Selecting appropriate Magnetic Nanoparticles for Hyperthermia

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Abstract

Due to immature cells, low blood flow rate, high density and lack of oxygen environment inside the tumour, it is experimentally seen that, tumour cells at temperature between 42°C and 46°C the viability of the cancerous cells is reduced (e.g. [5], [14]). Therefore efficiency of chemotherapy and radiation are increased. In recent years, due to the development in the area of nanotechnology, magnetic nanoparticle (MNPs) hyperthermia has been deeply studied as a promising new tumour therapy, because in presence of alternating magnetic field they show remarkable heating effects.

In order to achieve efficient and safe operational hyperthermia conditions, it is necessary to study or investigate detail about what heating model or magnetic loss processes dominant over the other in the ensemble of nanoparticles which are injected at the cancerous tumour sites. Because there are more than one heat loss process involved in generating heat by MNPs. First experimental work on magnetic materials for hyperthermia was carried out by Gilchrist in 1957(e.g. [1]). He heated various tissue samples with the help of different sizes of γ *-* Fe_2O_3*. Since then, there have numerous theoretical and experimental work been done by so many people on different nanoparticles. Here, in this work we compare theoretical results given by different MNPs. And taking into account cellular uptake mechanism it is showed that at a low frequency of applied magnetic field maghemite and at a high frequency of applied magnetic field FeCo are the best magnetic particle to use for the hyperthermia.*

Keywords - *Magnetic Nanoparticles (MNPs), Nanoparticles (NPs), Relaxation time, Critical size, blocking temperature.*

I. INTRODUCTION

"Those who cannot be cured by medicine can be cured by surgery. Those who cannot be cured by surgery can be cured by heat. Those who cannot be cured by heat are probably incurable**"** *Hippocrates - 470-377 B.C.*

Generally, tumour is the cluster of cells undergoing uncontrolled growth of cell in the body. These cancerous cells are more sensitive to temperature in the range 42-46°C compared to healthy cells (e.g. [5]). Therefore different theoretical and experimental studies have been done in last few decades on the field of oncology to kill cancerous cells by increasing the temperature of the cancer cells. Main problem involved in the traditional tumour or cancer therapy are that this method also damages the healthy tissue along with the cancer cells. And also in this process the use of powerful toxic drugs results in an unwanted side effect in our body. Development in nanotechnology has provided magnetic nanoparticles hyperthermia, one of the most promising approaches in cancer therapy to come out with a solution of above problems by localized heating inside the tumour. Magnetic naoparticles hyperthermia has negligible side effect compare to other process.

In magnetic nanoparticles hyperthermia, MNPs are injected near the tumour site. Once the MNPs are deposited on the site then an alternating magnetic field is applied for maximum 40-50 mins. The energy of this alternating magnetic field is absorbed by the magnetic nanoparticles and these particles are being exited to higher energy level. This excess energy of the particles is dissipating as heat to the surrounding. Since, in tumour low blood flow rate, high density condition is present, this helps localised heating inside the tumour. Thus healthy tissue will be unaffected by this treatment.

Different mechanism is involved in the heating process of the MNPs in the presence of alternating magnetic field. And also dependency of heating powers on the size of the MNPs makes the process more interesting and theoretical. First experimental investigations of the application of magnetic materials for hyperthermia are carried out by Gilchrist in 1957 (e.g. [9]). He heated various tissue samples different sizes particles of γ -Fe_2O_3 exposed to a 1.2 MHz magnetic field. After that many other theoretical as well as experimental work have been performed with different MNPs. Here in this novel work we also take into account cellular uptake mechanism and we theoretically showed that maghemite and FeCo will be the best nanoparticles for hyperthermia process.

II. THEORETICAL BACKGROUND

MNPs are subjected to an alternating magnetic field to turn them into a heat source. There are three different mechanisms by which magnetic materials can produce heat in presence of an alternating magnetic field. These are

1. Generation of eddy currents in magnetic particles.
2. Hysteresis losses in multi-domain MNPs,

3. Relaxation losses in 'super paramagnetic' single-domain MNPs,

But for the case of MNPs, heat produce due to eddy current decrease considerably as the size of the magnetic particles reduced to nanometer range. And also to generate heat by eddy current required high frequency alternating magnetic field. At a high frequency field eddy current also generates heat in the normal tissue. This causes the serious side effect to the patients. So in modern magnetic nanoparticle hyperthermia eddy current loss does not take into account.

The hysteresis loop of magnetic materials is characterized mainly by three typical material dependent parameters: Saturation magnetization M_S, Remnant magnetization M_R and coercivity H_C. All these parameters are important for the heat output of nanoparticles and may vary considerably for different particle types.

The power dissipated by a per unit mass magnetic material per oscillation subjected to an alternating magnetic field is often called the "Specific Absorption Rate" (*SAR*)of magnetic hyperthermia. For a field amplitude H it is expressed as (e.g. [3])

$$\text{SAR (H)} = 0 \qquad H \le H_C$$

$$= \frac{4 B_R H_c f}{\rho}\left(1 - \left(\frac{H_C}{H}\right)^5\right) \qquad H > H_C$$

B_R is remnant flux density.

One of the most unique things in magnetic nanoparticle is that the value of coercivity is strongly dependent on the size of the particles. At first as the size of the particle decrease to nanoscale, coercivity increase, but at particular size of the nanoparticle, coercivity achieve the maximum value afterwards it decrease sharply as the size of the particle further decrease. This size dependent coercivity value for particle size D can be expressed as (e.g. [3])

$$H_C(D) = H_M\left(\frac{D}{D_1}\right)^{-0.6}\left[1 - \exp(-D / D_1)^5\right]$$

Where, D_1 is a constant. Since SAR value is strongly depend on H_C, so *SAR* value also changes with size of the nanoparticles. So, for a very fine small particle hysteresis contribution to heat dissipation is very small (e.g. [12]).

Mainly, in nanoscale range relaxation loss is alone responsible over the other two mechanisms for heat generation process of MNPs.

A. *Relaxation loss*

Magnetic domains exist in macroscopic samples in the magnetic materials, and they are separated by domain walls. Because of spin-orbital interactions of the electrons in the NPs produce magnetic anisotropy. For isolated systems, the magnetic anisotropy is responsible for keeping the spins in a particular direction. Since atomic orbital have non-spherical shapes, therefore they try to align in a specific direction which is called the easy direction. Energy is required in order to rotate the magnetization away from the easy direction. This required energy is called the anisotropy energy. In general, the anisotropy energy per particle is expressed by $E = KV^2 \sin\theta$ where K is the anisotropy constant (it includes all sources of anisotropy), V (=r^3) is the volume of the particle, and θ is the angle between the particle magnetization and the easy magnetization axis of the particle (e.g. [4], [13], [14]). The higher order terms can be neglected from the above equation. It is seen that the anisotropy energy directly depends on the particle size and the anisotropy constant. For a fixed anisotropy constant *K*, as the size of the particle *r* decreases, anisotropy energy *E* also decreases. At nanoscale size, the particle prefers to have only one magnetic domain and it is called as single-domain NP. At this very small size, the anisotropy energy become smaller than the thermal energy, $E_{th} = k_B T$ (k_B is the Boltzmann constant). Therefore, in the absence of an external magnetic field the particle magnetic moment starts to rotate freely in all probable directions leading to zero net magnetization. While the particle orientation is fixed, if the flipping of magnetic moment start, then the relaxation time of the moment is called the Neel relaxation time τ_N, and is given by: (e.g. [2], [13], [14])

$$\tau_N = \tau_0 \exp(KV / k_B T).$$

Where, $\tau_0 \sim 10^{-9}$ s.

In a fluid medium of viscosity η, additionally a second relaxation mechanism occurs due to rotation of the particles itself is commonly referred to as Brown relaxation with the characteristic relaxation time (e.g. [2])

$$\tau_B = \tau_0 . \frac{3\eta V_h}{k_B T}.$$

V_h (=r_h^3) is the hydro-dynamically effective volume, which is differ from the geometrical volume. Including the ligand layer, hydrodynamic volume can be written as: (e.g. [2])

$$V_h = \left\lceil \frac{\Pi (D + 2\delta)^3}{6} \right\rceil .$$

Where D is the diameter of MNP and δ is the ligand layer thickness.

Of course, particles will choose the energetically 'easiest way' for reversal of magnetization. This means that reversal will occur via the process which has the smaller relaxation time. Neel relaxation decreases faster compare to Brown relaxation due to the exponential dependent of volume of the particle. An effective relaxation time τ_{eff} can be defined by

$$\tau_{eff} = \frac{\tau_N \tau_B}{(\tau_N + \tau_B)}.$$

B. Blocking temperature

Imagine that the magnetization of a single super-paramagnetic nanoparticle is measured in time τ_m. If $\tau_m > \tau_{eff}$, the nanoparticle magnetization will flip several times during the measurement, then the measured magnetization will average to zero. If $\tau_m < \tau_{eff}$, the magnetization will not flip during the measurement, so the measured magnetization will be what the instantaneous magnetization was at the beginning of the measurement. In the former case, the nanoparticle would appear to be in the super paramagnetic state whereas in the latter case it would appear to be "blocked" in its initial state. The state of the nanoparticle depends on the measurement time. A transition between super paramagnetism and blocked state occurs when $\tau_m = \tau_{eff}$. In several experiments, the measurement time is kept constant but the temperature is varied, so the transition between super paramagnetic and blocked state is seen as a function of the temperature. The temperature for which is called the blocking temperature

$$T_B = \frac{KV}{k_B \ln\left(\frac{\tau_m}{\tau_0}\right)}.$$

C. Power Dissipation

The internal energy of a magnetic system in an adiabatic process is $U = -\mu_0 \oint MdH$. (e.g. [2], [4], [13], [14]). The power dissipation in unit second due to magnetic field of frequency *f*, is $P = Uf$ (e.g. [4]). The volumetric power dissipation of magnetic nanoparticles can be defined as $p = \pi\mu_0 \chi'' H^2 f$ (e.g. [4]). Where μ_0 is the permeability of the free space and χ'' is the imaginary part of the susceptibility $\chi(\chi = \chi' - i\chi'')$ and it is defined as (e.g. [2], [4], [13])

$$\chi'' = \frac{\omega\tau}{1 + (\omega\tau)^2}\chi_0.$$

Where

$$\chi_0 = \chi_i \frac{3}{\xi}\left(\coth \xi - \frac{1}{\xi}\right).$$

Where ξ and χ_i are the Langevin parameter and initial susceptibilityis respectively

$$\xi = \frac{\mu_0 M_D H V_M}{k_B T}.$$

$$\chi_i = \frac{\mu_0 M_s M_D V_M}{3 k_B T}.$$

Here, M_D and V_M are the domain and saturation magnetization, respectively. From the above equations the heat losses by MNPs in a fluid medium when exposed to an ac field are not only dependent on the amplitude and frequency of the applied magnetic field, but also depend on the physical and magnetic properties of the MNP and the material parameters of the carrier fluid.

D. Cellular Uptake

Heat dissipation by hyperthermia is an intercellular process. So for efficient hyperthermia high cellular uptake rate of the nanoparticles is very mush necessary. Generally surface of the cell membrane covered with receptors. When particles come close to the receptors they selectively bound the particles. As a result, some chemical energy is released, which is equal to $L_b \varepsilon$. Where L_b is the number of receptors in the membrane that bound the particles and ε is the chemical energy that released for each bound receptors. Using this chemical energy, receptors pull the nanoparticles towards the inside of the membrane to intercellular compartment. Considering all the mechanism that are effecting the cellular uptake process it is calculated that there is a critical size for which cellular uptake of the particles is maximum, which is equal to (e.g. [1])

$$R_c = \sqrt{\frac{2\kappa A}{k_B T \varepsilon}} = (\sim 19\text{nm}).$$

Where, κ (~$20k_BT$) is the bending modulus of the membrane and A is the area of the each receptors. For the nanoparticles which are smaller than this size cellular uptake is negligibly small. And also as the size increase above this critical value cellular uptake decrease linearly with the size.

E. Analysis

In hyperthermia we need high heat dissipation loss by the nanoparticles. From the figure1 we see that various nanoparticles have maximum heat dissipation for certain size of the particle. Above and below this size heat dissipation value drops down quickly. From this we can conclude that size distribution of the nanoparticle should be very small for efficient hyperthermia treatment. And among the various particles FeCo has high heat dissipation.

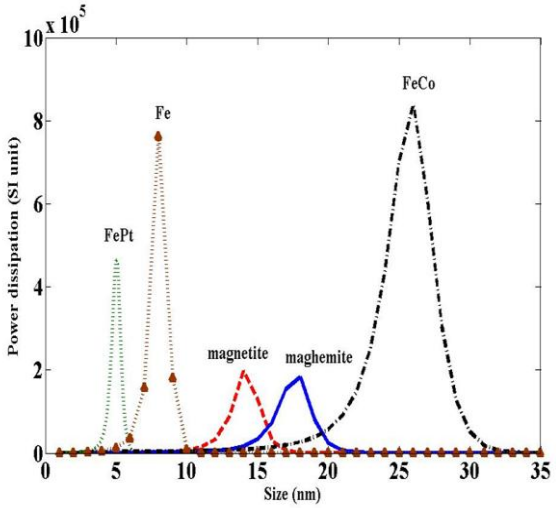

Fig 1: Profile of Power Dissipation with Variation in Size of the Magnetic Nanoparticles for Different Nanoparticles.

Different particles with maximum heat dissipation critical size particle are the given below:

Materials	$Q_{max\ (w/m^3)}$	Critical size (nm)
FePt	4.5×10^5	5
Fe	7.9×10^5	8
FeCo	8.2×10^5	27.5
Fe_3O_4	2.1×10^5	13.5
γ -Fe_2O_3	2×10^5	19

Now using the data for maghemite we plot a profile of heat dissipation with variation in size of the particle for different frequency of the applied ac magnetic field at constant field amplitude.

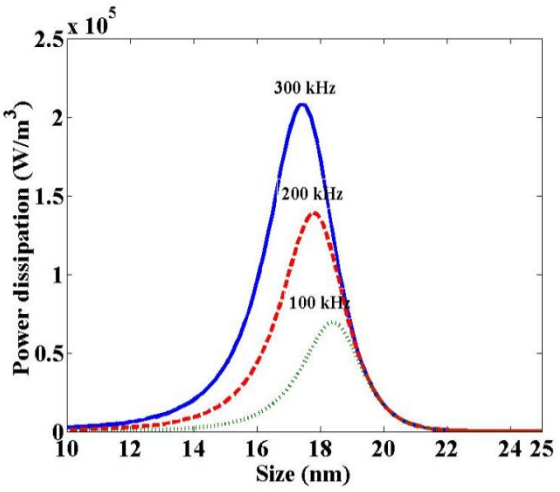

Fig 2: Profile of Power Dissipation with Variation in Size of the Magnetic Nanoparticle at Different Frequency of Alternating Magnetic Field for Maghemite.

Similarly using the same equation for maghemite we plot heat dissipation profile with variation in size of the particle for different amplitude of the field at a constant frequency. It is observed the figure that as the amplitude of the magnitude field increase heat dissipation also increases sharply. But critical size of the particle does not change with the field unlike the change in the frequency of the ac field.

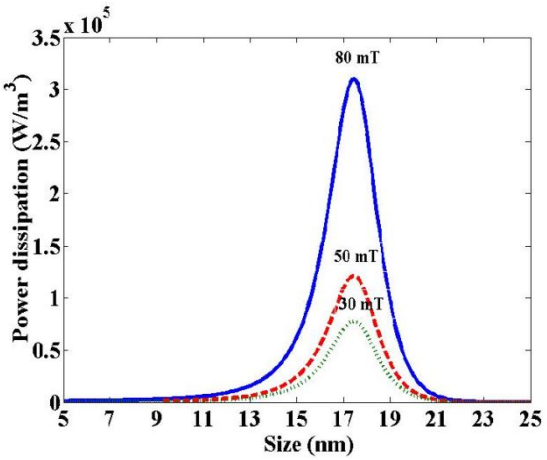

Fig 3: Profile of Power Dissipation with Variation in Size of the Maghemite Nanoparticle at Different Amplitude of Magnetic Field.

Result

From the figure 2 we have seen that power dissipation increase as we increased the frequency of the magnetic field. Another point we conclude from the profile is that critical size at which maximum dissipation occur is decrease as we increase the frequency of the field. The profile of variation of critical size with the variation in frequency of the field is shown in the figure 4.

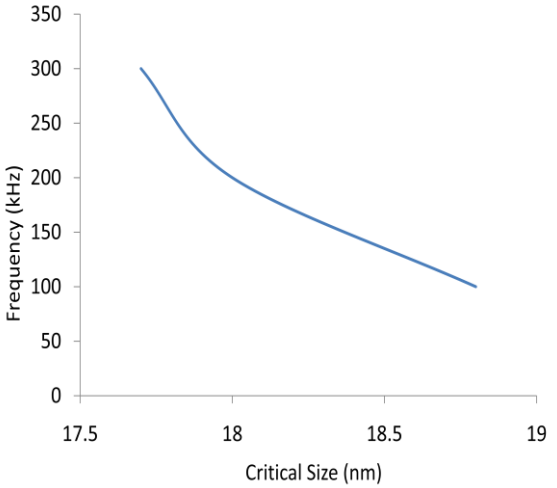

Fig 4: Profile of Critical Size at Which Maximum Dissipation Occurs With Variation in Frequency of The Applied Field as Per the Figure 2.

As we already discussed that hyperthermia would be efficient only when cellular uptake has a high value. From the cellular uptake mechanism we know that cellular uptake has an optimal value for the critical size of the particle near the size 19 *nm* (e.g. [1]). And from the above figure we see that maghemite has the maximum value of heat dissipation at the critical size 18.8 *nm* for 100 kHz frequency of applied magnetic field. So from these two points we can conclude that maghemite is an efficient nanoparticle for hyperthermia.

And since cellular uptake has an optimal value for range 19-25*nm* (e.g. [1]), hence FeCo also can be used as MNP for hyperthermia for high frequency of applied magnetic field. Because FeCo has a very high heat dissipation values in the range 22-28 *nm.*

Though FePt and Fe have high heat dissipation but due to their low cellular uptake they are not consider for efficient hyperthermia.

It is an interesting and challenging task for future research to achieve efficient and safest magnetic particle hyperthermia.

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