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Magnetically modulated drug delivery system

S.V. Kali Dinesh Kumar*, Salman khan *, S. Ravindra*, P Sai Teja*, G. Usha kiran, Y. V. Veerendranadh, Y.A. Chowdary

Student , III B .Pharmacy, NRI college of Pharmacy, Vijayawada, Andhra Pradesh, India

Corresponding Author: S V Kali Dinesh Kumar*

ABSTRACT

There are several novel drug delivery systems have been developed in various routes of administration to produce control and targeted drug delivery, magnetic micro tablets are one them. This micro carriers includes magnetic microspheres, magnetic liposomes, magnetic nano particles, magnetic released erythrocytes, magnetic emulsions, magnetic suspensions ,etc. magnetic micro or nano particles and magnetic emulsions are used to treat several disorders and imaging of effected organs. This project is depend on the principles of magnetic targeting and mechanism of magnetic targeted drug delivery. Advantages and disadvantages (i.e. Benefits and drawbacks) of magnetic targeting, magnetic micro carriers and application of magnetism in targeted drug delivery and some other field magnetically drug delivery by particulate carriers is an efficient method of delivering drug to localised disease such as tumors non targeted application of magnetic nano spheres are used as contrast agents and as drug reservoirs they act a magnet applied outside the body historic applications of a magnetic micro spheres will be applied as well as future directions of effects to be overcome for the effective and profitable use of magnetic micro spheres in pharmacy practices[5].

Keywords: Magnetic Targeting, Magnetic Microsphere, Magnetic Nanosphere, Magnetic Neutrophiles, Magnetic Liposomes. Magnetic Emulsion.

INTRODUCTION

Selective targeting of therapeutics is one of the greatest challenges in designing site-specific drug delivery system in which drugs are required to accrue at the exact location for its pharmacological action. Increased drug concentration remains a critical concern as drugs are unable to accumulate at the specific receptor, organ or any other part of the body resulting in toxicity to the healthy tissues. To overcome such problems in site-specific targeting, different chemical properties are modified including partition coefficient, attachment of ligands, altered charge density and creation of various biodegradable polymers. Mononuclear phagocytes of Reticular Endothelial System (RES) also creates an apparent obstacle by sequestration of these careers. Magnetic responsive drug delivery systems are designed for the site specific targeting of drugs without disturbing RES in which external magnetic field is applied to increase the drug concentration at tumor site after administration of magnetic particles. These careers are restricted to RES by biophysical means to localize them specifically at the desired site of action. Such system is also titled as “drug delivery polymeric magnetic particles” because different biocompatible and biodegradable polymers are used to envelope magnetic particles along with the drug. Non-magnetic micro careers are also used for targeting of drug but due to their clearance by RES, they show poor site-specific action[7].

Principles of Magnetic Targeting

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. Fig. 1 highlights the concept of magnetic targeting by comparing systemic drug delivery with magnetic targeting. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into a patient's blood stream, and then stopped with a powerful magnetic field in the target area.[5] Depending on the type of drug, it is then slowly released from the magnetic carriers (e.g. release of chemotherapeutic drugs from magnetic micro-spheres) or confers a local effect (e.g. irradiation from radioactive microspheres hyperthermia with magnetic nanoparticles). It is thus possible to replace large amounts of freely circulating drug with much lower amounts of drug targeted magnetically to localized disease sites, reaching effective and up to several-fold increased localized drug levels. Magnetic carriers receive their magnetic responsiveness to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt, neodymium–iron–boron or samarium–cobalt. 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 1–100 nm are magnetic microspheres. In included when speaking about magnetic carriers[5].

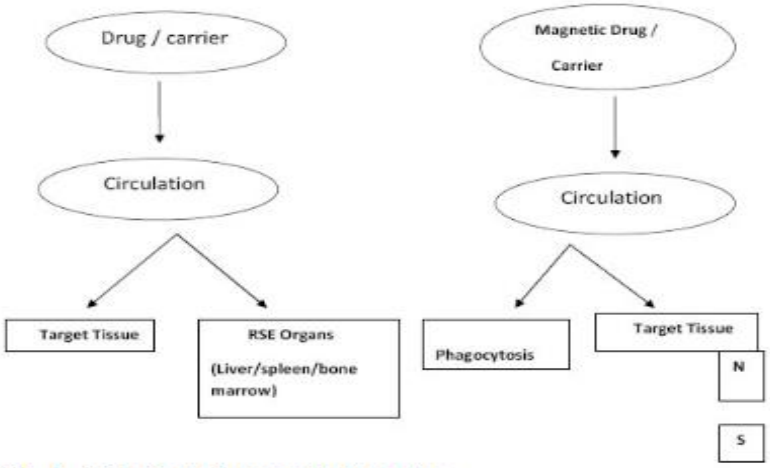

Fig. 1. Principle of magnetic targeting

Flowchart of Principle of Magnetic Targeting

The principle of magnetic targeting by comparing systemic drug delivery with magnetic targeting. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into a patient's blood stream, and then stopped with a powerful magnetic field in the target area. The magnetic fields are believed to harmless to biological system and adaptable to any part of the human body. Up to 60% of an injected dose can deposited and released in controlled manner in selected non reticuloendothelial organs (i.e. not in liver / spleen / bone marrow).

Mechanism Of Action

Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microspheres.

When the magnetic carrier is given through I.V route the accumulation takes place within area at where the magnetic field is applied.

⬇

An external magnetic field is applied at desire area to move and concentrate the drug.

⬇

The accumulation of magnetic carrier depends on physiological parameters such as particle size, surface morphology, blood flow rate.

⬇

This technique have a major benefit i.e. target the specific area and reduce the systemic distribution of drug (i.e. we can skip ADME.). And produces the therapeutical efficacy at low dose.

MAGNETICALLY MODULATED MICROCARRIERS

Magnetic microcarriers are site specific and by localization of these microcarriers in the target area, the problem of their rapid clearance by RES is also surmounted. Linear blood velocity in capillaries is 300 times less i.e. 0.05cm/sec as compared to arteries, so much smaller magnetic field, 6-8 KOE, it is sufficient to retain them in the capillary network of the target area10.Magnetic carrier technology appears to be a significant alternative for the bimolecular malformation (i.e. composition, inactivation or deformation). These microcarriers includes:-

A). Magnetic microsphere
B). Magnetic nanoparticles
C). Magnetic liposomes
D). Magnetic resealed erythrocytes
E). Magnetic emulsion
F). Magnetic neutrophils[5].

Magnetic Microsphere

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4 m) but are sufficiently susceptible (ferromagnetic) to be captured in micro vessels and dragged in to the adjacent tissues by magnetic fields of 0.5-0.8 tesla (T). Magnetic microspheres were prepared by mainly two methods namely phase separation emulsion polymerization (PSEP) and 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 microsphere are characterized for different attributes such as particle size analysis including 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 in microspheres[5].

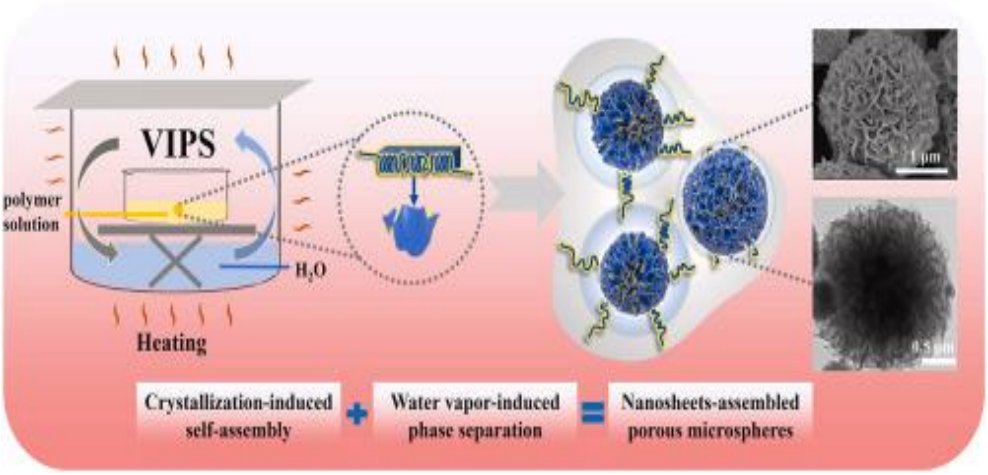

Figure 1 : Concept of Magnetic Microsphere

Magnetic Nanoparticles

Recent decades have shown a vast range of applications in the field of magnetic nanotechnology as it has expanded its scope to oncological, cardiovascular and neurological disorders. They have been under keen investigation in different fields as next generation drug carriers due to their physical properties. Magnetic nanoparticles have displayed a great potential in drug loading proficiency due to their magnetic core intrinsic capabilities and physico-chemical properties due to the coating efficiency. These particles having size less than 100 nm, are employed under the influence of magnetic field and manipulated by different materials such as iron, nickel, cobalt. Enhanced performance is delivered below a critical value of their size which is around 10-20 nm. These nanoparticles show super magnetic behavior above blocking temperature and acts like paramagnetic atoms showing less resonance. They can be used in different ways like magnetic resonance imaging, vascular contrasting agents, diagnosing agents, as theranostic in targeting of cancer treatment targeting of genes, tissue engineering, bio separations, cell tracking However, problems of intrinsic instability can occur over longer period of time as they can easily oxidize in air causing loss of the magnetic property.

Synthesis of Magnetic Nanoparticles

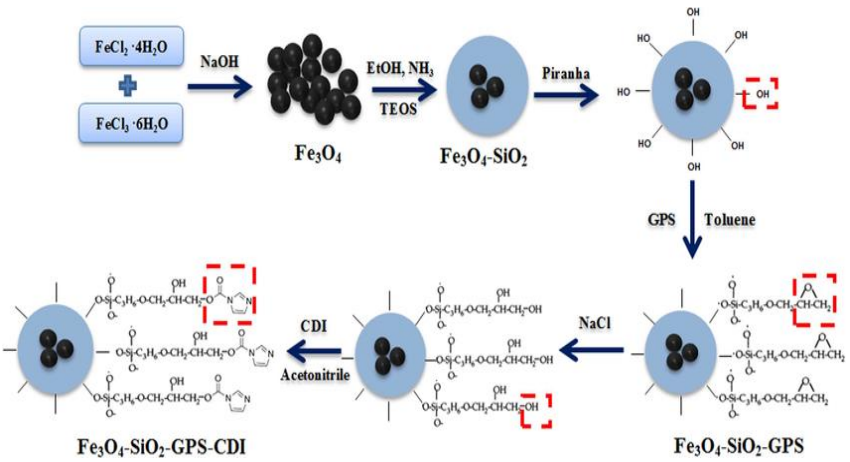

Figure 2 : Concept of Magnetic Nanoparticles

Magnetic nanoparticles have been prepared by using different compounds like cobalt, nickel, iron, ferrous oxides, ferrites like MFe2O4 (where M can be Cu, Mg, Mn, Ni etc.) and metal alloys. They can be synthesized using different methods like co-precipitation, thermal decomposition and micro emulsion method[7].

Magnetic Liposomes

Magnetic liposomes consist of bilayered layered compositional structure in which lipid layer and aqueous layer are designed in alternative patterns. These are biocompatible vesicular shaped structure having nanometric size, being used to encapsulate water soluble and oil soluble therapeutic agents. Water soluble active ingredients are incorporated in aqueous layer of magnetic liposomes and lipid soluble active drugs are incorporated in lipid layer of magnetic liposomes (Martin, 1989). Generally, two kinds of magneto liposomes exist: one containing metal oxides ion the aqueous layer while other consisting of meta oxides enveloped in lipid layer after being stabilized with laureth[5].

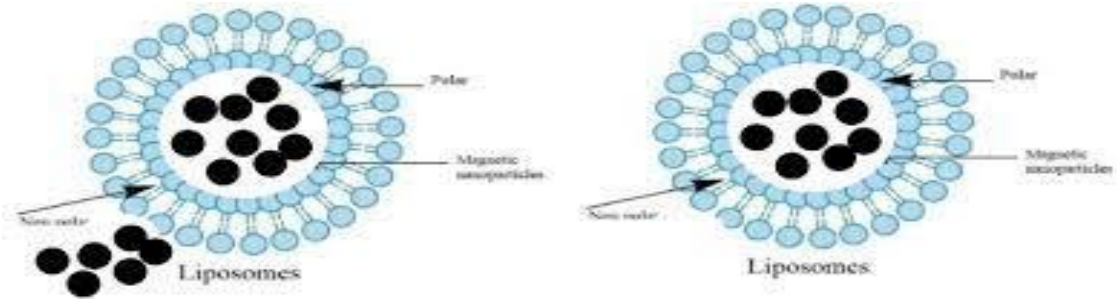

Figure 3 : Structure of Magnetic Liposomes

Magnetic 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. The erythrocytes loaded with ibuprofen and magnetite (ferrofluids) using the press well technique18. 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 prepared by press well technique and characterized for various in vitro parameters. Prevention of Arterial Thrombosis by Aspirin loaded Magnetic Resealed erythrocytes. Thrombosis absorbed or flushed due to the Force exerted by flow of Magnetic Erythrocytes under magnetic field, aspirin also released in vicinity of thrombosis (Thrombolytic effect) Local thrombosis in animal arteries was prevented by means of magnetic targeting of aspirin loaded red cell. Thrombosis was induced in 18 dogs and 16 rabbit's arteries by surgically inverting a vascular wall flap into its lumen. A completely occluding red thrombus was developed inside the vessel after 4 to 5 hours in 80% of cases. SmCo5 magnet was secured externally to one of the arteries. The constant magnetic field produced by the magnet had no influence on the clot formation. Autologous red cells loaded with ferromagnetic colloid compound and aspirin were administered intravenously, and completely aborted arterio-thrombosis on magnet application side with no deterioratory effect on clot formation in the control artery was recorded[5].

Magnetic Emulsion

Emulsion is a colloidal system consisting of two immiscible liquids and being stabilized by polymers or surfactants known as emulsifying agents. Water compose oil in water type emulsion when it is based as continuous external phase while as internal dispersed phase, it constitutes reverse water in oil type emulsion. Magnetic emulsion is an emulsion type in which ferrofluids, containing the stable dispersion of magnetic nanoparticles, constitutes the internal phase[5].

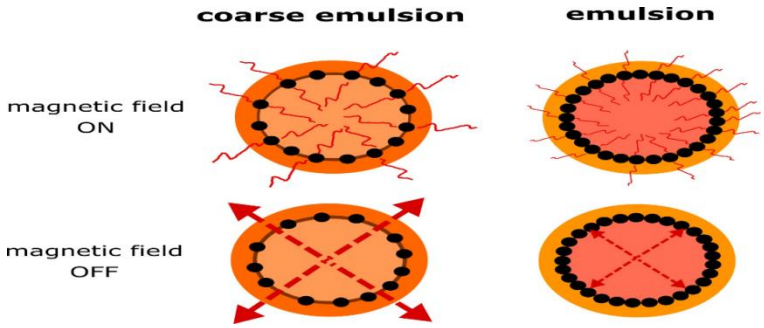

Figure 4 : Concept of Magnetic Emulosion

Magnetic Neutrophils

In certain clinical conditions, where patient sera contains chemotactic factor in activators and neutrophils directed inhibitors of chemotaxis , an indirect approach of targeting white cells by chemo attraction fails. These disorders include chronic lymphocytic leukemia, alcoholic cirrhosis, Crohn's disease, haemodialysis, sarcoidosis and Hodgkin's disease. Even though failure of chemotaxis is not observed in all patients, such conditions are life threatening. Therefore, a means of making neutrophils ingest magnetite base system ought to be developed, so that the sites of severe infection can be selectively approached for therapy[5].

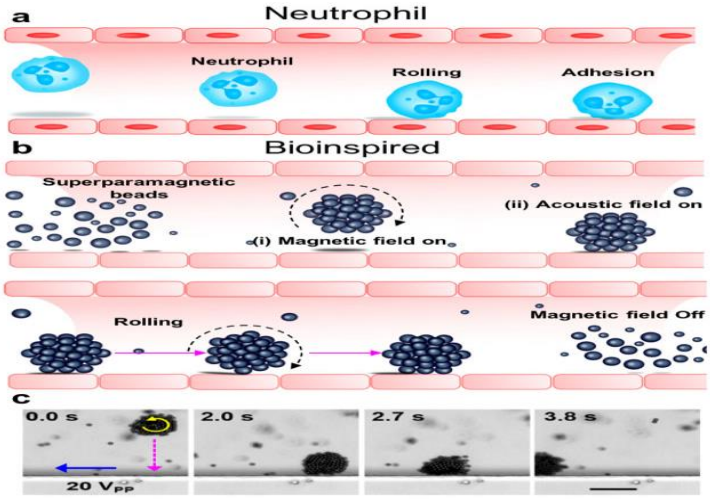

Figure 5 : Concept of Magnetic Nanoparticles

APPLICATIONS

Magnetic drug delivery system since its origination has shown tremendous applications in biomedical and biophysical fields of science. We will discuss here some of its main contributions towards modern drug delivery

Treatment of Tumors

Magnetic microspheres can be used in chemotherapy of anti-cancer drugs in their delivery to tumors e.g. doxorubicin. For such kind of site-specific targeting, magnetically modulated drug targeting systems have been successfully applied. Magnetic field in such cases is applied to concentrate the drug at tumor site thus eliminating systemic side effects. Different rats suffering from sarcoma were assessed after giving both free doxorubicin and doxorubicin with magnetic microspheres. It was evaluated that rats treated with free doxorubicin had increased tumor size while those treated with magnetic microspheres showed a significant 83 % decrease in the tumor size.

Targeting of Radioactive compounds

Radioisotopes in therapeutic range can be delivered under magnetic field to target tissues. Dose can be increased rendering damage to the normal tissues with improved anti-tumor activity. Selective radiation of the targeted tissues is carried out with the help of magnetic particles being coupled with different isotopes and an external magnetic field is applied to bind them . In recent years, radio labeling with isotopes such as 188Re; 90Y, 111ln and 125I have been successfully.

Magnetic Hyperthermia

Magnetic hyperthermia has been established to destroy the diseased tissues with the help of elevated temperature as they are more sensitive to the temperature compared to the healthy tissues. The other advantage is its restriction to the diseased tissues only. Recently liposomal nanoparticles have been established according to this mechanism as successful approach to the cancer therapy. Magnetic liposomes have also been prepared and studied for hyperthermia treatment of cancer through magnetic particles coated with phospholipids.

Diagnostic Applications

One of the modern and useful applications of magnetic delivery system is its diagnostic applications which involves;
**In-vivo Applications:* With the development of NMR imaging technique, a new pharmaceutical class known a magneto pharmaceuticals.
**In-vitro Applications:* Magnetic solid phase extraction method is used in isolation and determination of components and impurities from testing samples in large volume as compared to conventional extraction processes which are more time consuming[7].

ADVANTAGES

1. Therapeutical efficacy in magnetic modulated drug delivery system at the target organ is 10^{th} part of the free curative dose
2.Prolonged drug release within target organ reduces for intervals of 30 minutes to 3 hours.
3. We can alter accumalation of drug on liver and toxicity against endothelium and normal parenchymal cells.
4. It can be given to any body parts.
5. This curative delivery can skip phases like disintegration, dissolution and absorption.

6. This drug delivery system will decrease the circulating concentration of drug by 100 or more[5].

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. Magnetically modulated drug release from implants, successfully compensate any decay in drug release against time. Moreover, it minimizes the cost, size and complexity of implanted devices. However, utility of such implants has been compromised due to irreproducibility of magnetic modulation and necessity of surgery to replace such implants after complete drug release. Externally programmable infusion pump, need magnetic modulation only to a limited extent for activating radiometry circuits to allow a bi-directional information transfer[5].

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