

## Effect of Magnetic Field on Cancer Cells

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### ABSTRACT

In 16<sup>th</sup> century physician were of the opinion that magnet can be used for the treatment or eliminate the diseases from the body. Here the reports about the chemical synthesis, protection, functionalization and application of magnetic nanoparticles of nano structured system. Research of magnetic nanoparticles for targeted drug delivery system and function of magnetic nanoparticles on particular area are reviewed. Use of magnetic nanoparticles for cancer diagnosis has been advancing day by day. This review is related to the multifunctional use of magnetic nanoparticles probes and their use in bio imaging and nano medicine.

**Keywords:** Magnetic Field, Cancer Cells, tumors, paramagnetic

### INTRODUCTION

In middle age doctors used magnets to treat gout, arthritis etc. First time magnetic therapy was introduced in 1970s when researcher Albert Roy Davis reported that positive and negative magnetic field or charges play great role with human biological system. He also noticed that controlled amount of magnetic field can kill cancer cells in animal and is useful in treatment of glaucoma, arthritis pain, infertility and different other diseases. Now a day's magnetic therapy become an industry for the treatment of disease and widely used in China, Japan, United State and Europe.

In recent years different methods are used for the treatment of cancer but magnetic fields have their own value for the cancer cell and have no any side effect or very less side effect for the normal cells. Most methods of intervention involve combinations of surgery, chemotherapy, and ionizing radiation. Both chemotherapy and ionizing radiation can be

effective against many types of cancer, but they also harm normal tissues. The use of magnetic fields has shown early promise in a number of in vitro and animal studies. One study tested the effect of varying durations of magnetic exposure on tumor growth (Tatarov, Panda et al. 2011)<sup>[1]</sup>. Magnetic field can be used in the form of magnetic therapy or oral medicine with magnetic charge and magnetic charge medicine effective only for cancer cell not for normal cell. Nanotechnology has developed to a stage that makes it possible to produce, characterize and specifically tailor the functional properties of nanoparticles for clinical applications. This has led to various opportunities such as improving the quality of magnetic resonance imaging, hypothermic treatment for malignant cells, site-specific drug delivery and the manipulation of cell membranes. To this end a variety of iron oxide particles have been synthesized (Berry and Curtis 2003)<sup>[2]</sup>.

### Type of cancer Treatment

**Surgery**

Surgery is the best chance for the treatment of cancer when cancer has not spread to other part of body.

**Chemotherapy**

In this medicine or drugs is used for the treatment of cancer.

**Radiation Therapy**

In this very high energy particles or wave is used to destroy the cancer cells.

**Hyperthermia**

Heating of certain cancer cell or tissue or organ up to temperature between 41<sup>0</sup> c to 46<sup>0</sup>c for cancer therapy is called "Hyperthermia", above this temperature is called "Thermo-ablation". Both mechanisms have different nature with cancer cell and tissue. Modern clinical hyperthermia trial focus mainly on the optimization of thermal homogeneity at moderate temperatures (42-43<sup>0</sup>c) in the target volume (Jordan, Scholz et al. 1999)<sup>[3]</sup>. As we know that many cellular effects are important for thermal inactivation. After few minute of hyperthermia cells produce a special class of proteins that called as heat shock proteins. This type of proteins protect the cell from further heating or thermal treatment and lead to an increase of cell survival after pre heating, this type of effect is called as thermotolerance. Combination of hyperthermia with radiation therapy or chemotherapy used for the treatment of many type of cancer such as sarcoma, melanoma and cancer of the head and neck, brain, lungs oesophagus, breast, bladder, rectum, liver, appendix, cervix and peritoneal lining.

In this heat is applied to a small area, such as a tumor, using various techniques that deliver energy to heat the tumor. Different types of energy may be used to apply heat, including microwave, radiofrequency, and ultrasound. Depending on the tumor location, there are

several approaches to local hyperthermia :(Saniei 2009)<sup>[4]</sup>.

**External hyperthermia**

When tumours or cancer cell just below the skin then external hyperthermia is used...

**Intraluminal or endocavitary**

When tumors present near the body cavity (Ex- rectum or oesophagus) than hyperthermia instrument placed inside the cavity and inserted into the tumor to produce energy and heat the area directly.

**Interstitial**

Interstitial techniques are used for treatment of tumors which present within the deep of the body (Ex- brain tumor). In this a needle or probes are inserted inside the tumors after that heat source inserted into the probe to generate the heat for tumors. In this technique we can also use radio wave to heat and kill cancer cells.

**Regional perfusion**

Arms, leg liver and lungs cancer are treated by these techniques. In this case first blood of patient is removed, heated and then pumped back into the organ. Patient can take anticancer drugs during this process.

**Whole-body hyperthermia**

When cancer spread throughout the body than whole body hyperthermia technique is used. In this case whole body temperature can be raised up to 42<sup>0</sup>c to 43<sup>0</sup>c by the use of hot water blanket or by the use of thermal chamber.

**Photodynamic Therapy**

Drugs which have photosensitizing agents used for the treatment of cancer. This type of drugs is active only in presence of certain kind of light.

### Laser Treatment

In this very precise beam of light is used for the treatment and very careful surgical work for cancer.

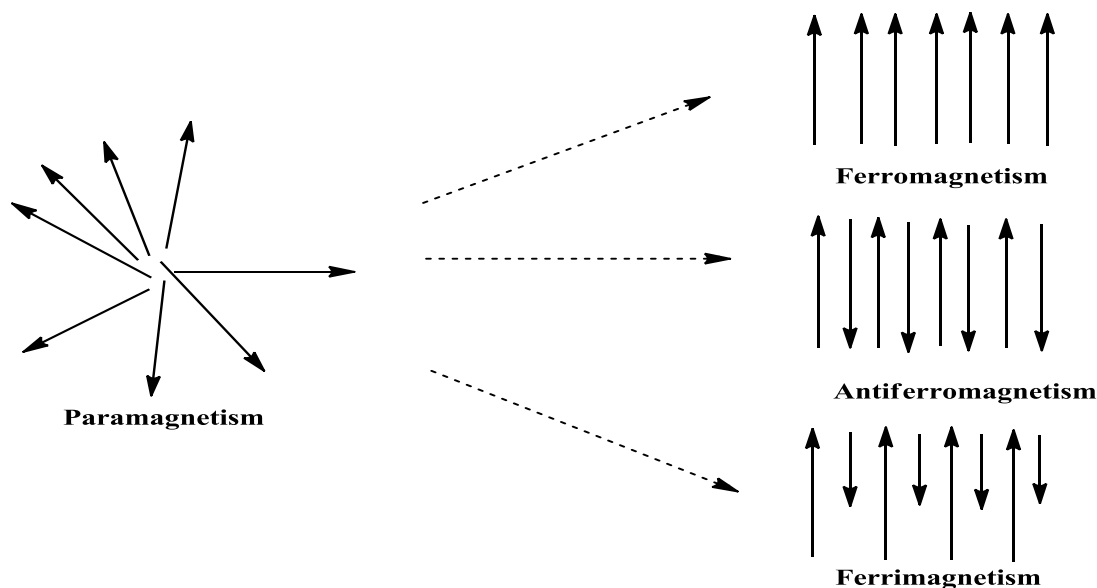
All above techniques are used for the treatment of cancer which are very painful, expensive and time consuming. Now we can use magnetic nanoparticles for the treatment of cancer because magnetic nanoparticles prepared with a layer or coating of cancer medicine and active only in particular region.

### Magnetic nanoparticles

#### Magnetic properties

Atomic number of iron atom is 26 and its electronic configuration is  $1s^2, 2s^2, 2p^6, 3s^2, 3p^6,$

$4s^2, 3d^6$  and this electronic configuration have four unpaired electron in d orbital. When crystals are formed than different magnetic field arises due to presence of unpaired electron of d orbital. Substances in paramagnetic state have magnetic moment zero due to align of all unpaired electron. If external magnetic field is applied on the substance, some of magnetic moment aligns and crystal will generate magnetic moment. Ferromagnetic substance can generate magnetic moment in absence of external magnetic field. Ferrimagnetic substance generates two type of magnetic moment with antiparallel mode of electron (Teja and Koh 2009) <sup>[5]</sup>.



**Individual atomic magnetic moment in different types of material**

(Teja and Koh 2009) <sup>[5]</sup>.

Magnetic properties of the substance depend upon its magnetic susceptibility ( $\chi$ ). Magnetic susceptibility ( $\chi$ ) is the ratio of the induced magnetization (M) and applied magnetic field (H). Diamagnetic substance gives very small or negative susceptibility ( $-10^{-6}$  to  $-10^{-3}$ ) because its magnetic moment is antiparallel to H. Thus diamagnetic substance do not show any magnetic properties when external magnetic

field is removed. When substance generates magnetic moment parallel to H and susceptibility lies in the order of  $10^{-6}$  to  $10^{-1}$  than substance called as paramagnetic. Ferrimagnetic and ferromagnetic substance also generate magnetic moment which is parallel to H. Magnetic susceptibility depends upon atomic structure, temperature and external magnetic field. (Sun, Lee et al. 2008) <sup>[6]</sup>.

### Metallic nanoparticles

Metallic nanoparticles are now utilizing in biomedical science and engineering. Today we can synthesize and modify the magnetic nanoparticles with various chemical functional groups and allow them to react or conjugated with antibodies, ligands, and drug. A metallic nanoparticles opens the wide range of application in the field of biotechnology, magnetic separation, drug delivery, and vehicle for gene and drug delivery and mainly important in the field of diagnostic imaging for Example MRI, CT, PET, Ultrasound, optical imaging and SERS. Different magnetic nanoparticles are iron oxide ( $\text{Fe}_3\text{O}_4$ ), gold and silver nanoparticles. (Mody, Siwale et al. 2010)<sup>[7]</sup>.

Metallic magnetic nanoparticles are made of iron, cobalt or nickel. Metallic MNPs are used in biological activity due to their chemical stable nature. Metallic nanoparticles forms oxide in presence of water and oxygen. Metallic nanoparticles can be protected by the use of coating of silica or gold to prepare core-shell structure. For example, iron oxide nanoparticles acquire comparatively high magnetic field property and can maintain Superparamagnetism at larger scale (Sun, Lee et al. 2008)<sup>[6]</sup>. Combination of metallic nanoparticles and magnetic nanoparticles are opening the new application in the field of biomedicine (Corr, Rakovich et al. 2008)<sup>[8]</sup>.

### Synthesis of Magnetic Nanoparticles

There are many chemical methods which can be used for the synthesis of magnetic Nanoparticles for the multifunction use such as medical imaging, micro emulsion, sol-gel synthesis, sonochemical reaction, hydrothermal reaction, hydrolysis and thermolysis, flow injection synthesis and electro spray synthesis. Chemical co precipitation technique of iron salts is the most important technique for the

production of magnetite nanoparticles. (Laurent, Forge et al. 2008)<sup>[9]</sup>.

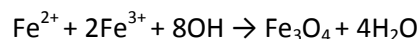
### Iron oxide nanoparticles

Magnetic nanoparticles gives biocompatibility and easy to synthesis therefore used in biomedical application. Magnetic nanoparticles are made of nanocrystalline magnetite ( $\text{Fe}_3\text{O}_4$ ) or maghemite ( $\gamma\text{Fe}_2\text{O}_3$ ) or ( $\alpha\text{-Fe}_2\text{O}_3$ ) and these nanoparticles are polymeric coated, these magnetic nanoparticles posses a spine crystal structure and in this oxygen ion forms a closed-packed cubic lattice. In closed packed cubic lattice, iron ions are located at the interstices position. Iron oxide ( $\text{Fe}_3\text{O}_4$ ) generates magnetic field due to electron switch between  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  ions and these particle are coexist at the octahedral site. During metabolism process, the iron ions of magnetic nanoparticles attached with iron of body and finally included by erythrocytes as haemoglobin (Sun, Lee et al. 2008)<sup>[6]</sup>.

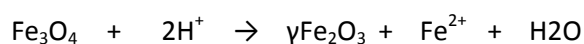
These three iron oxide exist in closed packed planes. In these iron cations and oxygen anion occupied the interstitial site of octahedral or tetrahedral arrangement. In hematite oxygen anions present in hexagonal closed-packed arrangement and iron gets octahedral sites arrangement. In magnetite and maghemite, the oxygen ions are present in cubic close-packed arrangement. The other name of magnetite is also known as black iron oxide, magnetic iron ore, ferrous ferrite, loadstone and Hercules stone (Teja and Koh 2009)<sup>[5]</sup>.

### Synthesis of Magnetic nanoparticles by Coprecipitation method

Coprecipitation technique is most suitable technique for the synthesis magnetic particle. In this method  $\text{Fe}_3\text{O}_4$  or  $\gamma\text{Fe}_2\text{O}_3$  is prepared by the use of mixture of ferrous ferric salt in aqueous medium. Chemical reaction is as,



in above chemical reaction,  $\text{Fe}_3\text{O}_4$  is formed in the form of precipitation and it will complete precipitate, if pH is between 8 and 14 with stoichiometric ratio of 2:1( $\text{Fe}^{3+}/\text{Fe}^{2+}$ ). Compound  $\text{Fe}_3\text{O}_4$  is very sensitive towards oxygen environment. Thus magnetite ( $\text{Fe}_3\text{O}_4$ ) convert into maghemite ( $\gamma\text{Fe}_2\text{O}_3$ ) in the presence of oxygen. (Laurent, Forge et al. 2008)<sup>[9]</sup>



Shape and size of nanoparticles depends upon the ionic strength, pH, and temperature, nature of salt and concentration ratio of  $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ . On above parameters we can adjust the size of magnetic nanoparticles from 2 nm to 17 nm (Laurent, Forge et al. 2008)<sup>[9]</sup>.

Now a day's magnetic nanoparticles used in many disciplines such as magnetic fluid, catalysis, biotechnology/biomedicine, magnetic resonance imaging and environmental remediation. There are many methods for the synthesis of magnetic nanoparticles of various different compositions. All research depends upon its stable nature under a different composition and different condition. Magnetic nanoparticles provide the best result when its particle size is below its critical condition of the range of 10 to 20 nm. Each magnetic nanoparticles generate own magnetic domain and shows super paramagnetic behaviour above the blocking temperature, thus magnetic nanoparticles behaves like a huge paramagnetic atom. This huge paramagnetic atom gives fast response towards applied very a lesser amount of magnetic field. Due to this type of activity, magnetic nanoparticles widely used in biomedical application, (Lu, Salabas et al. 2007)<sup>[10]</sup>.

#### Preparation of iron oxide ( $\text{Fe}_3\text{O}_4$ ) nanoparticles

He prepared a solution mixture of 0.85 ml of 12 mol/l HCl, 25 ml of deoxygenated DI water, 5.2 gm of  $\text{FeCl}_3$  and 2.0 g of  $\text{FeCl}_2$  in atmosphere of nitrogen gas. After that he transferred the solution drop-wise into 250 ml of 1.5 mol/l NaOH solutions under energetic stirring and than he diluted the obtained precipitate to 7 g/l by tetramethylammonium hydroxide (TMA) and three time washing of deoxygenated DI water. (Wang, Xiao et al. 2006)<sup>[11]</sup>.

#### Coating of magnetic nanoparticles

Magnetic nanoparticles can be synthesized by many methods and it is very sensitive towards precipitation or oxidation, the main important issue is that to protect the magnetic nanoparticles for long term against precipitation or oxidation. Pure metal such as Fe, Co and Ni and their metal alloys are very sensitive towards air. Therefore it is necessary to develop as such nanoparticles which are chemically stable and free from oxidation by oxygen and erosion by acid or base. As result of protection strategies generates a magnetic nanoparticles with core shell, in this magnetic nanoparticles as a core is coated by a shell. Magnetic nanoparticles with core/shell structure have many advantages like good dispersion and high stability against oxidation (Chomoucka, Drbohlavova et al. 2010)<sup>[12]</sup>. This type of coating method isolates the magnetic nanoparticles from environment. Coating technique can be divided into two groups that is organic coating and inorganic coating. Organic coating contains surfactant and polymers and inorganic coating contain silica, carbon, precious metal (such as Ag, Au) or oxides which formed by gentle oxidation of outer part of magnetic nanoparticles. It is formed in the form of  $\text{As}_2\text{O}_3$  (Lu, Salabas et al. 2007)<sup>[10]</sup>.

#### Polymeric coatings

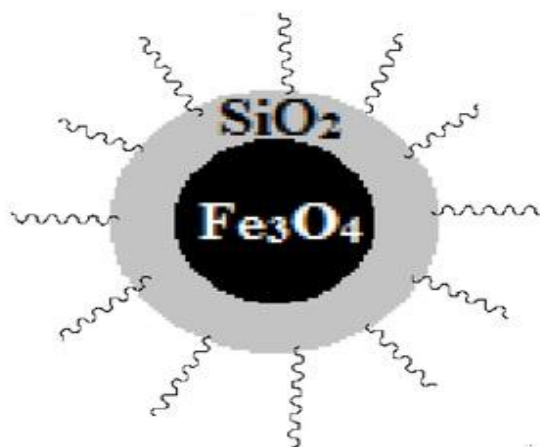
Polymeric coating on magnetic nanoparticles prevents the direct contact of iron oxide with cellular substance (Berry 2009)<sup>[13]</sup>. Polymeric

coating material can be classified into two groups that are synthetic and natural. Poly (vinylpyrrolidone) (PVP), poly (lactic-co-glycolic acid) (PLGA), poly (vinyl alcohol) (PVA), poly (ethylene glycol) (PEG), etc. are the example of synthetic polymers. Gelatin, dextran, chitosan, pullulan, etc. are the example of natural polymer (Gupta and Gupta 2005)<sup>[14]</sup>. For biomedical application, it is necessary that all magnetic nanoparticles should have coated surface. Polymeric coating on magnetic nanoparticles provides a steric barrier against agglomeration and increases the surface activity such as surface charge and chemical functionality. Monomeric species such as bisphosphonates, dimercaptosuccinic acid and alkoxy silanes can be used as polymeric coating. (Sun, Lee et al. 2008)<sup>[6]</sup>.

#### Silica coatings

Silica coated magnetic nanoparticles prevents the direct contact of magnetic nanoparticles with additional agents and avoids unwanted interaction. Therefore a silica shell first coated on the magnetic core and than dye molecules coated on silica shell. Silica coated magnetic nanoparticles have several advantage such as stability under aqueous condition and easy

control of interparticle interaction. The surfaces of silica-coated magnetic nanoparticles are hydrophilic in nature and easily can be modified with other functional group. Silica coated magnetic nanoparticles are potentially of use in bio labelling, drug targeting and drug delivery. Silica coating can perform on oxide surface easily. In this commercially available ferro fluid can be directly coated with silica by the method of hydrolysis of tetraethylorthosilicate (Xia and co-workers). First dilute the water based ferro fluid (EMG 340) with deionized water and 2-propanol, Stirred the whole solution and than add ammonia solution with continuously stepwise add of various amount of tetraethylorthosilicate under stirring condition. The coating thickness can be changed by continuous change of various amount of tetraethylorthosilicate. The whole mixture should be stirred for 3 hour under continuous stirring. As we know that iron oxide nanoparticles surface has a strong tendency of affinity towards silica, in this case no any primer or adhesive is required to promote the deposition and adhesion of silica. In water, silica coated magnetic nanoparticles are easily re dispersible without any need of other surfactants. (Lu, Salabas et al. 2007)<sup>[10]</sup>.

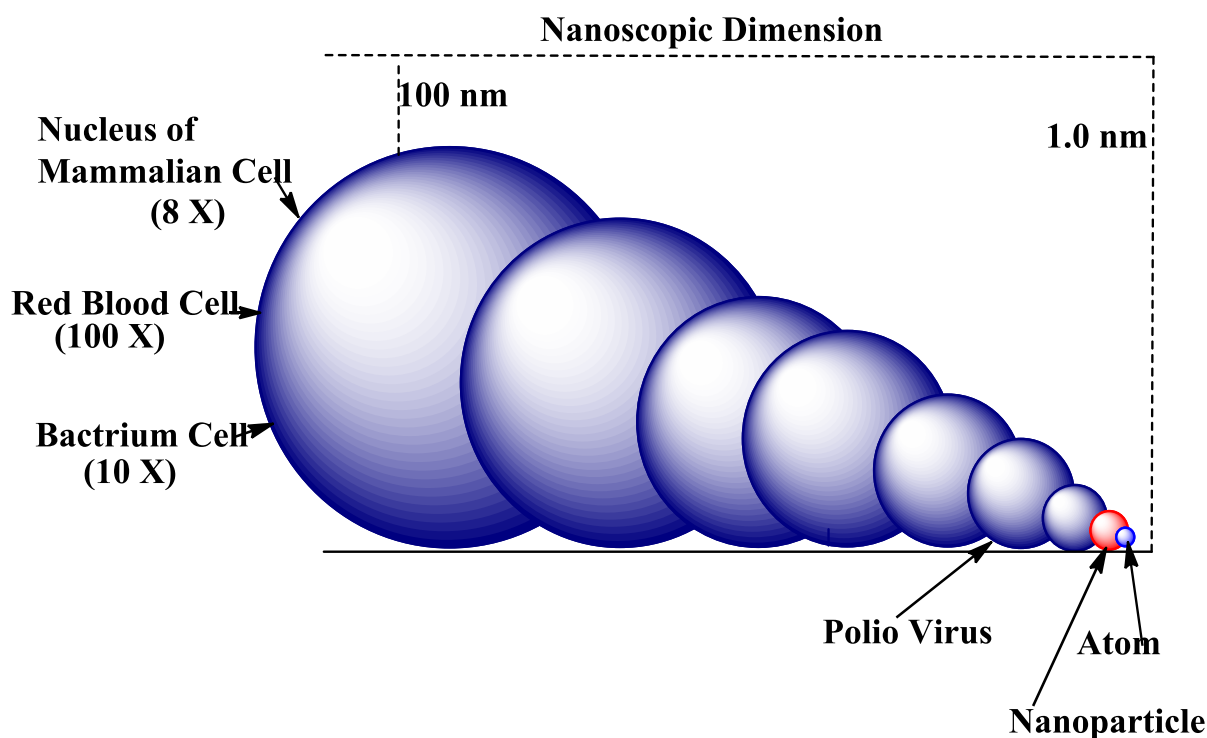


(Wang, Xiao et al. 2006)<sup>[11]</sup>

### Magnetic nanoparticles in biomedicine

Magnetic nanoparticles are future biomedicine because these biomedicines are having very controllable size ranging from few nanometres up to tens of nanometres. Magnetic nanoparticles are as much smaller as cell (10-100 $\mu$ m), a virus (20-450nm), a protein (5-50nm), a gene (2 nm wide and 10-100 nm long). this data prove that magnetic nanoparticles can get close biological nanoparticles (Figure 1). Magnetic nanoparticles provide a lot of benefit means this can coated with biological molecule to make them interact with or bind to biological unit. Magnetic coated biological molecule can

be manipulated by an external magnetic field because magnetic particle obey coulomb's law, due to this type of activity of magnetic coated biological particle (magnetic nanoparticles) opens many application such as transport and control. Therefore magnetic coated biological molecule can be used as anticancer drug or target the region of tumour. When heat is transfers to the magnetic nanoparticles than magnetic nanoparticles works as hyperthermia agents and delivers toxic amounts of thermal energy to target area of tumour of body. For chemotherapy and radiotherapy, magnetic nanoparticles are used very well (Pankhurst, Connolly et al. 2003)<sup>[15]</sup>.



(Gu, Xu et al. 2006)<sup>[16]</sup>

Nanoparticles are present in controlled size and shape which make these particle useful in biomedical purpose. These particles also have optical, magnetic and electronic properties. This property of nanoparticles helps in development of new tool to detect and control biological active process at the molecular and cellular level.

### Drug carriers

In 1970s, first polymer magnetic nanoparticles and microparticle developed for the delivery of drugs at specific location in lab. Magnetic part

of nanoparticles coated with biocompatible polymer such as dextran or inorganic coating such as silica. This type of coating works as a shield from the surrounding environment and

works when attached with carboxyl groups, carbodi-imide, biotin, avidine and other molecules. The carrier of magnetic nanoparticles consists of different structural configuration of magnetic particle core such as  $\text{Fe}_3\text{O}_4$  or  $\text{Fe}_2\text{O}_3$ . (Pankhurst, Connolly et al. 2003)<sup>[15]</sup>.

### **Superparamagnetic iron oxide nanoparticles: Magnetic nanoplatforms as drug carriers.**

In 1970s, first time the concept of magnetism introduce in medicine and after that a lot of research has been done in this specified area and design the many magnetic particle for the treatment of disease. (Wahajuddin 2012)<sup>[17]</sup>.

A magnetic iron oxide nanoparticles shows activity in presence of external magnetic field therefore this principle is used for the development of super paramagnetic iron oxide nanoparticles (SPIONs). SPIONs may be in range of 10 nm to 100 nm Ex-  $\gamma\text{-Fe}_2\text{O}_3$  (maghemite) or  $\text{Fe}_3\text{O}_4$  (magnetite). Now SPIONs open the wide range of research for novel drugs in cancer treatment.<sup>[17]</sup>

Shape of magnetic nanoparticles play very important role for the flow of blood because magnetic nanoparticles may be in shape of short rod or in shape of long road, spherical, and non spherical. Non spherical magnetic nanoparticles take long time for blood circulation in comparison to spherical shape. Thus we can say that shape of magnetic nanoparticles direct affects the cell and their toxicity.<sup>[17]</sup>

Sizes of nanoparticles are very important for blood circulation. If size is less than 10 nm than removed by renal clearance whereas size larger than 200 nm become concentrated in the spleen or taken by phagocyte. Only nanoparticles size range 10-100 nm considered by our circulation system for long term circulation. Magnetic nanoparticles size can be measured by transmission electron microscopy, dynamic light scattering and scherrer method

using X-rays diffractograms. (Wahajuddin 2012)<sup>[17]</sup>.

Magnetic nanoparticles have positive and negative zeta potential therefore magnetic nanoparticles have colloidal stability nature and dispersion stability nature. This charge also helps in the distribution of magnetic nanoparticles in the body.

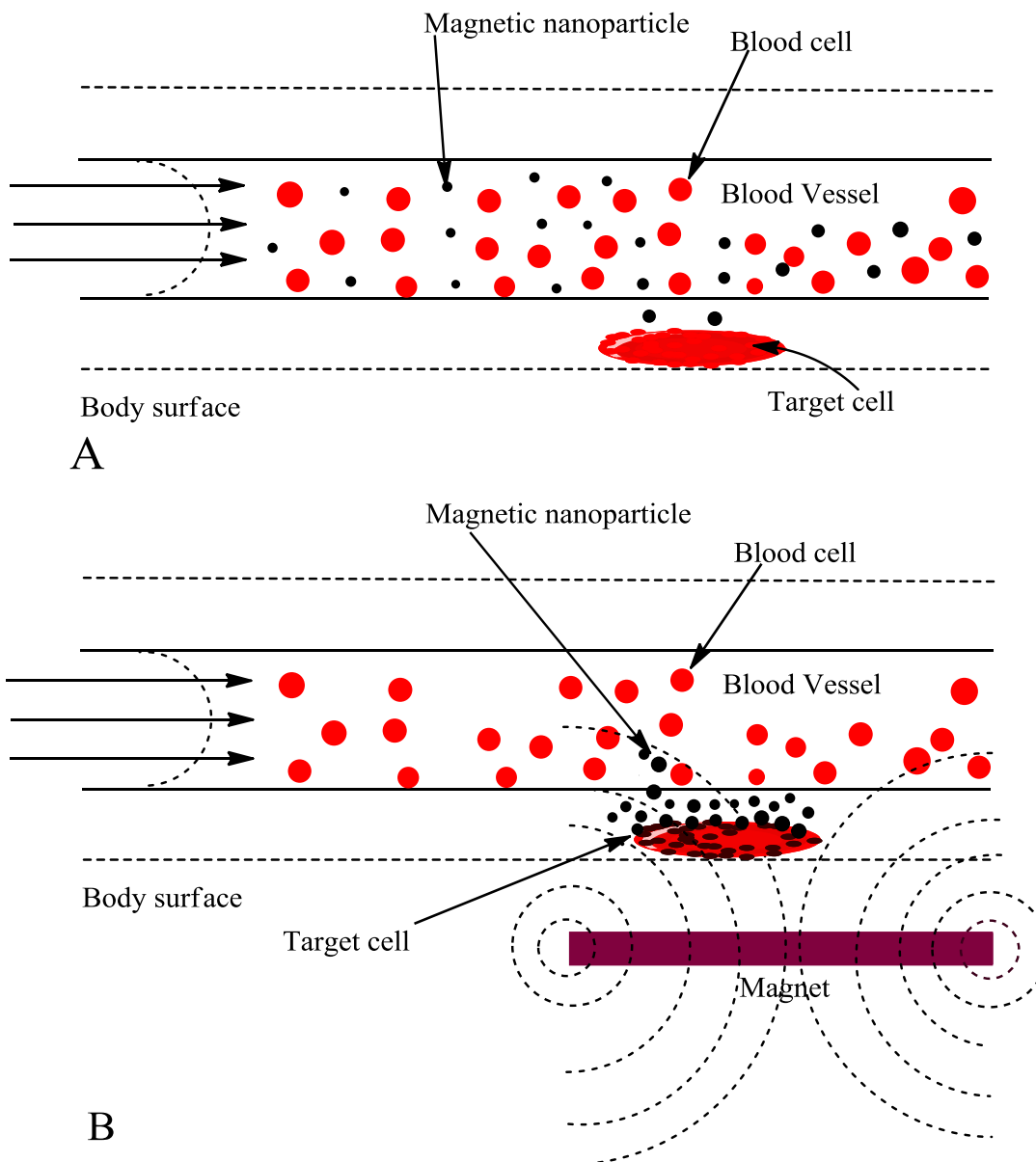
### **Drug delivery**

Now a day's nanotechnologies are commonly used in medicine, pharmaceutical industries, namely disease detection, controlled drug delivery, as biosensors, in tissue engineering and so on. Magnetic nanoparticles are designed for drug delivery. These types of particle are most successful among other nanosystem for drug delivery. (Chomoucka, 2010)<sup>[12]</sup>. Magnetic nanoparticles are very useful due to its unique properties of biological interaction which makes them a suitable agent for magnetic resonance imaging (MRI). Magnetic nanoparticles also have unique proprieties such as magnetic moment, non-fouling surface in detection, diagnosis and treatment of malignant tumors, cardiovascular disease and neurological disease (Sun, Lee et al. 2008)<sup>[6]</sup>. This review article based on the make use of MNPs as carriers for drug delivery. To target specific area in the body [Widder et al., 1978; Senyei et al., 1978; Mosbach and Schroder, 1979] Widder and others developed magnetic micro- and nanoparticles. They mix the magnetic nanoparticles with drugs and then injected into the specific area through intravenous or through intra-arterial injection (Dobson 2006)<sup>[18]</sup>. An external rare earth permanent magnetic field applied on the tumour cell to guide and concentrate the drugs. When drugs are concentrating at the site than beneficial drugs is released from magnetic carrier through the action of enzymatic activity or via change in physiological activity such as pH change, osmolality or temperature change. This technique give us a major advantage that target



the specific area of tumour and reduce the systemic distribution of cytotoxic drugs and

result in effective treatment at lower doses (Dobson 2006)<sup>[18]</sup>.



Magnetic-nanoparticle based drug delivery system in presence of external magnetic field

A-Magnetic nanoparticle in absence of magnetic field

B-Magnetic nanoparticle in presence of magnetic field

### MAGNETIC CHEMOTHERAPY

Treatment of cancer with drugs is called chemotherapy and chemotherapy destroys the

growth and reproduction of cancer cell. Normally, it can also harm healthy cells, which causes side effects.

Chemotherapy based on person's unique situation and it depends upon the stage of cancer and condition of patients. Chemotherapeutic drugs attack on reproducing cells; they cannot differentiate between reproducing cell of normal tissue and cancer cell. Chemotherapy destroys the normal cell and called as side effects yet chemotherapy is the best solution for curing or controlling cancer.

Currently scientists are working on new technique in which magnets are used to pull chemotherapy drugs into the tumours. For this technique, cancer killing drugs are infused with magnetic particle and then transfer into the blood vessel because blood vessel feeds the tumour. External magnetic fields applied on the patient body directly on the site of tumour therefore drug-carrying magnetic particle lodge in the tumour and treat the cancer.

### SUMMARY

After many research, yet it is not possible to predict nanoparticles bio distribution according

to physiological process and physicochemical properties. Coated nanoparticles distribution always affected by the biological system and their molecules such as proteins. Therefore, it is essential to design specific nanoparticles for specific cell organelles. Research work should base on either particle size dependent tissue growth or targeting extracellular part to achieve specificity. Thus research should base on to develop high-performance magnetic nanoparticles probes for deep treatment of tissue.

### CONCLUSION

Magnetic nanoparticles play an important role in the diagnosis of cancer and other disease because of it peculiar activity such as small size and non toxic effect on the other neighbor living cell. Now magnetic nanoparticles are using in the cancer diagnosis of liver, spleen, and bone marrow. The use of magnetic nanoparticles in the medical field shows a new interest for selective treatment of tissue or cell without any side effects. Thus magnetic nanoparticles may be the feature of medical diagnosis application.

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