Magneto Hyperthermia and Cancer Therapy

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Introduction

Cancer derives its name from the fact that the tumours were observed by the earliest doctors to look like crabs. Even the earliest doctors recognized the difference between malignant cancers, which spread slowly through the lymph system to all parts of the body and slowly killed the victim, and the other more benign variety. The causes of cancer though have always been a subject of controversy and through the annals of time we can observe various attempts at explaining and treating cancer, which to a modern mind may sound frivolous but were once upon a time influential enough to have an effect on the wellbeing of the sufferer. With the birth of modern medicine and the improvement of hygiene, surgery became the preferred option for the treatment of cancer. Also the discovery of the cellular structure of tissue fundamentally changed mankind's understanding of cancer. This led to the investigation of treatment methods based on the promotion of selective death of cancerous cells such as radiation and chemotherapy.

The idea of using heat as a mode of treatment is certainly not a new one. All traditional systems of medicine place a lot of emphasis on the therapeutic value of heat. The use of heat in cancer therapy is not new with the first provable (in western medicine) account being that of Hypocrites. The method was revived in the late 19th century using electromagnetic principles.

The method works primarily on the basis of the fact that the cancerous cells die when elevated to temperatures of the range of 42 − 46 °C. Even though there were some significant efforts, there was not enough interest and the idea never really caught on for a long time.

The first experimental investigations in the destruction of cancer cells by the heating of magnetic particles in a magnetic field were by Gilchrist et al in 1957 [1]. They heated various tissue samples with γ−Fe_2O_3 ranging from 20-100 nm in a 1.2 MHz magnetic field. Magnetic hyperthermia has come a long way in the last 50 years, during which time a variety of magnetic materials, methods of energizing them and delivering them to the site of the cancer have been tried out and reported. Now it is accepted as one of the most important methods of secondary treatment to be carried out as a supplement to radiotherapy and chemotherapy.

1. Magnetic Hyperthermia

Magnetic Hyperthermia is a relatively new method used for cancer therapy. Magnetic particles are inserted into the blood stream and they go and bind to the cancerous cells. The cancerous cells are destroyed by increasing their temperature to about 40–43° C. An alternating magnetic field is applied and these particles generate heat due to the hysteresis loss and the heat generated destroys the cancer cells. Usually, ferromagnetic and superparamagnetic particles are used for cancer therapy. The latter is preferred however because of the lower magnetic fields required to generate heat.

In Magnetic Fluid Hyperthermia, a fluid containing the magnetic nanoparticles is injected directly into the tumours. This magnetic fluid should be biocompatible, have a neutral pH and physiological salinity. The particles should evenly disperse throughout the fluid and must be small enough to avoid precipitation due to gravitational forces. Fe_3O_4 is commonly used.

Several methods for delivering the fluids exist. If the tumour location is known, direct injection concentrates fluid in the diseased tissue. The fluid can also be injected into an artery that supplies the tumour with blood.

If the tumour location is unknown, an intravascular injection delivers the magnetic nanoparticles throughout the body. The heating however can be localized by applying the magnetic field only to the region containing the tumours [1].

2. Modes of Hyperthermia

Hyperthermia modes are classified in terms of the nature of the heating source and the nature of the heated target. Some of major modes in investigation are: contact with external heated liquid, contactless applicator (radiation) and inserted heating sources (like probes).

Heating with an external liquid or contactless applicator is not preferred due to the lack of target specificity. None of these methods are able to precisely deliver heat energy to deeply situated cancers without destroying the surrounding normal tissues, which has lead to the parallel development of technologies based on internal heating sources. However internal heating sources, in particular those which require surgical intervention, are not preferred. Therefore using magnetic micro or nano scale mediators (devices which convert the electromagnetic energy into heat when exposed to an electric or magnetic field), which are injected as particle dispersions, seems to be a more robust method.

The energy dissipation is caused by capacitive applicators, which use the electric component of the electromagnetic (E.M) field or by inductive applicators where the magnetic component predominates in the heating process. For capacitive hyperthermia, mediators have to be materials of high

electrical conductivity (because heating happens *via* eddy currents), and for inductive hyperthermia they have to be magnetizable. Nevertheless capacitive applicators may lead to uncontrollable heating of the body because of the tissues' intrinsic electrical conductivity and/or due to electrical field heterogeneities due to differences in tissue dielectrical permeabilities. Since the tissues do not contain any intrinsic magnetic materials (with potential to heat up in a magnetic field), this renders inductive mediators more relevant for usage in therapy [2].

These micro or nano scale mediators are applied using three broad strategies, namely:

- Arterial Embolization Hyperthermia (AEH)
- Direct Injection Hyperthermia (DIH)
- Intracellular Hyperthermia (IH)

These methods are most promising in cancer therapy because of better temperature homogeneity. Before the heating, their distribution in tissues can determined using an MRI scan by making use of their magnetic properties. Also, the intracellular route, which is based on administering magnetic nanoparticles designed for selective uptake by tumour cells, is the best method to selectively overheat tumour cells even in isolated cancerous cells in any region of the body.

3. Modes of heat loss from Magnetic Particles

3.1 Hysteresis Loss

Ferromagnetic materials when placed in an alternating magnetic field tend to lose heat due to hysteresis loss. When exposed to an external field, the magnetic moments all start to align in the direction of the field. This is the phenomena of **magnetization.** This usually happens only at high field magnitudes. Essentially, those domains whose magnetic moments are along the external field axis grow while those which are aligned oppositely shrink. This 'domain wall displacement' carries on till the point of saturation when the growing domain encompasses the entire volume.

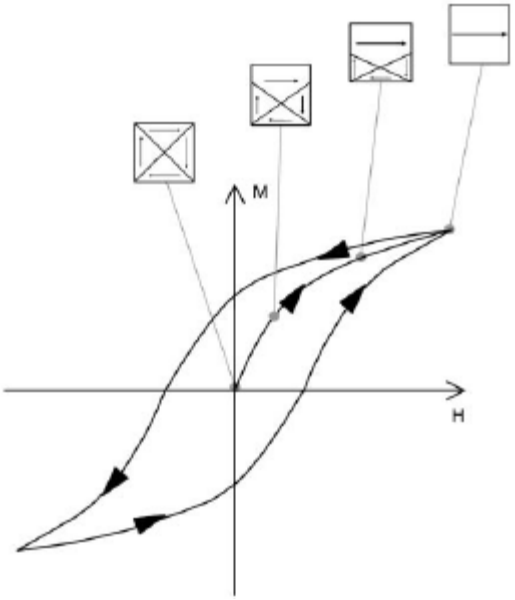

Figure1. Hysteresis cycle of a multidomain magnetic material (H is the magnetic field amplitude, M is the magnetization of the material) and domain wall displacements in such a material. The arrows indicate the direction of magnetization in the respective domain.[2]

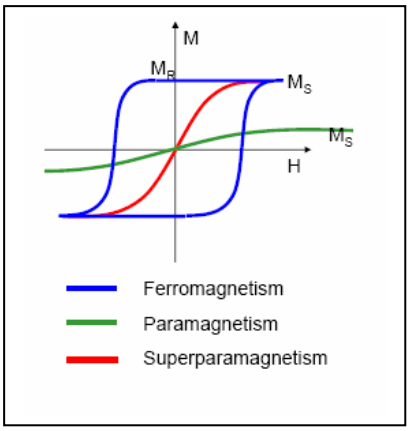

Figure2. Graph showing the differences in the M vs H curves for ferro, para and supermagnetic materials.

Now, if the direction of the external field is reversed, the irreversible nature of magnetization becomes evident. The magnetization curves for increasing and decreasing amplitudes do not coincide and the material is said to exhibit 'hysteresis behaviour' and produces heat.

3.2 Relaxation losses

This heat loss is attributed to the relaxation phenomena of moments. In an external AC magnetic field, energy is supplied to assist magnetic moments of the particles to rotate in overcoming the energy barrier E= KV, where K is the anisotropy constant and V is the volume of the magnetic core. This energy is dissipated during relaxation when the moment returns to its equilibrium orientation. This is the phenomena of **Nèel Relaxation.** The Nèel relaxation, t_N is a characteristic measurable property and is given by

$$t_N = t_0 e^{\frac{KV}{kT}} \quad \text{- (1)}$$

Where
$t_0 \sim 10^{-9}$ s,
k- Boltzmann constant.
T – Temperature (K)

The frequency of the alternating field (f_N) for maximal heating via this mode of heat loss is related to t_N as,

$$2\pi f_N t_N = 1 \quad \text{- (2)}$$

This corresponds to the maximum complex magnetic susceptibility $\chi''(f)$, which is given by:

$$\chi''(f) = \chi_0 \phi / (1+\phi^2) \quad \text{- (3)}$$

Where,

$$\phi = f t_N \quad \text{- (4)}$$

$$\chi_0 = \mu_0 M_s^2 V / (kT) \quad \text{- (5)}$$

M_s - magnetization value at saturation.

Another heat dissipation phenomena observed is due to the rotational Brownian motion of the particle within the carrier liquid. In essence, this is attributed to the rotation of the magnetic particle as a whole because of the torque exerted on the magnetic moment by the external AC magnetic field. Energy has to be provided to overcome the rotational friction offered by the surrounding liquid. This energy is released during relaxation is called **Brown relaxation**. Analogous to Nèel relaxation time we have t_B, Brown relaxation time given by

$$t_B = \frac{3\eta V_B}{kT} \quad \text{- (6)}$$

Where
V_B - Hydrodynamic volume of the particle.
η - Viscosity of the fluid.

Similar to Nèel relaxation, the frequency (f_B) for optimal heating is given by

$$2\pi f_B t_N = 1 \quad \text{-(7)}$$

$$P(f, H) = \mu_0 \pi \chi''(f) H^2 f \quad \text{-(8)}$$

P (f , H) –loss power density (Wm^{-1})
H- external magnetic field amplitude (Am^{-1})

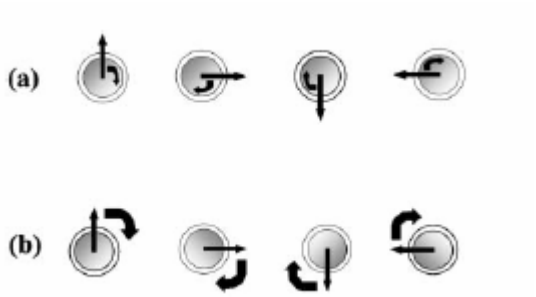

Figure3. (a) Neel rotation of magnetization in a magnetic particle (the particle does not rotate). (b). Brown rotation (the particle as a whole rotates).[2]

4. Parameters influencing the choice of mediator

4.1 Specific Loss Power (SLP)

Any form of injective therapy needs to be very selective in its action. In all cases, it is advantageous to achieve the temperature enhancement needed for a special application with as low as possible amount of magnetic nano particles (MNPs). Therefore, the specific loss power (SLP), also called specific absorption rate (SAR), of the MNP, which is measured in watts per gram of magnetic material to be applied, must be high enough. This is particularly important for applications where the target concentration is very low, for instance in antibody targeting of tumours.

Typically, a large number of parameters affect the value of SLP for a substance namely, size, size distribution, shape and chemical composition particles, frequency and amplitude of the magnetic field etc. Also depending on which mode of heat loss is dominant we need to adjust the external field (frequency and amplitude) so as to maximize the SLP. In heating through hysteresis losses, high magnetic field amplitudes (at least coercive field value) are needed for using the loop area fully and consequently maximizing SLP_H value. However due to other physiological and technical restrictions on the field amplitudes (for e.g. $H.\upsilon < 5\times10^{8} Am^{-1}s^{-1}$ is the safety condition which must be obeyed to prevent any damage to the patient.) the hysteresis loop can rarely be fully used.

Today's particles used for hyperthermia take advantage of Nèel relaxation because, for small field amplitudes, superparamagnetic particles give higher SLP than ferromagnetic particles.

4.2 Particle size

Hysteresis losses increase with decreasing particle size due to increasing remenance and coercivity and then abruptly decrease (Fig.3) [2]. This is because, when the diameter of the magnetic core is decreased, a transition

from ferromagnetic to superparamagnetic behaviour takes place. It is no more a multi domain structure. It is also evident from Fig.4 that when hysteresis losses diminish, Nèel losses increase.

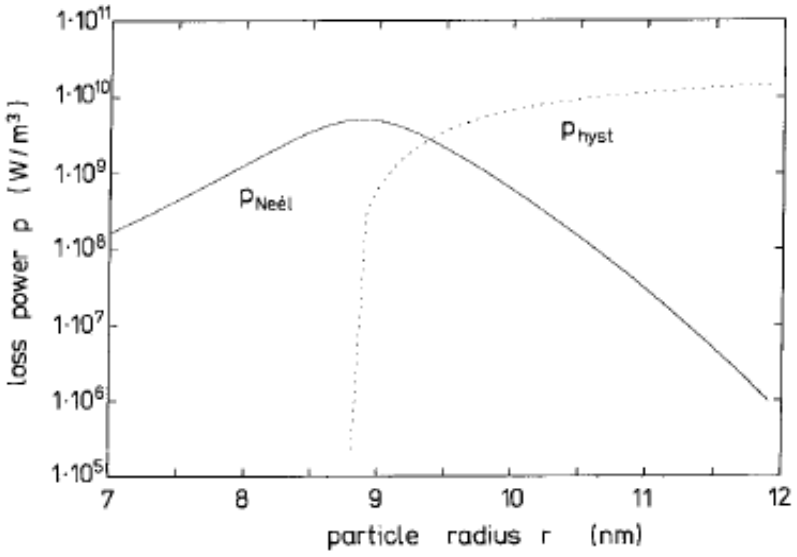

Figure4. Dependence of magnetic loss power density on particle size for magnetite fine particles (dotted line—hysteresis losses, full line— Nèel losses; frequency $2\times10^{6}s^{-1}$; field amplitude 6. 5 kA/m) [2]

It is tough to distinguish the contributions of Brown and Nèel heating mechanisms. Theoretically, a critical diameter Dc is defined at which t_N equals t_B. For particles of diameter less than Dc, Nèel relaxation is predominant. For larger particles, heating would be due to Brownian rotation. When the diameter of the particle is close to Dc, an effective relaxation time is defined, $t_{eff} = t_N t_B /(t_N + t_B)$. The Brownian relaxation contribution can be verified by preventing the free rotation of the particle. Also, Brownian losses seem to have less effect on SLP for uncoated superparamagnetic particles than uncoated ferromagnetic particles. But Brownian relaxation depends on the hydrodynamic volume of the particle and not on the volume of the magnetic core; therefore a coating would greatly influence the heating via a Brownian mechanism.

Nowadays, dispersions of superparamagnetic nanoparticles seem promising since they are used as ferrofluids. Such a technology is presently under development as Magnetic fluid hyperthermia (MFH). But still, ferromagnetic particles are potentially useful because of the Curie temperature which provides a robust method for temperature control during the therapy.

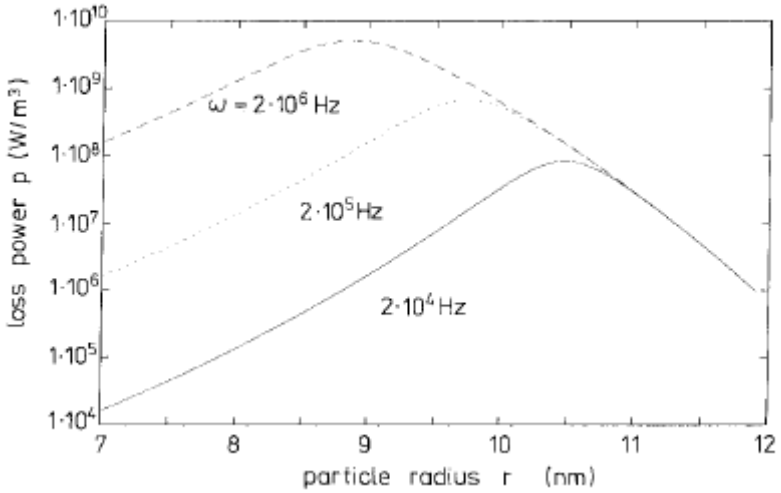

Figure5. Grain size dependence of the loss power density due to Nèel relaxation for small, ellipsoidal particles of magnetite (field amplitude 6. 5 kA/m). ($\omega = 2\pi f$) [2]

Another important factor affecting SLP_N values is the size distribution of the magnetic cores. It has been shown that the narrower the size distribution of the magnetic cores, higher is the SLP values.

4.3 Applied external field

For MFH, the heat loss also depends on the amplitude and frequency of applied magnetic AC field.
Also, there is a strong dependence on the structural particle properties like mean size, width of size distribution, particle shape and crystallinity.

4.4 Temperature control

High temperatures, in excess of 42°C can cause burns, blisters and discomfort. Therefore, an effective method of temperature control needs to be devised. By using magnetic particles with low Curie temperatures, there is the possibility of a self-limitation of the temperature.
The *Curie temperature* (T_C) is the temperature below which there is a spontaneous magnetization *M* in the absence of an externally applied magnetic field, and above which the material is paramagnetic, thereby significantly reducing the heat loss due to lack of hysteresis. Above T*c*, thermal energy is high enough to overcome the coupling force holding the magnetic moments in a particular orientation and this causes a disruption in the alignment. Therefore the Curie temperature would act like an upper bound to maximum temperature that can be reached.
This safety mechanism (just like a fuse) can be employed by choosing magnetic mediators with suitable curie temperatures. The graph shown below depicts different material with different curie temperatures and how the temperature profile with time behaves accordingly.

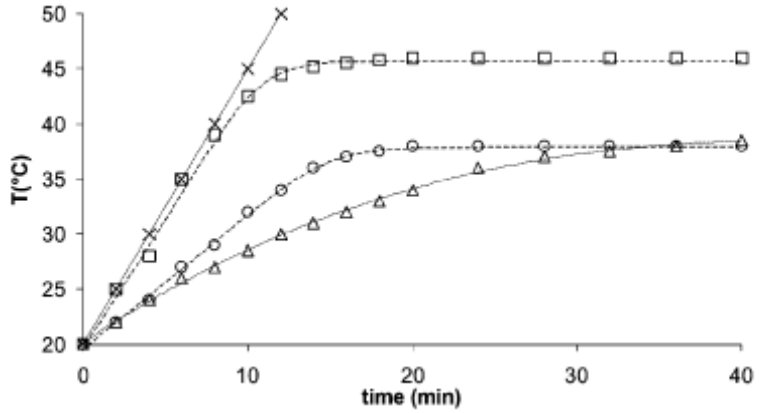

Figure6. Temperature profile with time for the following mediators:
× - dextran-coated Fe3O4; □ - La0.75Sr0.25MnO3; O - La0.8Sr0.2MnO3; ▵ - 'ZnFe2O4. [2]

The above materials were tested in an AC magnetic field (800 kHz, 7.2 kA/m). For La0.75Sr0.25MnO3, the maximum reported temperature was 46.3°C (T_c= 56°C) and for La0.8Sr0.2MnO3 was found to be 37.8°C (T_c = 48°C). This lower than expected maximal temperature is explained by the decrease in the saturation magnetization in the vicinity of the theory and also by the heat exchange balance that is taking place. For the other two particles, no maximal temperature within the time span was reported, although in the case of ZnFe2O4, a decrease in the rise in temperature was noted.

4.5 Biocompatibility

The nanoparticles that are sent in the body must not be recognized by the immune system as a foreign body. If it is recognized, the mononuclear phagocyte system (MPS) engulfs the nanoparticle through opsonization and subsequent phagocytosis. These nanoparticles then end up in the liver or the spleen. Sometimes when the targeting cell is in the liver or the spleen, this method is used. It is referred to as passive targeting. [2]
The idea usually however is to increase the circulation time of the nanoparticle in the blood and prevent it from phagocytosis. For this purpose, the nanoparticles are coated with hydrophilic molecules like dextrans to make them biocompatible. The smaller, the more neutral and the more hydrophilic the carrier surface, the greater is the circulation time.
Even though there are many magnetic materials available, most are not usable. Magnetic materials like some spinal ferrites, magnetic iron oxides Fe_3O_4 (Magnetite) and γ -Fe_2O_3 (Maghemite) have been proved to be well tolerated by the human body.

5. Cancer cell targeting

The best way to reach the target organs and tissues is through intra-venous administration. These MNPs are dispersed in certain fluids (drug carriers) and are then injected. These drug carriers are either liposomes or polymeric particles. Liposomes are similar to water-insoluble polar lipids. In excess of water, they rearrange themselves into concentric, closed membranes. The MNPs are then trapped either in the inner aqueous phase or in the lipid bilayers depending upon the hydrophobicity/hydrophilicity ratio.
To see to it that the nanoparticles specifically attach to the cancer cells, they need to be functionalized. This can be achieved by attaching specific ligands like folic acid, oligopeptides, oligosaccharides and antibodies to the surface of the nanoparticles which bind to specific receptors on the surface of the malignant cells. However, coupling antibodies with the nanoparticles has two major drawbacks, (1) the overall dimensions increase which hinders particle diffusion through biological barriers, (2) it might evoke an immune response within the body. Some of the common receptors are,

5.1 Alpha(V) Beta(3) Integrins

The surfaces of most endothelial cells in the body are spanned by molecules called integrin receptors. These receptors play an important role in binding of cells to proteins in the extra-cellular matrix (ECM). These integrin receptors bind the proteins in the extra-cellular matrix by recognizing the Arg-Gly-Asp (RGD) sequence of residues in those proteins. They bind ECM proteins and interact with the cytoskeleton at focal adhesion complexes .This can initiate the production of intracellular messenger or can directly mediate nuclear signals. In general, integrins serve important cellular bio-sensing roles and convey both outside ("outside-in" signalling) and, ("inside-out" signalling). Collectively, these are integrated by the cell to yield various responses, including changes in cell growth, locomotion & differentiation.

One of these integrins is the Alpha(V) Beta(3) integrin. From cancer point of view, this integrin plays an important role in tumor angiogenesis, tumour cell survival, invasion and metastases. Molecules which inhibit the activity of Alpha (V) Beta(3) integrin have been used for some time for cancer therapy. [3] Also, there is greater density of Alpha(V) Beta(3) receptors in the cell membrane of tumor cells than normal endothelial cells. This property of tumor cells is used for targeting.

The nano particles to be used for magnetic hyperthermia are bound to peptides containing repeats of Arg-Gly-Asp (RGD) residues. As there are many recognition sites on the surface of tumor cells compared to that on normal endothelial cells, the nanoparticles coated with peptides bind

specifically to tumor cells with greater efficiency. Presence of many peptides on the nanoparticles surface ensures tight binding. [4]

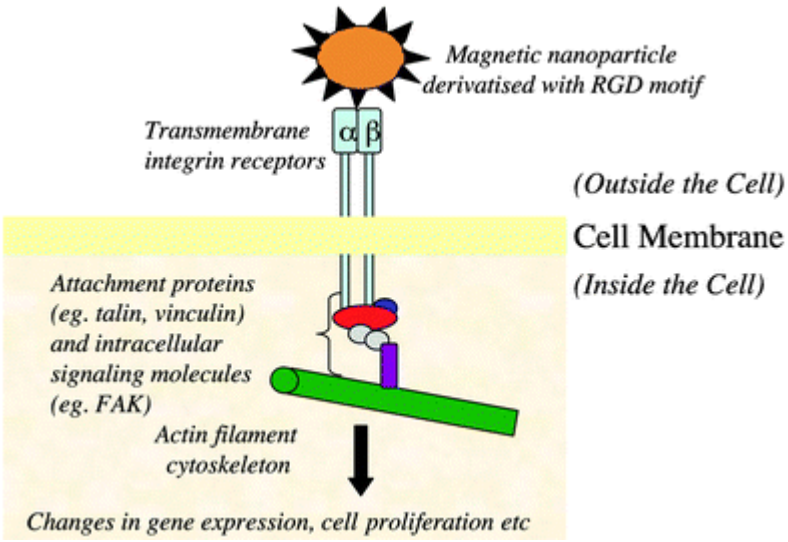

Figure7. Schematic illustrating the possible interaction of RGD-derivatised magnetic nanoparticles with transmembrane integrin receptors [5]

5.2 Folic acid and cross link receptors

Folate receptors have been very crucial for targeting of cancer cells specifically over other normal cells. The receptor for folic acid constitutes a useful target for tumor-specific drug delivery, primarily because: (1) it is upregulated in many human cancers, including malignancies of the ovary, brain, kidney, breast, myeloid cells and lung, (2) access to the folate receptor in those normal tissues that express it can be severely limited due to its location on the apical (externally-facing) membrane of polarized epithelia, and (3) folate receptor density appears to increase as the stage/grade of the cancer worsens. Thus, cancers that are most difficult to treat by classical methods may be most easily targeted with folate-linked therapeutics. To exploit these peculiarities of folate receptor expression, folic acid has been linked to both low molecular weight drugs and macromolecular complexes as a means of targeting the attached molecules to malignant cells. [6]

Folic acid receptor targeting is tried in various methods of functionalizing the nanoparticles to target specific cells. In one of the methods, a polymer (polyethylene glycol, PEG) was taken and folic acid was attached to it. To the other side of the polymer, thioctic acid was attached. Thioctic acid contains two sulfur atoms in the form of molecular tweezers. Sulfur atoms bind avidly to Gold. So when this engineered polymer was added to gold nanoparticles, it formed a tight surface coating. The resulting coated gold nanoparticles had an average diameter of 10 nm, were biocompatible and soluble in water (due to PEG coating) and had folic acid attached to it for targeting malignant cells specifically. [7]

In another method, folic acid conjugated shell cross-linked nanoparticles (SCKs) were used. Shell cross-linked nanoparticles (SCKs) constitute a unique class of materials with amphiphilic core-shell morphology. SCKs are prepared by intramicellar cross-linking of polymer chains located within the shell domain of polymer micelles and are characterised by their structural integrity and available functionality to attach receptor-recognising or receptor-specific ligands on the shell surface. In this method, a folate-PEG-amine was prepared by coupling of bis-PEG-amine with folic acid and was then allowed to undergo amidation based attachment to preformed SCKs bearing carboxylic acids within their shells. [8]

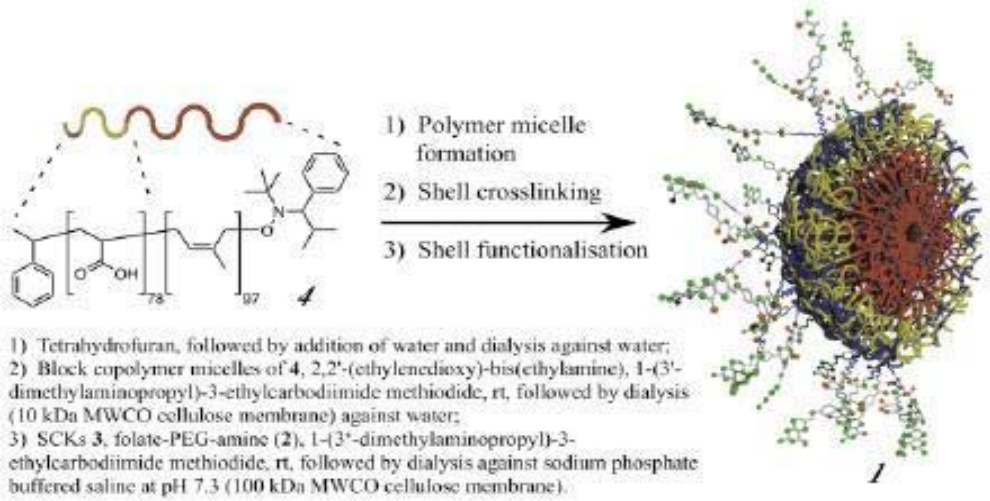

Figure8. The preparation of folate-functionalised SCK nanoparticles involving a three-step methodology from an amphiphilic diblock copolymer [8]

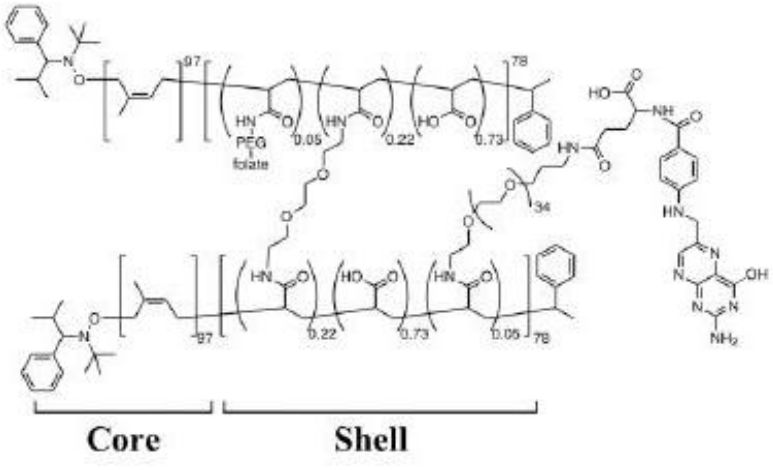

Figure9. The core and the shell of the SKC [8]

6. Uptake of nanoparticles by the cell

The magnetite nanoparticles can be modified by coating with aminosilane or dextran groups. The uptake of these modified nanoparticles is 500-2000 times larger in cancer cells than in normal cells. So, without a targeting ligand, differential particle endocytosis can be a targeting strategy. Aminosilane group is preferred over dextran group for two reasons, (1) dextran corona of dextran-magnetite nanoparticles is attacked by enzymes in the lysosomes and (2) Uptake of aminosilane-magnetite particles by the cell is 100 times faster than dextran-magnetite particles.
The uptake of these coated nanoparticles is achieved by the process of clathrin mediated endocytosis. The uptake procedure involves membrane invagination, clathrin coated pit formation, coated pit sequestration, detachment of the newly formed vesicle via action of the small GTPase dynamin and finally movement of this new endocytic compartment away from the plasma membrane into the cytosol.

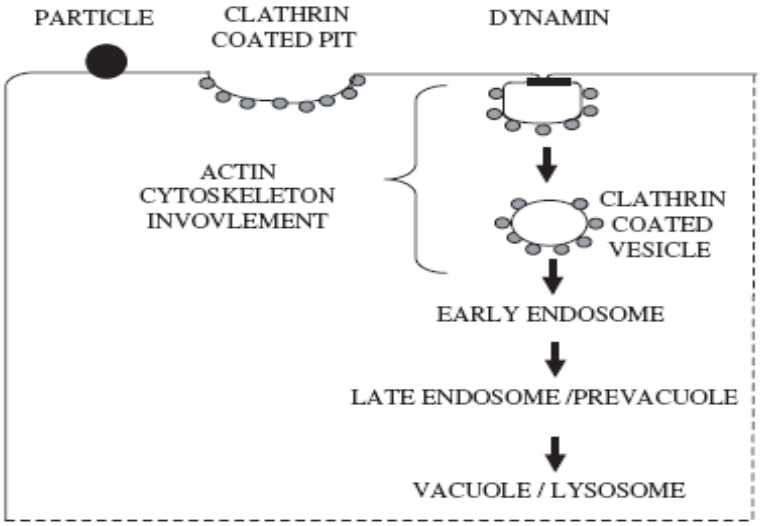

Figure10. Schematic of the basic cell events occurring during clathrin mediated endocytosis. Once the coated nanoparticle has docked at its receptor, receptor-mediated endocytosis usually occurs. Clathrin coated pit invaginations are observed at the cell membrane, which with the combined action of the GTPase dynamin, pinch off from the membrane to form isolated vesicles leading to the formation of vacuoles.[9]

Moreover, tumor cells could be loaded with thousands of nanoparticles and they would not be able to get rid of them. Daughter cells from a particle containing parent cell would contain at least 50% of the particle amount of the parent cell. So the descendants would still be cured by future therapy sessions.

7. Heat Transfer Modelling of Hyperthermia [10,11]

One of the most important things to be kept in mind while actually using hyperthermia as a cancer treatment is that as little as possible of the surrounding tissue should be damaged. The quantity of magnetic particles injected into the stream as also the time for which the particles are excited both need to be minimized while still achieving the conditions required for treatment. This necessitates the modelling of the heat transfer problem in hyperthermia.

The heat transfer can be modelled both analytically as well as experimentally. For experiments, after animal tissues (rats, dogs etc.) (both *in vitro* and *in vivo)* the preferred mediums are either carageenan or agar gels, both of which are sea-weeds derivatives. Both these gels have been found to have thermal properties similar to that of tissues.

7.1 Assumptions

For the greater part, biological tissue can be assumed to have thermal properties similar to that of water or they can be found out experimentally i.e. k = 0.64W/m−K, C = 4.18×10^6 J/m^3, and v = 1.5×10^3m/s [10] Substituting these values in the equation for the mean free path:

$$\Lambda = \frac{3k}{Cv} \text{ - (9)}$$

We find that the mean free path comes out to be 0.3 nm. This is significantly lesser than the size of the nanoparticles used, and hence the classical Fourier heat equations remain valid.

For tissues for which the values of the thermal properties vary greatly from these values, the values are found out experimentally.
The variation in the power delivered from the magnetic particles is usually assumed to be constant, although it is possible to solve taking the variation due to the variation in the magnetic field into account. The magnetic particles are assumed to be uniformly distributed throughout the area and the contact resistance between the particle and the tissue is also neglected.
Also, in the case of hyperthermia using conducting particles, it is usually the case that the conductivity of the nanoparticle is many times that of the surrounding medium. In such cases, the magnetic particle is assumed to be a perfect conductor with respect to the surrounding medium.

7.2 Blood perfusion

Blood circulating through the capillaries takes away a lot of heat from the tissues. This phenomenon is called blood perfusion. Owing to the fractal nature of the capillaries, taking it into account in models is quite difficult. For smaller tumours in muscular/fatty tissues like the breast the blood perfusion is not significant and it can be taken care of by modifying the heat equations by adding a constant value for heat lost due to the blood perfusion. However, organs like the liver have a lot of blood perfusion, which cannot be treated in the same way. For such tissues it is necessary to take the blood perfusion into account. For such a system, the blood perfusion, with it's variance with temperature needs to be taken into account.

7.3 Constituent equations

As mentioned above, the Fourier heat equation is valid for hyperthermia modelling. Assuming a spherical nanoparticle, the problem is reduced to a one dimensional transient problem in (r, t). The equations are:

$$\rho_1 c_1 \frac{\partial T_1}{\partial t} = \frac{k_1}{r^2}\frac{\partial}{\partial r}[r^2 \frac{\partial T_1}{\partial r}] + P$$
$$\rho_2 c_2 \frac{\partial T_2}{\partial t} = \frac{k_2}{r^2}\frac{\partial}{\partial r}[r^2 \frac{\partial T_2}{\partial r}] \quad \text{- (10)}$$

The first equation is for the interior of the sphere and the second one is for the exterior. The indices indicate the same. These equations are solved simultaneously with the boundary conditions that T at infinity is the same as the body core temperature, and also the temperature at the surface of the nanoparticle is continuous at all temperatures.

7.4 Mean parameters

The direct values of the ρ, c and k can't be used as there is significant change due to the composite nature of the system of tissue and magnetic particles.
This is taken care of by using effective values for the same. For the c and the ρ the value is a simple weighted mean over the volume, while for the k, the value is taken as the volume weighted harmonic mean.

7.4 Solution to the model

Solving the model analytically, one gets the following solutions,

$$\Delta T_1(r,t) = \frac{PR^2}{3k_2}\left[1+\frac{q_k}{2}\left(1-\frac{r^2}{R^2}\right)+\frac{6}{\pi}q_k^{\frac{3}{2}}\frac{R}{r}\int_0^\infty f(z;r,t)g_1(z;r)dz\right] \quad \ldots\ldots (11)$$

And,

$$\Delta T_2(r,t) = \frac{PR^3}{3k_2 r}\left[1+\frac{6}{\pi}q_k\int_0^\infty f(z;r,t)g_1(z;r)\frac{dz}{z}\right] \quad \ldots.. (12)$$

where,

$$q_k = \frac{k_2}{k_1}, q = \frac{\rho_2 c_2}{\rho_1 c_1}, \qquad s(z) = (q_k - 1)\sin z + z\cos z \quad \ldots.. (13)$$

and,

$$f(z;r,t) = z^{-2}\ \exp\left(-\frac{k_1 t z^2}{\rho_1 c_1 R^2}\right)\frac{z\cos z - \sin z}{[s(z)]^2 + q_k q(z\sin z)^2} \quad \ldots. (14)$$

$$g_1(z;r) = \sin\left(\frac{rz}{R}\right) \quad \ldots. (15)$$

$$h(z;r) = (q_k q)^{1/2} z\left(\frac{r}{R}-1\right) \quad \ldots. (16)$$

$$g_2(z;r) = s(z)\sin[h(z;r)] + (q_k q)^{1/2} z\sin z\cos[h(z;r)] \qquad \ldots. (17)$$

This model shows the following curves for various values of the parameters involved.

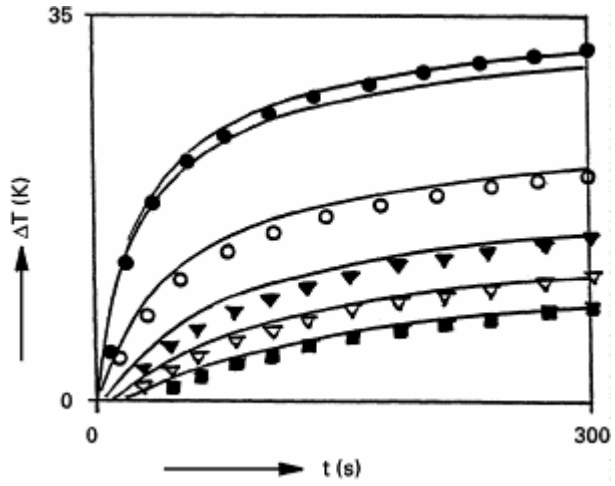

Figure11. Temperature increase ΔT as function of time for different reduced distances r/R from the composite centre. The points are experimental points for similar values.[10]

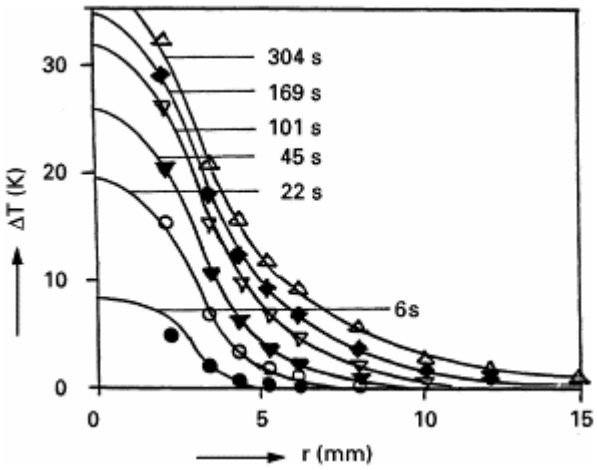

Figure12. Temperature increase ΔT as function of the distance from the composite centre for different exposure times. Measured values for the same parameters are plotted with symbols indicating the different exposure times. [10]

The model shows us that, initially the tumour with the magnetic particles heat up faster. This suggests the use of a very large amount of the material allowing a very fast increase in the temperature difference with respect to the body temperature. This will allow the exposure lengths to be restricted and hence prevents the damage to the other cells in the neighbourhood. This however makes it necessary to control the time of the exposure very accurately. The use of a calculated minimum amount of magnetic particles on the other hand allows us to be fairly free with the time scales, but this minimizes the temperature differences between the tumour and the surrounding tissues. One needs to optimize between the two to get the best results, killing the maximum number of cancerous cells and limiting damage to the healthy cells. [10]

7.5 Size Limitations

Although hyperthermia is very effective in a large number of tumour cases, it has to be pointed out that owing to the limitation in the volumetric power output of the magnetic materials, and their extremely small size, there is a limit to the accuracy of the treatment. It is claimed by certain authors, that by means of intracellular hyperthermia, it may be possible to kill even a single cell by heating it using magnetic-hyperthermia. Rabin, by similar analysis in his 2002 [11] work found that the temperature rise due to the presence of a single magnetic particle and also the effect of a field on a single cell, loaded with magnetic particles is negligible. In fact, for significant temperature rise to occur, the size of the tumour-magnetic particle composite was found out to be 1.1 mm for typical values of the magnetic field and SAR. As this analysis was made without considering the blood perfusion, the actual value is likely to be higher.

Though this might call into question the design of the particle for uptake by the cells, it might be observed that design for selective uptake by cancerous cells allows for accurate targetting.

8. Ferromagnetic Embolisation Hyperthermia

In some tissues, the blood perfusion is not negligible. Instead it becomes a major factor [12]. For example in liver tumours the blood perfusion in the tumours is less than that in the liver. This allows a greater degree of protection to the healthy tissue. It is thought that the tumours in such tissues be cooled by arterial embolisation hyperthermia. In this method, magnetic microspheres are injected into the liver via the hepatic artery. Owing to the dense agglomeration of capillaries near the tumour, the particles also end up there. When the diameter of the capillaries becomes lesser than the size of the particle, the particles get lodged in the capillaries.

Such a method of introducing the particles to the body leads to a heterogenous distribution of the magnetic particles and renders the above analysis invalid for such cases. Hence the distribution of the magnetic particles on the periphery of the tumour has to be taken into account while calculating the temperature distributions within. This is done by assuming the fractal growth of the blood vessels while simultaneously modifying that to take into account the greater randomness in the growth of blood cells in and around the tumours.

The placement of the microspheres is predicted using a probability model, and then the whole system of tumour core, periphery and healthy tissue is solved using a Finite Element Method formulation.
The solutions for such a model show a very high temperature gradient near the surface of the tumour, which drops off as we go away from it. It also shows that a very tiny part of the healthy liver tissue is damaged, allowing us to conclude that a distribution of the particles on the surface leads to a good amount of malignant cell death and relatively less healthy cell death.

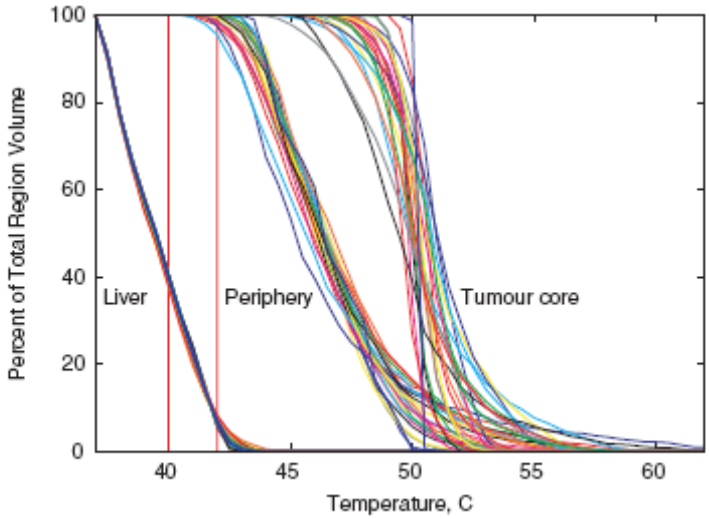

Figure13. Temperature–volume histogram for the liver, tumour periphery and tumour core regions. Vertical lines are at 40°C and 42°C. Thin lines are the heterogeneous cases, and thick lines are the homogeneous case [12]

9. Effects of Hyperthermia on different parts of the body

Brain: Hyperthermia by conventional methods for the brain is generally out of scope. Oncothermia, however, has found to have excellent results for treating brain tumours.

Liver: Liver is a sensitive organ and is susceptible to large blood profusion and high sensitivity to chemo-toxicity from previous treatments. So, hyperthermia might be a risky way of treating cancerous growth around the liver.

Pancreas: The Pancreas Carcinoma is a very rapid and aggressive disease. Basic hyperthermia has a moderate success rate in treating it, but oncothermia shows better results, as in the case with the brain.

Lung: The lung is a problematic area for hyperthermia application. This is because, by nature itself, the lung has a cooling-ventilation mechanism, which results in the heat produced by the treatment unit, being dissipated away. So, the hyperthermia should be performed such that it accounts for this natural heat loss, when dealing with the lungs.

Bone: Bone tumours are particularly difficult to pinpoint and treat because the usual mechanism for pinpointing cancerous cells is through their abnormal growth rates. But since even normal tissues in the Bone marrow have a high growth rate, as they produce bone marrow continuously, this method of finding out the cancerous tissues becomes invalidated. Apart from

this, the bone itself has a low density, compared to adjoining tissues, making it a complicated part to do a Hyperthermia treatment on.

10. Future scope

Low-Curie-Temperature nanoparticles and cancer-specific binding agents are promising areas for future research. The advantage with using Low-Curie temperature nanoparticles with appropriate sizes and magnetic properties is that they will heat more efficiently and maintain therapeutic temperatures. Iron-platinum (FePt) and nickel-palladium (NiPd) nanoparticles have been found to meet this criteria.

Attaching cancer-specific binding agents to magnetic nanoparticles would make MFH treatment much more selective than radiation treatments and chemotherapy. Chemotherapy destroys a wide range of rapidly dividing cells, including many types of cancer but it also damages healthy cells with multiply rapidly, such as those found in hair, bone marrow, and the lining of the gastrointestinal tract. Also, high systematic doses are required to achieve high local concentrations and this leads to a lot of side effects. Likewise, external beam radiation treatments can eliminate tumors but also harm healthy tissues between the tumor and radiation source. MFH on the other hand uses frequencies that pass harmlessly through the body and only generate heat in tissues containing magnetic nanoparticles.

Attaching cancer-specific binding agents to these nanoparticles would enable doctors to target both a specific chemical and physical locations. This would reduce the chances of damage of the healthy tissue. This approach would also treat small tumors that might otherwise be missed.

Cancer-specific binding agents could include hormones, antibodies, and viruses. Several types of cancers have hormone receptors. Some forms of breast cancer, for example, have estrogen receptors. Current breast cancer treatments often include anti-estrogen drugs such as tamoxifen. Magnetic particles coupled with estrogen would therefore target hormone-sensitive breast cancer. Similarly, testosterone and thyroid hormone could be used in MFH treatments for prostrate cancer and thyroid cancer, respectively.

Monoclonal antibodies, which are antibodies cloned from the same parent cell, can also be used to target cancer. These antibodies react with matching antigens on cancerous cells, and can be produced for many types of cancer. The American Cancer Society has successfully managed to couple monoclonal antibodies with chemotherapy drugs and radioactive particles. These tagged antibodies increase the effectiveness of chemotherapy and radiation therapy by delivering therapeutic agents to cancerous sites. Therefore, the same

benefits could be achieved by coupling antibodies with magnetic nanoparticles.

Finally, attaching magnetic nanoparticles to viruses (Fig. 2) has promising implications for MFH cancer treatment. Viruses can be modified to latch onto receptors on several types of cancerous cells. The genetic material contained in the viruses can also be replaced with chemotherapy drugs. These viruses can then be engineered to release the drugs at elevated temperatures. Viruses coupled to magnetic particles could therefore locate cancerous cells and deliver heat and therapeutic drugs directly to these locations.

Conclusion

Cancer therapy has come a long way since the time it was first detected. Hyperthermia has been tried in various forms *viz.* optical, microwave, Radio waves, magnetic hyperthermia. Magnetic hyperthermia is a promising therapeutic strategy and has attracted a lot of interest recently. More so, because of the relatively high transparency of the human body to magnetic fields and the possibility of conjugating the treatment with MRI machines which can be used for online monitoring and for which the basic infrastructure is already in place. In future, magneto hyperthermia in combination of chemotherapy and radiotherapy could prove to be an effective treatment for most cancers.

As with most treatment methods, magneto hyperthermia also has certain ethical issues. Issues regarding nano-toxicity and incomplete biocompatibility of MNPs are also important and need to be dealt with a serious thought. Regulatory standards and accurate and reliable manufacturing technology is also a concern area.

The need is for the people working in as diverse fields as electro-magnetics, biotechnology, material sciences, medicine and inorganic chemistry to work together and create technologies for future applications. The basic aim should not only be longevity but to improve the quality of life.

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