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Review on Magnetic Drug Delivery Systems

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ABSTRACT: Magnetic fields are belived to be harmless to biological system and adaptable to any part of the body .With the support of a magnetic field, it avoids reticuloendothelial system and directs the drugs to reach the target precisely. Magnetic carriers like nanoparticles, microspheres, liposomes and emulsion have been found advantageous of the fact that they reduces the free drug concentration in the blood and to minimize the adverse effects provoked by these drugs. It has made the most crucial tumor targeting possible without damaging the healthy tissues. In this review, we will summarize the facts about magnetic drug delivery systems comprehensively.

Keywords: Magnetic Drug Targeting, Magnetic Microspheres ,Magnetic nanoparticles , Magnetic liposomes , Microemulsions , Thermal Decomposition

I. 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 reticuloendothelial 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 .

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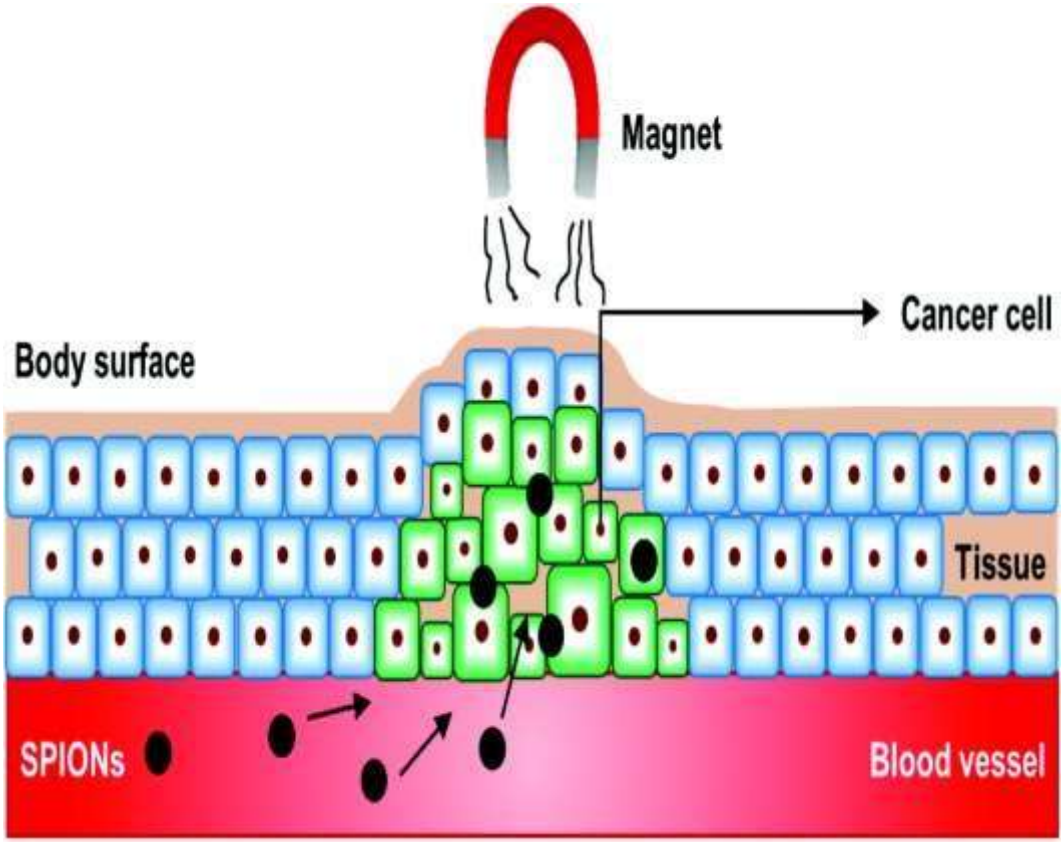

Figure 1:Magnet design: F= M ΔH, F is the force on particles, M is magnetic movement of particles, ΔH is magnetic field gradien

II. PRINCIPLE OF MAGNETIC DRUG TARGETING

In this technique, drug is bound to a magnetic compound , injected into a patient's blood stream, and stopped with a powerful magnetic field in the target area. Depending upon the type of drug , it is then slowly released from the magnetic carriers. Very high concentrations of chemotherapeutic or radiological agents can be achieved near the target site ,without any toxic effects to surrounding tissue or to the whole body.

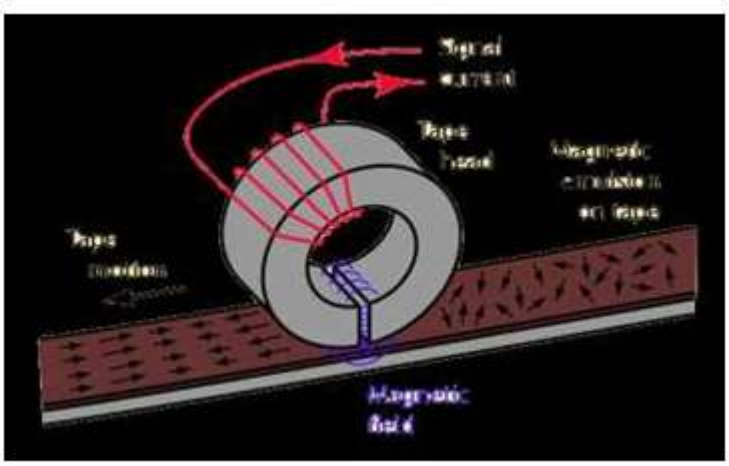

Figure 2 Principle of Magnetic Drug Targeting

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III. MECHANISM OF MAGNETIC DRUG TARGETING

- Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere (or nanosphere) or conjugated on the surface of the micro/nanosphere.
- When the magnetic carrier is intravenously administered, the accumulation take place within area to which the magnetic field is applied.
- An external permanent magnetic field is applied on desired area to guide and concentrate the drugs.
- Accumulation of the carrier at the target site allows them to deliver the drug locally.

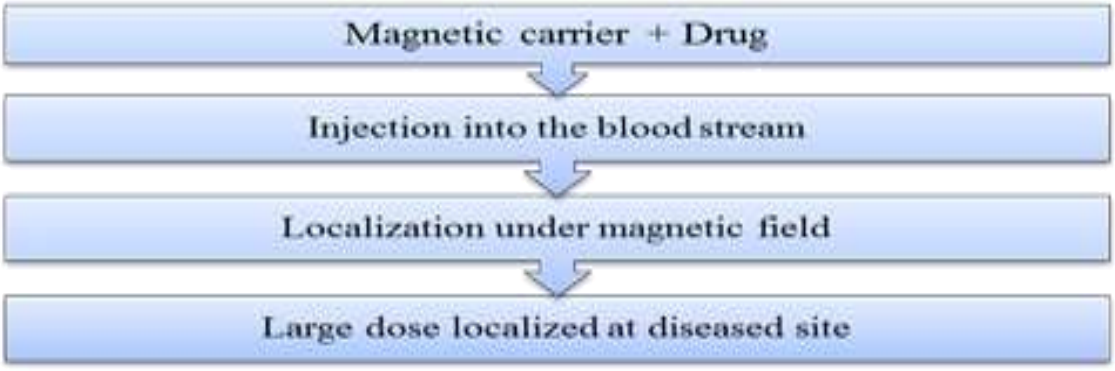

Figure 3: Mechanism of action for magnetic targeted drug delivery systems

IV. ADVANTAGES OF LOCALIZATION OF DRUGS

Magnetic carriers localize the drug at targeted diseased sites, to accomplish following advantages :

- Efficient drug delivery to the target tissues (increase up to 60%)
- Reduced toxicity risk
- Minimizes side effects risk
- Free drug concentration in blood stream is reduced by factor of 100
- Decline in normal cell tissue damage rate.
- Therapeutics responses in target organs at only one tenth of the free drug dose.
- Adaptable to any part of the body.
- Delivery 60% drug to the target tissue.
- Minimally reactive with blood components.

V. CLASSIFICATION OF MAGNETIC DRUG DELIVERY SYSTEMS

To achieve controlled and targeted delivery of drug, magnetic carrier drug delivery systems (DDS) can be categorized further into (Akhtar et al., 2009);

1. Magnetic nanoparticles
2. Magnetic microspheres
3. Magnetic liposomes
4. Magnetic emulsions

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 .

1.Advantages of Magnetic Nanoparticles

- Excess amount of drug is reduced minimizing unwanted effects
- Frequency of administration is reduced

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- Reduced side effects of drugs as compared to conventional dosage forms
- Targeted organ receive prolonged delivery of drug
- Diseased organ receive sustained drug delivery.

5.1.2 Synthesis of Magnetic Nanoparticles

Magnetic nanoparticles have been prepared by using different compounds like cobalt, nickel, iron, ferrous oxides, ferrites like MFe_2O_4 (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.

(a) Co-precipitation

Co-precipitation is one of the facile, preferred and convenient route for the synthesis of spherical magnetite particles in nanometric size. This method is preferred over other methods due to its lower temperature, time and environment friendly (water as solvent) as compared to other processes. In this method, metal oxides and metal ferrites based magnetic nanoparticles are synthesized from aqueous salt solutions which transform their properties to the latter one. Morphology as well as composition of the nanoparticles depends on the type of salt solution, metals ratio, temperature of the reaction, pH and ionic strength of the medium . It is said that particle size generally decrease as the pH and ionic strength increase, illustrating that these two factors can control the size of the particles as a whole. Magnetic nanoparticles can synthesized by this method in two ways in which one uses oxidizing agents to oxidize the metal hydroxides while in the second one, metal hydroxides are mixed together in presence of aqueous media. Finally aggregation occurs within metal hydroxide to form spherical particles

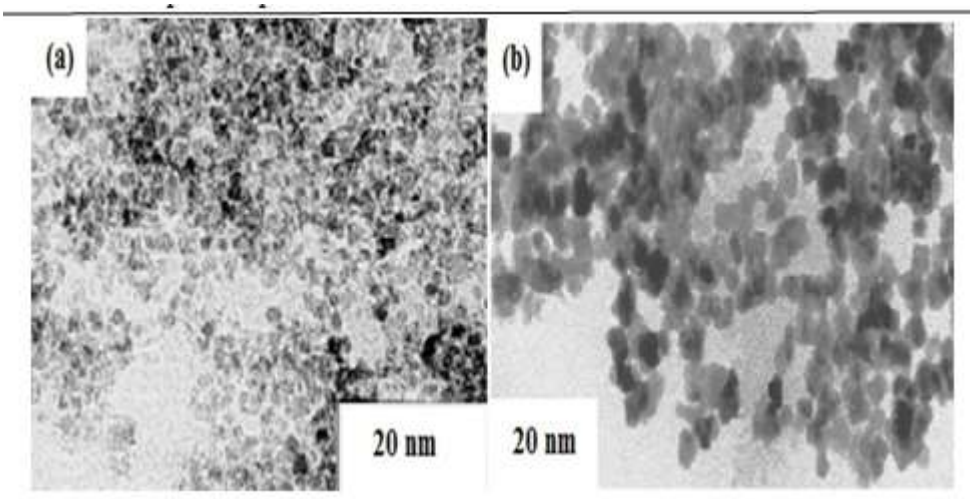

Figure 4: Magnetic nanoparticles prepared by: (a) co-precipitation method (b) microemulsion technique

(b) Microemulsions

Microemuslion is widely used technique for formation of uniform particle sized magnetic nanoparticles due to water in oil type emulsion . It is an identical thermodynamic scattering of water and oil, stabilized by surfactant molecules which lower the surface tension between the liquids to form a transparent solution. Rapid coalescence takes place resulting in mixing and aggregation of the nano droplets to form magnetic nanoparticles in a spherical shaped water pool. Size of the nanoparticles can be controlled by changing size of the water pool which surrounds the nano droplets. A precipitate formation can take place in micelles by collision and coalescence of two similar micro emulsions.

(C)Thermal Decomposition

Magnetic nanoparticles by this process are synthesized at high temperature decomposition of organometallic precursors like metal acetylacetonates, metal cupferronates, carbonyls and surfactants like fatty acids, oleic acids and hexadecylamine. Precursors with zerovalent metals forms metallic nanoparticles but if oxidation takes place then mono disperse particles are formed. On the other side, cationic metals decompose directly to metallic oxide nanoparticles . Ratios of the

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organometallic precursors, surfactants, organic solvents along with the reaction temperature and reaction time play a vital role in determining the particles morphology and magnitude .

5.1.3 Characterization

- Magnetic nanoparticles can be characterized through following analysis.
- Transmission electron microscopy for determination of size and shape
- X-ray diffraction for structural determination
- Particle size analysis DLC
- Magnetic density by using SJZP-1 Gauss/Tesla-Meter
- Chemical composition by using analytical spectroscopic technique like atomic adsorption spectroscopy
- TGA inductively coupled plasma atomic emission spectrometer for determination of magnetite contentsVibrating sample magnetometer to determine its magnetic property.

2.Magnetic Microspheres

Magnetic microparticles comprise of different materials, having strong magnetic moment which can successfully deliver non-magnetic substances like cells, antibodies, drugs, nucleic acids and enzymes to the magnetic field . These are smaller in size i.e. less than 4 µm, which provides an efficient flow rate to pass through capillaries without formation of embolus . They consist of biocompatible proteins or synthetic polymer to which the drug is bound and are formulated to be used in depot form near targeting site by nearby placing suitable magnet. To avoid unwanted distribution of drug to non target organ help in drug localization and avoid toxicity. It was propounded by Gupta and Hung that magnetic microspheres can cause 16 fold increase in drug concentration, 6 fold increase in drug exposure and 6 fold increase in targeting efficiency of the system

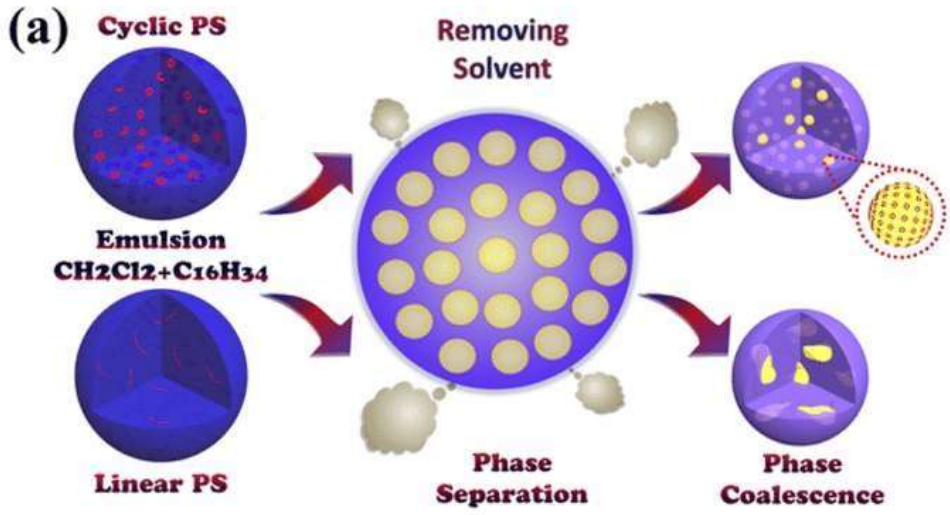

Figure 5: Formation of Magnetic Microsphere

1.Preparation of Magnetic Microsphere

Magnetic Microspheres are prepared generally by two methods. One is Phase separation emulsion polymerization method and other is continuous solvent evaporation method. Microspheres prepared by these two techniques are known to be biocompatible with the blood and are stabilized by addition of albumin. Magnetic field having greater field strength is required for a fast moving arterial system .

(a) Phase Separation Emulsion Polymerization

In phase separation emulsion polymerization method, an aqueous suspension is prepared by incorporation of polymer, drug and magnetite into sufficient amount of water. Emulsifying agent is added to the solution for formation of oily phase which is stabilized by heating at appropriate temperature of 100-150˚C followed by drop wise addition of cross linking agentwith constant stirring that result in formation of magneticmicrospheres. Washing procedure is used to separate oil from suspension by subjecting it to freezing temperature at 4˚C.

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(b) Continuous Solvent Evaporation Method

Polymer, drug and magnetite solution should be added to the volatile organic solvent at constant stirring to form an auxiliary homogeneous solution at temperature of 22-30˚C. Evaporation of the organic solvents takes place to form microspheres followed by centrifugation, freeze drying and storage at 4˚C

5.2.2 Characterization

Magnetic microspheres are subjected to different tests to verify its morphological structure and different physico-chemical properties. They include particle size analysis , scanning electron microscopy , flow properties through angle of repose and compressibility index , thermal analysis, determination of % age yield, drug content, determination of drug loading, incorporation efficiency of microscopy, determination of solubility and dissolution studies of microspheres .

3.Magnetic Liposomes

Magnetic liposomes consist of bilayered 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 . Generally, two kinds of magnetoliposomes exist: one containing metal oxides ion the aqueous layer while other consisiting of meta oxides enveloped in lipid layer after being stabilized withlaureth.

1.Method of Preparation

Magnetic liposomes can be prepared by incorporation of magnetic partices in the phospholipid linkage which acts a nanoreactor while in second method; phosphatidylcholine/ phosphatidylethanolamine are used in the 2:1 ratio covering the magnetic paricles, which produces agglomerates of the magnetic particles.

These linkages are stabilized by using pullalan hydrazide. Magnetoliposomesare also advantageous because of the fact that they escape from reticuloendothelial system very easily and their lipid layer is sensitive to the magnetic field .

5.3.2 Characterization

The internal structure of the magnetoliposomes is observed through time resolved neutron scattering TR-SANS at ILL-D22 and time resolved electron microscopy TR-EM using a stopped-flow mixing device .

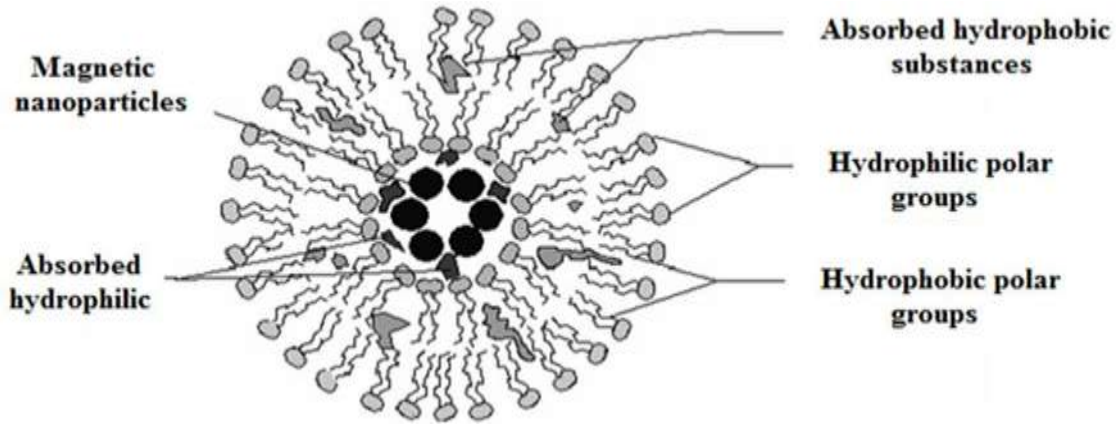

Figure 6: Structure of magnetic liposome

4 . Magnetic Emulsion

Emulsion is a colloidal system consisting of two immiscible liquids (water and organic solvent) 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.

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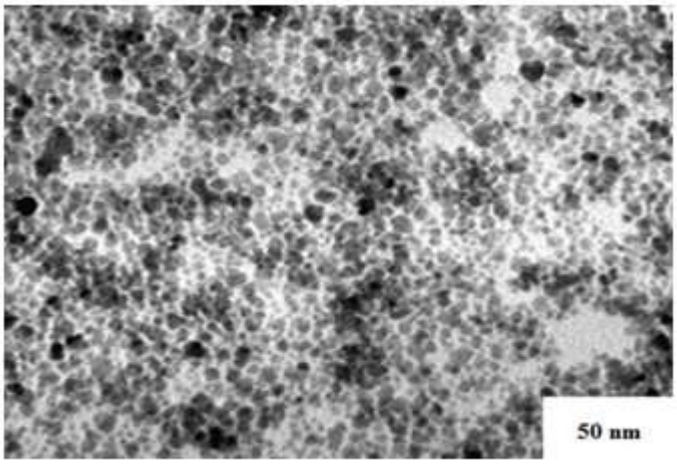


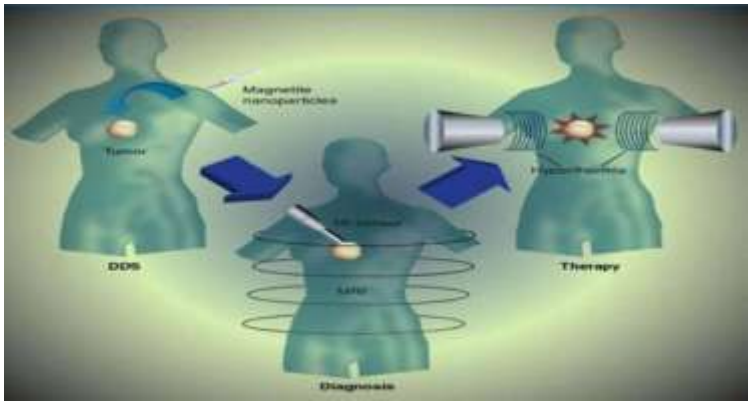
Figure 7: Transmission electron micrograph of the ferrofluids

5.4.1 Characterization

- Magnetic emulsions can be analyzed through following tests:
- Infrared spectroscopy to evaluate the adsorption of surfactants on magnetic particles.
- Elemental analysis to evaluate the ferrofluids and magnetic particles.
- X-ray diffraction to investigate the crystallographic structure of the iron oxides and magnetic particles size distribution.
- Thermogravimetric analysis of the ferrofluids in dried state.
- Transmission electron microscopy.
- Freeze fracture to investigate the internal structure of the ferrofluids.
- Gas chromatography to determine the octane concentration in the magnetic emulsion

6.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.



1.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 .

2.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 employed

3.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.

4.Diagnostic Applications

One of the modern and useful applications of magnetic delivery system is its diagnostic applications which involves;

a) In-vivo Applications

With the development of NMR imaging technique, a new pharmaceutical class known amagnetopharmaceuticals has been established, providing following advantages

- Improvement in distinguishing of diseased to normal tissue
- To determine normal function of organ

b) 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

6.Miscellaneous Applications

It is used in
a. Cancer Therapy
b. Magnetic fluid hyperthermia
C. Miscellaneous of Drug Release

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VII. CONCLUSION

Magnetically targeted drug delivery by particular carriers is an efficient method of delivering drug localised diseased site such as tumours ,also in order to increase the efficiency and reduce the unpleasant side effects. Also magnetic drug delivery improves the controllability , targeting and regulation of drug.

In oral and other delivery system require more dose to be given from which less amount of drug will reach to particular target area. While in this drug delivery less dose required because drug is directed to the affected area.

Over the years, despite of a defect that magnetic drug delivery carriers constitute of a strong magnetic field, it has still proved to be an efficient drug delivery system by successfully achieving the selective targeting and controlled drug delivery. It's challenging future demands an extensive research area to combat the most chronic diseases of modern ages

Thus , magnetic drug delivery system is more efficient and beneficial means of drug delivery.

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