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MAGNETIC DRUG DELIVERY IN THERAPEUTICS

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ABSTRACT

Magnetic modulated drug delivery system addresses the major problem of initial biodistribution of drug carrier. It involves the use of particulate carriers to a localized diseased site. Magnetic microspheres can be used for site-specific drug targeting as in case of tumors, magnetic bioseparation and also can be used for non-targeted drug delivery as in case of contrast agents (MRI) and drug reservoirs that can be activated by a magnet of suitable strength applied outside the body. This delivery system has the distinct advantage of locally congregating high concentrations of the drug at the diseased site thereby minimizing drug requirement and side effects. Though it is expensive and requires high technical approach, it can be adapted to any part of the body. Various magnetic microspheres developed include magnetic nanoparticles, magnetically resealed erythrocytes and magnetic liposomes. Stereotaxis Inc. and FeRx Inc., are major commercial developers of magnetic guidance system for the medical industry.

INTRODUCTION: In recent years, polymeric controlled drug delivery systems have evolved as one of the most attractive areas in drug delivery research. The drug release is controlled by the properties of the polymer-drug system. Despite having several advantages, one most important problem to this field is that all the systems so far developed, give release rates that are either constant or decrease with time. Patients suffering from Diabetes mellitus, arrhythmia or angina pectoris needs augmented delivery on demand, which can be achieved by the systems, which are associated with external or feedback control such as magnetic control.

For Drug targeting, various carrier systems have been exploited like liposomes, nanospheres, microspheres, macromolecules etc. The difficulty of targeting drugs in vivo using these carrier systems is that the body contains 3 major tubes: the vascular, extracellular & intracellular compartments. Reticuloendothelial organs resist extravasations of drug carriers above 3-5 nm in molecular diameter. Other problems associated with in-vivo drug targeting i.e. the initial bio-distribution of drug carrier & bioengineering problems that must be addressed before the possibility of cell-receptor binding & cell uptake can be meaningfully explored.

To overcome these problems, an alternative to these systems has been found i.e. to magnetize the carriers so that these particles can be retained at or guided to the target site by the application of an external magnetic field of appropriate strength.

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This retention of magnetic carrier at target site will delay reticuloendothelial clearance, facilitate extravasations & thus prolong the systematic action of drug.

History: Magnetically Modulated system for drug delivery is a young field. In 1957, the surgeon Gilchrist published a seminar paper on selective inductive heating of lymph nodes after injection of 20-100nm sized magnetite particles into the lymph nodes near surgically removed cancer [1]. Later in 1975, Turner & Rand combined this radiofrequency heating method with embolization therapy [2]. Gilchrist even didn't know envision that his magnetic particles could be magnetically guided & delivered to target areas.

In 1963, Meyers described that how much they were able to accumulate small iron particles intravenously injected in leg veins of dogs using a horse shoe magnet externally [3].

Hilal in 1974, engineered catheters with magnetic ends & described how they could be used to deposit & selectively embolize arterio-venous malformations with small magnets [4].

The more defined spherical magnetic microspheres were made for the first time by Dr. Kenneth Widder & Colleagues in 1979. They developed albumin microspheres, which encased drugs & magnetite (Fe_3O_4) Their magnetic albumin microspheres worked well in animal experiments for tumor therapy & as magnet resonance agents, but were not explored in clinical trails [5].

Wu et al. (1995) & Jones and Winter (2001) used the magnetic particles for embolization therapy of liver cancer [6, 7].

Principle: Magnetic drug delivery by particulate carriers is an efficient method of drug delivery to a localized disease site.

A drug or therapeutic radioisotope is encapsulated in a magnetic compound; injected into patient's blood stream & then stopped with a powerful magnetic field in the target area.

Depending on the type of drug, it is then slowly released from magnetic carriers or confers a local effect, thus it reduces the loss of drug as freely circulating in body (**Fig. 1**).

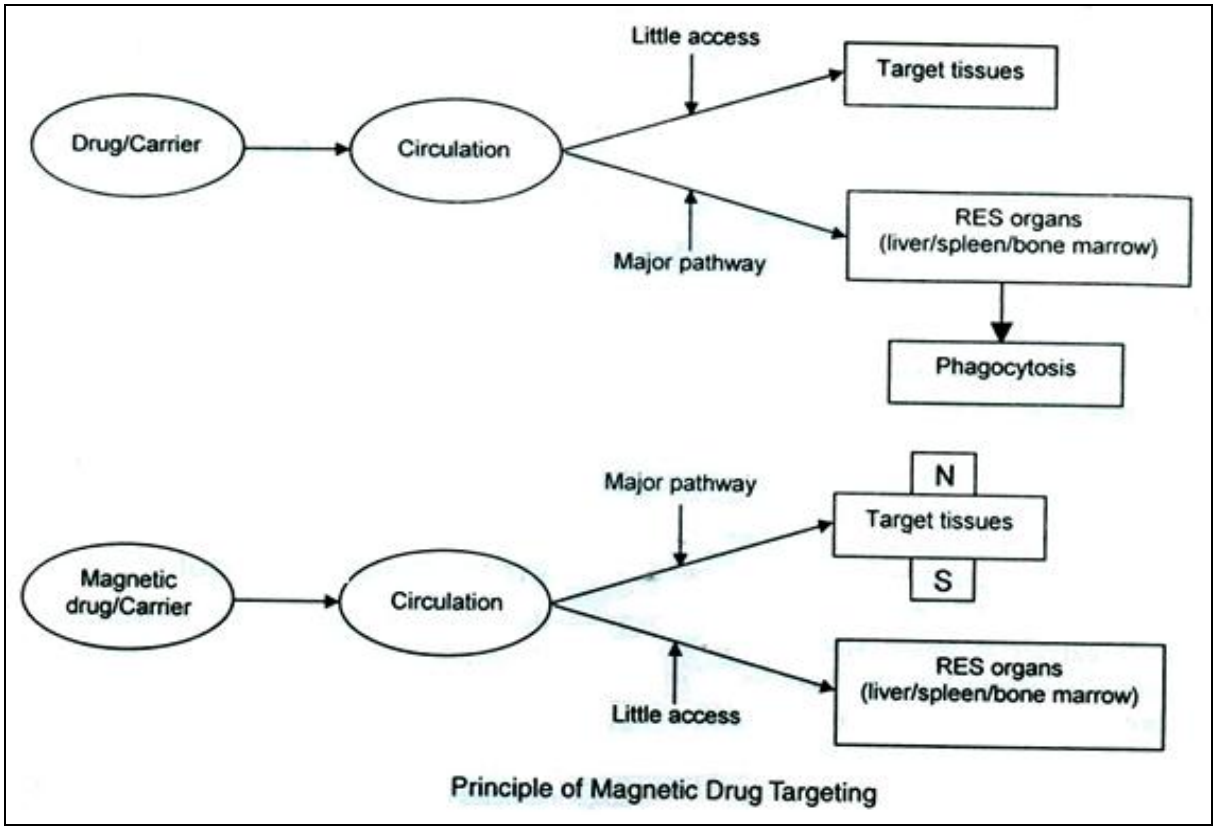

FIG-1: MAGNETIC DRUG TARGETING INVOLVES TARGETING DRUG TO TARGET SITE USING A MAGNETIC DRUG CARRIER RESULTING IN HIGHER CONCENTRATIONS OF DRUG AT TARGET SITE AS COMPARED TO CONVENTIONAL DRUG DELIVERY

Very high concentration of chemotherapeutic or radiological agents can be achieved near the target site, such as tumor, without any toxic effects to surroundings tissues.

Non targeted applications of magnetic microsphere & nanospheres include their use as contrast agents (MRI) & as drug reservoir that can be activated by a magnet applied outside the body.

The Efficiency of magnetic carriers depends on physiological parameters e.g. particle size, surface characteristics, field strength & blood flow rate, etc. Some kind of channel opened by the force of the magnet is thought to be associated with process of extrusion by magnetic targeted carriers.

Advantages:

- Therapeutic responses in target organs at only one tenth of the free drug dose.
- Controlled drug release within target tissues for intervals of 30 min to 30 hours, as desired.
- Avoidance of acute drug toxicity directed against endothelium and normal parenchymal cells.
- Adaptable to any part of the body.

However, this system suffers from some disadvantages also as given below:

- It is an expensive, technical approach and requires specialized manufacture and quality control system.
- It needs specialized magnet for targeting, for monitoring, and trained personnel to perform procedures.
- Magnets must have relatively constant gradients, in order to avoid focal over-dosing with toxic drugs.
- A large fraction (40-60%) of the magnetite, which is entrapped in carriers, is deposited permanently in target tissues.

Due to these limitations, magnetic drug targeting is likely to be approved only for certain disease conditions.

Magnetic Microspheres: Microspheres are spherical polymeric particles with size less than 4µm. They are small enough to circulate through capillaries without producing embolic occlusion and are sufficiently susceptible (ferromagnetic) to get captured in microvessels by magnetic fields of 0-5-0.8T. These were prepared by mainly 2 methods :-

- Phase separation emulsion polymerization (PSEP)
- Continuous solvent evaporation (CSE)

By injecting microspheres in a physiological solution containing 0.1% w/v Tween 80 or a viscosity enhancing agent such as 50% (w/v) dextran, aggregation in target vessels can be minimized. For Spheres smaller than 3 µm, initial biodistribution (5-30min) is a function of,

1. The dose relative to the capacity of target capillaries.
2. The degree to which the magnetic field overlaps microvessels supplied by the injection vessels.
3. The extent of venous shunting before microspheres reach the field.
4. The flow rates in target vessels.

The amount and rate of drug delivery via magnetic responsive microsphere can be regulated by varying size of microspheres, drug content, magnetic content, hydration state and drug release characteristic of carrier. Factors that influence drug release from carrier in vivo viz., enzymatic digestion of microspheres accelerated drug release and retrodiffusion of the drug back to micro vessels enhances drug clearance. Estimates of free tissue drug can be made at different intervals from the simultaneous interpretation of results obtained from carrier localization studies in tissue and drug release profile in vitro. The accurate & precise results can be obtained by measuring the drug levels of the target site per se using magnetic resonance methods.

Magnetite: Also known as ferrous ferrite, is a combination of two magnetic oxides of Iron, FeO & Fe_2O_3. It is in the form of fine particles and has been used for various applications in vivo, in transmission radiography, ad contrast gastrointestinal agent, in inducing clotting in arteriovenous malformation, as a tracer of blood flow and in radionuclide angiography. Others include immunoassays, drug targeting, drug transporting & biosensing. Certain studies show that iron particles could be magnetically controlled in the vasculature of experimental animals [3]. Iron particles of 50-200 Å in diameter could pass through even the smallest capillaries in the body [8].

A magnoresponsive fluid is also available, known as ferro fluids. These normally contain anionic surface active agents for the purpose of stabilization which have haemolytic properties. These haemolytic properties can be removed by addition of Amberlite, MB_2.

Another novel magnetic material dextran- magnetite conjugate (DM) was proposed by Hasegawa & Hokkuku [9]. It is a submicron complex consisting of magnetic iron-oxide core surrounded by dextran chains. These particles have low toxicity than conventional magnetite.

Magnetic Targeting: Targeting by magnetic microspheres i.e. incorporation of magnetic particles in to drug carriers (Polymers) and using an externally applied magnetic field is one way to physically direct this magnetic drug carrier to a desired site.

Widder showed that in the presence of a suitable magnetic field, the microspheres are internalized by the endothelial cells of target tissues in healthy as well as tumor bearing animals [5].

The relationship between magnetic force and magnetic moment of particles after saturation is given by

$$F = M \blacktriangledown H$$

F - Force on Particles

M - Magnetic moment of particles

$\blacktriangledown H$ - Magnetic field gradient

This explains that spheres with increased magnetic moments will experience forces sufficient for extravascular migration at proportionally lower field gradients. The magnetic moments of magnetic particles can be increased by –

1. By magnetizing the sphere to saturation levels prior to vascular targeting.
2. By clustering magnetite at the center of each sphere to produce larger macrodomains.
3. By substituting one of the newer ferromagnetic materials that has higher susceptibility than Fe_3O_4

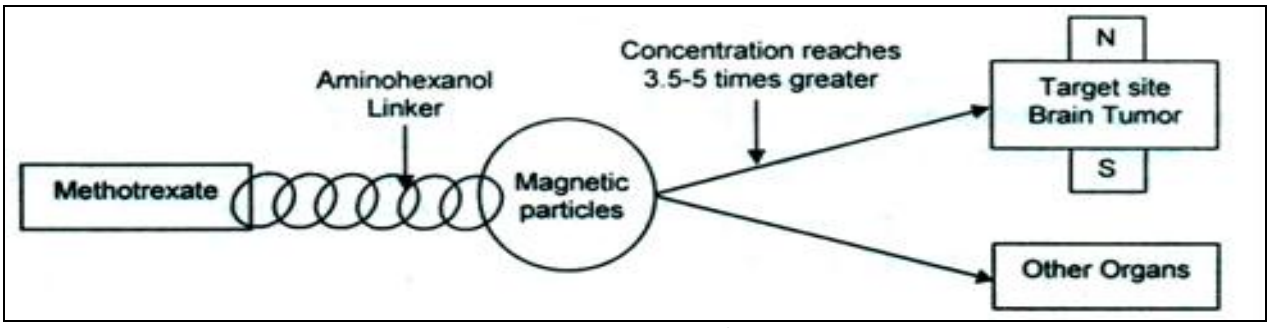

FIG-2: ACTIVE PHARMACEUTICAL DRUG IS BOUND TO MAGNETIC CARRIER/PARTICLE USING A LINKER, IN THIS CASE AMINOHEXANOL BEING THE LINKER BETWEEN METHOTREXATE AND MAGNETIC PARTICLES WHICH IS EFFICIENT IN TREATING BRAIN TUMOR

Gupta and Hung suggested that in presence of magnetic field, the microspheres demonstrated 16 fold increases in the maximum drug concentration, 6 fold increase in drug exposure and 6 fold increase in the drug targeting efficiency to rat tail target segments [10].

A novel magnetic microsphere-methotrexate (MM-MTX) drug delivery system was developed and evaluated in rats bearing rat glioma-2 humour. The drug is administered to Male fisher 344 rats bearing tumour in the form of either as MM-MTX or as methotrexate solution (MTX-S) and magnetic field was

applied for 15min. After analysis, it was shown that MTX concentration was 3.5 to 5 fold greater in the brain of MM-MTX treated group compared to the MTX-S treated group. MTX concentrations in all other organs were comparatively low following administration of MM-MTX than MTX-S (Fig-2).

Magnetic Liposomes: Liposomes are microscopic particles in the form of multilamellar, concentric, bilayer vesicles with layers of aqueous media separating the lipid bilayers, having diameters from 25 nm to 4 µm. Magnetic liposomes can be prepared by entrapment of ferrofluid within core of liposomes. Other components include phospholipids and cholesterol. Magnetic liposome can also be produced by covalent attachment of ligands to the surface of the vehicles or by incorporation of target lipids in the matrix of structural phospholipids.

Alternatively magnetic liposomes are prepared using the phospholipid vesicle as a nanoreactor for the in-situ precipitation of magnetic nanoparticles. These liposomes are characterized for their physical attributes i.e. size, shape & size distribution, surface charge, percent capture, percent magnetite content, entrapped volume lamillarity through freeze fracture microscopy and P-NMR, phase behavior drug release, quantitative determination of phospholipids and cholesterol analysis.

Research carried out by Margolis et al, 1983 showed the utilization of magnetic liposomes in cellular sorting [11]. The magneto liposomes were biophysically characterized and the potentialities of liposomes in symmetric and asymmetric phospholipids transfer process were explored. They presented classical binding characteristics and thermal behavior of cytochrome-C oxidase bearing magnetic liposomes [12, 13]. The preparation, physicochemical properties and their possible use as a targeting carrier have also been described [14].

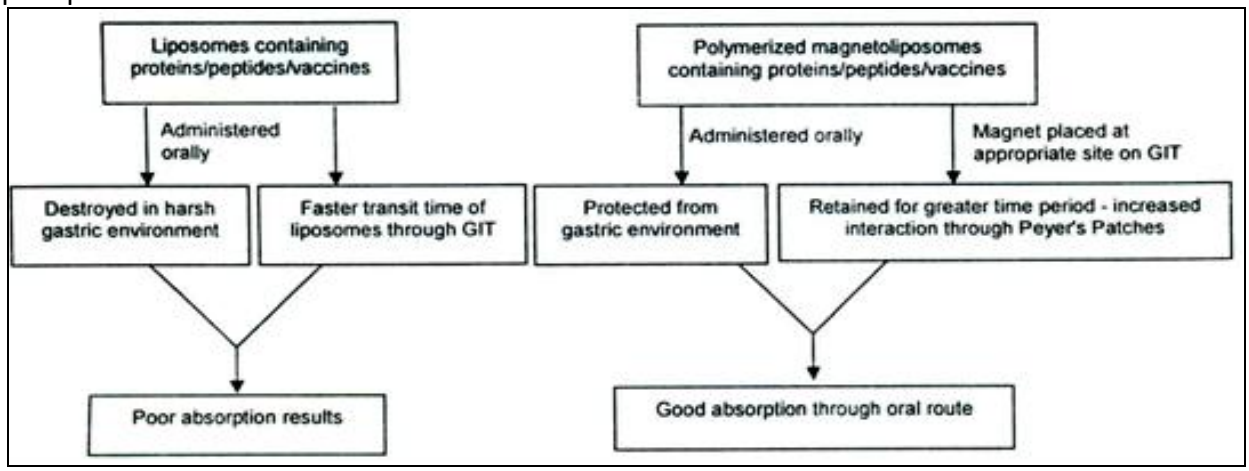

FIG. 3: DRUGS/PEPTIDES DESTROYED BY GASTRIC ENVIRONMENT CAN BE GIVEN ORALLY BY POLYMERIZING THE MAGNETOLIPOSOMES ENSURING PROTECTION FROM GASTRIC pH, TARGETING DELIVERY AND INCREASING DRUG-ABSORPTION TIME IF REQUIRED

Chen and Langer prepared magnetically responsive polymerized liposomes as potential oral delivery vehicles to protect complex molecules such as protein & peptide from harsh gastrointestinal environment and targeting them to the peyer's patches [15] (**Fig. 3**).

Babincova *et al*., showed that magnetoliposomes could be heated to higher temperatures which may lead to a leakage of encapsulated drug [16]. Kubo *et al*., designed magnetoliposomes to act as anticancer drug carriers which could be effectively delivered to solid tumor via intravenous route [17].

Magnetic Nanoparticles: Magnetic nanoparticles are particles containing polymers and drug along with ferromagnetic particles (magnetite), with diameter of 200 to 500 nm. Materials used in the preparation of nanoparticles are sterilizable, non-toxic and biodegradable; examples are albumin, ethylcellulose, casein and gelatin. Magnetic colloidal iron oxide nanoparticles were prepared with the method of co-precipitation. Ferromagnetic iron-dextran nanoparticles were prepared by the reaction of a mixture of ferrous chloride & ferric chloride with dextran polymers under alkaline conditions.

Interfacial polymerization was also applied to synthesize magnetic nanoparticles. Indomethacin bearing magnetic nanoparticles of polymethyl-methacrylate were prepared by the emulsion polymerization technique [18].

Magnetically responsive nanoparticles were prepared from enzymatically hydrolyzed starch and magnetite. Two different monoclonal mouse anti-rat Ig kappa light chain antibodies were covalently coupled to the particles. Using these particles, a very high depletion of surface Ig positive cells from one million rat peripheral blood mononuclear cells could be achieved.

Super paramagnetic iron oxide particles represent a new class of contrast agents that increase the detectability of hepatic & splenic tumour by MRI. The main steps of biodegradation and metabolism of magnetite-dextran nanoparticles in rats were investigated [19] (**Fig. 4**).

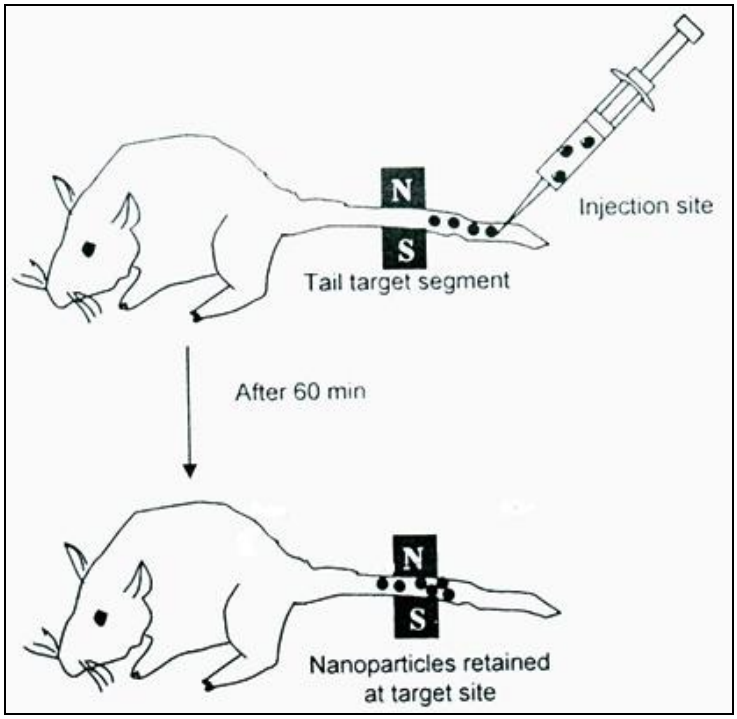

FIG. 4: ELEMENTARY MODEL DEMONSTRATING TARGETING DRUG AT A SPECIFIC SITE BY USING MAGNETIC FIELD EXTERNALLY

Colloidal aqueous suspension of superparamagnetic nanoparticles(diameter 9nm) was covalently coupled with lectins, enzymes or antibodies and their application in specific targeting of cells was studied [20]. Mono crystalline iron oxide containing nanoparticles were prepared with an oxidized starch coating for positive contrast MR angiography [21].

Magnetically Resealed Erythrocytes: Magnetically resealed erythrocytes contains ferrofluids (magnetite) along with loaded drugs within the cell. Erythrocytes are suspended in a hypotonic medium. They swell to about one and a half times their normal size and the membrane ruptures, resulting in the formation of pores with diameters of 200 to 500 Å. With drugs & ferrofluids present in the extracellular solution, it is possible to entrap up to 40% of the material into erythrocytes. If the ionic strength of the medium then is adjusted to isotonicity and the cells are incubated at 37°, the pores will close and cause the erythrocytes to "reseal".

These resealed erythrocytes came into existence due to various advantages such as

- Biodegradable, fully biocompatible and nonimmunogenic.
- Exhibit flexibility in circulation time depending on their physicochemical properties.
- The entrapped drug is shielded from immunological detection.
- Chemical modification of drug is not required.

Autologous red blood cells loaded with ferromagnetic colloid compound & aspirin were administered intravenously and completely aborted arterio-thrombosis on magnet application side with no deterioratory effect on clot formation in the coronary artery was recorded [22].

In another study by Vyas & Jain, erythrocytes were loaded with ibuprofen and magnetite using presswell technique [23]. The loaded cells effectively responded to an external magnetic field of 8.0 KOe. Various process variables including drug concentration, magnetite concentration, sonication of ferrofluids were optimized. The loaded erythrocytes were characterized for *in vitro* drug efflux, haemoglobin release, morphology, osmotic fragility, turbulence shock, in vitro magnetic responsiveness and prevent cell recovery. The drug release profile from the cellular system was observed to follow zero order kinetics.

In the continuous study, diclofenac sodium bearing erythrocytes were characterized for in vitro parameters.

Magnetic Emulsions: The emulsion is magnetically responsive oil in water type of emulsion bearing a chemotherapeutic agent which could be selectively localized by applying an external magnetic field to specific target site. It appears to have potential in conferring site specificity to certain chemotherapeutic agent. Akimoto and Morimoto prepared magnetic emulsion by utilizing ethyl oleate based magnetic fluid as the dispersed phase, casein solution as the continuous phase and anticancer agent, methyl CCNU (1-(2-chloroethyl)-3- (trans-4-methylcyclohexyl)-1-nitrosourea) trapped in the oily dispersed phase as active chemotherapeutic agent[24]. The emulsion showed high retention by a magnetic field in vitro. After i.v. injection in the rat, the emulsion was mainly localized in the lungs by application of an electromagnet over the chest.

Applications: Magnetic drug delivery system has vivid areas of use & its use is increasing tremendously. The major areas of its use are accounted below:

1. **Treatment of Tumors via magnetic drug targeting**: Magnetism can play very important role in cancer treatment. The first clinical cancer therapy trials using magnetic microspheres were performed by Lubbe et al. in Germany for the treatment of advanced solid tumor while current preclinical research is investigating use of magnetic particles loaded with different chemotherapeutic drugs such as mitoxantrone, paclitaxel [25].

   Magnetic drug targeting allows the concentration of drugs at a defined target site generally and importantly, away from the Reticular Endothelial System (RES) with the aid of a magnetic field. The drug & an appropriate Ferro fluid are formulated into a pharmaceutically stable formulation which is usually injected through the artery that supplies the target organ or tumour in the presence of an external magnetic field. For effective retaining of magnetic drug carrier, the magnetic forces must be high enough to counteract linear flow rates within the organ or tumor tissue (between 10 & 0.05 cm/s depending on vessel size & branching pattern) Liver, brain, pancreatic & renal cell carcinomas are generally treated through this method.

2. **Magnetic Control of Pharmacokinetic parameters:** Langer *et al*., (1980) embedded magnetite or iron beads in to a drug filled polymer matrix and they showed that they could activate or increase the release of drug from the polymer by moving a magnet over it or by applying an oscillating magnetic field [26]. The microenvironment within the polymer seemed to have shaken the matrix or produced 'micro cracks' & thus made the influx of liquid, dissolution and efflux of drug possible thereby achieving magnetically controlled drug release. In this way, it was possible to magnetically activate the release of insulin from a depot underneath the skin [27].

   Another mechanistic approach based on magnetic attraction is the slowing-down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach & intestines can be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption in stomach or intestines. Slowing down the passage of magnetic liposomes with magnet actually increased the blood levels of a drug [15].

3. **Magnetic Bioseparation:** Bioseparation is an important phenomenon for the success of several biological processes. Therefore, prospective bioseparation techniques are increasingly gaining importance. Amongst the different bioseparation techniques, magnetic separation is the most promising. Particles that are bound to magnetic fluids can be used to remove cells and molecules by applying magnetic fields and in-viva- to concentrate drugs at anatomical sites with restricted access. Additional modifications of the magnetic particles with monoclonal antibodies, lecithin's, peptides, or hormones make these applications more efficient & are also highly specific.

   The isolation of various molecules such as enzymes, enzyme inhibitors, DNA, RNA, Antibodies and antigens etc from different sources including nutrient media, fermentation broth tissue extracts and body fields, has been done by using magnetic absorbents.

In case of enzyme Separation, the approximate affinity ligands are immobilized on polymer coated magnetic carrier or magnetizable particles.

Isolation & purification of IgG can be done by immobilization of protein A or protein G on Silanized magnetic along with fine magnetotactic bacteria.

Isolation of mRNA, genomic DNA and proteins can be done by monosized super paramagnetic particles, Dyna beads.

The therapeutic applications of immunomagnetic cell selection are based on antibodies that bind to cancer cell antigens such as CD10, CD19 or CD20 [28].

4. **Treatment of tumors with magnetically induced hyperthermia:** Heat treatment of organs or tissues, such that the temperature is increased to 42-46° C and the viability of cancerous cells reduces, is known as hyperthermia. It is based on the fact that tumor cells are more sensitive to temperature than normal cells. In hyperthermia it is essential to establish a heat delivery system, such that the tumor cells are heated up or inactivated while the surrounding tissues (normal) are unaffected.

   Magnetic fluid hyperthermia is based on the fact that sub domain magnetic particles produce heat through various kinds of energy losses during application of an external AC magnetic field. If magnetic particles can be accumulated only on the tumour tissue then cancer specific heating can be achieved. Cationic magnetoliposomes and affinity magnetoliposomes have been used for hyperthermia treatment.

   Ongoing investigations in magnetic hyperthermia are focused on the development of magnetic particles that are able to self-regulate the temperature they reach.

5. **Magnetic systems for the diagnosis of diseases:** One of the most important applications of magnetic particles is as contrast agent for magnetic resonance imaging (MRI) in diagnosis of diseases. Saini *et al*., (1987) tested 0.5-1 micrometer sized ferrites in vivo for the first time [29]. Since then, smaller superparamagnetic iron oxides (SPIOs) have been developed into unimodular nanometer sizes. The most commonly used superparamagnetic material is Fe_3O_4 with different coatings such as dextrans, polymers and silicone. SPIOs have mainly found their application as a liver-specific contrast agent for intravenous application, detection of metastases in non-enlarged lymph nodes, to distinguish loops of the bowel from other abdominal structures.

6. **Magnetic Targeting of Radioactivity:** Magnetic targeting can also be used to deliver therapeutic radioisotopes [30]. The advantage of this method over external beam therapy is that the dose can be increased, resulting in improved tumor cell eradication, without harm to nearby normal tissue. Different radioisotopes can treat different treatment ranges depending on the radioisotope used the B-emitters ^{90}Y for example will irradiate up to a range of 12 mm in tissue. Unlike chemotherapeutic drugs, the radioactivity is not release, but rather the entire radioactive microspore is delivered to and held at the target site to irradiate the area within the specific treatment range of isotope. Once they are not radioactive anymore, biodegradation of the microspheres occurs (and is desired). Magnetic targeted carriers, which are more magnetically responsive iron carbon particles have been radiolabeled in last couple of years with isotopes such as ^{188}Re [30], ^{90}Y, ^{111}In, and ^{125}I [31] and are currently under trails.

7. **Study of focal pathological lesions accompanied by Blood Brain Barrier modifications**: Blood Brain Barrier (BBB) permeability to magnetic dextran nanoparticles (MD_3) after osmotic disruption in rats was investigated. After i.v. mannitol infusion, the BBB breakdown was temporary & immediate as judged by soluble molecule diffusion. MD_3 nanoparticles crossed the BBB 12h after intravenous mannitol injection, at a time when brain permeability for molecules or small particles returns to normal. Magnetic crystals were found in cytoplasmic vesicles of glial cells. On MRI, signal intensity decreased after injection of MD_3, even 12h after mannitol injection (**Fig. 5**).

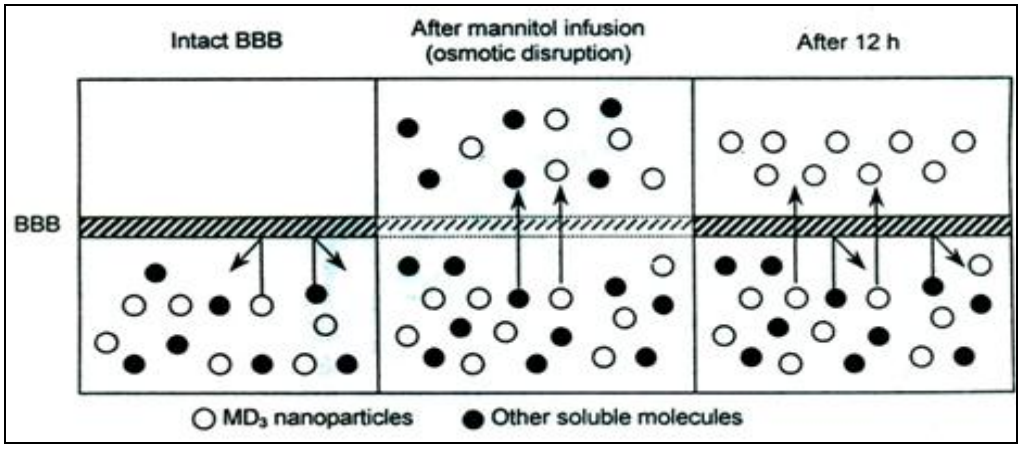

FIG. 5: MAGNETIC DEXTRAN PARTICLES' PATTERN OF DIFFUSION ACROSS BBB AFTER MANNITOL INFUSION

This could be particularly useful in the study of focal pathological lesions accompanied by BBB permeability modifications. In such conditions, super paramagnetic particles based contrast agents could be caught by BBB areas without detectable cellular lesions.

8. **Monitoring of Tissue Levels:** Determination of naturally occurring ^{31}P metabolites & ^{13}C labeled metabolic precursors by magnetic resonance spectroscopy provides a means to monitor tissue responses to localized drugs. This method included either monitoring of decrease in spectral peaks or acute broadening of spectral peaks.

9. **Application in Contraceptive Drug Delivery:** Magnetically Controlled Systems release the desired drug in a controlled fashion on exposure to aqueous media. The rate can be altered & modulated on application of an oscillating external magnetic field. These systems may be useful when drug delivery is designed responsive to the changes in steroid secretion during menstrual cycle.

10. Miscellaneous Applications:

i. The use of magnetic nanospheres for the well directed delivery of radionuclides to a tumour after the i.v. Administration of the biodegradable colloidal suspension is well documented and proposed [32].

ii. Magnetic elements have been successfully used in gastrointestinal surgery for tissue fixation, which form hermetic seal after surgery & possibility of the gastrointestinal tract is maintained & the patient can able to eat immediately after operation.

iii. Magnetically guided ferrofluid nanoparticles were used in retinal repair. Magnetically guided interstitial diffusion of the nanoparticles up to 20mm of the gel over periods of 72 hours was shown to be possible, thus demonstrating that essentially all points on the retinal surfaces are reachable from elsewhere in the ocular interior.

iv. Monocrystalline iron oxide containing nanoparticles were prepared with an oxidized start coating, and ore recently being used for positive contrast MR angiography.

v. Magnetoliposomes coupled with HIV receptor proteins can be effective treatment modules against HIV virus [33].

Delivery Strategy:

STEREOTAXIS, Inc.'s Delivery Strategy [34]: Stereotaxis, Inc. is the leading commercial developer of magnetic stereotaxis systems (MSS) for the medical industry. The first prototype magnetic guidance system was a 6-coil superconducting multicoil helmet built by Wang NMR as a fifth generation device. This device was built for the University of Virginia by Wang NMR and in 1994 characterization of the system was underway in preparation for experimental studies.

It was subsequently sold to Stereotaxis Inc. where it developed a leak in 1998, and it is currently warehoused with an estimated cost of approximately $200,000 to fix. Based in part on this prior Wang design, Stereotaxis's primary product is the "TELSTAR".

It represents the sixth generation of MSS. It uses a 3-coil superconducting system to guide a magnetic tipped catheter throughout the arterial system. The next generation system that Stereotaxis is focusing on is a more compact and cost effective system, utilizing permanent instead of superconducting magnets. The position of the permanent magnets will be mechanically moved instead of varying current to alter the force on the magnetic tipped catheter.

FeRx Inc.'s Delivery Strategy [35]: In comparison, FeRx has focused on the use of external permanent magnets and particle transport through tissue. FeRx's strategy has been to use milled 1 µm iron-activated carbon which has a much higher magnetic moment when compared to magnetite. Iron is injected into blood vessels near the target organ and then a single external permanent magnet pulls the particles out of the bloodstream and into the epithelium layers of the organ. The field is removed from the target organ after approximately 15 minutes and an angiogram is performed to make sure blockage of the main arteries has not occurred.

Various drugs are attached to the iron activated carbon depending on the application. This method for drug delivery has been performed for both the liver and bladder. Potential downfalls of this method are the toxicity of the iron, which directly relates to the body's ability to rid itself of excess iron. There is a condition called hemochromatosis in which the liver fails after a slow buildup of too much iron caused by the liver's inability to excrete this waste. Superconducting Quantum Interference Devices (SQUIDS), the most sensitive detector of magnetic flux, have been used to noninvasively determine iron concentration in organs to prevent hemochromatosis.

However, FeRx plans to keep the doses in the body under toxic levels by limiting and controlling the amount of infused iron.

In summary, there have been many uses of magnetic particle manipulation in the human body. However, a single system has yet to emerge that combines the techniques presented into a simple tool with a wide range of applications extensively used by the medical community.

CONCLUSION: Magnetic drug targeting and delivery has enormous potential in the field of therapeutics. Despite of certain snags and high expertise requirement, site-specific drug targeting and maintaining its optimized concentration can be achieved. Efficiency of magnetic carriers depends on certain physiological parameters and magnetic field strength. Various magnetic microspheres , each having its own distinct advantage, has been developed and can be widely used for the treatment of tumours, cell separation, diagnosis of diseases, biological studies, contraception and many more.

Future is quite promising and challenging for development of magnetic drug delivery as a novel drug delivery system. Research needs to be done on development of methods to abate its disadvantages so that it can be used for treatment of many more diseases in future.

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