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Magnetic Microspheres: A Novel Drug Delivery System

Abstract

A well designed controlled drug delivery system can provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration for the specific period of time. A number of approaches are available in delivering therapeutic substance to the target site in sustained and controlled release fashion. One such approach is using magnetic microspheres as carriers for drugs. Microsphere drug delivery system has gained vast attention due to its diverse applications that range from targeting the drug to specific site to imaging and helping the diagnostic features.

One of its important application is that it is used for targeting tumors using anticancer drugs. Being more stable, it has an advantage over other delivery systems like liposomes. The main objectives of this review are to highlight some important aspects of magnetic microspheres as a novel drug delivery system. The review shall cover definitions, concepts, types, mechanism of targeting, evaluation and characteristics of magnetic microspheres as well as various methods and techniques used in their preparations. The review also entails various applications and future prospects of magnetic microspheres.

Keywords: Magnetic microspheres; Preparation; Evaluation; Novel drug delivery

Review Article

Volume 3 Issue 5 - 2016

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Received: October 24, 2016 | **Published:** November 23, 2016

Introduction

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4μm)but are sufficiently susceptible (ferromagnetic) to be captured in micro-vessels and dragged into the adjacent tissues by magnetic field of 0.5-0.8 tesla [1,2]. Magnetic microspheres are very much important which localizes the drug to the disease site. In this respect, larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug [3].

Microspheres are characteristically free flowing small spherical particles consisting of proteins or synthetic polymers, which are biodegradable in nature and having a particle size ranging from 1-1000μm [1]. They are considered as one of the important approach in delivering therapeutic substance to the target site in sustained and controlled release fashion [4].

The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. While a variety of devices have been used for controlled release drug delivery, biodegradable polymer microspheres including magnetic microspheres are one of the most common types and hold several advantages [4]. The development of new delivery systems for the controlled release of drugs is important in order to increase patient compliance through prolonging drug action and reducing adverse effects by lowering peak plasma concentration [5]. Microspheres can be used for the controlled release of drugs, vaccines, antibiotics, and hormones and are easily administered through a syringe needle. Microspheres could provide a larger surface area and possess an easier estimation of diffusion and mass transfer behavior also the encapsulated small molecules could diffuse out of the barrier with precise kinetics modelling and control-release of drugs to the body fluid [6]. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time. Several commercial products are based on polymer microspheres including Lupron Depot® and Nutropin Depot® [5].

Nowadays several targeted treatment systems including magnetic field, electric field, ultrasound and temperature, UV light and mechanical force are being used in many diseases treatments (e.g. cancer, nerve damage, heart and artery, anti-diabetic, eye, etc.). One of the most attractive and promising strategy for delivering the drug to the specific site is the magnetically controlled drug delivery targeting that aims to deliver the drug at a rate directed by the needs of the body during the period of treatment and target the drug to the site of action in order to overcome two major problems encountered in drug targeting namely; reticuloendothelial clearance and target site specificity. The amount and rate of drug delivery via magnetic responsive microspheres can be regulated by varying the size of microspheres varying drug content, varying magnetite content, varying the hydration state and varying drug release characteristic of the carrier [7].

Magnetite offers great potential for advancements in a number of fields including magnetically guided drug carriers for targeting the therapy. Targeted drug delivery is an effective method to assist the drug molecule to reach preferably to the desired site. The main advantage of magnetic microsphere is the reduction in the dose and side effects of the drug. The magnetic targeted chemotherapy has better tumor targeting, therapeutic efficacy

and lower toxicity. 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 microsphere drug delivery system [4].

Magnetic microspheres as an alternative to traditional radiation methods which use highly penetrating radiation that is absorbed throughout the body. Its use is limited by toxicity and side effects. Magnetic radioactive microspheres are applied in methods similar to non-radioactive spheres. A magnet, placed outside the body, is directed to the target site. The magnet can be a rod-shaped permanent magnet of any size or can be contained in equipment that looks like an open magnetic resonance imaging scanner. The loaded microspheres are introduced into a blood vessel, and in as little as half an hour, they gather at the target site to emit radiation that kills surrounding cancer cells. The therapeutic action usually a couple of days or weeks, depending on the material used. If necessary, the treatment can be repeated. Spheres need to be peppered with microscopic magnetic particles, such as iron, so they will be attracted to the magnet for applications requiring *in vivo* magnetic targeting, for example, magnetic drug delivery, the magnetic carriers must have a proper size range between 200nm and 3mm and high magnetizations to enable technically feasible external magnetic guidance within the vasculature. In these applications the microspheres having a size of 1–2mm would be more advantageous than nanospheres in terms of better targeting and easier capture [4].

Advantages of Magnetic Microspheres [8]

a. Therapeutic responses in target organs can be achieved by only small fraction of the free drug dose.

b. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.

c. Controlled drug release within target tissues for prolonged therapeutic effect.

d. Reduce the dosing frequency and thereby improve the patient compliance.

e. They could be injected into the body due to the spherical shape and smaller size.

f. Microsphere morphology allows a controllable variability in degradation and drug release.

Disadvantages of Magnetic Microspheres [8]

a. It is an expensive technical approach and requires specialized manufacture and quality control system.

b. It needs specialized magnet for targeting, for monitoring, and trained personnel to perform procedures.

c. Magnets must have relatively constant gradients, in order to avoid focal over-dosing with toxic drugs.

d. A large fraction of the magnetite, which is entrapped in carriers, is deposited permanently in tissues.

e. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.

Types of Magnetic Microspheres

Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres such as chitosan, dextran etc [3]. The different types of magnetic microspheres include:

I. Therapeutic microspheres that is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system [9].

II. 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 [6].

Principle 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 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 (Figure 1) and often augmented by magnetic agglomeration. The accumulation of the carrier at the target site allows them to deliver 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. The magnetic field helps to extravasate 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 amounts of drug targeted magnetically to localized disease site, reaching effective and up to several fold increased drug levels [4,5].

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. The magnetic core generally consists either of magnetite (Fe_3O_4) or magnetite (gamma Fe_2O_3) with super paramagnetic or ferromagnetic properties. Some magnetic cores can also be made with magnetic ferrites, such as cobalt ferrite or manganese ferrite. Super para magnetism 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 non-magnetic when an external magnetic field is applied, but do develop a mean magnetic moment in an external magnetic field (Figure 2 & 3) [4].

The ferromagnetic particles are those particles having a permanent mean magnetic moment (Figure 4 & 5). Here, the larger effective magnetic anisotropy suppresses the thermally activated motion of the core moments.

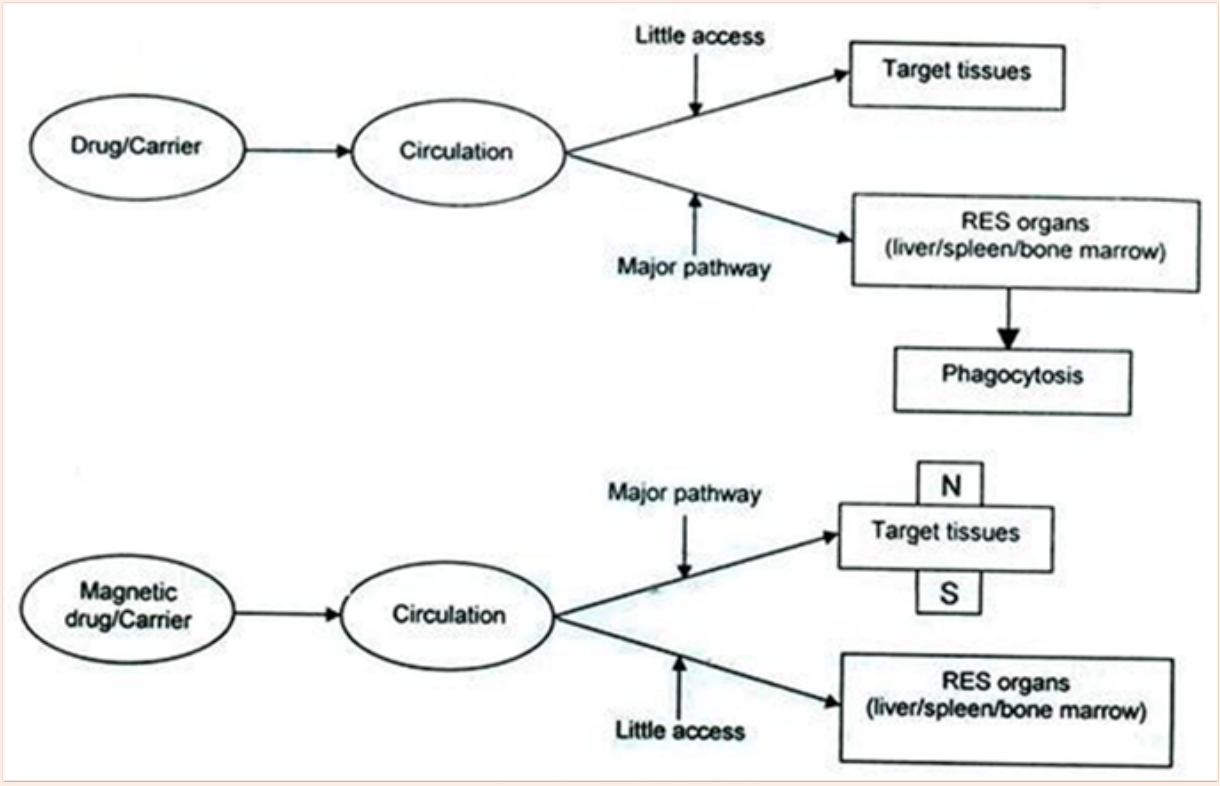

Figure 1: Principle of Magnetic Drug Targeting.

Figure 2: Super paramagnetic particles under the influence of external magnetic field [5].

Figure 3: Super paramagnetic particles in absence of an external magnetic field, monodisperse particle distribution [5].

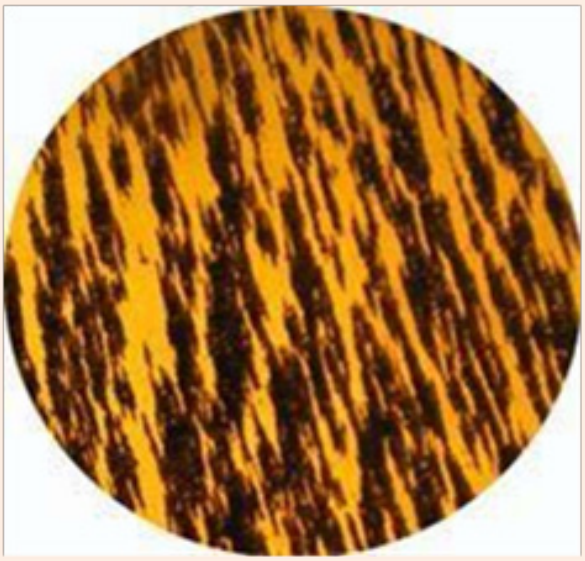

Figure 4: Ferromagnetic particles under the influence of an external magnetic field [5].

The superparamagnetic and ferromagnetic particles are generally recommended for automatic DNA/RNA separation/purification. 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 robot systems work with different processing methods or magnetic separation systems, either superparamagnetic or ferromagnetic SiMAG-DNA beads will lead to optimal results [4,10].

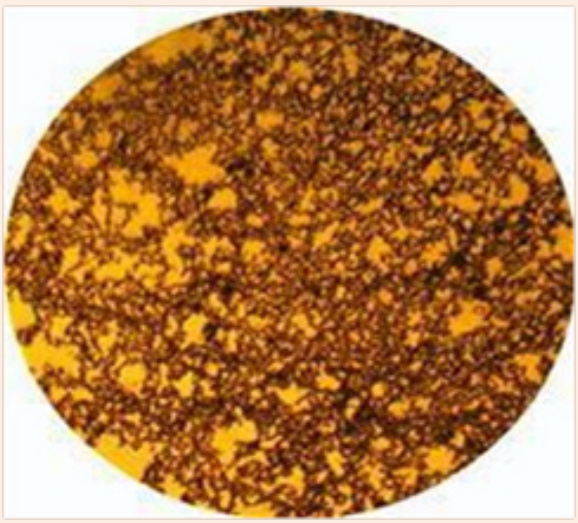

Figure 5: Ferromagnetic particles in absence of an external magnetic field [5].

Methods of Preparation of Magnetic Microspheres

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 auxiliary solution on stirring. The resulting solution is then homogenized and stirred at a temperature in the range of 22-30°C. The formed magnetic microspheres are separated by centrifugation. The product is then freeze-dried & stored at 4°C [4,11].

Multiple emulsion method

It involves the formation of the multiple emulsions of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates the protein contained in dispersed aqueous phase. The primary emulsion is the subjected to homogenization or sonication before addition to the aqueous solution of the poly vinyl alcohol. This results in the formation of a multiple emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like indomethacin, leutinizing hormone releasing hormone agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using this method [12,13].

Phase separation emulsion polymerization

In this method, the aqueous solution of polymer, drug and magnetite are added to a vegetable oil which is then emulsified using a magnetic stirrer. The resultant emulsion is stabilized by heating at the temperature (100-150°C). The cross linking agent is then injected drop wise into the emulsion with continuous stirring. The formed magnetic microspheres are then separated from oil by washing procedures. The product is then freeze-dried & stored at 4°C [4].

Emulsion solvent extraction method

The preparation involved first the dispersion of an aqueous phase, containing magnetite nanoparticles and a water-soluble homo-polymer, into droplets in an organic medium using an amphiphilic block copolymer as the dispersant. This was followed by water distillation at a raised temperature from the aqueous droplets to yield polymer magnetite particles. The structure of the particles was then locked in by a reagent being added to cross-link the water-soluble copolymer block and homo-polymer. Since the hydrophobic block of the copolymer consisted of a protected polyester, the removal of the protective moieties from the coronal chains yielded poly (acrylic acid) or other functional polymers to render water dispensability to the spheres and to enable biomolecule immobilization [4].

Hot melt microencapsulation

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50μm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°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, e.g. 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 disadvantage of this method is moderate temperature to which the drug is exposed [11].

Dispersion copolymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed, one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase. Amphiphilic magnetic microspheres in the range of 5 to 100µm were prepared by dispersion copolymerization of styrene and poly ethylene oxide vinyl benzyl (PEO-VB) 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 [4].

Microwave-assisted preparation of magnetic albumin microspheres

Microwave-assisted method was used to prepare magnetic bovine albumin microspheres. It produces smaller particles and is faster than traditional methods. The optimum conditions to prepare magnetic microspheres containing albumin were 4 minutes at 160°C that yielded smaller sized microspheres of 30 µm in diameter. This microwave process could become a preferred method for the synthesis of magnetized protein microspheres [14].

Evaluation & Characterization of Magnetic Microspheres [1]

Particle size and shape [1,4,15]

The most widely used procedures to visualize microspheres are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microspheres. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the

microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Confocal fluorescence microscopy is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size.

Electron spectroscopy for chemical analysis: [1,4,15]

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. The spectra obtained using ECSA can be used to determine the surface degradation of the biodegradable microspheres.

Thermal analysis [16]

Thermal analysis of microcapsule and its component can be done by using differential scanning calorimetry (DSC), thermo gravimetric analysis (TGA), differential thermometric analysis (DTA) Accurately the sample was weighed and heated on alumina pan at constant rate of 10°C/min under nitrogen flow of 40 ml/min.

Attenuated total reflectance fourier transform-infrared spectroscopy: [16,17]

ATRFTIR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring attenuated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

Swelling Index [4]

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance. The hydrogel microspheres then dried in an oven at 60°C for 5h until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula:

$$\text{Swelling index} = \frac{\text{mass of swollen microspheres} - \text{mass of dry microspheres}}{\text{mass of dried microspheres}} \times 100$$

Flow properties: [1,4,15]

Density

a. **Bulk density:** It is determined by pouring a sample of microspheres of known weight into a measuring cylinder without tapping and measuring its volume, then dividing the weight by the volume.

b. **Tapped density:** It is determined by pouring a sample of microspheres of known weight into a measuring cylinder & thoroughly tapping it & measuring its volume, then dividing the weight by the volume.

Hausner ratio: Hausner ratio is the ratio of the tapped density to the bulk density of microspheres & can be used to predict of microspheres flow. Low Hausner ratio of < 1.2 indicates a free flowing microspheres.

Angle of repose: It is defined as the maximum angle to the horizontal that is attainable by a heap of microspheres. Among methods available for measuring the angle of repose are the fixed height cone and the fixed base cone. High angle of repose indicates poor flowing microspheres, while low angle indicates a free flowing microspheres.

Surface charge analysis [16]

Surface charge can be determined using the micro-electrophoresis. It is an apparatus used to measure the

electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different pH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1mm. By using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge and ion absorption nature of the microspheres.

Drug release profiles [16]

***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 [17-20] and basket [21,22]. 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-vivo* methods are the use of animal models and buccal absorption tests:

A. **Animal models:** Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations. A number of animal models have been reported in the literature, however, very few *in vivo* (animal). Animal models such as the dog [23,24], rats [25], rabbits [26,27], cat [28], hamster [29,30], pigs [31], and sheep [32] 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 analyzed.

B. **Buccal absorption test:** The buccal absorption test was developed by Beckett & 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 [33].

C. ***In vitro-In vivo* correlations:** Correlations between *in vitro* dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "*in vitro-in vivo* correlations" [34]. Such correlations allow one to develop product specifications with bioavailability.

D. **Percent of drug dissolved *in vitro* vs peak plasma concentration:** In this method the percent of the drug released from different dosage forms is correlated to the peak plasma concentrations achieved by them. It is expected that a poorly formulated dosage form releases less amount of drug than a well formulated dosage form, and, hence the amount of drug available for absorption is expected to be less.

E. **Percent of drug dissolved vs percent of drug absorbed:** In case of hydrophobic drugs where the dissolution rate is the limiting step in the absorption of the drug, then a linear correlation may be obtained by comparing the percent of the drug absorbed to the percent of the drug dissolved. For hydrophilic drugs where the absorption is the rate limiting step in the bioavailability of the drug, a change in the dissolution rate may not be reflected in a change in the rate and the extent of drug absorption from the dosage form.

F. **Dissolution time vs absorption time:** In the analysis of *in vitro* and *in vivo* drug correlation, rapid drug absorption may be distinguished from the slower drug absorption by observation of the absorption time for the dosage form. The quicker the absorption of the drug, the less is the absorption time required for the absorption of the certain amount of the drug. The time required for the absorption of a certain amount of drug from the dosage form is correlated with the time required same amount to dissolve *in-vitro*.

G. **Percent of drug dissolved vs serum drug concentration:** For drugs whose absorption from GIT is dissolution rate limited, a linear correlation may be established between the percent of drug dissolved at specified times and the serum drug concentrations at corresponding times.

Percent of drug dissolved vs percent of the dose excreted in urine: Since the percent of a drug dissolved and the percent of drug absorbed can be linearly correlated, then a correlation between the amount of drug in body and the amount of drug excreted in the urine is expected. Therefore, a linear relation may be established between the percent of the drug dissolved and the percent of the dose excreted in the urine [12].

Determination of microspheres drug content or entrapment efficiency [35,36]: Accurately weighed amount of microspheres are crushed using glass mortar and pestle & the powder microspheres is then suspended in a specific volume of suitable solvent. After 12 hours the solution was filtered and the filtrate is then analyzed for the drug content using UV-Visible spectrophotometer. drug content is equal to entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.

Factors Influencing the Properties of Microspheres [4]

Polymers commonly used to form microspheres should be stable, biocompatible, biodegradable, exhibit a wide range of erosion times, has tunable mechanical properties, favorable degradation characteristics and possibilities for sustained drug delivery. It's by-products should be toxicologically safe and are easily eliminated by the normal metabolic pathways. The polymer used must be able to deliver its payload with appropriate duration, bio-distribution and concentration for the intended therapeutic effect.

Choice of solvent/co-solvent system

The solvent system chosen should be able to dissolve the chosen polymer. Poorly soluble in the continuous phase. High volatility and a low boiling point with low toxicity.

Other components

a. **Porosity generator:** increases degradation rate of polymer and improves drug release. e.g. Incorporating sephadex into insulin-loaded polylactide microspheres significantly increases microsphere porosity [37].

b. **Surfactants:** They reduce the surface tension of continuous phase. Avoid the coalescence and agglomeration of drops. Stabilize the emulsion, widely used surfactants include; non-ionic: methylcellulose, tween, span. Anionic: sodium dodecyl sulphate. Cationic: cetyl tri methyl ammonium bromide (CTAB).

c. **Antifoaming agents:** foaming problem will disturb the formation of microspheres. Anti-foams of silicon such as dimethicone and non-silicon constituents such as spans are used.

Applications of Magnetic Microspheres

a. Magnetic microsphere carriers have received considerable attention, because of their wide applications in the fields of biomedicine and bioengineering, biological and biomedical developments and trends such as enzyme immobilization, cell isolation, protein purification, and target drugs [4,38].

b. Magnetic vehicles are very attractive for delivery of therapeutic agents as they can be targeted to specific locations in the body through the application of a magnetic field gradient. The magnetic localization of a therapeutic agent results in the concentration of the therapy at the target site consequently reducing or eliminating the systemic drug side effects [4,39].

c. Magnetic microspheres are used in targeting drugs like mitoxantrone, paclitaxel [32] and doxorubicin [1,2] to tumor sites. Magnetic microsphere carriers labeled with radionuclide such as Rhenium-188 and Yttrium-90 have been also used in a preclinical study to treat liver and brain tumors [40].

d. Magnetic microspheres of cisplastin and paclitaxel were used in localized hyperthermia for treatment of cancer [41].

e. Magnetic microspheres can be used for stem cell extraction and bone marrow purging [42].

f. Magnetic polystyrene microspheres have been used as specific cell labeling [43].

g. Improvement in methods for isolating DNA, proteins, cells or cell organelles has been made and more recently, methods that rely on the use of solid phase have been proposed. Adsorbents such as silica that provide fast, efficient DNA purification are important for making this procedure amenable to automation. One of these kits involves isolation of DNA using silica coated magnetic particles [44].

h. Nowadays, several instruments are available from different companies that couples separation of biomolecules with its detection in terms of its quantification or its interactions with other biomolecules. These instruments either use directly ferromagnetic particle as label (magneto assay) or couples magnetic particles with other detection methods such as fluorescence or chemiluminescence [45].

i. Magnetic microspheres are now increasingly used as carriers for binding proteins, enzymes and drugs. Studies have shown that proteins and enzymes can be bound covalently to naked magnetic particles in the presence of carbodiimide. Such immobilization procedures for proteins, enzymes or drugs will have a major impact in various areas of medicine and biotechnology. The immobilized biomolecules can be used directly for a bioassay or as affinity ligands to capture or modify target molecules or cells [46].

j. Streptavidin coated magnetic beads were used for bacteria detection [47].

k. Supra-magnetic iron oxide microspheres have been used for detection of metastases in non-enlarged lymph nodes [48].

l. Magnetic Dynabeads have been used in immune-magnetic techniques for the enrichment and detection of isolated breast carcinoma cells in bone marrow and peripheral blood [49].

m. Magnetic microspheres carriers of contraceptive has been designed responsive to the changes in steroid secretions during menstrual cycle [50].

Future Prospects

Future prospects of magnetic microspheres look bright particularly in the area of medicinal field because of its wide spectrum of application in molecular biology, e.g. microsphere based genotyping platform is used to detect six single nucleotide polymorphism, yittrium-90 microspheres are used to prevent tumor after liver transplantation and its advanced way in delivery of vaccines and proteins [1]. It might be possible in near future that magnetic particles would be used as detection probes for a variety of assays, replacing labeling techniques such as fluorescence, chemiluminescence and radioactivity. Future work shall involve developing a detection method for bio-molecular interaction using magnetic particles as label. The method that is planned to be developed would have special emphasis in microarray technology, where bio-molecular interactions like cDNA-mRNA or DNA-DNA are the basis for determining gene expression or allelic variation [47].

Conclusion

It has been observed that magnetic microspheres are among the best novel drug delivery systems, as it has the advantage of target specificity and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumors, detecting bio-molecular interaction etc. So in future by combining various other strategies, magnetic microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

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Citation: Farah FH (2016) Magnetic Microspheres: A Novel Drug Delivery System. J Anal Pharm Res 3(5): 00067. DOI: 10.15406/japlr.2016.03.00067