Review on 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. Moreover focusing on engineering aspect of hyperthermia.**

Keywords- **Magnetic nanoparticle (MNP)**

I. INTRODUCTION

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.

II. LITERATURE REVIEW

Alison E. Deatch, Benjamin A. Evans hav 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.

$$\tau_N = \frac{\tau_0}{2}\sqrt{\pi\frac{kT}{kV}}\; e^{\frac{kV}{kT}} \text{ ....(1)}$$

$$T_B = \frac{3\eta V_H}{\kappa T} \text{.......................................(2)}$$

$$\frac{1}{\tau} = \frac{1}{\tau_B} + \frac{1}{\tau_N} \text{.......................................(3)}$$

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.

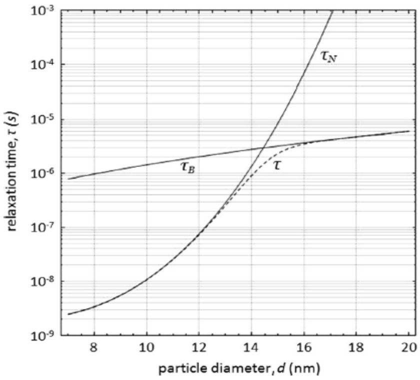

Figure 1: Relaxation times for single-domain magnetite nanoparticles. τ_N is the Neel relaxation time and τ_B is the Brownian relaxation time, dashed line is the effective relaxation time τ.

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. From Fig.1. It is observer that Brownian relaxation are an the order of 10^{-5} s and to maintain $\omega\tau=1$ ω would need to be 10^5 rad/s (f=15kHz) which is very low than frequency reported in hyperthermia studies. Typical reported frequencies ranges from 100 to 300 kHz which shows relaxation time on order of 10^{-6}sTherefore for particles diameter ranging from 7 to 15 nm Neel relaxation is expected to be dominant. Eq.(1). Shows exponential relation with particle volume thus SAR is highly sensitive to diameter.

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. Author selected human cells of cancerous nature A549, Saos-2, and HepG2 for experimental study. The major things observed are there is effect on cellular spreading and cellular area after treatment. There is no nuclear fragmentation or condensation. Fig.3. shows the relative cell viability as per the dose.

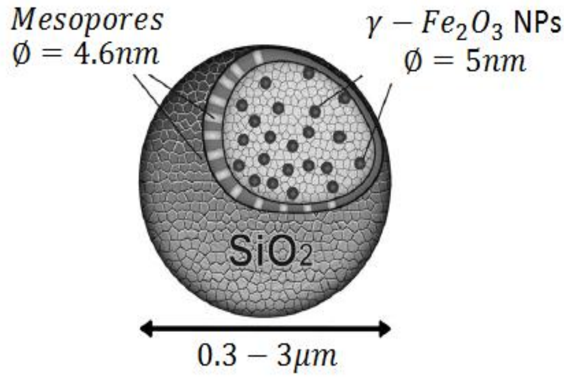

Figure 2: Schematic representation of MMS.

This shows that the particle internalized per HepG2 cell is lower compare to other two cells and at the high dose cell viability dropped up to 60%

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.4 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. This 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. The solution-1 prepared in water is denoted as dispersion and when the contribution of Brownian relaxation is removed by aggregation called aggregate solution. The heating ability under external magnetic field increases from Brownian to Neel relaxations. From the investigation of SAR values of solution 1 shows linear relation with square of field strength (H). The major result shown is that the aggregated solution shows the same relation i.e. H^2-law of SAR and the heat generated is mainly from Neel relaxation. $MnFe_2O_4$@Sio_2@Ag satisfying the hyperthermia treatment requirement.

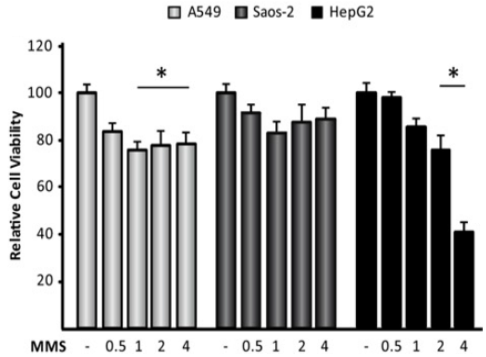

Figure 3: Relative cell viability exposed to MMS for 3 days.

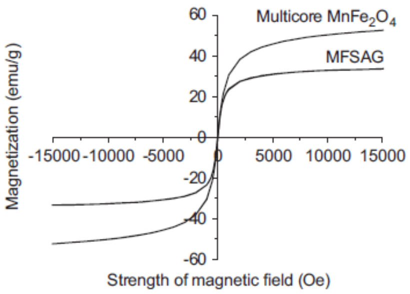

Figure 4: Magnetization curve of MC-MNPs & MFA-MNPs

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.

$La_{0.7}Sr_{0.3}MnO_3$ (LSMO) has higher magnetic moment at room temperature and their curie temperature can be easily adjusted between 315 and 350 K. Following reaction using 99.9% pure La_2O_3, MnO_2 and $SrCO_3$ gives nanopowder of $La_{0.7}Sr_{0.3}MnO_3$ of size ranging from 20 to 50 nm.

$$La_2\,O_3 + 0.3SrCO_3 + MnO_2 \rightarrow La_{0.7}Sr_{0.3}MnO_3 + \frac{0.7}{4}O_2 + 0.3CO_2$$

During the process of preparation of nanoparticles it is clearly observed that particle size increases with increase in annealing temperature.

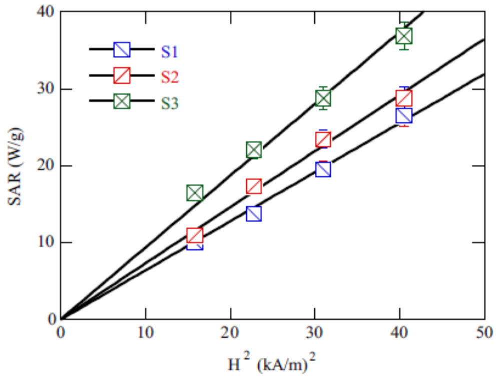

Figure 5: Graph of SAR Vs Strength of magnetic field (H)

Spherical shape obtained for most of the particles. Theoretical density of LSMO is 6.45 g/cm^3. Specific surface area increases with decrease in diameter of particle. The particles shows the single domain below the critical diameter calculated by formula as follows

$$d_c = \frac{18\sqrt{A_{ex}K}}{\mu_0 M_s^2}$$

Where K is the uni-axial anisotropy constant, A_{ex} is the xchange stiffness; μ_0 is the vacuum permeability and M_s the saturation magnetization. Critical diameter mainly depends on type of material, for Fe it is about 6nm, 60nm for Fe_3O_4, 80nm for $La_{0.7}Ca_{0.3}MnO_3$ and for $La_{0.7}Sr_{0.3}MnO_3$ it is 70nm.

This researcher has used particle size ranging from 20 to 50nm. They concluded that the SAR value depends on the size of the particle and the applied AC magnetic field frequency. For sample of 50nm the observed specific absorption rate is 36.87 W/g. Sample S1 sintered at 700°C gives size 20nm, sample S2 sintered at 800°C gives size 30nm and third sample S3 sintered at 900°C gives size 50nm shows the effect on SAR shown in fig. 5

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$f\tau = 1$.

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

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.

Huoqing Yang reported his work on MEMS temperature sensor in his paper. Precise measurement of temperature of cancerous cell in human body is the big challenge. Most of the temperature sensors are manufactured on one side of the silicon film which cannot sense uniformly the temperature inside the tumor from all sides thus they tried to develop helical sensor on the capillary tube. For the manufacturing of such MEMS sensor they used spray coating on capillary surface and cylindrical projection lithography. Platinum is selected as material for key sensing element. Capillary is of dimension 300µm outside diameter. And the platinum coated is of 0.12µm thickness. This temperature sensor can be used in several monitoring devices in several biomedical applications.

III. CONCLUSION

Neel relaxation mechanism is the key for achieving heat generation. But we focus on improving Brownian relaxation time will result in more effective for treatment. Fluid with low viscosity improves the Brownian relaxation time. Multi-core thermal seed generates high heat energy. Different materials has different critical size of diameter.

IV. FUTURE SCOPE

This review of nanoparticles used for hyperthermia treatment highlights the area where there is large scope for the research on material selection to achieve more biocompatibility. The second area for research is the MEMs technology for developing sensor for the same treatment.

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