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IRON OXIDE NANOPARTICLES AS THERMAL SEEDS IN MAGNETIC HYPERTHERMIA THERAPY

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ABSTRACT

we present the short review on Magnetic nanoparticle specifically for biomedical application. This study shows the overview on magnetic material properties and its biocompatibility. Here we are discussing some results of manufacturing iron nano particle in lab and its thermal propertie srelated to hyperthermia. Keywords- Magnetic nanoparticle (MNP).

INTRODUCTION

RATIONALE

Hyperthermia may be defined more precisely as raising the temperature of a part of or the whole body above normal for defined period of time. Hyperthermia is a type of cancer treatment in which body tissue is exposed to high temperatures, using external and internal heating devices. Research has shown that high temperature can damage and kill cancer cells, usually with minimal injury to normal tissues. The effect of hyperthermia depends on the temperature and exposure time. The difficulty in limiting heating close to the tumor region without damaging the healthy tissue is a technical challenge in hyperthermia. Use of magnetic nanoparticles can overcome the difficulty in spatial adjusting of power absorption by cancerous tissue.

Magnetic nanoparticles are designed to selectively be absorbed in tumor. Once in the tumor, they agitate under an alternating magnetic field and generate heat within tumor. Heat generation is due to different magnetic loss processes such as moment relaxation, mechanical rotation leading to the destruction of the tumor, whereas most of the normal tissue remains relatively unaffected. Engineering aspect of hyperthermia is selection of magnetic nanopartricle material. An important requirement of all selected materials is biocompatibility. CAD aspect of engineering requires modeling for treatment planning and computation of temperature distribution. More attention is now on development of most precise equipment for measurement of different parameters especially at clinical practice.

LITERATURE REVIEW

Alison E. Deatch, Benjamin A. Evans have talked about the fundamental concept of heat energy generated from magnetic nanoparticles. Magnetic field with high frequency causes heat generation by changing magnetic flux induces eddy current which produces resistive heating. This eddy current is significant in only centimeter scale or large material. Second is the hysteresis loss also produces the thermal energy. Hysteresis loss is nothing but the shifting of magnetic domain wall in multi-domain material. Third mechanism is relaxation including Neel and Brownion relaxation. Heating accomplished by moment rotation is the neel relaxation and heating due to physical rotation of particles is the brownion relaxation. Actually Both relaxation accour simultaneously.

He discussed the parameters which affect the heating efficiency. First parameter is the applied magnetic field: Magnetic field with high frequency and large amplitude may generate local heating tissues other than infected tissues. Super-paramagnetic particles generate heat at low magnetic field strength. If the product of field strength H and frequency f is limited to $Hf< 4.85x\ 10^8\ Am^{-1}s^{-1}$ does not produce excessive heating in patients. Second parameter he discussed is the nanoparticle diameter: particle size greater than critical grain volume dominate the hysteresis losses but that size may be greater than 100nm which do not penetrate easily and disperse within tumors. For magnetite the critical grain volume is at 15nm diameter. Below this size particle becomes super paramagnetic and both neel and Brownian relaxation become relevant mechanisms in iron oxide particles. Exactly where this neel and Brownian relaxation is significant is strongly depends on anisotropy constant. 13nm iron oxide particle shows high anisotropic constant thus Brownian relaxation become significant while for low anisotropy particles it becomes significant above 20nm. Specific Absorption Rate (SAR) strongly depends on applied magnetic frequency. As per study of the other SAR is maximum when $\omega\tau=1$ where ω is the field frequency and the τ is the effective relaxation time.

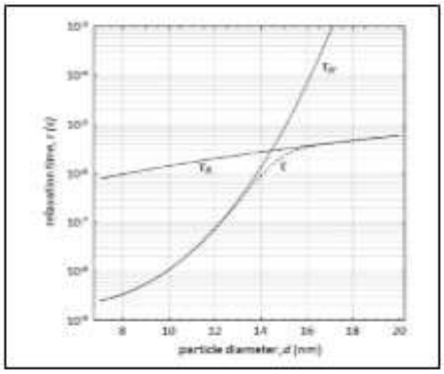

Figure 1 Relaxation times for single-domain magnetite nanoparticles. τ_N is the Neel relaxation time and τ_B is the Brownian relaxation time, dashed line is the effective relaxation time τ.

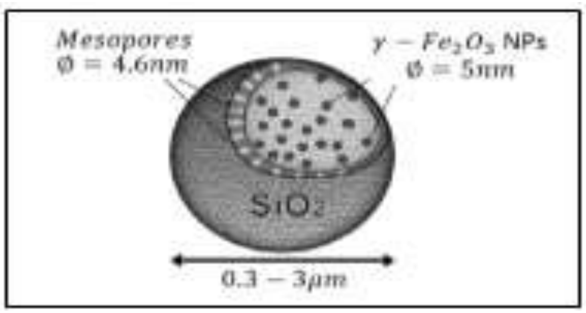

Figure 2 Schematic representation of MMS.

F. M. Martin-Saavedra reported his study about ability to conduct hyperthermia by using magnetic microspheres (MMS) of composite of mesoporous silica-matrix covered with biocompatible maghemite. The concept is to achieve excellent power absorption property by using alloy seeds showing significant advantage over magnetic hyperthermia. The desirable properties like colloid dispersion and biocompatibility can be enhanced by coating superparamagnetic nanoparticles of silica with inorganic or polymeric layers. MMS used for their work having size ranging from 0.3 to 3μm in diameter. High surface area of 479 m^2g^{-1} gives smooth surface with mesopores on these spheres having diameter of 4.6 nm. Fig.2. Shows schematic representation of MMS. Maghemite nanoparticles (5nm diameter) are encapsulated within a solid mesoporous silica sphere.

Jr-Jie Lai have prepared thermal seed of multicore $MnFe_2O_4@Sio_2@Ag$ for hyperthermia treatment. Silver and gold nanoparticles used as thermal seeds. They reported that these nobel materials could generate very high heat energy. The average particle size calculated by scherrer's method is 8.3 nm. Figure no.3 shows magnetization curve of $MnFe_2O_4$ magnetic nanoparticles (MC-MNPs) and multicore $MnFe_2O_4@Sio_2@Ag$ (MFA-MNPs). Curve gives saturation magnetization (57emu/g), specific remanent magnetization (0.003) and coercivity (318A/m) respectively for 8.3 nm MC-MNPs. and same parameters for MFA-MNPs saturation magnetization is 36 emu/g i.e. 63% of MC-MNPs. The size of MFA-MNPs is above 200nm. his indicates that all three parameter values of MC-MNPs are below the corresponding values of ferromagnetic MNPs which means that large size MC-MNPs shows superparamagnetic property. MFA-MNPs also show superparamagnetic property.

During experimentation on MFA-MNPs they used magnetic field from 1.3 kA/m to 4.7kA/m at 200 kHz. $MnFe_2O_4@Sio_2@Ag$ satisfying the hyperthermia treatment requirement.

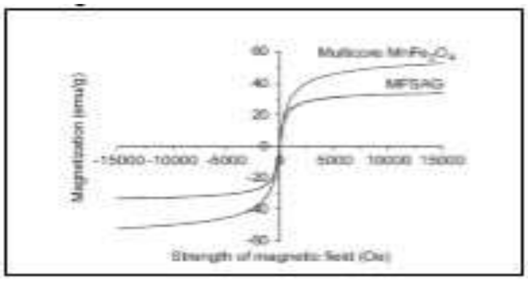

Figure 3 Magnetization curve of MC-MNPs & MFA-MNPs

D.H. Manh investigated the magnetic and structural properties of $La_{0.7}Sr_{0.3}MnO_3$. Transition metals like Fe, Co and Ni or metal oxides Fe_3O_4 and g-Fe_2O_3 have highly saturated magnetization. Highest saturation magnetization present in pure metals but pure metal is very sensitive to oxidation and highly toxic therefore nanoparticles of pure metals are not suitable for biomedical application. To achieve biocompatibility from pure metals additional surface treatments are carried out. Number of researcher studied about biocompatibility of magnetite and maghemite material which is very less sensitive to oxidation. Therefore these two candidates are more promising in hyperthermia application.

In the previous papers we have seen the spherical shape of the particles now the researcher from IIT Bombay Dr. G. seshadri have shown the study about optimization of nanorods size for heating application. Through the variety of synthesizing methods several group of study synthesized isotropic and anisotropic nanoparticles. They have shown relation between relaxation mechanism and the particle size. As the particle size decreases Neel relaxation time increases and Brownian relaxation time decreases. Therotical study of anisotropic MNP's shows that the optimally sized mono-disperse rod shaped and spherical shaped nanoparticles generates equal maximum power density. If the spherical and rod shaped nanoparticles compared according to the similar size distribution it shows that there is drastic increase in power generation by nanorods. In case of small size nanoparticles the heat loss predominantly due to Neel relaxation and for large sized nanoparticles heat loss is due to Brownian relaxation. When the entire particle physically rotates in the solution it is called Brownian relaxation therefore Brownian relaxation time is directly proportional to the viscosity of the medium. Model of rod shaped particle is of prolate ellipsoid. The moment of inertia about the axial rotation is low compare to other round and perpendicular axis rotation therefore friction factor related to axial rotation is considered. Power generated per unit volume of nanoparticle is given by equation no. 4. It shows that power generated varies linearly with the external applied oscillation frequency when$f\tau \gg 1$, if $f\tau \ll 1$ power generated tends to zero. Maximum power generation occur when$f\tau = 1$.

$$P = \pi\mu_0\chi_0 H_0^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2} \quad ....(4)$$

Researcher observed that the MNP's generating the heat in volumetric nature and the shape affects on Brownian relaxation time and the anisotropic constant (k). In case of rod shaped nanopaticles we have to consider not only magneto-crystalline anisotropic constant (k_{mag}) but also shape anisotropy (k_{shape}). Researcher concluded that the monodisperse rod-shaped particle have the same maximum power generation as monodisperse spherical particles gives the greater anisotropic energy of rod shaped particles. This anisotropic energy increases the spread of the power density distribution curve. The loss power density generated by rod-shaped particles is greater than that generated by spherical particles with the same deviation in the radius.

T.-H.Tsai reported his work on thermal conductivity of nanofluid of Fe_3O_4 and Al_2O_3 with various base fluids. The variation in the volumetric fractions between two fluids changes the viscosity of mixed fluid. Their team observed that the consideration of effect of Brownian relaxation in conventional Maxwell model is zero. Therefore the experimental results shows the higher thermal conductivity of nanofluid compared to model result. During experiment they tried two nanofluids one of Fe_3O_4 with base fluid of viscosity 4.188cP and second with base fluid of viscosity 140.4cP. Nanofluid of 1.12% volume fraction of Fe_3O_4 with oil base as diesel with viscosity of 4.188cP shows $K_{ano}/K_{bf} > K_{maxwell}$. And the oil with viscosity 140.4cP shows $K_{ano}/K_{bf} = K_{maxwell}$. Therefore it is concluded that the brownion motion of nanofluid with high viscosity disappear.

MANUFACTURING OF IRON NANOPARTICLES

Among the various methods for producing nanoparticles, co precipitation has the advantages of being relatively simple and providing good control over particle properties. Introducing a suitable surfactant during or after the synthesis prevents aggregation of the nanoparticles and makes a stable colloidal dispersion possible. Study shown that alkyl phosphonates and phosphates also bind to magnetite particles well and render their surfaces hydrophobic. Aqueous colloidal dispersions of magnetic nanoparticles hold great potential for use in a variety of new and existing bioprocesses because of the compatibility of the aqueous medium with bio systems.

Nanoparticle Synthesis

Magnetite particles were prepared by co precipitation of Fe3O4 from a mixture of FeCl2 and FeCl3 (1:2 molar ratio) upon addition of NH4OH. In a typical reaction, 4 g FeCl2 and 10.904 g FeCl3 were mixed in 186.4mL water and heated to 80 °C under Nitrogen in a three-necked flask. While vigorously stirring the reaction mixture, 23.25 ml of NH4OH was introduced by syringe, and the heating continued for 30 min. After that, 4.65 g of Citric Acid in 9.3mL water was introduced, the temperature was increased to 95°C, and stirring continued for an additional 90 min. stirring is done at two different speeds one is at 400 rpm and second at 800 rpm. A small aliquot of the reaction mixture was withdrawn, diluted to twice its initial volume, placed in a vial, and then subjected to a static magnetic field of several hundred Gauss. The particle remained dispersed in the fluid even in the presence of

Figure 4 Manufactured magnetic Iron nano particles

the external field indicating that a stable colloidal solution had formed.
At this stage particle formed were coated with citric acid and there is excess amount of citric acid present in solution. To remove excess citric acid, centrifugation has to be given. The solution is rotated at 15000 rpm for about 15 minutes. The particles were settled at bottom and the excess citric acid was removed. The solution was washed three times with distilled water. The aliquot of magnetite nanoparicles was collected in petri dish and it was kept in a vacuum oven for 16 hours at 600C temperature to obtain nano particles. Nanoparticles obtained were crushed in crucible to obtain fine powder. Figure 4 shows the manufactured power contains the magnetic property.

CHARACTERISATION OF MAGNETITE NANOPARTICLES

XRD can be used to look at single crystal or polycrystalline materials. 1A^0 is equal to 0.1 nm. To determine various characteristics of crystal Bragg's law is used. Used wavelength of x-ray is λ = 0.154 nm. XRD method is time consuming and requires large volume of sample. XRD determine the average size of particles, d-spacing and expected 2θ position with relative intensity. Figure 5 shows the XRD result at 400 rpm.

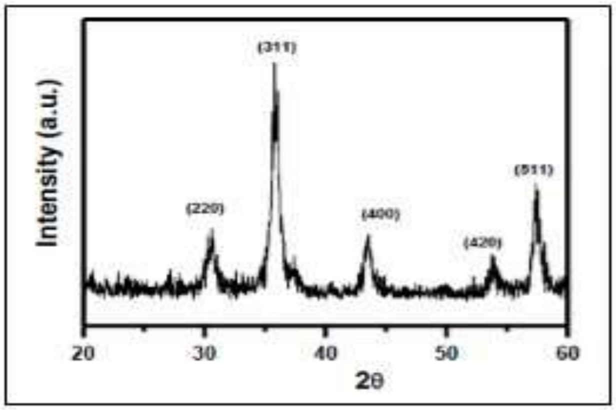

Figure 5 XRD plot @400 rpm

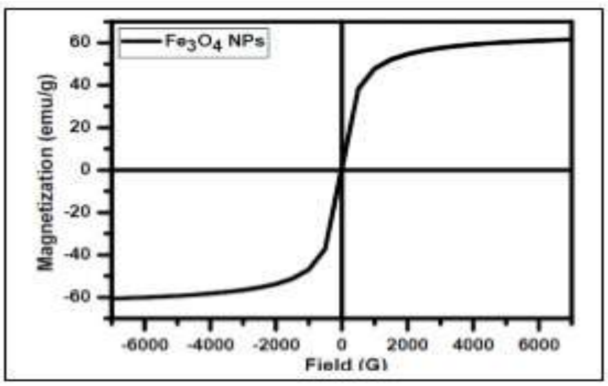

Figure 6 Output result of VSM test

As seen in table I and table II the two different stirring speeds used during synthesis affects on the average particle size and its uniformity. Table I shows the calculated and observed values from XRD result at 400 rpm and table II shows the calculated and observed values from XRD result at 800 rpm.

Vibrating Simple Magnetometer (VSM) measures the magnetic properties of material. When a material is placed within a uniform magnetic field is and made to undergo sinusoidal motion (i.e. mechanically vibrated), there is some magnetic flux change. This induces a voltage in the pick-up coils, which is proportional to the magnetic moment of the sample. From above Graph it is found that magnetisation is 62 emu/gm.

Fourier Transform Infrared Spectroscopy (FTIR) spectroscopy shows that the surface passivation of the particles occurs via the -COOH group. Figure shows the FTIR spectra of magnetite particles coated with citric acid (MP-CA).The 1650 cm-1 @ 800 rpm and 1630 cm-1 @ 400 rpm peak assignable to the C=O vibration in MP-CA. Carboxylate groups of CA should complex with the Fe atoms on the magnetite surface and render a partial single bond character to the C=O bond, weakening it, and shifting the stretching frequency to a lower value. This observation is similar to the citrate complex in γFeO3 studied by Todorovsky et al. It is proposed that CA binds to the magnetite surface by chemisorption of the carboxylate that is citrate ions.

TABLE I AVERAGE DIAMETER FROM XRD RESULT (@400 RPM)

Peak (plane)	**2θ**	**d-spacing (A0)**	**Peak Index**	**β (radian)**	**Diameter D (nm)**
220	30.53	2.926	8.089	0.0230	6.250
311	35.78	2.508	11.010	0.0138	10.576
400	43.68	2.071	16.147	0.0138	10.843
420	53.68	1.706	23.795	0.0113	13.706
511	57.63	1.598	27.121	0.0206	7.688
Average Diameter of particles=					**9.812**

TABLE II AVERAGE DIAMETER FROM XRD RESULT (@(800 RPM)

Peak (plane)	**2θ**	**d-spacing (A^0)**	**Peak Index**	**β (radian)**	**Diameter D (nm)**
220	30.29	2.937	8.028	0.0162	8.849
311	35.78	2.507	11.024	0.0161	9.076
400	43.41	2.082	15.976	0.0183	8.145
420	54.20	1.690	24.240	0.0298	5.220
511	57.36	1.604	26.920	0.0215	7.364
Average Diameter of particles=					7.730

FERRO-FLUID PREPARATION

Ferrofluids are the colloidal liquids made of nanoscale ferromagnetic particles suspended in a carrier fluid (usually an organic solvent and water). Each tiny particle is thoroughly coated with a surfactant to inhibit clumping. Large ferromagnetic particles can be ripped out of the homogeneous colloidal mixture, forming a separate clump of magnetic dust when, when exposed to strong magnetic fields. The magnetic attraction of nanoparticles is weak enough that the surfactant's Van Der Waals force is sufficient to prevent magnetic clumping or agglomeration. Ferro-fluids usually do not retain magnetization in the absence of an external magnetic field and thus are often classified as "Superparamagnets" rather than ferromagnets.

Surfactants used commonly are Citric acid, Oleic acid, Tetramethylammonium hydroxide, Soy lecithin, etc. Citric acid is hydrophilic in nature. Hence we can use water, Ethylene glycol etc. as a base fluid. Other surfactants are hydrophobic in nature and base fluids used are canola oil, silicon oil etc. Citric acid is hydrophilic in nature. Hence we can use water, Ethylene glycol etc. as a base fluid.

Measured density of Iron oxide nanoparticles is 1.667 gm/cm3. There are two sample prepared as 10mg/ml add 1.67 gm of nanoparticle in 100ml distilled water and for 5 mg/ml we have added 0.835 gm of nanoparticles in 100 ml of distilled water.

SONICATION PROCESS

All the test samples of Fe_3O_4 nanofluids are use subsequently for estimation of their properties were subjected to magnetic stirring process followed by ultrasonic vibration for about 5 hrs. The Fe_3O_4 nanofluid samples thus prepared are kept for observation and no particle settlement was observed at the bottom of the flask containing Fe_3O_4 nanofluids even after 4 hrs.

The thermal conductivity for concentrations 5mg/ml is 0.216 mS (Micro Siemens) and for 10mg/ml, it is 1.34 mS at room temperature.

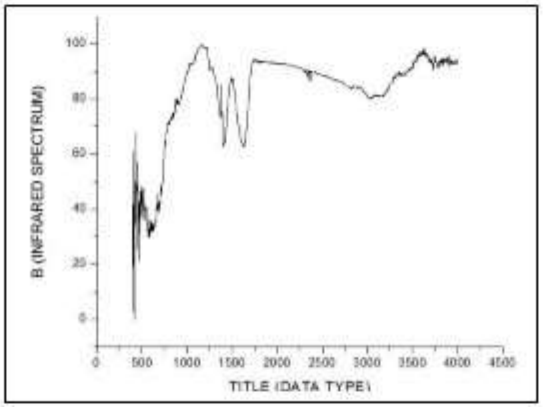

Figure 7 FTIR plot (@ 400 rpm steering sample)

INDUCTION HEATING OF PREAPRED IRON OXIDE NANO PARTICLES

In smaller single domain magnetic particles, called super paramagnetic nanoparticles – less than 20 nm in diameter for Iron Oxide Fe3O4 (Magnetite) MNP the difference between the magnetic moment maximum and minimum potential energy per unit volume of the particle is much smaller than its thermal energy. Ferrofluid of concentration 10mg/ml shows rise in temperature suddenly to 29.5 °C from atmospheric temperature when held in induction coil. After one minute the temperature changes to 30.5 °C and as time passes per minute rise in temperature increases. As per process of hyperthermia treatment to kill cancer cell required temperature is 42°C to 45 °C. The results of induction heating are tabulated in table III. The interesting observation is that the rise in temperature up to 45°C requires 9 min for sample-I and after nine minute the 45°C temperature remains constant for 1 Hr. and near about same case is observed for sample-II. Figure 8 shows the MATLAB simulation for generating heat in cancer tissue/ tumor due to nanofluid.

CONCLUSION

The prepared nanoparticles Fe3O4 are coated with citric acid (carboxylic groups) which is biocompatible. Hence, Nanoparticles are safe for hyperthermia treatment. At 400 rpm the average particle size is 9.81 nm and at 800 rpm the average particle size is 7.73 nm. Hence, we can conclude that at higher rpm we get fine particle size. As the surfactant used (citric acid) is hydrophilic in nature, hence we have used water as base fluid. The density of nanoparticle is found to be 1.66 gm/cm3. We prepared two samples of nanofluid of 100ml each for 10mg/ml and 5 mg/ml concentration. Thermal conductivity of 10 mg/ml solution is 1.34 mS and that of 5mg/ml is 0.216 mS. Hence, we can conclude that as concentration increases, conductivity also increases. Thermal conductivity has a effect on heat generation. More the thermal conductivity, less the time required for achieving uniform temperature.

TABLE III TEMPERATURE RESULT FOR BOTH SAMPLES

Sr. No	**Time (min)**	**Temperature (°C) For 10mg/ml (Sample-I)**	**Temperature (°C) For 5mg/ml (Sample-II)**
1	0	29.5	29.5
2	1	29.5	29.5
3	2	30.5	30.5
4	3	32	31.5
5	4	34	33
6	5	39	36
7	6	42	39
8	7	45	40
9	8	45	42
10	9	45	42

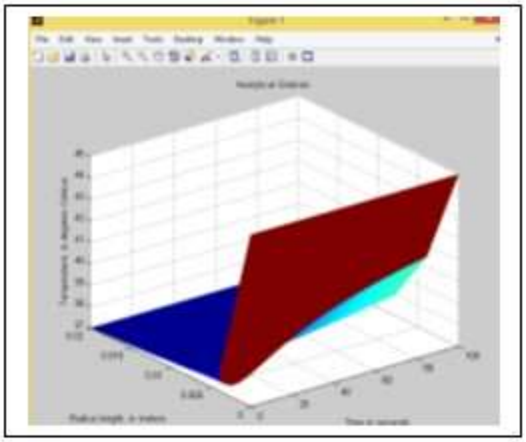

Figure 8 MATLAB Simulation

FUTURE SCOPE

This experimental study of manufacturing of iron oxide nanoparticles by biosynthesis is required. And the study of different reasons of stability in temperature is required.

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