

## Magnetically Modulated Drug Delivery Systems

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### Abstract

Magnetic drug delivery is a novel approach to delivery drug using engineered 'smart' micro carriers which appears to overcome a number of limitations facing current methods of delivering medicines. The drug and a suitable ferrofluid are formulated into a pharmaceutically stable formulation which is usually injected through the artery that supplies the target organ or tumor in the presence of an external magnetic field. Depending on the fabrication method, particle size and nature they are named as magnetic microspheres, magnetic nanoparticles, magnetic liposomes etc. This review gives the information regarding the all possible formulations that can be designed using magnetism as the drug delivery mode.

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### INTRODUCTION

Magnetically targeted drug delivery by particulate carriers is an efficient method of delivering drugs to localized disease sites such as tumors. High concentrations of the chemical agents can be achieved near the target site without any toxic effects to normal surrounding tissue. Non-targeted applications of magnetic microspheres and nanospheres include their use as contrast agents (MRI) and as drug reservoirs that can be activated by a magnet applied outside the body. Various nonmagnetic micro carries (nanoparticles, microspheres and microparticles etc.) are successfully utilized for drug targeting but they show poor site specificity and are rapidly cleared off by RES (reticuloendothelial system) under normal circumstances. Magnetism plays an important role in such cases. Magnetic particles composed of magnetite. Magnetic fields are believed to be harmless to biological systems and adaptable to any

part of the body. Up to 60% of an injected dose can be deposited and released in a controlled manner in selected nonreticuloendothelial organs. Magnetic micro carriers were developed to overcome two major problems encountered in drug targeting namely: RES clearance and target site specificity.

Magnetism has application in numerous fields like diagnostics, drug targeting, molecular biology, cell isolation, cell purification, hyperthermia, and radioimmunoassay.

Magnetic particles, ranging from nanometer-size to 1micron, are being used in an increasing number of medical applications. The important properties of magnetic particles for medical applications are non-toxicity, bio-compatibility, injectability and high-level accumulation in the target tissue or organ. Magnetic nanoparticles modified with organic molecules have been widely used for biotechnological and biomedical applications as their properties can be magnetically controlled by applying an external magnetic field.

### History OF Magnetic Targeting

Magnetic drug targeting is a young field. The surgeon Gilchrist published a seminar paper in 1956 on the selective inductive heating of lymph nodes after injection of 20–100-nm sized magnetite particles into the lymph nodes near surgically removed cancer [1]. Turner and Rand combined this radiofrequency heating method with embolization therapy [2]. Gilchrist apparently did not, however, envision that his magnetic particles could be magnetically guided and delivered to the target area. In 1963, Meyers described how they were able to accumulate small iron particles intravenously injected into the leg veins of dogs, using a large, externally applied horse shoe magnet [3]. They imagined that it might be useful for lymph node targeting and as a contrast agent. Hilal then engineered catheters with magnetic ends, and described how they could be used to deposit and

selectively embolize arterio-venous malformations with small magnets [4]. The use of magnetic particles for the embolization therapy of liver cancer followed and has recently found renewed interest.

More defined spherical magnetic microspheres were made for the first time at the end of the 1970s by Widder [5]. Their magnetic albumin microspheres worked well in animal experiments for tumor therapy and as magnet resonance contrast agents, but were not explored in clinical trials [6].

### Principle of Magnetism for micro particles

Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to a localized disease site. Very high concentrations of chemotherapeutic or radiological agents can be achieved near the target site, such as a tumor, without any toxic effects to normal surrounding tissue or to the whole body.

Magnetic carriers are normally grouped according to size. At the lower end, we have the ferrofluids, which are colloidal iron oxide solutions. Encapsulated magnetite particles in the range of 10–500 nm are usually called magnetic nanospheres and any magnetic particles of just below 1–100µm are magnetic microspheres. In general, magnetic liposomes are also included when speaking about magnetic carriers.

### MAGNETIC CARRIERS

#### Magnetic Microspheres:

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4 µm) but are sufficiently susceptible (ferromagnetic) to be captured in microvessels and dragged in to the adjacent tissues by magnetic fields of 0.5-0.8 tesla. Magnetic microspheres were prepared by mainly two methods:

1. Phase separation emulsion polymerization (PSEP) and
2. Continuous solvent evaporation (CSE).

The amount and rate of drug delivery via magnetic responsive microspheres can be regulated by varying size of microspheres, drug content, magnetite content, hydration state and drug release characteristic of carrier. The amount of drug and magnetite content of microspheres needs to be delicately balanced in order to design an efficient therapeutic system. Magnetic microspheres are characterized for different attributes such as particle size analysis includes size distribution, surface topography, and texture etc using scanning electron microscopy (SEM), drug entrapment efficiency, percent magnetite content, and in vitro magnetic responsiveness and drug release.

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 carriers to a desired site, Widder first reported on the use of magnetic albumin microspheres [7]. Widder also 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 [8].

Gupta and Hung suggested that in presence of magnetic field, the microspheres demonstrated 16 fold increases in the maximum drug concentration, 6 fold increases in drug exposure and 6 fold increases in the drug targeting efficiency to rat tail target segments<sup>11</sup>. Morimoto and Natsume studied the utilization of magnetic microparticulate system for cancer therapy by formulating a novel cationic delivery system based on magnetic aminodextran microspheres (MADM) and compared with the neutral magnetic dextran microspheres (MDM)<sup>12</sup>. The magnetic microspheres were effectively used for drug targeting to tumor cells, cell separation,

diagnosis of disease and magnetic targeting of radioactivity.

### **Magnetic Liposomes:**

Liposomes are simple microscopic vesicles in which lipid bilayer structures are present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecule. There are a number of components present in liposomes with phospholipids and cholesterol being the main ingredients but in case of magneto liposomes magnetite is one of the components of the liposomes. Generally these are magnetic carriers which can be prepared by entrapment of Ferro fluid within core of liposomes. 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. Vesicles are also prepared containing didodecyl methyl ammonium bromide; contain an ionic magnetic fluid. These magnetic liposomes were effectively used for site specific targeting, cell sorting & as magnetic resonance contrast enhancing agent. Thermo sensitive magnetic liposomes can release the entrapped drug after selective heating caused by the electromagnetic fields. Magnetic fluorescent liposomes were used for increasing sensitivity of immunofluorescence. The magnetic liposomes are characterized for their physical attributes i.e. size, shape, and size distribution, surface charge, percent capture, percent magnetite content, entrapped volume lamellarity through freeze fracture microscopy and P-NMR, phase behavior drug release, quantitative determination of phospholipids and cholesterol analysis. Various researches have been carried out on magnetic liposomes. The finding of Margolis *et al*. demonstrates utilization of magnetic liposomes in cellular sorting[9]. The feasibility of magnetic

liposomes as a targeting device in tumor cell was explored by Kiwada[10]. The preparation, physicochemical properties and their possible use as a targeting carrier have been described by Ishii[11]. The possibility of dextran magnetite incorporated thermo sensitive liposomes was studied by Mausko et. al.[12]. Antibody coated magnetic liposomes for hyperthermia treatment of cancer were prepared by coating phospholipid on to magnetic particles were studied by Shinkai et. Al.[13]. Chen and Langer prepared magnetically responsive polymerized liposomes as potential oral delivery vehicles for complex molecules such as protein and peptide to protect them from gastrointestinal environment and targeting them to the payer's patches[14].

#### **Magnetic nanoparticles:**

Magnetic nanoparticles are particles of nano size range, containing polymers and drug along with ferromagnetic particles (magnetite). In recent years the separation of cells, viruses, and bio-molecules using magnetic micro particles has gained increasing popularity. Hence, new technologies using magnetic micro particles or nanoparticles are emerging. With magnetic separation, it is possible to achieve very high efficiency of separation in complex media. Other applications of magnetic particles include immunoassays, drug targeting, drug transporting, and biosensing.

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 and ferric chloride with dextran polymers under alkaline condition. Interfacial polymerization was also applied to synthesize magnetic nanoparticles. Pedro Trataj et al. review article described synthetic routes for the preparation of magnetic nanoparticles useful for biomedical applications[15].

Bacterial magnetite nanoparticles obtained from magneto tactic bacteria after disruption of the cell wall & subsequent magnetic separation have been used for a variety of bioapplications. Due to the presence of the lipid layer these particles are biocompatible, their suspensions are very stable & the particles can be easily modified. Vyas and Malaiya were prepared indomethacin bearing magnetic nanoparticles of polymethylmethacrylate by the emulsion polymerization technique[16]. Surface modification of super paramagnetic nanoparticles (Ferro fluid) with particle electrophoresis and their application in the specific targeting of cells was studied by sestier et al[17].

#### **Magnetically resealed erythrocytes:**

Resealed erythrocytes have various advantages as drug carriers such as it is biodegradable, biocompatible, large quantity of variety of material can be encapsulated within small volume of cell and can be utilized for organ targeting etc. Due to these advantages of resealed erythrocytes, magnetic resealed erythrocytes came in to existence which contains ferrofluids (magnetite) along with loaded drugs within the cell. Magnetically responsive ibuprofen-loaded erythrocytes were prepared and characterized in vitro by Vyas and Jain[18]. The erythrocytes loaded with ibuprofen and magnetite (Ferro fluids).The loaded cell effectively responded to an external magnetic field. Various process variables including drug concentration, magnetite concentration, sonication of ferrofluids that could affect the loading of drugs and magnetite were studied. The loaded erythrocytes were characterized for in vitro drug efflux, hemoglobin release, morphology osmotic fragility, in vitro magnetic responsiveness and percent cell recovery. In the continuous study, diclofenac sodium bearing erythrocytes were and characterized for various in vitro parameters. Local thrombosis in animal arteries was prevented by means of magnetic targeting of

aspirin loaded red cell was studied by Orekhova et al[19].

#### **Magnetic emulsions:**

Besides magnetic modulated systems, like microcapsules/microspheres magnetic emulsion was also tried as drug carrier for chemotherapeutic agents. 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. 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 trapped in the oily dispersed phase as active chemotherapeutic agent[20]. Magnetic emulsion appears to have potential in conferring site specificity to certain chemotherapeutic agent.

#### **Magnetically Modulated Systems and Devices**

Magnetically modulated polymeric controlled drug delivery systems that deliver the drugs at increased rate on demand have been developed extensively in recent years.

These systems consist of polymeric matrix wherein drug powder is dispersed.

The polymeric matrix is generally composed of ethylene vinyl acetate copolymer (EVAc), with some magnetic beads. The beads used are either magnetic steel beads composed of iron (79%), chromium (17%), carbon (1%), manganese (1%), silicon (1%), molybdenum (0.75%), and phosphorus (0.04%) or small amount of samarium cobalt magnets. These systems are formulated by adding approximately 50% of drug-polymer mixture to a glass mould, which is cooled to -80C using dry ice, then the magnetic particles, are added followed by the remaining drug-polymer mixture. An oscillating external magnetic field, which is generated by a

device that rotates the permanent magnets below the vials, controls the release rates.

#### **Mechanism:**

The release of macromolecules from EVAc systems without magnetic beads, suggests that molecules with molecular weight greater than 300 cannot permeate the polymer.

The direct incorporation of macromolecules in the polymer-macromolecule using cast procedure caused a tortuous and complex series of pores formation within the matrix.

The release rates are determined by factors affecting permeation of water into the polymer and drug out of these pores.

#### **Magnetically modulated, implantable, hemispheric drug delivery device:**

Polymeric drug delivery devices associated with a magnetically operated or triggered mechanism can improve the release rates of macromolecules from the polymeric controlled drug delivery devices. A zero order drug release profile could be achieved by using a hemisphere shaped geometric design. Taking this into consideration, subdermally implantable, magnetic modulated hemispheric drug delivery device has been developed. This device is composed of a doughnut shaped magnet at the center of a biocompatible polymer matrix, the latter contains a homogenous dispersion of a macromolecular drug at a high drug: polymer ratio, to form a hemi-spheric magnetic pellet. This pellet is then coated with pure polymer (ethyl vinyl acetate copolymer or silicone elastomers) on all sides, except the cavity at the center of the flat surface, to permit the release of macromolecular drug only through the cavity. Under non-operative condition, the hemispheric magnetic delivery device can release macromolecular drug at a controlled basal rate, following a diffusion mechanism. However, when external magnetic field

is applied, it tends to release the drug at higher rate under the activation.

### Magnetic Systems In Contraceptive Drug Delivery

In these magnetically controlled systems, the drug and small magnetic beads are uniformly dispersed within a polymer material. On exposure to aqueous media, the drug is released in a diffusion controlled fashion. Moreover, the rate can be increased or 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.

### Magnetically Programmable Infusion Pumps

Magnetic technology is widely used for external programming of pacemakers. The same principle was adapted to an implantable infusion pump. The development of such pumps to a prototype stage, the newer method of radiofrequency signaling could improve the magnetic approach because of greater programming flexibility and bi-directional transmission capability. In rf-programmable pump, the receiver is initially switched to a programmable mode by a permanent magnet located in the extracorporeal programming head. When the magnetic field and a recognizable rf pulse sequence are applied simultaneously, the re-programming occurs.

### CONCLUSION:

Magnetic Vesicular systems have been realized as extremely useful carrier systems in various scientific domains. Over the years, magnetic microcarriers have been investigated for targeted drug delivery especially magnetic targeted chemotherapy due to their better tumor targeting, therapeutic efficacy, lower toxicity and flexibility to be tailored for varied desirable purposes.

In spite of certain drawbacks, such as strong magnetic field requires for the ferrofluid and deposition of magnetite the magnetic microcarriers still play an important role in the selective targeting, and the controlled delivery of various drugs.

It is a challenging area for future research in the drug targeting so more researches, long term toxicity study, and characterization will ensure the improvement of magnetic drug delivery system. The future holds lot of promises in magnetic microcarriers and by further study this will be developed as novel and efficient approach for targeted drug delivery system.

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