REVIEW ARTICLE ON MAGNETIC MICROSPHERES

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ABSTRACT: Recently a number of novel drug delivery system have emerged to minimize drug dose and loss to prevent harmful side effects [1], excess drug bioavailability and to achieve controlled and targeted drug delivery. Microspheres constitute an important part of this particulate drug delivery system by virtue of its small size and efficient carrier characteristics Magnetic microspheres has been alternatively traditional method for delivery of drug to the targeted site by reducing the amount of free drugs circulating the whole body by reducing excess dose dumping for limiting toxicity and for reducing the side effects of the drug. The magnetic microspheres are delivered using an external magnetic energy to help and reach the carrier to the targeted site. This review gives an overview of the size, properties, mechanism, benefits, drawbacks, different preparations and applications of the magnetic microspheres [2].

KEYWORDS: Magnetic Microspheres, Magnetic targeting, Magnetic properties, Biomedical Applications

INTRODUCTION: Design and development of novel drug delivery system has two basics. First, it should distribute the drug in accordance with a predetermined rate, and second, it should release therapeutically effective quantity of drug at the site of action. Conventional drug delivery undergoes from several drawbacks such as increased variation in the circulatory drug level, extra frequential of dosage administration, increased gastrointestinal irritation, and dose related side effects. To solve this disadvantages, control release drug delivery systems have been planned for even and constant drug release over a prolonged period. [3]The study drug released is achieved by use of different kinds of polymeric systems; biodegradable polymer microspheres are one of the most common types which are used as a targeted drug delivery system. Microspheres can encapsulate many types of drugs with small molecules, proteins and nucleic acid are easily administered through a syringe needle. They are normally bio-compatible, can give high bioavailability, and are capable of constant release for long period. Magnetite offers a large potential for innovation in electronics, pot electronics, magnetic storage, biomedical ferrofluid, separation, and magnetically guide drug carriers for targeting the therapy.

Microspheres are free flowing powders consisting of encapsulate drug spherical particles of size ideally <125p that can be suspended in aqueous vehicle and injected by an 18 or 16 number needle. Magnetic(μ) microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (4μm) but are sufficiently (ferromagnetic) to be captured in micro vessels and dragged in to the adjacent tissues by magnetic fields of 0.50.8T.[4] Methods of preparation of magnetic micro-spheres are 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(i) Size of microspheres;(ii) Drug content'(iii) Magnetite content' (iv) Hydration state'(v)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 therapeutics system. Magnetic microspheres are characterized for different attributes such as (i) Particle size analysis including size distribution, surface topography, and texture etc. using scanning electron microscopy(SEM);(ii) Drug entrapment efficient ;iii) % magnetite content;(iv) In vitro magnetic responsiveness ; (v) Drug release.

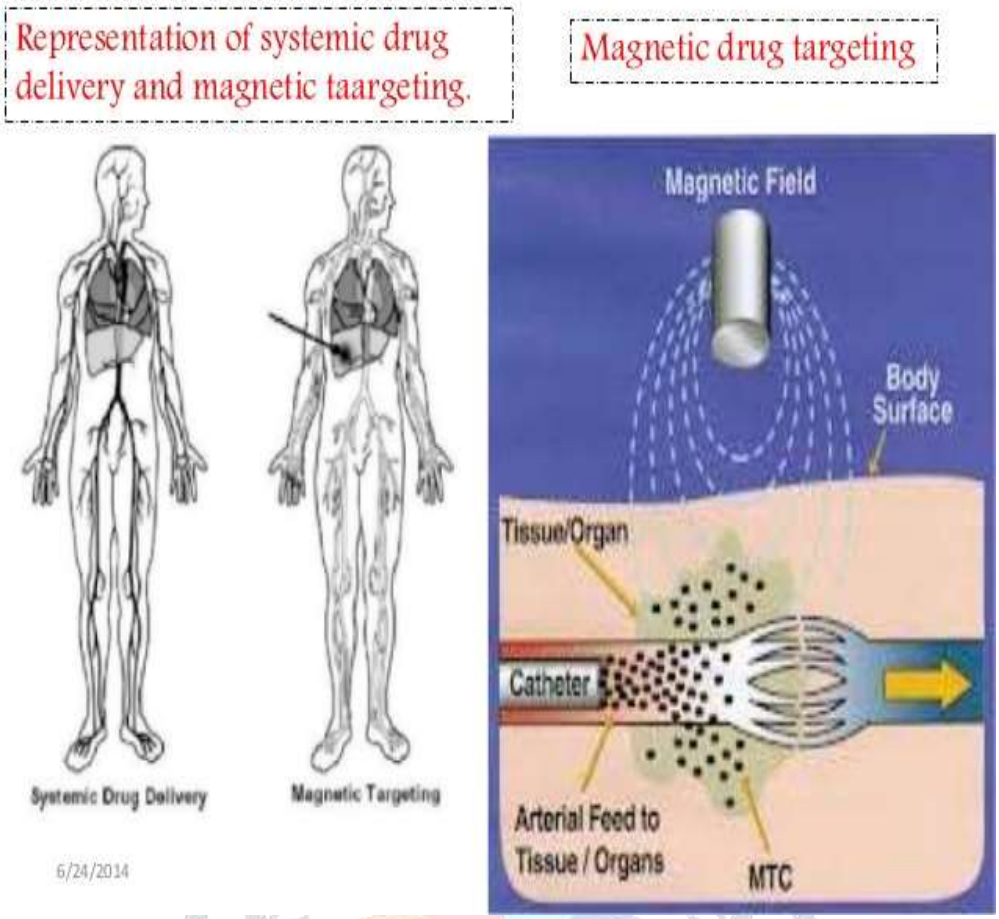
Targeting by magnetic microspheres i.e.in corporation of magnetic particles in to drug carrier [5] (polymers) and using an externally applied magnetic field is one way to physically direct these magnetic drug carrier to a desired site. Drug targeting is the delivery of drug to the receptor or organ or any specific part of the body to which one wishes to delivered the drug exclusively various nonmagnetic microspheres carrier (nanoparticles, microspheres, and magnetic particles .etc.,) are successively utilized for drug targeting but they show poor site specificity and are rapidly clear off by RES (reticulo endothelial system) under normal circumstances. Magnetism placed an important role in these cases, magnetic particles composed of magnetite which are tolerated by the body, [6] Up to 60% of an injected dose can be deposited and released in a controlled manner in selected non reticuloendothelial organs. So magnetic micro carrier 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 radio immunoassay.

TYPES OF MAGNETIC MICROSPHERES:

Magnetic carrier receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres such as chitosan, dextran etc. [7] The different types of magnetic microspheres include (i).Therapeutic microspheres that is used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system. (iii) Diagnostic microspheres that can be used for imaging liver metastases and also to distinguish bowel loops from other abdominal structures by forming nanosize particles supra magnetic iron oxides.

PRINCIPLES OF MAGNETIC MICROSPHERES DRUG TARGETING:

Drug targeting is a specific form of drug delivery where the drug is directed to its site action or absorption. This [8] could be a particular cell, organ structure or tissues. The aim of the specific targeting is to enhance the efficiency of drug delivery and at the same time to reduce the toxicity & side effects. Magnetic drug transport technique is based on the assumption that the drug can be either encapsulated into a magnetic microsphere or conjugated on the surface of the microsphere. When the magnetic carrier is intravenously administered, then accumulation takes place within the area to which the magnetic field is applied and often augmented by magnetic agglomeration. The accumulation of the carrier at the target site allows them to liver the drug locally. Efficiency of accumulation of magnetic carrier on physiological carrier depends on physiological parameters e.g. particle size, surface characteristic, field strength, & blood flow rate etc.[9] The magnetic field helps to extra vacate the magnetic carrier into the targeted area. Very high concentration of chemotherapeutic agents can be achieved near the target site without any toxic effect to normal surrounding tissue or to whole body. It is possible to replace large amount of drug targeted magnetically to localized disease site, reaching effective and up to several increase.

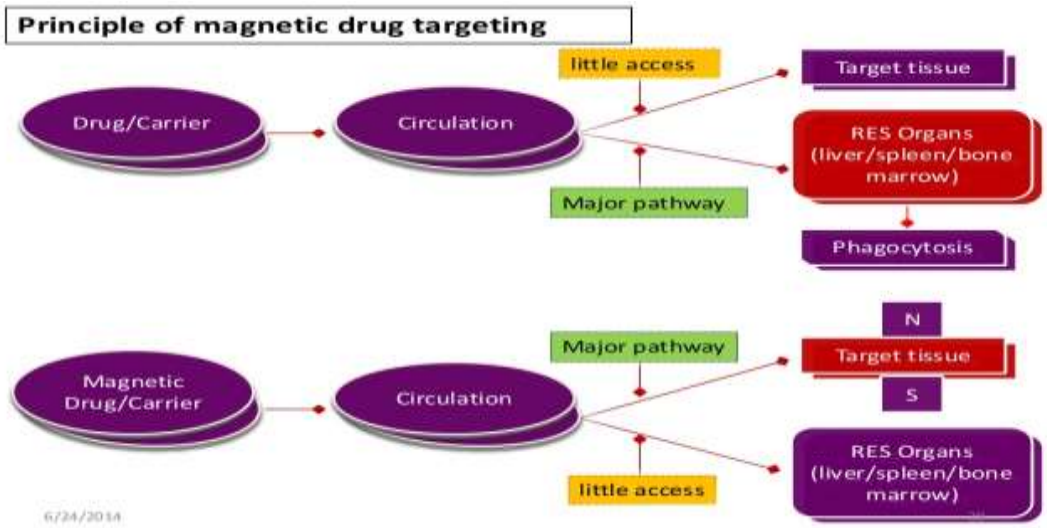


COMPARSION OF MAGNETIC & NON-MAGNETIC TARGET:

Nonmagnetic targeting	Nonmagnetic targeting
Capillaries of human body are in microns, so one can easily target the capillaries of lungs, blood, liver etc. by the use of microspheres.	Magnetic microspheres are injected into an artery that supplies a given site. As the microspheres would be selectively and magnetically localized at the capillary level, they would have free flow access through the large arteries. Thus the microspheres would serve as time-release capsule system sitting in the desired location.
No magnetic field strength needed	A much lower magnetic field strength is necessary to restrict the microspheres at the slower moving flow velocities of blood in capillaries.
A much lower magnetic field strength is necessary to restrict the microspheres at the slower moving flow velocities of blood in capillaries.	After removal of the magnetic field, the microspheres still continued to lodge at the target site, presumable because they had lodged in the vascular endothelium, penetrated in to the interstitial space, resulting in their retention.

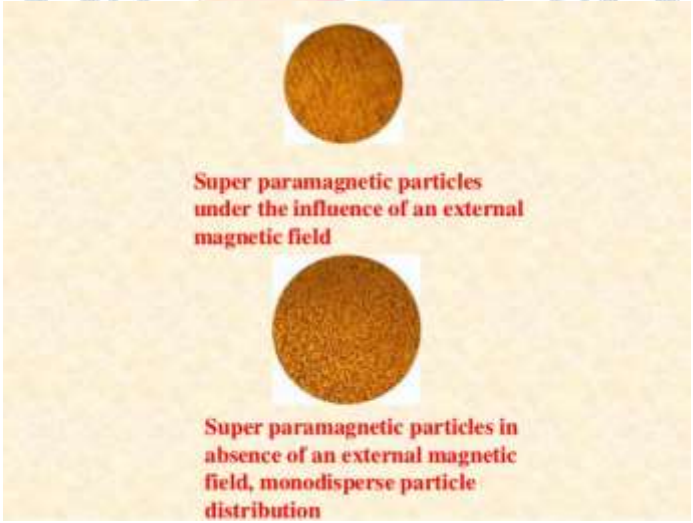
PRINCIPLES OF MAGNRTIC DRUG TARGETING:

The principle of this treatment shows that the magnetic drug can be retained at or made to flow toward the target site by the application of an external magnetic field.[10] Retention of magnetic carrier at target site will decrease reticuloendothelial clearance and increase site specificity.



MAGNETIC PROPERTIES OF MICROSPHERES:

Magnetic particles for bio separation consist of one or more magnetic cores with a coating matrix of polymers, silica or hydroxyl apatite with terminal functionalized groups. [11]The magnetic core generally consists either of magnetite (Fe_3O_4) or magnetite (gamma Fe_3O_4) with super paramagnetic properties. Some magnetic cores can also be made with magnetic ferrites, Super paramagnetism is when the dipole moment of a single-domain particle fluctuates rapidly in the core due to the thermal excitation.



So, that there is no magnetic moment for macroscopic time scales. Thus, these particles are nonmagnetic when an external magnetic field is applied, but do develop a mean magnetic moment in an external magnetic field.[12]The ferromagnetic particles are those particles having a permanent mean magnetic moment. Here, the large effective magnetic anisotropy of the core moments suppress the thermally activated motion.

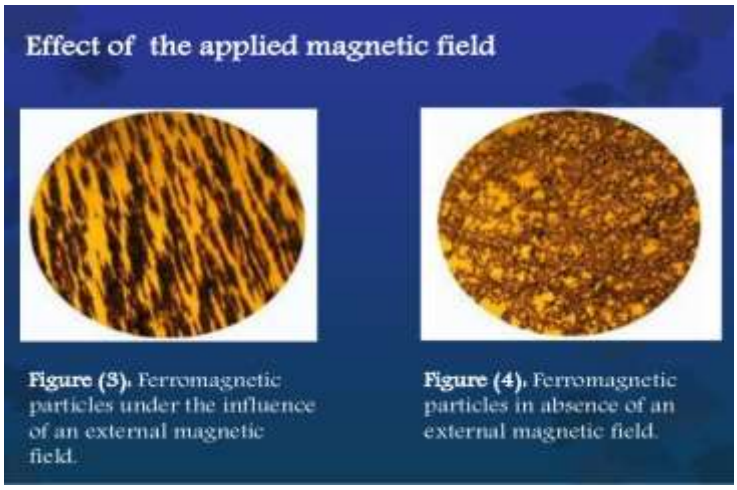


Figure (3). Ferromagnetic particles under the influence of an external magnetic field.

Figure (4). Ferromagnetic particles in absence of an external magnetic field.

The super paramagnetic and ferromagnetic particles are generally recommended for automatic DNA/RNA separation/purification.[13]For example, SiMAG/K-DNA and SiMAG/MP-DNA beads have been developed for automatic DNA/RNA separation such as genomic DNA, plasmid DNA, total RNA and PCR products. DNA/RNA bind to this porous silica surface under high salts conditions (5M guanidinium thiocyanate.) The superparamagnetic SiMAG/K-DNA beads and the ferromagnetic SiMAG/MP-DNA beads have excellent magnetic properties and are therefore most suited for automatic DNA/RNA separation/purification. Since different processing methods or magnetic separation systems, either super paramagnetic or ferromagnetic SiMAG/DNA beads will lead to optimal results.

ADVANTAGES OF MAGNETIC MICROSPHERES:

- Incorporation [14] of magnetically responsive materials into microspheres makes them susceptible to applied magnetic field, so that they are connected to the target site, by application of magnetic field externally that site. Due to this, rapid clearance of these microspheres by RES is prevented.
- Differences occurs maximally in capillary network so efficient delivery of drug to diseased tissue is achieved.
- Microspheres can transit into extra vascular space creating an extra vascular depot of drug for sustained release of drug within the targeted areas.
- Increase of tumour cell due to its much- increased phagocytic activity as compared to normal cell. So the problem, of drug resistance due to inability of drug to be transported across the cell membrane can be prevented.
- Controlled and predictable rate of drug release with smaller doses of drug can be achieved.
- Linear blood velocity in capillaries is 300 times less as compared to arteries, so much smaller magnetic field is sufficient to retain them in the capillary network of the target area.
- Avoidance of acute toxicity parenchyma cell, controlled release within target tissue for intervals of 30 min to 30hr as desired, adapatable to any part of body.

DISADVANTAGES OF MAGNETIC MICROSPHERES:

- It is an expensive, technical approach and need specialized manufacture and quality control system.
- It needs specialized magnet for targeting, for monitoring, and trained personnel to perform procedures.
- Magnets must contain relatively constant gradients, 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 tissues.

FACTORS AFFECTING MAGNETIC TARGETING OF DRUG:

- Factors related to ferrofluid.
- Size of the particles in ferrofluid.
- Surfactant characteristics of particles.

- Concentration of the ferrofluid.
- Volume of the ferrofluid.
- Reversibility and strength of drug/ferrofluid binding.
- Access to the organism (infusion rate).
- Duration or rate of injection /infusion.
- Size, weight, body surface of patient.
- Total blood volume.
- Blood flow in tumour.

LIMITATIONS OF MAGNETIC DRUG TARGETING:

- Magnetic targeting is an expensive, technical approach and requires specialized manufacture and equality control system.
- It needs specialized magnet for targeting, advanced techniques for monitoring and trained personnel to perform procedures.
- A large fraction of magnetite, which is entrapped in carriers, is deposited permanently in targeted tissue.

MATERIALS USED IN MAGNETIC MICROSPHERS:

✓ Synthetic polymers.
✓ Biodegradable: Glycolides, Epoxy polymers.
✓ Non-biodegradable: Polyanhydrides, Lactides, Polymethylmetharylate, Acrolein, Glycidyl methacrylate.
✓ Natural polymers.
✓ Carbohydrates: Agarose, Starch, Chitosan.
✓ Chemically modified carbohydrates: Polydextran, Polystarch.

METHODS OF PREPARATION:

Solvent evaporation:

Polymer encapsulated microspheres are synthesized by continuous solvent evaporation technique. A solution of polymer, drug and magnetite is added to the volatile organic solvent, which forms auxillary solution on stirring. The resulting solution is then homogenized and stirred at a temperature in the range of 22-30^{0}C .The formed magnetic microspheres are separated by centrifugation. The product is then freeze-dried & stored at 4^{0}C.

Phase separation polymerization method:

Freeze dried and stored at 4 Homogenous aqueous suspension is prepared by adding albumin water-soluble drug and agent with magnetite in appropriate quantity of water (if magnetic microspheres). This aqueous suspension is then emulsified in the presence of suitable emulsifying agent to form spheres in emulsion. This aqueous proteineous sphere thus, formed in the emulsion are stabilized either by heating at 100-150^{0}C or by adding hydrophobic cross linking agents like formaldehyde, glutaraldehyde or 2-3 butadiene, microspheres thus produced are centrifuged out and washed ether or some other appropriate organic solvent to remove excess of oil.

Hot-melt extrusion:

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to <50 µm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5^{0}C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, such as poly anhydrides. Microspheres with diameter of 1-1000µm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only temperature to which the drug is exposed.

Dispersion co-polymerization:

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelope the dispersed phase. In this technique two reacting monomers are employed, one of which is dissolved in the continuous phase while the other in the dispersed phase. Amphiphilic magnetic microspheres in the range of 5-100µm were prepared by dispersion copolymerization of styrene and poly ethylene oxide vinyl benzyl macro monomer in the presence of Fe_3O_4 magnetic fluid. The average particle size of the microspheres was found to increase with increasing styrene concentration as well as decreasing the molecular weight of PEO-VB.

Cross-linking method:

Here, the following reagent is used as follows: Acetate buffer used as solvent for the chitosan polymer, Glutaraldehyde used as cross linker, Sodium hydroxide solution as medium.

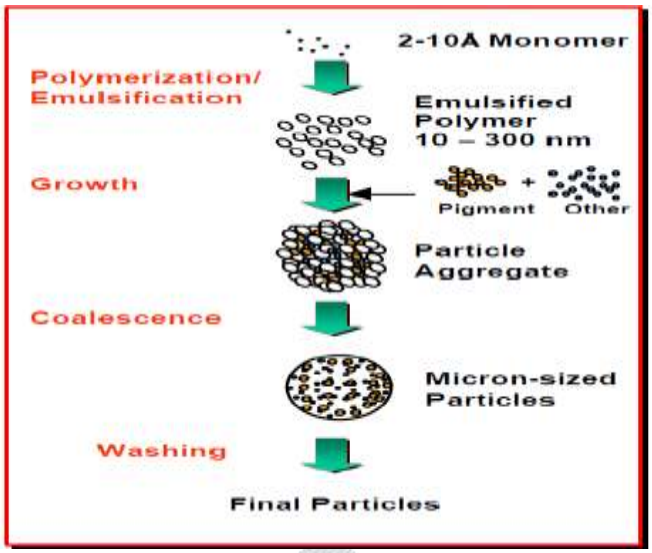
Magnetic fluid: 35% (w/v) ferrous sulphate solution, 5-4% (w/v) ferric chloride solution and 36% (w/v) of sodium hydroxide solution were prepared using distilled water. Then, the ferric salt and ferrous salt were mixed, stirred, and heated. The alkaline solution was added when the temperature reached 55^0C. The mixture was stirred for 30 minutes, and then 5g of PEG-10000 was added. The temperature was raised up to 80^0C and maintained for 30 minutes. The mixture was then neutralized while cooling, and the magnetic fluid was prepared. 1% (w/w) chitosan was dissolved in acetate buffer. The dissolved chitosan was added dropwise on the magnetic microspheres were washed with deionized water and soaked in 1,3, and 5% of glutaraldehyde solution for 2 hrs and then washed with deionized water.

Swelling and penetration method:

For swelling of polymer micro particles, researchers mixed 0.25 g of PS (Micro-size polystyrene) particles with 35ml of a N-methyl-2-pyrrolidone(NMP) water solution in a specific v/v NMP-Water ratio of 3:1 containing 200mg of PLGA (first w/o emulsion was prepared using a homogenizer in an water bath at 26000rpm for 2.5 min). Fifteen ml of 1% PVA solution directly poured in to the primary emulsion. w/o/w emulsion immediately poured in to a beaker containing 85ml of 1% PVA solution and stirred in a hood under on overheated propeller for allowing the solvent to evaporate. Whereas, solidified microspheres harvested by centrifugation at 2500 rpm, for 10 min and washed with distilled water.

Sonochemical method:

In this method, the microspheres consists of iron oxide filled with coated globular BSA. Here, magnetic microspheres were prepared from BSA and iron penta carbonyl or from BSA and iron acetate. Protein microspheres have a number of biomedical applications, i.e., used as echo contrast agent for sonography. The microspheres was formed by two ways (i) Either by heating denaturation at various temperatures or (ii) by cross linking with carbonyl compounds in the ether phase. Cross linking was completed as the microspheres are formed by chemically cross-linking cysteine residue of the protein with water radical formed around a non-aqueous droplet. The chemical cross-linking is known to be responsible for the formation of the microspheres. This is due to the chemical ejects of the ultrasound radiation on an aqueous medium.



CHARACTERIZATION OF MAGNETIC PARTICLES:

1. Particle size[18] and size distribution:

The particle size of microspheres has been determined by using an optical microscope with the aid of a calibrated ocular micrometer.

Here, total 100 particles were measured for size and then the average of these particles taken as average particle size.

2. Surface characterization;

Surface characterization can be determined by using:

a. High-resolution microscopy
b. Scanning electron microscopy(SEM)
c. Scanning tunnelling microscopy

3. Surface charge analysis:

They can be achieved by using:

a. Micro electrophoresis
b. Laser Doppler anemometry.

4. Density:

a. Tapped density

It is determined by pouring accurately weighed microspheres in measuring cylinder and tapped 100 times from a stable height to determine the tapped volume and finally tapped density is to be calculated.

True density = weight of powder/tapped volume of powder.

b. Bulk density

It is determined by pouring accurately weighed microspheres in measuring cylinder and thus determining its bulk volume.

Bulk density = weight of powder/bulk volume of powder

5. Flow properties:

Flow properties are measured by following ways:

a. Angle of repose

Angle of repose is the angle that a static heap of particles makes with the horizontal. The flow properties makes with the horizontal. The flow properties of microspheres can be determined by fixed funnel flow method, which is used to calculate angle of repose.

$\tan \theta = h/r$

$\theta = \tan^{-1} hr/r$

b. Hausner ratio

It is determined from the ratios of tapped density and bulk density.

Hausner ratio = tapped density/bulk density

6. Hardness:

Hardness is defined as the force requires breaking the microsphere. It can be tested by using Monsanto hardness apparatus.

Hardness = final reading- initial reading

7. Friability:

For thus, a rosche Friabilator is used for determining the friability.

% Friability = initial weight-final weight/initial weight ×100

8. Surface area

9. Porosity

10. Drug content

11. Drug release profiles

EVALUATION OF MAGNETIC MICROSPHERES[19]:

Particle size and shape:

Magnetic particles synthesized by above methods are of variable sizes. Their properties are quite different from other type of micro and nanoparticles. The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both techniques can be used to determine the shape and outer structure of the micro particles. Particle size and its distribution are determined by light microscopy, scanning electron microscopy, transmission electron microscopy, etc. Confocal laser scanning microscopy is applied as a non-destructive visualization technique for micro particles. CLSM allows visualization and characterization of structures not only on the surface, but also inside the particles, provided the material is sufficiently transparent and can be fluorescently labelled. By collecting several coplanar cross sections, a three- dimensional reconstruction of the inspected object is possible.

Chemical Analysis:

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical-analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface Fourier Transform Infrared Spectroscopy (FTIR) is used to determine the degradation of the polymeric matrix carrier system. The surface of the microspheres is investigated measuring total attenuated reflectance (ATR). The surface carboxylic acid residue is measured by using radioactive glycine. The radioactive glycine conjugate is prepared by reaction of 14C-glycine ethyl ester hydrochloride with the microspheres. The radioactivity of conjugate is measured using scintillation counter. Surface associated amino acid residue is determined by the radioactive 14C- acetic acid conjugate. The carboxylic acid residue is measured through the liquid scintillation counter and hence the amino acid residue can be determined indirectly.

Drug Loading:

The capture efficiency or the drug loading of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse the lysate is then subjected to the determination of

% Entrapment = (actual content/theoretical content)×100

Magnetic Properties:

Magnetic properties of nano composite particles were characterized by using vibrating sample magnetometer (VSM). The magnetic moment of each dried magnetic particles measured over a range of applied fields between -800 and+800 Guass with a asensitivity of 0.1 emu/g. The prepared samples can be characterized by weight or volume in VSM. The dry samples are weighed (0.075g), While the fluids are injected into the sample holder (0.05 ml). In this system, when a magnetic sample is placed between two coils of an lectromgnet creating a uniform magnetic field gradient, the applied field induces the magnetic domains to line up with the field through dipole interactions. As the magnetic field is increased, number of domains will be also enhanced until the particles reach saturation levels, the particles undergo a sinusoidal motion and produce an electrical signal in a set of stationary pick-up coils. This signal is set of proportional to magnetic moment, vibration amplitude and vibration frequency. After the measurements, magnetic saturation values of the materials are calculated for each sample by dividing the saturation magnetization by the weight of samples.

Thermo Gravimetric Analysis:

Different scanning calorimetry and other gravimetric methods are used to determine the extent of interaction of polymers with magnetite and such other magnetic materials. Moreover the stability of ferrous and ferric ions can be assessed by thermos gravimetric methods.

Measurement of swelling kinetics of Microspheres:

Swelling kinetics of the composite magnetic microspheres can be determined by swelling rate at given time. Dried microspheres are immersed in distilled water at each predetermined time at room temperature. Then the sample is removed from distilled water and is frequently weighed after trapped with filter paper. Thus, the wet weight of the microsphere is record during the swelling period at regular time intervals. The SR,(Ws+Wd, is defined as the ratio of total weight of the dried microspheres, where Ws is the weight of adsorbed water and "Wd" is the weight of the microspheres at dry state.

Stability Measurements:

Stability measurements can be performed by using separation analyser. Measurements are made in glass tubes at accelerated velocities from 50 to 300rpm. The slope of sedimentation velocity and stability data can be found. Potential Measurements:-potential measurements can be made using an instrument like zetasizer 2000. The zeta potential is measured at different pH values and stability of magnetic particles can be predicted.

Effect of pH on Magnetic Microspheres:

Measurement of pH sensitive behaviour is similar to the measurement of swelling kinetics of the microspheres. It is determined by the equilibrated swelling rate (ESR) at given pH data. ESR of the microspheres is measured by immersing dry and known weight of microspheres into buffer solution with different pH data for at least 1h at room temperature. Then the microspheres are removed from the buffer solution and frequently weighed after trapped with a filter paper to remove excess of water on the surface. ESR is calculated from the following formula We/Wd, where We is the weight of the solution in equilibrated swollen microspheres at each predetermined buffer solution with different pH data, the symbol of "Wd" is the same as defined earlier.

Drug release profiles:

In vitro methods:

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of in vitro and in vivo techniques have been reported. In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production and product development. Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both rotating elements, paddle and basket. Dissolution medium used for the study varied from 100-500ml and speed of rotation from 50-100rpm.

In vivo methods:

The most widely used in vitro methods are

A) **Animal models:** Animal models are used mainly for the screening of test series of compounds, investigating the mechanism and usefulness of permeation enhancers of evaluating a set of formulations. A number of animal models has been reported in the literature, however, very few in vivo. Animal models such as the dog, rats, rabbits, cat, hamster, pigs, and sleep have been reported. In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the esophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn an analysed.

B) Buccal absorption test:

The buccal absorption test was developed by Beckette & Triggs in 1967. It is a simple and reliable method for measuring the extent of drug loss of the human oral cavity for single and multi-component mixtures of drugs. The test has been successfully used to investigate the relative importance of drug structure, contact time, initial drug concentration and pH of the solution while the drug is held in the oral cavity.

APPLICATIONS:

Tumour Targeting via Magnetic Microspheres:

Magnetism can play very important role in cancer treatment. The first clinical cancer therapy trials using magnetic microspheres were performed by Lubb *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. Permanent magnetic field for one hour way found to induces lethal effects on several rodent and human cancers. Anticancer drugs reversibly bound to magnetic fluids and could be concentrated in locally advanced tumours by magnetic field that or arranged at tumour surface outside of the subject. Various novel biodegradable magnetic microspheres are synthesized and their targeting to brain cationic magnetic amino dextrin microspheres has been synthesized. Its potentiality for drug targeting to tumour was studied. These particles were retained in brain tissue for longer period of time .

Loco regional Cancer Treatment with Magnetic Drug Targeting:

The specific delivery of chemotherapeutic agents to their desired targets with a minimum of systemic side effects is an important, ongoing challenge of chemo-therapy. One approach, is the i.v. injection of magnetic particles [ferrofluids (FFs)] bound to anticancer agents that are then concentrated in the desired area (e.g., the tumour) by an external magnetic field. Where as an external magnetic field was focused on the tumour. Application of FF-MTX is successful in treating experimental squamous cell carcinoma. This "magnetic drug targeting "offers a unique opportunity to treat malignant tumours loco regionally without systemic toxicity. Furthermore, it may be possible to use these magnetic particles as a "carrier system" for a variety of anticancer agents, e.g., radionuclide's, cancer-specific antibodies and genes.

Magnetically Induced Hyperthermia for Treatment of Cancer:

Heat treatment of organs or tissues, such that the temperature is increased to 42-46^{o}C,and the bioavailability of cancerous cells reduces, is known as hyperthermia. It is based on the fact that tumour cells are more sensitive to temperature than normal cells. In hyperthermia it is essential to establish a heat delivery system, such that the tumour cells are heated up or inactivated while the surrounding tissues (normal) are unaffected.

Magnetic Delivery of Chemotherapeutic Drugs to Liver Tumours:

The first clinical cancer therapy trial using magnetic microspheres (MMS) was performed by Lubbe in Germany for the treatment of advanced solid cancer in 14 patients. Their MMS were small, about 100 nm in diameter and filled with 4-epidoxorubicin. The phase I study clearly showed the low toxicity of the method and the accumulation of the MMS in the target area. However, MRI measurements indicated that more than 50% of the MMS had ended up in the liver. [20]This was likely due to the particles' small size and low magnetic susceptibility which limited the ability to hold t hem at the target organ. The start up company FeRx in San Diego developed irregularly shaped carbon coated iron particles of 0.5–5 m in diameter**.**

Human Cholangiocarcinoma Xenografts:

Cholangiocarcinoma, a malignant disease, poses a severe hazard to human health. It constitutes2.32% of biliary tract disease and the incidence ratio of male to female is 1.461.The incidence of cholangiocarcinoma has shown a tendency to rise in recent years. Treatment includes mainly operation and combined chemotherapy and radiation. But cholangiocarcinoma can be located deep, be anatomically concealed and difficult to diagnose early. As a result, the outcome of operation can be unsatisfactory and the survival rate is very low. Single or combined application of chemotherapeutic drugs is usually less than 30% successful in the clinic. The targeting drug with magnetic microspheres is used to treat human cholangiocarcin-oma xenografts. It scan inhibit the growth of human cholangiocarcinoma xenografts in nude mice.

Magnetic Control of Pharmacokinetic Parameter and Improvement of Drug Release[21]:

Magnetite or iron beads into a drug filled polymer matrix and then showed that they could activate or increase the release of drug from the polymer by moving a magnet over it or by applying an oscil

lating magnetic field. The microenvironment within the polymer seemed to have shaken the matrix or produced micro cracks' and thus made the influx of liquid, dissolution and efflux of drug possible there by achieving magnetically controlled drug release. Macr-
omolecules such as peptides have been known to release only at a relatively low rate from a polymer controlled drug delivery system, this low rate of release can be improved by incorporating an electr
omagnetism triggering vibration mechanism into the polymeric delivery devic--
es with a hemispheric design; a zero-order drug release profile is achieved.

Combination Therapy:

There also exists the combination therapy which would induce hyperthermia treatment followed by chemo-therapy or gene therapy. [22] A combination of chemo-therapy or radiation
therapy with hyperthermia is found much more effective than hyperthermia itself. The approach involves us e of magnetic microspheres containing a drug to cause hyperthermia using the
standard procedure, followed by the release of encapsulated drug that will act on the injured cells. It is anticipated that the combined treatment might be very efficient in treating solid tu-
mour. Ongoing investigations in magnetic hyperthermia are focused on regulate the temperature they reach. The ideal temperature for hypothermia is 43°C-45°C and particles with a curie temperature in this range have been described by kuznetsov. In addition, Magnetic microspheres have wide range of applications. Various applications have been listed. Various preparations of Marketed products of magnetic microspheres are available which are characterized by their I NCI names, size, oil abs, refractive index and density shows comparison of magnetic and non magnetic targeting microspheres.Machines for magnetic cell separation ha-
ve recently the development of magnetic particles that are able to selfregulate the temperaturethey reach. The ideal temperature for hypothermia is 43^{o} **c**-45^{0} c and particles with a curie temperature in this range.

CONCLUSION:

Over the years,[23] magnetic microsphere has been investigated for targeted drug delivery especially magnetic targeted chemotherapy due to their better tumour targeting. Targeted drug delivery is an effective method to assist the drug molecule to reach preferably to the desired site. It gives the idea that drugs reach the right site in the body, at the right time, at the right concent-ration. It does not exert side effects, neither on its way to the therapeutic target, not at the target site, nor during the clearance process. Thus, magnetic micro-spheres have the potential for these objectives. The main advantage of this technique is the reduction in the dose and side effects of the drug. [24]The magnetic targeted chemotherapy has better tumour targeting, therap eutic efficacy, and lower toxicity. As the targeted drug delivery system implies selective and effective local i-zation of drug into the target at therapeutic concentr-ations with limited access to non-target sites. Magnetic microspheres hold great promises for reaching the goal of controlled and site specific drug delivery. It is a demanding area for future research in t he drug targe-ting so more researches, long-term toxicity study, and characterization determinations to give guarantee for the upgrading of magnetic drug delivery system. The future holds a lot of promises in magnetic micro-spheres, and by more study, this will be developed as novel and efficient approach for targeted drug delivery system.

REFERENCE:

1)Amit, Ramandeep, Chandna, singh.b: A review On target drug delivery: magnetic microspheres, Journal of Acute disease, vol 2,issue 3, pg 189-195 .

2) Satinder, Ujjwal, Kaka.ra,Nautiyal.b, Magnetic microspheres as magical novel drug delivery system: Journal of Acute disease,vol2,issue1,2013,pg1-15.

3) Dikshasharma, Abhishek Sharma,A review on magnetic microsphere as emerging drug delivery system: Asian journal of pharmaceutical &clinical research,vol10,issue6,2017.

4) Anurekha jain, Satinder,kakar: A review on magnetic microsphere, international journal of biomedical science & engineering:vol 5,issue 5,oct2017,pg:48-52.

5) P.keerthi, T.lakshmi Teja, DebarshiDatta, M.Niranjan Babu, V.lavakumar, S.sheema Nafees, MAGNETIC MICROSPHERES A nobel approach ,vol 3,issue1,320-323,25 Dec 2013.

6) DeepaBatra, Ramandeepsingh, UjjwalNasstiyal, Magnetic microspheres as a targeted drug delivery system: an overview,1volume1, issue3,2012.

7) Tarun.p, soni.s, Thakur.B, pandya.v, Bharadiap: magnetic microspheres as a targeted drug delivery system, vol1, issue2,2012.

8) Vidyavati.s, Koppisetti & sahiti.B. : Magnetically modulated drug delivery system,vol 3,issue1,jan-march, 2011.

9) Shaikh siraj, G.J.khan, patel afroza, patelhuzaifa, Wedachhiyasufiyan, shaoor .Ahmad, sanjay padvi, Magnetic microspheres drug delivery system,vol5,issue1,3 37-346.

10) Amit chandna,Deepa Batra, satinderkakr, Ramandeep singh: Areview on target drug dlivery & 58:magnetic microspheres,vol2,number3,2013,pg:189-195(7).

11) Siddharth.k, Gajja, G.U.sailor, Purva.B, Patel; A review on targeted drug delivery: Magnetic drug delivery system; 12 oct 2011.

12) Nisha Sharma, Neha parwar & prakash Chandra guota: Microspheres as drug carriers for controlled drug delivery: Au,2015, pg no:4379-87.

12)Chandna, A.D.Batra, S.kalka, 2013, Areview on target drug delivery: Magnetic microspheres, journalof acute disease,2(3):189-195.

13) Anurekha jain, satinder kakr : A review on magnetic microspheres, vol 5,issue5,2011,pg no:48-52.

14)Kim KK, pack D.N: Microspheres for drug delivery Bio: Biommedical Technology 2006:1; 19-20.

15)Vyas SP. Khan Rk Targeted and controlled drug delivery novel carrier systems.CBpublications:2004, pg no; 456-483.

16) Molday RS, yen SP, Rembaum A. Application of magnetic microspheres in labelling and separation of cells, Nature 1997:268;437-438.

17) Lachman LA, liberman HA, Kanig JL. The theory & practice of industrial pharmacy, Mumbai, india, Varghese publishing house, 2005, 3; 414-415.

18) Aggarwal A, Chhajaer p, Maheshwari S. Magnetic drug delivery in therapeutics.int J pharm sciences Res 2012:3(2);4670-4680.

19) Lokwani P. Magnetic particles for drug delivery: an overview international Res pharm Biomed sciences 2011:2 (2)465-473).

20) Gallo JM. Gupta PK, Hung CT, prier DG, Magnetic particles for drug delivery. J pharm sciences 1989; 78: 190.

21) Asmatulu R, Zalich MA, Claus RO. Synthesis, characterization and targeting of biodegradable magnetic nanocomposite particles by external magnetic fields. J Magn Magn Mater 2005; 292: 108

.

22) Salim MD, Shukla VK, Bhardwaj V, Garg VK, Sharma PK. Magnetic microspheres as a magnetically targeted drug delivery system. J Glob Pharm Technology 2010; 2(3):36-46.

23) Nasra MK, Mohamed MM, Elblbesy MA, Hefney BA.Preparation of biocompatible magnetic microspheres with chitosan. J Biomater Nanobiotechnol 2011; 2: 194-200.
24)Fricker J. Drugs with a magnetic attraction to tumours. Drug Discover Today 2001; 6: 387-389.