

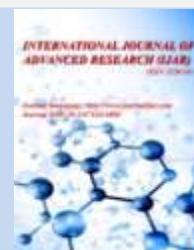


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### RESEARCH ARTICLE

#### MAGNETIC MICROSPHERE AS NOVEL DRUG DELIVERY SYSTEM: A REVIEW

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#### Abstract

A therapeutic amount of drug at proper site in the body and its maintenance for a specific period of time are controlled by a well-designed drug system. A number of drug delivery systems hold great promises for achieving the goal of controlled and site specific drug delivery, one of them is magnetic microsphere, a novel drug delivery system. Novel drug delivery system has been advanced to achieve controlled and targeted drug delivery to meet the needs of the body during the period of treatment. Magnetic microsphere, a newer approach in pharmaceutical field is magnetically controlled releasable supramolecular particles having a particle size ranging from 1-1000  $\mu\text{m}$ . A number of limitations facing current methods of delivering medicines are overcome by using a novel approach of magnetic drug delivery which uses engineered 'microcarriers'. Magnetic microsphere drug delivery system is captured in microvessels and dragged into adjacent tissues by magnetic field of below 1.0 tesla. Magnetic responses are received by magnetic carriers to a magnetic field from incorporated materials like chitosan, dextran etc. that are used for magnetic microspheres. Various carrier materials can be used in magnetic microsphere, one of the most utilized is serum albumin from human. Thus, the problem of conventional therapy can be overcome by a well-designed controlled drug delivery system. Microsphere drug delivery system has eminent importance as it has wide applications ranging from drug targeting at a specific site to imaging the diagnostic features and also in targeting tumours using anticancer drugs. It is more stable than liposomes, offering an advantage over it. The review shall include definitions, concepts, types, characteristics, advantage as well as methods and techniques used in preparations; it will also entail various applications and future prospects of magnetic microspheres as a novel drug delivery system.

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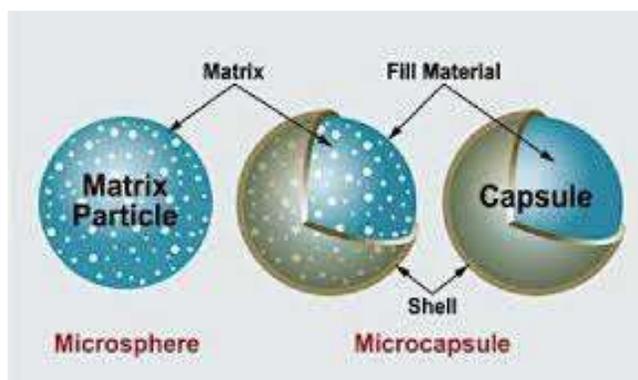
#### Introduction:-

The most preferable route for taking medications is the oral route drug administration, the simplest, convenient and safest means of drug administration. However, an unconventional dosage form, the oral administration of most of

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the drugs possess some limitations due to their short circulating half-life and restricted absorption via a defined segment of intestine. To overcome this, various approaches are in use for delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach for obtaining maximum therapeutic efficacy is the use of microspheres as carriers for drug. One of the most interesting fields of research in pharmaceutical science is the development of new delivery systems for the controlled release of drugs through which maximum therapeutic efficacy can be achieved by delivering the agent to the target tissue in the optimal amount in the right period of time thereby causing minimal side effects and little toxicity. The release of drug in a controlled and site-specific manner is achieved by a novel drug delivery system which aims to deliver the drug at a rate directed by the needs of the body during the period of treatment to achieve controlled and targeted drug delivery. Microsphere-based drug delivery systems are one of them. Many types of drugs with small molecules, proteins and nucleic acids can be encapsulated by microspheres and are easily administered through a syringe needle. They can give high bioavailability, nontoxic, normally biocompatible and are capable of constant release for a long period of time, thus overcoming two major problems encountered in drug targeting namely reticuloendothelial clearance and target site specificity to reduce dosing frequency thereby improving patient compliance. Microspheres are classified as Bioadhesive microsphere, Magnetic microsphere, Floating microsphere, Radioactive microsphere, Polymeric microsphere (Biodegradable Polymeric microsphere, Synthetic Polymeric microsphere) of which Magnetic microsphere is the most efficient.



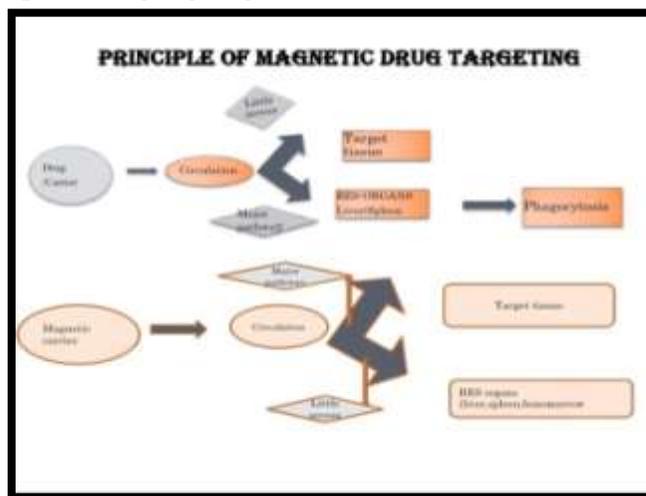
Magnetic microsphere, a newer approach in pharmaceutical field is magnetically controlled releasable supramolecular particles having a particle size ranging from 1-1000  $\mu\text{m}$  which uses engineered 'microcarriers'. Magnetic microsphere drug delivery system is captured in microvessels and dragged into adjacent tissues by magnetic field of below 1.0 tesla. Magnetic responses are received by magnetic carriers to a magnetic field from incorporated materials like chitosan, dextran etc. that are used for magnetic microspheres. Magnetic microspheres are prepared by phase separation emulsion polymerization (PSEP) method and continuous solvent evaporation (CSE) method. The magnetic microsphere's amount and rate of drug delivery can be regulated by varying size of microsphere, magnetic content, drug content, hydration state and drug release characteristic of carrier. Similar methods like non-radioactive spheres are applied to magnetic radioactive microspheres. Outside the body, a magnet is placed which can be contained in an equipment that looks like an open magnetic resonance imaging scanner or simply a rod-shaped permanent magnet of any size directed to the target site. The loaded microspheres are introduced into a blood vessel and gather at a site to emit radiations that kills cancer cells. This therapeutic action takes weeks or sometimes gets completed in a couple of days depending on material used. Moreover, magnetic cores constitute the magnetic polymer microsphere which ensures a strong magnetic response and polymeric shells to provide favourable functional groups, thus protecting particle aggregation. Magnetite content of microsphere plays an important role in drug delivery as they are well tolerated by the body, magnetic fields are supposed to be harmless to biological system and are adaptable to any part of the body. Many unique features are exhibited by these microspheres which are small and of uniform size, differ in shapes and morphologies and have wide applications in fields like diagnostics, molecular biology, drug targeting, cell proliferation, enzyme immobilization and radioimmunoassay.

#### History of Magnetic carriers:

1. A seminar paper was published by Gilchrist 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 in 1956.
2. The radiofrequency heating method with embolization therapy was combined by Turner and Rand.

3. Description of ability of magnetic carriers to accumulate small iron particles intravenously injected into the leg veins of dogs, using a large, externally applied horse shoe magnet was given by Meyers.
4. Hilal engineered magnetic endocatheters and gave description on their use to deposit and selectively embolize arterio-venous malformations with small magnets. For the embolization therapy of liver cancer, magnetic particles are used.
5. Widder proposed that at the end of the 1970s, defined spherical microspheres were made for the first time. Their magnetic albumin microspheres worked well as magnet resonance contrast and animal experiments for tumor therapy.

#### Principle of magnetic microspheres drug targeting:



It is an efficient method of drug delivery in which drug is delivered to a localized disease site by particulate carriers. The aim of specific targeting is efficiency of drug targeting should be enhanced; toxicity and side effects should be reduced at the same time. A therapeutic radioisotope or drug is encapsulated in a magnetic compound, injected into patient's blood stream and then stopped with a powerful magnetic field in the target area. The drug is slowly released from magnetic carriers or confers a local effect depending on the type of drug, thus it reduces the loss of drug as freely circulating in the body. A specific form of drug delivery where the drug is directed to its site of action or absorption is known as drug targeting. This could be a cell, a particular organ structure, tissue or even an intercellular region. Accumulation efficiency of magnetic carrier on physiological carrier depends on certain physiological parameters e.g. particle size, surface characteristic, field strength and blood flow rate etc. It is possible to achieve high concentration of chemotherapeutic agents near the target agent without any toxic effect and thus reaching several fold increased drug levels.

#### Magnetic properties:

Bio separation includes magnetic particles which consist of one or more magnetic cores with a coating matrix of polymers, hydroxyl apatite with terminal functionalized groups. Generally, the magnetic core consists either of magnetite ( $\text{Fe}_3\text{O}_4$ ) or magnetite ( $\gamma\text{-Fe}_2\text{O}_3$ ) with superparamagnetic or ferromagnetic properties. Magnetic cores can also be made with magnetic ferrites, such as manganese ferrite or cobalt ferrite. A single-domain particle's dipole moment fluctuates rapidly in the core because of the thermal excitation so that there is no magnetic moment for macroscopic time scales known as Superparamagnetism. Thus, when an external magnetic field is applied these particles are non magnetic.



Figure 1:- Superparamagnetic particles under the influence of external magnetic field.



**Figure 2:-** Superparamagnetic particles under the absence of an external magnetic field, monodisperse particles distribution.



**Figure 3:-** Ferromagnetic particles under the influence of an external magnetic field.



**Figure 4:-** Ferromagnetic particles in absence of an external magnetic field.

Those particles which are having a permanent mean magnetic moment are referred to as the ferromagnetic particles. Here, the larger effective magnetic anisotropy is suppressed by the thermally activated motion of the core moment. For automatic DNA/RNA separation/purification, generally the superparamagnetic and ferromagnetic particles are recommended. For example, automatic DNA/RNA separation/purification such as genomic DNA, plasmid DNA, total RNA and PCR products, K-DNA and SiMAG/MP-DNA beads have been developed. The superparamagnetic SiMAG/K-DNA beads and the ferromagnetic SiMAG/MP-DNA beads are most suited for automatic DNA/RNA separation/purification having excellent magnetic properties. Since different processing methods work with different robot systems, either ferromagnetic SiMAG-DNA or superparamagnetic beads will lead to optimal results.

#### **Types of Magnetic Microspheres (Farah, 2017):**

Magnetic responses are received by magnetic carriers to a magnetic field from incorporated materials such as chitosan, dextran etc. that are used for magnetic microspheres. Magnetic microspheres include the following types:

1. Therapeutic microspheres-For delivering chemotherapeutic agent to liver tumor, it is used. This system can also target drugs like proteins and peptides.
2. Diagnostic microspheres-It can be used to distinguish bowel loops from other abdominal structures by forming nanosize particles supra-magnetic iron oxides and for imaging metastases.

#### **Materials used in Magnetic Microspheres:**

1. Synthetic polymers.
2. Biodegradable: Epoxy polymers, Glycolides.
3. Non-biodegradable: Lactides, polyanhydrides.
4. Polymethylmethacrylate, Acrolein.

5. Natural polymers.
6. Proteins: Albumin, Collagen, Gelatin.
7. Carbohydrates: Agarose, Chitosan, Starch.
8. Chemically modified carbohydrate: Polystarch, Polydextran.

### **Characterization of magnetic microspheres:**

#### **1. Detection of particle size of microsphere:**

It can be determined by using an optical microscope. Here, size of total 100 particles were measured and then the average of these particles was taken as average particle size.

#### **2. Surface characterization:**

Surface characterization can be determined by using:

1. High-resolution microscopy
2. Scanning electron microscopy (SEM)

#### **3. Surface charge analysis:**

They can be achieved by using:

1. Micro electrophoresis
2. Laser Doppler anemometry

#### **4. Density:**

Its determination is done by pouring accurately weighed microspheres in measuring cylinder and to from a stable height it is tapped 100 times. Then the tapped volume is determined and finally calculation of tapped density is done.

#### **5. Bulk density:**

Its determination is done by pouring accurately weighed microspheres in measuring cylinder and thus its bulk volume is determined.

#### **6. Flow properties:**

Flow properties are measured by following ways:

- a. Angle of repose: It is the angle that a static heap of particles makes with the horizontal. Determination of flow properties of microspheres can be determined by fixed funnel flow method, from where calculation of angle of repose is done.
- b. Hausner ratio: Its determination is from the ratios of tapped density and bulk density.

#### **7. Hardness:**

The force which is required for breaking the microsphere is termed as hardness. Monsanto hardness apparatus can be used for testing hardness.

#### **8. Friability:**

For determination of friability, Rosche friabilator is used.

### **Methods of Preparation of Magnetic Microspheres:**

#### **i. Solvent evaporation method:**

Synthesis of polymer encapsulated microsphere is done by continuous solvent evaporation technique. Addition of a solution of polymer, drug and magnetite is done with a volatile organic solvent, which when stirred forms auxiliary solution. Then homogenization of resulting solution is done and stirred at a temperature in the range of 22-30°C. Then separation of formed magnetic microsphere is done by centrifugation. Lastly, the product is freeze-dried & stored at 4°C.

#### **ii. Multiple emulsion method:**

This method comprises of the formation of the multiple emulsions of type w/o/w which is best suited to water soluble drugs, peptides, proteins and vaccines. This method can be used with both natural and synthetic polymers. In a lipophilic organic continuous phase, the aqueous protein is then dispersed. May be the active constituents are the contents of this protein solution. The polymer solution that eventually encapsulates the protein contained in dispersed aqueous phase is generally the constituent of the continuous phase. Before addition to the aqueous solution of the

poly vinyl alcohol, primary emulsion is subjected to homogenization or sonication. As a result, multiple emulsions are formed. Then, either by solvent evaporation or by solvent extraction, solvent removal takes place. Successful incorporation of microspheres using this method includes hydrophilic drugs like indomethacin, leutinizing hormone and conventional molecules.

### iii. Phase separation emulsion polymerization method:

Addition of the aqueous solution of polymer, drug and magnetite with vegetable oil is done and is then emulsified using a magnetic stirrer. As a result, the emulsion is stabilized by heating at the temperature (100-150°C). Then dropwise, the cross-linking agent is added into the emulsion with continuous stirring. Then, the separation of formed magnetic microsphere is done from oil by washing procedures. Thus, product formed and freeze-dried and stored at 44°C.

### iv. Emulsion solvent extraction method:

The dispersion of an aqueous phase, containing a water-soluble homo-polymer and magnetite nanoparticles into droplets in an organic medium using an amphiphilic block copolymer which serves as the dispersant. Water distillation at a raised temperature from the aqueous droplets to yield polymer magnetite particles follows this. A reagent then locks the structure of the particles which was being added to the water-soluble copolymer block and homo-polymer for cross-linking.

### v. Hot melt microencapsulation:

This method comprises of melting of polymer and then mixing of it with solid drug particles that have been sieved to less than 50µm. In a non-miscible solvent (like silicone oil), the mixture is suspended and continuously stirred, and then heated to 5°C above the melting point of the polymer. The stabilization of emulsion is done, then it is cooled till the solidification of polymer particles. As a result, through decantation, microspheres are washed with petroleum ether. The development of a process suitable for the water labile polymers, e.g. polyanhydrides for microencapsulation is the primary objective of this method. Alteration of stirring rate can easily control size distribution of microspheres with diameter of 1-1000µm. Exposure of the drug at moderate temperature is the only disadvantage of this method.

### vi. Dispersion copolymerization:

The reaction of various monomers at the interface between the two immiscible liquid phases for formation of a film of polymer envelops the dispersed phase. Two reacting monomers are employed in this technique, one of which is dispersed in the continuous phase and other is dissolved in continuous phase. Example: Amphiphilic magnetic microsphere in the range of 5 to 100µm.

### vii. Microwave-assisted preparation of magnetic albumin microspheres:

Preparation of magnetic bovine albumin microsphere is done by this method. Smaller particles are produced through this method, being faster than traditional methods. Synthesis of magnetized protein microsphere can be done through this method.

**Table showing drugs and their polymers used in drug delivery (Batra, Singh, Nautiyal, 2013):**

Sl. no	Drug	Polymer	Application	Method used	Target site	Reference
1	Yttrium-90	Human serum albumin	Bimodal radionuclide-hyperthermia cancer therapy	Modified emulsification heat stabilization	Tumor cells	(Wunderlich, 2010)
2	Oxanzazole	Chitosan	Cancer therapy	Emulsion/polymer cross-linking/ solvent evaporation	Tumor cells	(Hassan, 1992)
3	Piperacillin/tazobactam	Dextran	Antimicrobial activity against <i>S. aureus</i>	Continuous solvent evaporation	Bind to penicillin-binding proteins (pbps) located inside the	(Kang & Koh, 1987)

					bacterial cell wall	
4	Aclarubicin	Gelatin	Intravascular tumour targeting	Water in oil emulsion polymerization	Bind to minor DNA groove(DNA intercalation)	(Kang &Koh, 1987)
5	5-Fluorouracil	Bovine serum albumin (BSA)	Tumor of hepatoma	Emulsion-ultrasound heat stabilization	Binds to the nucleotide-binding site of Thymidylate synthase	(Kaixiong, 1999)
6	Adriamycin	Albumin	Cytotoxic effect on tumor cells	Heat-stabilized protein methods	Interacts with DNA by intercalation	(Kaixiong, 1999)
7	Diclofenac	Gelatin	Reduced joint swelling	sodium Emulsification and cross linking	Bind to the enzyme that makes prostaglandins (cyclooxygenase) thereby blocking it	(Surini,2009)
8	Amphotericin B	Albumin	Treatment of visceral leishmaniasis	Spray drying	Binds with ergosterol, a component of fungal cell membranes	(Brunete, 2004)

#### Advantages of Magnetic Microspheres(Farah, 2017):

1. Only small fraction of the free drug dose can achieve therapeutic responses in targetorgans.
2. Patient compliance is improved by reducing dosing frequency.
3. This method ensures prolonged therapeutic effect within target tissues.
4. A controllable variability in drug release is allowed by microsphere morphology.

#### Disadvantages of Magnetic Microspheres(Farah, 2017):

1. This technique is expensive and specialized manufacture and quality control system is required.
2. For targeting and monitoring,a specialized magnet is needed.
3. Permanent deposit of large fraction of magnetite in tissues occurs which usually gets entrapped in carriers.
4. Generally,controlled release formulations consist of higher drug load and thus potential toxicity occurs if any loss of integrity of the release characteristics of the dosage form happens.

#### Applications of Magnetic Microspheres:

1. Considerable attention is achieved by magnetic microspheres as it possesses wide applications in the field of bioengineering and biomedical. Examples include enzyme immobilization,protein purification,targeting drugs etc.
2. Therapeutic agents are delivered through magnetic field gradient. This ensures site specificity of drug thereby eliminating systemic drug side effects.
3. Stem cell extraction and bone marrow purging uses magnetic microspheres.
4. Nowadays, magnetic microsphereshave been used as carriers for binding proteins, enzymes and drugs showing a major impact in various fields of biotechnology and medicine.
5. For bacteria detection,Streptavidin coated magnetic beads are used.
6. For specific cell labelling,magnetic polystyrene microsphere is used.
7. For detection of metastases in non-enlarged lymph nodes, supra-magnetic iron oxide microsphere is used.
8. For detection of isolated breast carcinoma cells in bone marrow and peripheral blood, magnetic dynabeads are used.

**Future Prospects:**

The area of medicinal field shows bright future prospects of magnetic microspheres as it has wide spectrum of application in molecular biology, e.g. microsphere based genotyping platform is used for detecting six single nucleotide polymorphism, to prevent tumor, yttrium-90. It can be expected that in near future, magnetic particles would be used as a detection probe for a variety of assays, such as fluorescence, radioactivity and chemiluminescence. Future work shall involve development of detection method for bio-molecular interaction using magnetic particles as label. Special emphasis through this technique is shown in microarray technology, where basis for determining gene expression or allelic variation are bio-molecular interactions like cDNA-mRNA or DNA-DNA.

**Conclusion:-**

Magnetic microspheres are observed as the best novel drug delivery system possessing the advantage of target specificity and better patient compliance. It shows enormous applications as they are not only used for delivering drugs but also for detecting bio-molecular interaction and imaging tumor etc. So, magnetic microspheres in future will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organs and tissues in the body. It can also be expected that many patent dosage forms can be obtained in the form of magnetic microspheres in future.

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