World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

MAGNETIC MICROSPHERE-A NOVEL APPROACH IN TARGETED DRUG DELIVERY SYSTEM

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Article Received on 30/10/2019 **Article Revised on 20/11/2019** **Article Accepted on 10/12/2019**

ABSTRACT

Recently a number of novel drug delivery systems have emerged with various routes of administration, minimize the drug degradation, to prevent side effects, desired drug concentration and to achieve controlled and targeted Drug delivery. Magnetic microspheres hold great promise in reaching the goal of controlled and site specific drug delivery. The magnetic properties of these particles add a new dimension upon application on an external magnetic field. Magnetic microspheres are supra molecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4micrometer). Magnetically targeted drug delivery by particulate carriers is an efficient method of delivering drugs to localized sites such as tumors. High concentration of chemotherapeutic or radiological agents can be achieved near the target site, without any toxic effects to normal surrounding tissues. These are various methods used to prepare magnetic microspheres along with different evaluation parameters. The review entails the current application of magnetic microspheres, as well as future prospects and problems to be overcome for the efficient and beneficial use of the magnetic microspheres.

KEYWORDS: Magnetic microspheres, magnetic targeting, drug targeting, supra molecular microspheres, applications, supramolecular particles.

INTRODUCTION

Microsphere can be defined as the particles that flow freely and are encapsulated spherical drug particle that deliver their action on target site with a probable concentration on a desired interest. They are consisting of synthetic polymers or proteins size between 1-1000µm. They not only prolong the release of the drugs but also control drug release Microsphere can also be classified as magnetic microsphere, floating microsphere, polymeric microsphere, bio adhesive microspheres, radioactive microsphere, bio-degradable microsphere and synthetic microspheres.[1] Drug targeting is the delivery of drugs to receptors or organ or any other specific part of the body to which one wishes to deliver the drug exclusively. Scientifically, it is extremely challenging, as the goal is to find a drug-delivery system with the capability for site-specificity as well as controlled release.[2] Magnetic Drug Targeting means the specific delivery of chemotherapeutic agents to their desired targets, e.g. tumors by using magnetic nanoparticles (ferrofluids) bound to these agents and an external magnetic field which is focused on the tumor. 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.[3,4] 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.[5] A drug or therapeutic radio isotope is encapsulated in a magnetic compound, injected into patient's blood stream through large arteries and then stopped with a powerful magnetic field in the target area. Depending on the type of drug, it is then slowly released from magnetic carriers and gives a local effect, thus it reduces the loss of drug as freely circulating in body.

When the microspheres are first pushed against the endothelial cells by the magnetic field, an endocytic response was triggered with continuous magnetic influence over certain period of time. Microspheres migrate from endothelial cells into the interstitial compartment and form a depot for sustained release over an extended period .Magnetic carriers receive their magnetic responsiveness to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt, and neodymium-iron-boron or samarium- cobalt. Magnetic microsphere were developed to minimize renal clearance and to increase target site specificity.[6] Magnetism has application in numerous fields like

diagnostics, drug targeting, molecular biology, cell isolation, cell purification, hyperthermia, and radioimmunoassay. Magnetic particles, ranging from nanometer-size to a micron, are being used in an increasing number of medical applications. The important properties of magnetic particles for medical applications are non- toxicity, bio-compatibility, and high- level accumulation in the target tissue or organ. Magnetic nanoparticles modified with organic molecules have been widely used for biotechnological and biomedical applications as their properties can be magnetically controlled by applying an external magnetic field.[7]

Magnetism plays an important role in non-magnetic micro carrier which show poor site specificity and are rapidly cleared off by RES under normal circumstances, magnetic particles composed of magnetite which are well tolerated by the body, and magnetic fields are believed to be harmless to biological systems and adaptable to any part of the body [8]. Up to 60% of an injected dose can be deposited and released in a controlled manner in selected non reticuloendothelial organs. Magnetic micro carriers were developed to overcome two major problems encountered in drug targeting namely RES clearance and target site specificity.[9]

Principle of Magnetic Targeting

Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to a localized disease site. Very high concentrations of chemotherapeutic or radiological agents can be achieved near the target site, such as a tumor, without any toxic effects to normal surrounding tissue or to the whole body. Figure 3 highlights the concept of magnetic targeting by comparing systemic drug delivery with magnetic targeting. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into a patient's blood stream, and then stopped with a powerful magnetic field in the target area (Figure 1). Depending on the type of drug, it is then slowly released from the magnetic carriers (e.g., release of chemotherapeutic drugs from magnetic micro-spheres) or confers a local effect (e.g., irradiation from radioactive microspheres; hyperthermia with magnetic nanoparticles). It is thus possible to replace large amounts of freely circulating drug with much lower amounts of drug targeted magnetically to localized disease sites, reaching effective and up to several-fold increased localized drug levels.

When 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 (Figure 2). The accumulation of the carrier at 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 characteristics, field strength, and blood flow rate etc. The magnetic field helps to extravagate the magnetic carrier into the targeted area (Figure 3).[10,11]

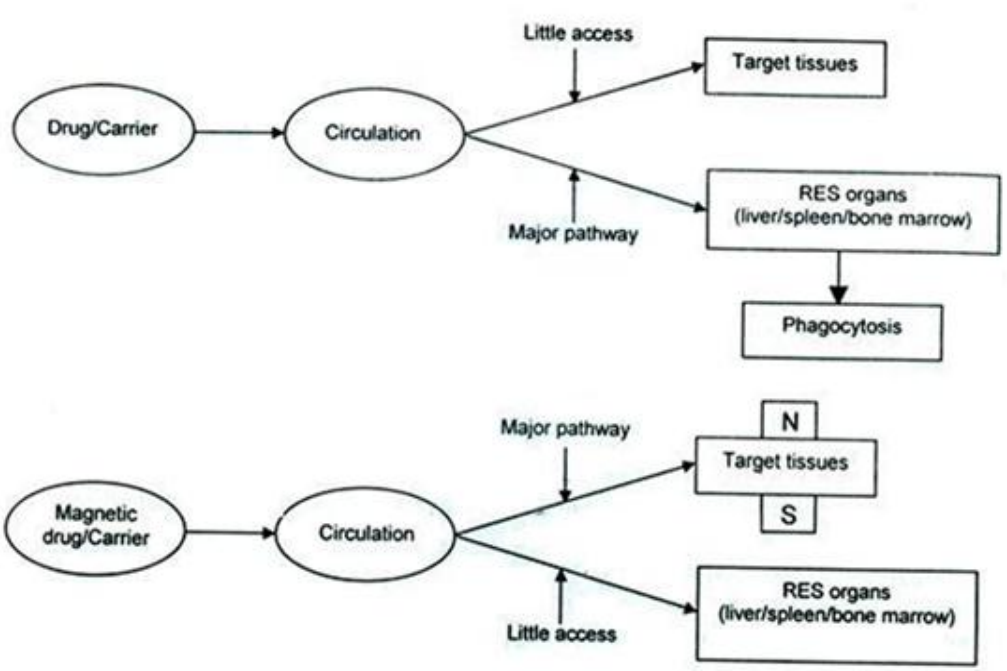

Figure 1: Principle of magnetic drug targeting.

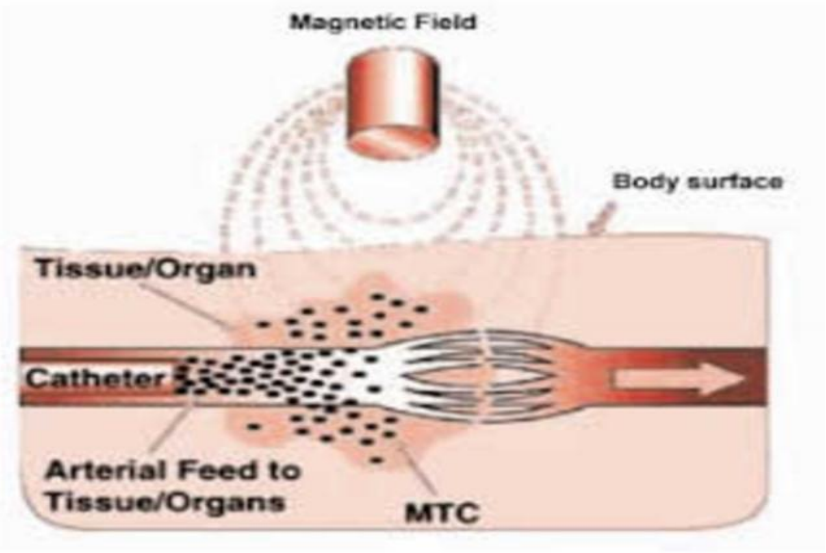

Figure 2 Drug targeting using MTCs. MTCs are composite of elemental iron and activated carbon with anticancer.

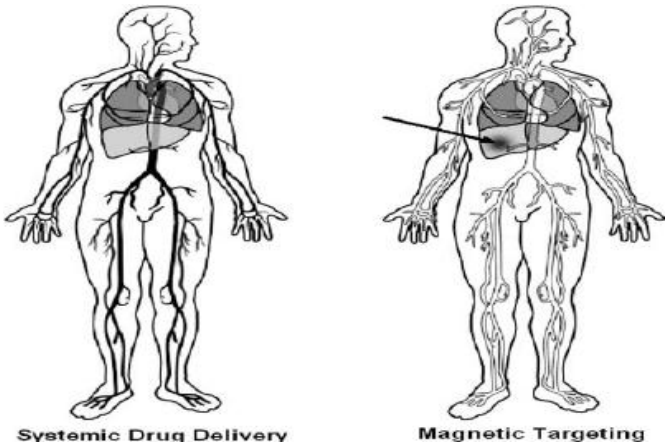

Figure 3: Representation of systemic drug delivery and magnetic targeting.

Advantages of Magnetic Microsphere

- Magnetic micro carriers are site specific and by localization of these micro carriers in the target area, the problem of their rapid clearance by RES is also surmounted.
- This drug delivery system reduces circulating concentration of free drug by a factor of 100 or more. Injected into the body due to the spherical shape and smaller size.
- Controlled and predictable rate of drug release with smaller doses of drug can be achieved. In case of tumor targeting, microsphere can internalize by tumor cells due to its much increased phagocytic activity as compared to normal cells [12, 13, 14].
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects. Microsphere morphology allows a controllable variability in degradation and drug release [15].
- Reduce the dosing frequency there by improve the patient compliance. First pass effect can be avoided and reduce toxicity,
- Bitter taste and smell can be masked and physical stability can be improved.
- Stabilization of gastric enzyme and reduce irritation of gastric area [16, 17].

Disadvantages of Magnetic Microspheres

- Toxicity of magnetic beads can occur in liver and the regions of RES, unknown localization of drug are seen.
- The dangerous effect of self-flocculation of the magnetic particle and thrombosis occur at the site of catheterization. It needs specialized magnet for targeting, for monitoring, and trained personnel to perform procedures
- The magnet must have relatively constant gradients in order to avoid local overdosing with toxic drugs. Due to this limitation magnetic drug targeting is likely to be approved only for very severe diseases that are refractory to other approaches.
- Magnets must have relatively constant gradients, in order to avoid focal over dosing with toxic drugs. A large fraction of the magnetite, which is entrapped in

carriers, is deposited permanently in tissues.

- Removal is difficult once injected. It is expensive technical approach and requires specialized manufacture and quality control system.
- Interaction and formation of complexes with blood components can occur due to parenteral delivery. Magnetic microspheres cannot be crushed or chewed.[18]

Types of Magnetic Microsphere

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

1. **Therapeutic microspheres** that are used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system (WWW.pharmainfo.net/review/ bioadhesivemicrospheres-review).
2. **Diagnostic microspheres** that can be used for imaging liver metastases and also to distinguish bowel loops from other abdominal structures by forming Nano size supramagnetic iron oxide particles.[19]

Factor Affecting Magnetic Targeting of Drug

Factors related to ferrofluids, Size of the particles in ferrofluid, Surface characteristics of particles, Concentration and Volume of the ferrofluid, Reversibility and strength of drug/ferrofluid binding (desorption characteristics), Access to the organism (infusion route), Duration or rate of injection/infusion, Geometry, strength and duration of the magnetic field application, Physiological parameters related to patient (or animal),Size, weight and body surface of patient (or animal),Total blood volume, Cardiac output and systemic vascular resistance, Circulation time, Tumor volume and location, Vascular content of tumor and Blood flow in tumor.

Magnetic Properties of Microsphere

Magnetic particle 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 consists 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. These particles are non-magnetic when an external magnetic field is applied, and develop a mean magnetic moment in an external magnetic field (Figure.5).

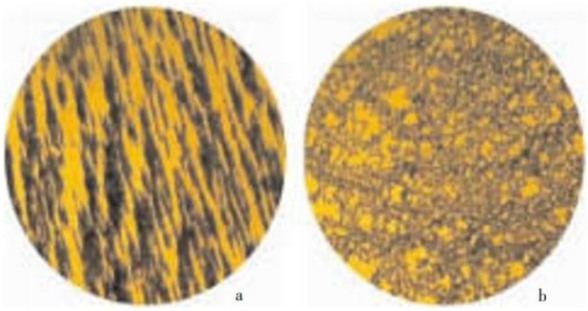

Figure 4: Ferromagnetic particles.

a) Under the influence of external magnetic field; (b) in absence of an external magnetic field (slideshare.net).

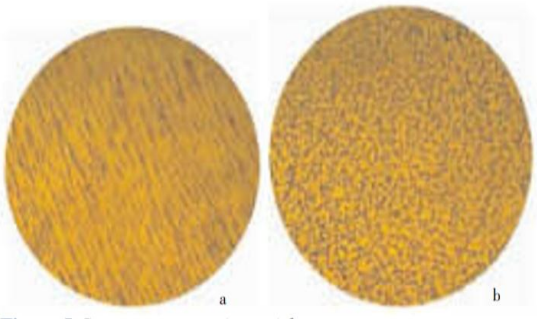

Figure 5: Super magnetic particles.

A. Under the influence of external magnetic field B. in absence of an external magnetic field, monodisperse particle distribution (researchgate.net).

The ferromagnetic particles are those particles having a permanent mean magnetic moment.

The super paramagnetic and ferromagnetic particles are generally recommended for automatic DNA/RNA separation/ purification (Figure 4).[20]

Magnetically Modulated Micro Carriers

Magnetic micro carriers are site specific and by localization of these micro carriers in the target area, the problem of their rapid clearance by RES is also surmounted. Magnetic carriers' technology appears to be a significant alternative for bio molecular malformation (i.e, composition inactivation or deformation).These micro carriers include

A) Magnetic microspheres

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4 m) but are sufficiently susceptible (ferromagnetic) to be captured in micro vessels and dragged in to the adjacent tissues by magnetic fields of 0.5-0.8 tesla (T). Magnetic microspheres were prepared by mainly two methods namely phase separation emulsion polymerization (PSEP) and continuous solvent evaporation (CSE). The amount of drug and magnetite content of microspheres

needs to be delicately balanced in order to design an efficient therapeutic system.

B) Magnetic liposomes

Liposomes are simple microscopic vesicles in which lipid bilayer structures are present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecule. There are a number of components present in liposomes, with phospholipids and cholesterol being the main ingredients but in case of magneto liposomes magnetite is one of the component of the liposomes. Generally these are magnetic carrier which can be prepared by entrapment of Ferro fluid within core of liposomes. Magneto liposome can also be produced by covalent attachment of ligands to the surface of the vehicles or by incorporation of target lipids in the matrix of structural phospholipids . These magneto liposomes were effectively used for site specific targeting, cell sorting and as magnetic resonance contrast enhancing agent. Thermo sensitive magneto liposomes can release the entrapped drug after selective heating caused by the electromagnetic fields.[21]

C) Magnetic nanoparticles

Magnetic nanoparticles (MNPs) possess unique magnetic properties and the ability to function at the cellular and molecular level of biological interactions making them an attractive platform as contrast agents for magnetic resonance imaging (MRI) and as carriers for drug delivery. MNPs with higher magnetic moments, non-fouling surfaces, and increased functionalities are now being developed for applications in the detection, diagnosis, and treatment of malignant tumors, cardiovascular disease, and neurological disease .The important properties of magnetic particles for medical applications are non-toxicity, biocompatibility, injectability and high-level accumulation in the target tissue or organ .Furthermore, a novel application of magnetic nanoparticles and magnetic forces for tissue engineering, termed 'magnetic force-based tissue engineering' has been proposed.[22]

D) Magnetic Resealed Erythrocytes

Resealed erythrocytes have various advantages as drug carriers such as it is biodegradable, biocompatible, large variety of material can be encapsulated within small volume of cell and can be utilized for organ targeting etc. Due to these advantages of resealed erythrocytes, magnetic resealed erythrocytes came in to existence which contains ferrofluids (magnetite) along with loaded drugs within the cell.[23] The loaded erythrocytes were characterized for in vitro drug efflux, hemoglobin release, morphology osmotic fragility, in vitro magnetic responsiveness and percent cell recovery.

E) Magnetic emulsion

The emulsion is magnetically responsive oil in water type of emulsion bearing a chemotherapeutic agent which could be selectively localized by applying an external magnetic field to specific target site [24]. Magnetic emulsion appears to have potential in conferring site specificity to certain chemotherapeutic agent.

F) Magnetically Modulated System and Devices

Magnetically modulated polymeric controlled drug delivery systems that deliver the drugs at increased rate on demand have been developed extensively in recent years These system consist of polymeric matrix where the drug powder is dispersed. The polymeric matrix is generally composed of ethylene vinyl acetate copolymer (EVAc), with someone magnetic beads. These systems are formulated by adding approximately 50% of drug polymer mixture to a glass mould, which is cooled to -8^{o}C using dry ice, then the magnetic particles, are added followed by the remaining drug polymer mixture. An oscillating external magnetic field, which is generated by a device that rotates the permanent magnets below the vials, controls the release rates.

G) Magnetically Modulated, Implantable, Hemispheric Drug Delivery Device

Polymeric drug delivery devices associated with a magnetically operated or triggered mechanism can improve the release rates of macromolecules from the polymeric controlled drug delivery devices. When external magnetic field is applied, it tends to release the drug at higher rate under the activation.

H) Magnetic System in Contraceptive Drug Delivery

In these magnetically controlled systems, the drug and small magnetic beads are uniformly dispersed within a polymer material. On exposure to aqueous media, the drug is released in a diffusion controlled manner. Moreover, the rate can be increased or modulated on application of an oscillating external magnetic field. These systems may be useful when drug delivery is designed in responsive to the changes in steroid secretion during menstrual cycle.

I) Magnetically Programmable Infusion Pumps

Magnetic technology is widely used for external programming of pacemakers. The sample principle was adapted to an implantable infusion pump. The development of such pumps to a prototype stage, the newer method of radiofrequency signaling could improve the magnetic approach because of greater programming flexibility and bio directional transmission capability.

Synthetic polymer

Examples of Biodegradable synthetic polymers are Glycolides, epoxy polymers and example for Non – Biodegradable synthetic polymers are Polyanhydride, lactide, poly-methylmetharylate, acrolein.[25,26]

Natural Polymer

Examples of protein as natural polymers are Albumin, gelatin, collagen, examples of. Carbohydrate natural polymers are Agarose, starch, chitosan; examples of

chemically modified carbohydrate are polydextran, and polystarch

Some Example of the Drugs used in the preparation of Magnetic microspheres is Dexamethasone, Indomethacin, Oxantrazole, Diclofenac sodium, 5-fluorouracil, Nimesulide, Verapamil hydrochloride

METHOD OF PREPARATION OF MAGNETIC MICROSPHERES

Selection of drugs: In the selection of a drug for formulation of magnetic microspheres, following points are taken into consideration:-

- The drug is not so dangerous or labile that we cannot allow it to circulate freely in the blood stream.
- The agent is so expensive, that we cannot afford to waste 99.9% of it.
- Requires a selective, regional effect to meet localized therapeutic objective.
- Requires an alternative formulation to continue the treatment in patient whose systemic therapy must be temporarily discontinued due to life threatening toxicity at selective organs.

Methods

Solvent Evaporation Method

In this method the drug and polymer (Carrier) are dissolved in appropriate volatile organic solvent and then magnetite is added to this solution along with stirring in order to form a homogeneous suspension. The resulting solution is then homogenized and stirred at a temperature in the range of 22-30^{o}C. The formed magnetic microsphere is separated by centrifugation. The product is then freeze dried and then stored at 4^{o}C.

Phase Separation Emulsion Polymerization Method

Homogenous aqueous suspension is prepared by adding albumin water-soluble drug and agent with magnetite in 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 protein sphere thus formed in the emulsion are stabilized either by heating at 100- 150°C or by adding hydrophobic cross linking agents like formaldehyde, glutraldehyde, microspheres thus produced are centrifuged out and washed either in ether or some other appropriate organic solvent to remove excess of oil. Microspheres are freeze dried and stored at 4°C.[27,28]

Multiple Emulsion Method

It involves the formation of the multiple emulsions type of w/o/w and is best suited to water soluble drugs, like 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 then subjected to homogenization or sonication before addition to the aqueous solution. This results in the formation of a multiple emulsion which is then subjected to solvent removal either by solvent evaporation or by solvent extraction.[29,30] (Figure 6)

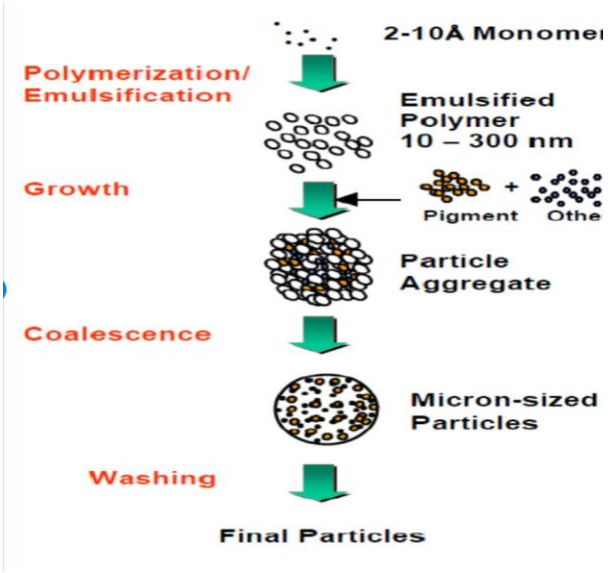

Figure 6: multiple emulsion method.

Cross Linking Method

Reagents used: Acetate buffer–used as solvent for the chitosan polymer; Glutraldehyde-used as the cross-linker; Sodium solution-used as medium. Synthesis of magnetic fluid: A 35% (w/v) ferrous sulfate solution, 54% (w/v) ferric chloride solution and 36% (w/v) sodium hydroxide solution were prepared using distilled water. Then the ferric salt and ferrous salt were mixed, stirred and heated. When the temperature reached 55°C, the alkaline solution was added. The mixture was stirred for 30 min and then polyethylene glycol-10000 (PEG-10000) was added. The temperature was raised to 80°C and maintained for 30min. The mixture was then neutralized while cooling and the magnetic fluid was prepared. 1% (w/w) chitosan was dissolved in acetate buffer at pH 4.5. The dissolved chitosan was added drop wise on the magnetic fluid. Formed chitosan magnetic microspheres were washed with deionized water and soaked in 1, 3 and 5 mole% glutraldehyde solution for 2 h and then washed with deionized water.[31]

Alkaline Co-Precipitation Method

Treat poly (acrylic acid–divinylbenzene) microspheres with dilute aqueous sodium hydroxide solution (0.5 M) for hours at suitable temperature to transform the carboxylic acid groups to sodium carboxylates and then washed thoroughly with water to remove the excess sodium hydroxide till neutral ph. Purged the microsphere suspension with nitrogen for 30 min. To this suspension add an aqueous solution of ferrous chloride and Ferric chloride that had been purged with nitrogen. The mixture was stirred overnight under nitrogen atmosphere for ion

exchange. The resulting microspheres were washed repeatedly with water under nitrogen atmosphere to remove excess iron salts. Added drop wise aqueous NaOH solution (3M) to a suspension of the microsphere taken up with iron ions under nitrogen atmosphere to adjust the pH value to be > 12. The mixture was then heated to 60^{o}C and kept for another 2 h. The resulting magnetic microsphere were suspended in an aqueous HCL solution (0.1M) to transform the –COONa to COOH and then washed thoroughly with water to neutral pH, dried under vacuum at 50°C overnight giving magnetic microsphere.[32]

Inverse Phase Suspension Polymerization Method

A 250ml three-neck flask fitted with a mechanical stirrer used for performing the reaction. Continuous phase includes: 100 ml of castor oil and 10 ml of span 80. Determined (DVB) and N, N-Methylene-bisacrylamide (BIS) dissolved completely in DMSO and the organic phase was added drop wisely into the flask, with 70°C heating using an oil bath. Ammonium per sulfate (INITIATOR) added drop wise using a syringe. The reaction proceeded for 8 h with continuous stirring. The resulting microspheres were separated by centrifugation. Further washed with diethyl ether and then by deionized water.[33]

Sonochemical Method

Bovine serum albumin, albumin are used. Decane and iron pentacarbonyl Fe_2 (CO) $_3$ are layered over a 5% w/v of protein solution. The bottom of the high – intensity ultrasonic horn is positioned at the organic interface. The mixture is irradiated for 3 min, employing particular acoustic power with the initial temperature of 23^{o}c in the reaction cell. The pH is adjusted to 7 by addition of Hydrochloric acid. Products are separated from the unreacted protein and from the residues of iron acetate or pentacarbonyl by centrifugation (1000 r/min for 5 min), washing is done and the magnetic microspheres are obtained .The magnetic microspheres were washed a few times with sufficient volumes of water to remove the residues of the precursors.

Swelling and Penetration Method

For swelling of polymer micro particles, PS (Micron-size polystyrene) was mixed with of a NMP/water solution in a specific v/v NMP (N-methyl-2- pyrrolidone)-to-water ratio. The NMP/water mixture with PS spheres was left soaking for 24 hours at room temperature while stirring. Super paramagnetic nanoparticle dispersion was added to the mixture of PS sphere and NMP/water solution at 30°C while shaking (at 140 r/min) for 1-5 days to allow the magnetic nanoparticles to penetrate into the interior of the PS particles. Afterwards, the polymer particles were separated from the solution by centrifugation. Finally, particles were sequentially washed with methanol, deionized water and vacuum dried at room temperature for 1-2 days to yield the magnetic polymer microspheres.[34]

Characterization and Evaluation of Magnetic Particles

Particle size and shape

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. 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.[35]

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).[36] FTIR studies for drug excipient interaction were carried out by Potassium Bromide pellet method.

Thermal Analysis

Thermal analysis of microcapsule and its component can be done by using differential scanning calorimetric (DSC), thermo gravimetric analysis (TGA), differential thermometric analysis (DTA) accurately the sample was weighed and heated on alumina pan at constant rate of 10c/min under nitrogen flow of 40ml/min.[37]

Percentage yield

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula, Percentage yield = (Weight of microspheres/Weight of polymer + drug) ×100.

Swelling index

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. Swelling index = mass of swollen microsphere -mass of dry microsphere/mass of dried microsphere×100.

Flow properties

Bulk density 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. Tapped density was 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 is the ratio of the tapped density to the bulk density of microspheres and can be used to predict of microspheres flow. Hausner ratio of < 1.2 indicates a free flowing microsphere. Angle of repose is defined as the maximum angle to the

horizontal that is attainable by a heap of microspheres.

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 and the lysate is then subjected to the determination of active compound. The percent encapsulation efficiency is calculated using following equation: % Entrapment = (actual content/theoretical content) x 100.

Surface charge analysis

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 electrophoretic mobility can be related to surface contained charge and ion absorption nature of the microspheres.[37]

Drug release profiles (In vitro and In vivo methods)

The release characteristics and permeability of a drug through membrane is to be determined. Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both paddle and basket method. Dissolution medium used for the study varied from 100-500ml and speed of rotation from 50-100rpm.The most widely used in-vivo methods are the use of animal models, buccal absorption tests, other tests like in vitro – in vivo correlations, percent of drug dissolved vs plasma concentration, percent of drug dissolved vs percent of drug absorbed, dissolution time vs absorption time, percent of drug dissolved vs percent of the dose excreted, and percent of drug dissolved vs Serum drug concentration.[37]

Determination of microspheres drug content or entrapment efficiency

Accurately weighed amount of microspheres are crushed using glass mortar and pestle and 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.[38]

Differential scanning calorimetry

The DSC analysis of pure drug, drug-loaded microspheres and blank microspheres without drug were carried out using Shimadzu DSC 60 to evaluate any possible drug polymer interaction. The analysis was performed at a rate 10 degree C 1 min. from 20-300 degree C temperature range under nitrogen flow of 25ml per min.

Scanning electron microscopy

A scanning electron microscope was used to characterize the surface morphology of the microspheres. A scanning electron photomicrograph of drug-loaded microspheres was taken. A small amount of microspheres was spread on glass stub. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber. The scanning electron photomicrograph was taken at the acceleration voltage of 10 kV, chamber pressure of 0.6 mm Hg, original magnification 500.11.

Stability studies

Stability studies were carried out as per ICH Guidelines. The microspheres were stored at 40 degree c ±2ºC/75% RH ± 5% RH for 6 months. The formulations were analyzed for appearance, entrapment efficiency and drug content.

Application of Magnetic Microsphere

- 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.
- 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.[39]
- Magnetic microspheres are used in targeting drugs like mitoxantrone, paclitaxel and doxorubicin 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]
- Magnetic microspheres of cisplastin and paclitaxel were used in localized hyperthermia for treatment of cancer.[41]
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging
- Magnetic polystyrene microspheres have been used as specific cell labeling.[42]
- 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.
- 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.[43]
- 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.[44]

- Streptavidin coated magnetic beads were used for bacteria detection.[45]
- Supra-magnetic iron oxide microspheres have been used for detection of metastases in non-enlarged lymph nodes.[46]
- 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.
- Magnetic microspheres carriers of contraceptive have been designed responsive to the changes in steroid secretions during menstrual cycle.

Storage

Microsphere suspensions should not be frozen, as freezing is likely to cause irreversible aggregation. Cold storage (2-8°C) is recommended to inhibit microbial growth. 'Standard' (non-protein coated) microsphere suspensions do not contain an antimicrobial agent. All suspensions should be handled using aseptic technique. Continuous rolling (e.g. 3-5 r/min on a cell culture roller) is recommended to keep microspheres in suspension, without generating foam (foam may cause particle loss through bead entrapment). If continuous rolling is not possible, particles should be thoroughly resuspended before use. Higher speed rolling (30-60 r/min for 2-4 h) is effective for the resuspension of settled material. Again, rolling speed is intended to effectively resuspend the beads without generation of foam.

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. 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 variation.

CONCLUSION

Targeting by means of magnetic fields seems to be a vital and most common function of opening a new vista of a multi-barrier of multi-step drug delivery. Their main advantage is the targeting of drug using an external magnet, which can be accomplished very easily thus Reticuloendothelial clearance can be minimized and target site specificity can be increased. Magnetic microspheres are novel drug delivery systems, having received attention from the early 1990s. Thus magnetic microspheres have the great potential for these objectives. It is also emerging as a challenging area for future research in the drug targeting, long term toxicity study, and characterization will ensure the improvement of magnetic drug delivery system. This is an effective tool for the cancer patients. The future holds lot of promises in magnetic microspheres and by further study this will be developed as novel and efficient approach for targeted drug delivery system. The review on magnetic microsphere concluded that it is the well developed new drug delivery system for targeting of drug in chronic diseases. It is safe and advantageous drug delivery system. The materials which are used in methods of preparation are economic and nontoxic in nature so it is most convenient drug delivery system.

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