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Magnetic microspheres as magical novel drug delivery system: A review

Satinder Kakar[1*], Deepa Batra[1], Ramandeep Singh[2], Ujjwal Nautiyal[2]

[1]*Department of Pharmacy, Doon valley Institute of Pharmacy & Medicine, Karnal (Haryana)*
[2]*Department of Pharmacy, Himachal Institute of Pharmacy, Paonta Sahib (H.P)*

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ABSTRACT

Magnetic microspheres hold great promise for reaching the goal of controlled and site specific drug delivery. Magnetic microspheres as an alternative to traditional radiation methods which uses highly penetrating radiations that is absorbed throughout the body. Its use is limited by toxicity and side effects. Now days, several targeted treatment systems including magnetic field, electric field, ultrasound, temperature, UV light and mechanical force are being used in many disease treatments (e.g. cancer, nerve damage, heart and artery, anti-diabetic, eye and other medical treatments). Among them, the magnetic targeted drug delivery system is one of the most attractive and promising strategy for delivering the drug to the specified site. Magnetically controlled drug targeting is one of the various possible ways of drug targeting. This technology is based on binding establish anticancer drug with ferrofluid that concentrate the drug in the area of interest (tumor site) by means of magnetic fields. There has been keen interest in the development of a magnetically target drug delivery system. These drug delivery systems aim to deliver the drug at a rate directed by the needs of the body during the period of treatment, and target the activity entity to the site of action. Magnetic microspheres were developed to overcome two major problems encountered in drug targeting namely: RES clearance and target site specificity.

1. Introduction

Microspheres are free flowing powders consisting of encapsulated (drugs) spherical particles of size ideally less than 125p that can be suspended in aqueous vehicle and injected by an 18 or 16 number needle. Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4 μm) but are sufficiently susceptible (ferromagnetic) to be captured in micro vessels and dragged into the adjacent tissues by magnetic fields of 0.5-0.8 Tesla (T). Methods of preparation of magnetic microspheres 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 therapeutic 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 efficiency; (iii) % magnetite content; (iv) *In vitro* magnetic responsiveness; (v) Drug release.

Targeting by magnetic microspheres i.e. incorporation of magnetic particles in to drug carriers (Polymers) and using an externally applied magnetic field is one way to physically direct these magnetic drug carriers to a desired site[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. Various nonmagnetic micro carriers (nanoparticles, microspheres

*Corresponding author: Satinder Kakar, Doon Valley Institute of Pharmacy & Medicine, Karnal (Haryana), India.
Tel: +91-9017138383
E-Mail: satinder.kakkar5@gmail.com

and micro particles etc.) are successfully utilized for drug targeting but they show poor site specificity and are rapidly cleared off by RES (reticuloendothelial system) under normal circumstances. Magnetism plays an important role in these cases, magnetic particles composed of magnetite which are well tolerated by the body, magnetic fields are believed to be harmless to biological systems and adaptable to any part of the body[2]. Up to 60% of an injected dose can be deposited and released in a controlled manner in selected non reticuloendothelial organs. So magnetic micro carriers 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 radioimmunoassay[3].

2. Concept of targeting of non magnetic targeting versus magnetic targeting

Table 1 shows comparison of magnetic and non magnetic targeting.

3. Concept and principle behind magnetic targeting

Magnetic drug delivery by particulate carriers is an efficient method of drug delivery to a localized disease site. A drug or therapeutic radioisotope is encapsulated in a magnetic compound; injected into patient's blood stream & then stopped with a powerful magnetic field in the target area. Figure 1 shows representation of systemic drug delivery and magnetic targeting. Depending on the type of drug, it is then slowly released from magnetic carriers or confers a local effect, thus it reduces the loss of drug as freely circulating in body[4]. 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 organ structure, a cell, subsetor even an intercellular region. Figure 2 shows magnetic drug targeting.

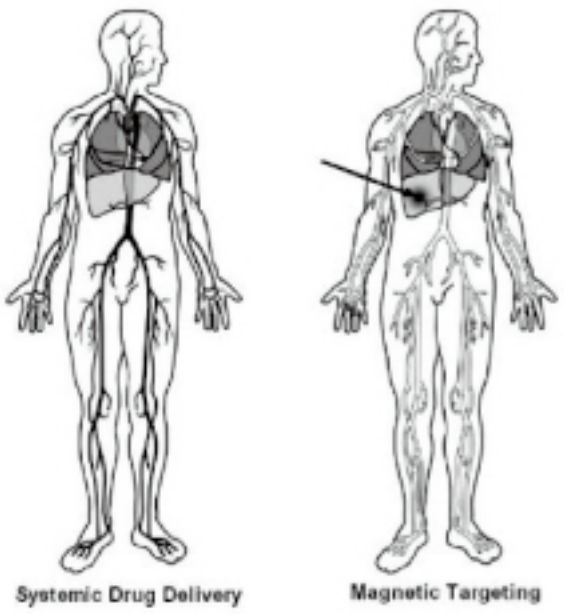

Figure 1. Representation of systemic drug delivery and magnetic targeting.

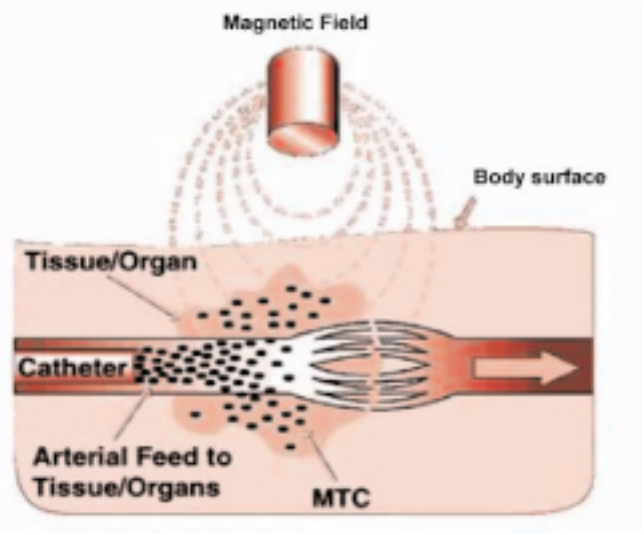

Figure 2. Magnetic drug targeting.

3.1. Approaches of targeting

Five different approaches of targeting are: (i) Chemical approach–prodrug; (ii) Compartment delivery; (iii) Natural targeting; (iv) Ligand mediated targeting; (v) Physical

Table 1
Comparison of magnetic and non magnetic targeting.

S. No.	Non magnetic targeting	Magnetic targeting
1.	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.
2.	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.
3.	No effect of magnetic field.	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.

approach of targeting.

3.2. Principle of magnetic drug targeting & principle of magnetic drug targeting in cancer

Principle of magnetic drug targeting & principle of magnetic drug targeting in cancer are shown in Figures 3 & 4.

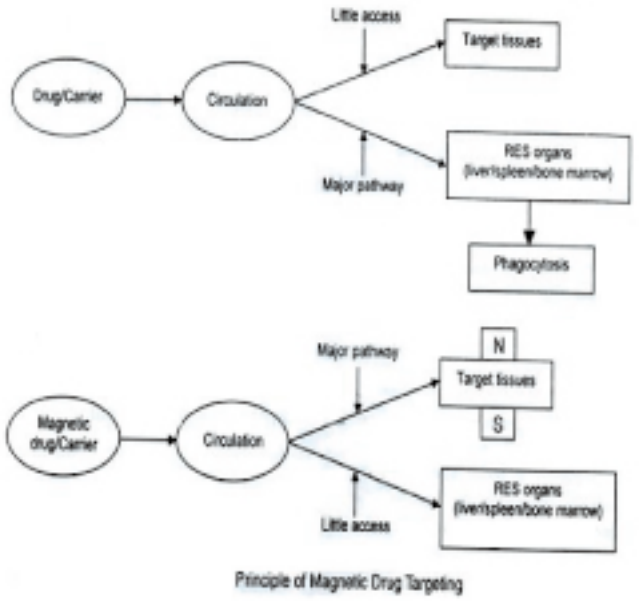

Figure 3. Principle of magnetic drug targeting.

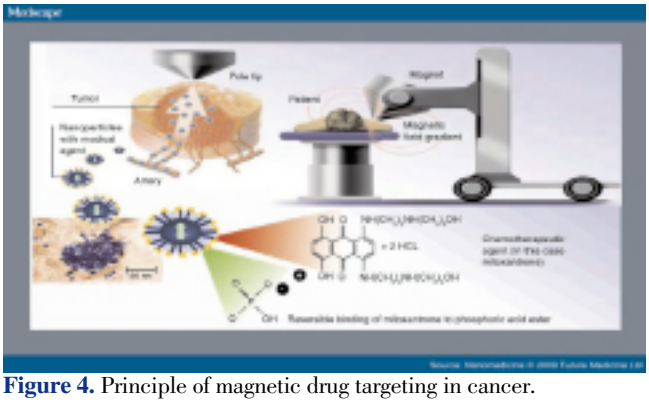

Figure 4. Principle of magnetic drug targeting in cancer.

4. Magnetic properties

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.

4.1. Super para magnetism

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 5)[5].

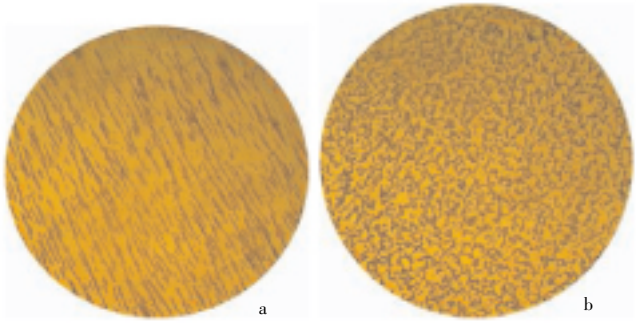

Figure 5. Super paramagnetic particles.
(a) under the influence of external magnetic field; (b) in absence of an external magnetic field, monodisperse particle distribution.

4.2. Ferromagnetism

Ferromagnetism means that the particles have a permanent mean magnetic moment. Here, the larger effective magnetic anisotropy suppresses the thermally activated motion of the core moments. Ferromagnetic particles are generally recommended for the separation of DNA/RNA (SiMAG/MP-DNA) (Figure 6)[6].

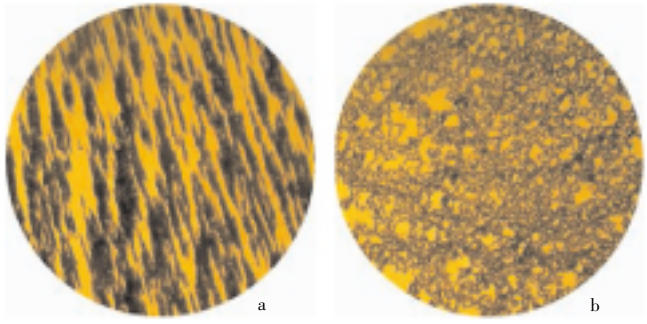

Figure 6. Ferromagnetic particles.
(a) under the influence of an external magnetic field; (b) in absence of an external magnetic field.

5. Magnetite

Also called as ferric ferrous oxide, tri iron tetra oxide, and black iron oxide. Magnetic iron oxide chemical formula $FeOfe_20_3$ having a molecular weight of 231.55 with a chemical composition of Fe=72.36%, O=27.64%.

The Ferro magnetic material when incorporated into microspheres makes them magnetically responsive, so that they can be concentrated to the desired site by applying some external magnetic field.

To prepare magnetite, nitrogen gas flushed through 500 mL round bottom flask fitted with condenser. Charged the flask with 8.9 g (0.1 mol) of goethite, 9.94 g (0.05 mol) of $FeCl_2 \cdot 4H_2O$ along with 250 mL deionized water. Added 50

mL of 2 M Sodium hydroxide. Reaction mixture was heated to reflux for 12 h. Its pH fell from 14 (orange) in to 8–9 (black precipitates). Particles washed and air dried[7,8].

6. Materials used in magnetic microspheres

Table 2 shows materials used in preparation of magnetic microspheres[9].

7. Factors regulating drug release from microspheres

(1) The amount bind rate or drug delivery via magnetically responsive microspheres is regulated by varying the size of the microspheres, drug content, magnetic content, and their hydration state and drug release characters of the carrier.

All the factors are inter-related.

(2) Drug content depends on size. Drug content, which in turn is governed by solubility characters of drug and their method of preparation.

(3) Hydration state of magnetic microspheres effects their distribution in the body.

(4) The magnetic content and the magnitude of applied magnetic field govern the retention of microspheres at the target site.

(5) In microspheres with high magnetic content, the external magnetic field strength required is less, but if high magnetic content is present than the space for drug available is less and hence the magnitude of magnetic content and drug should be delicately balanced to have effective therapeutic systems.

Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to a localized disease site. 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[10]. Depending on the type of drug; it is then slowly released from the magnetic microspheres. It is thus possible to replace large amounts of freely circulating drug with much lower amounts of targeted magnetically to locally diseased sites, reaching effective up to several fold increased localized drug levels[11-13].

Figure 7 shows various processes for preparation of magnetic particles viz. precursors, modification of the nanoparticles surface, targeted medicine, super paramagnetic particles preparation, functionalization by active biomolecules.

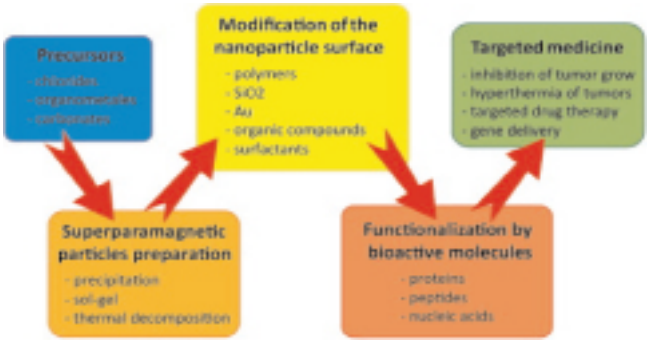

Figure 7. Processes of preparation of magnetic particles.

8. Methods of preparation of magnetic microspheres

8.1. Selection of drugs

In the selection of a drug for formulation of magnetic microspheres, following points are taken into consideration: (i) The drug is so dangerous or labile that we cannot allow it to circulate freely in the blood stream. (ii) The agent is so expensive, that we cannot afford to waste 99.9% of it. (iii) Requires a selective, regional effect to meet localized therapeutic objective.

Requires an alternative formulation essential to continue treatment in patient whose systemic therapy must be temporarily discontinued due to life threatening toxicity directed at selective organs[14].

8.2. Continuous solvent evaporation

In this method the drug and polymer (Carrier) are dissolved in appropriate volatile organic solvent and then magnetite (if magnetic microspheres) is added to this solution along with stirring in order to form a homogeneous suspension. This suspension is added to an immiscible auxiliary solution along with vigorous stirring. Now the volatile organic solvent is evaporated slowly at 22–30 °C to form microspheres. Microspheres are this centrifuged and freeze dried and stored at 4 °C[15-17].

8.3. Phase separation emulsion polymerization

Homogenous aqueous suspension is prepared by adding

Table 2
Materials used in preparation of magnetic microspheres.

S. No.	Material used	Types	Examples
1.	Synthetic polymers	a) Biodegradable b) Non biodegradable	Glycolides, Epoxy polymers, polyanhydrides, Lactides Polymethylmetharylate, Acrolein,Glycidyl methacrylate
2.	Natural polymers	a) Proteins b) Carbohydrates c) Chemically modified carbohydrates	Albumin, Gelatin, Collagen Agarose, Starch, Chitosan Polydextran, Polystarch

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 °C or by adding hydrophobic cross linking agents like formaldehyde, glutraldehyde or 2-3 butadiene, 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[15-17].

8.4. Multiple emulsion method

Water dispersible magnetite with a PEG/PAA coating was added to the BSA-containing inner water phase. 0.2 mL of a 1 mg/mL BSA solution added to a 4 mL mixture of DCM and EA at a ratio of 3 to 1 containing 200 mg of PLGA (first w/o emulsion was prepared using a homogenizer (Polytron PT10-35; Kinematica, Luzern, Switzerland) in an ice bath at 26 000 r/min for 2.5 min). Fifteen mL of a 1% PVA solution poured directly into the primary emulsion and re-emulsified using the same homogenizer under the same conditions for another 2.5 min. W/o/w emulsion immediately poured into a beaker containing 85 mL of 1% PVA solution and stirred in a hood under an overhead Propeller for 2 h, allowing the solvent to evaporate. Solidified microspheres harvested by centrifugation at 2 500 r/min for 10 min and washed with distilled water three times (Figure 8)[18,19].

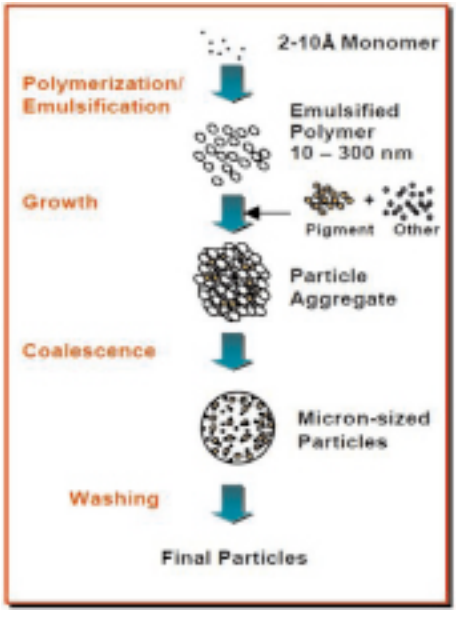

Figure 8. Preparation of microspheres by multiple emulsion method.

8.5. Cross linking method

Reagents used: Acetate buffer-used as solvent for the chitosan polymer; Glutraldehyde-used as the cross-linker; Sodium hydroxide 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 5 g of polyethylene glycol-10000 (PEG-10000) was added. The temperature was raised to 80 °C and maintained for 30 min. 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 mol % glutraldehyde solution for 2 h, and then washed with deionized water[20].

8.6. Alkaline co precipitation method

Treat poly (acrylic acid-divinylbenzene) microspheres with dilute aqueous NaOH 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 NaOH till neutral pH. Purged the microsphere suspension with nitrogen for 30 min. To this suspension add an aqueous solution of $FeCl_3$ and $FeCl_2$ that had been purged with nitrogen. Stirred the mixture 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 an aqueous NaOH solution (3 M) to a suspension of the microspheres taken up with iron ions under nitrogen atmosphere to adjust the pH value to be >12. The mixture was then heated to 60 °C and kept for another 2 h. The resulting magnetic microspheres were suspended in an aqueous HCl solution (0.1 M) to transform the -COONa to -COOH, and then washed thoroughly with water to neutral pH, dried under vacuum at 50 °C overnight, giving magnetic microspheres[21].

8.7. Inverse phase suspension polymerization method

A 250 mL 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 amount of itaconic acid (IA), Styrene (St), divinylbenzene (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 persulfate (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 (Figure 9)[22].

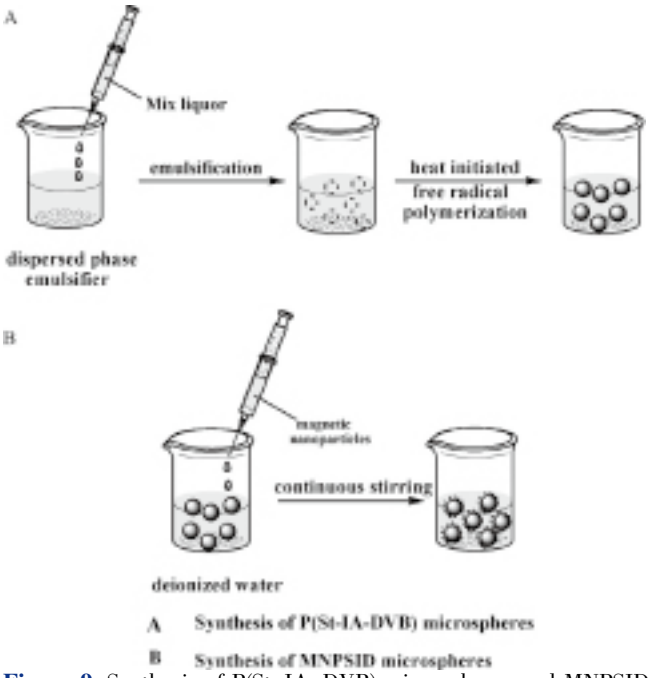

Figure 9. Synthesis of P(St-IA-DVB) microspheres and MNPSID microspheres.
P(St-IA-DVB) microspheres: P(styrene-itaconic acid-divinylbenzene) microspheres.
MNPSID microspheres: Magnetic nanoparticles-coated P (St-IA-DVB) microspheres.

8.8. Sonochemical method

The microspheres composed of iron oxide-filled and coated globular bovine serum albumin (BSA). The magnetic microspheres were prepared from BSA and iron penta carbonyl, or from BSA and iron acetate. Protein microspheres have a wide range of biomedical application, i.e. use as echo contrast agents for sonography. The microsphere were formed by either heat denaturation at various temperatures, or by cross linking with carbonyl compounds in the ether phase. Cross linking was done as: the microspheres are formed by chemically cross-linking cysteine residues of the protein with HO_2 radical formed around a non-aqueous droplet. The chemical cross-linking is responsible for the formation of the microspheres and is a result of the chemical ejects of the ultrasound radiation on an aqueous medium.

Two sonochemical methods for the fabrication of iron oxide nanoparticles were (i) Water as the solvent and (ii) Decalin as solvent.

Decane and iron pentacarbonyl $Fe(CO)_5$ (7.43U1034 M) were layered over a 5% w/v protein solution. The bottom of the high-intensity ultrasonic horn was positioned at the aqueous organic interface. The mixture was irradiated for 3 min, employing a power of W150 W/ 32cm with the initial temperature of 23 °C in the reaction cell. The pH was adjusted to 7.0 by adding HCl. This procedure was performed again with an aqueous solution of iron acetate, $Fe(CH_3CO_2)_2$ 95% (Sigma) (7.66U1033 M). After the synthesis, the products were separated from the unreacted protein and from the residues of iron acetate or iron pentacarbonyl by centrifugation (1 000 r/min for 5 min). The magnetic microspheres were washed a few times with sufficient volumes of water to remove the residues of the precursors[23-26].

8.9. Swelling and penetration method

For swelling of polymer micro particles, 0.25 g of PS (Micron-size polystyrene) particles was mixed with 35 mL of a NMP/water solution in a specific v/v NMP (N-methyl-2-pyrrolidone)-to-water ratio. In later preparations of magnetic microspheres, SDS (Sodium dodecyl sulfate) was added to the NMP/water solution. Whenever SDS was used, 0.025 g of SDS were added to each NMP/water solution. The NMP/water mixture with PS spheres was left soaking for 24 h at room temperature while stirring. 2.5 mL of the superparamagnetic nanoparticle dispersion (24 mg/mL or other specified concentration) 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[27].

8.10. Low-temperature hydrothermal method

0.1 g Fe_3O_4 was dispersed in the aqueous glucose solution without additives, the hydrothermal reaction catalyzed only by Fe_3O_4 was kept at 180 °C for 5 h[28].

9. Comparison between CSE and PSEP

For continuous solvent evaporation (CSE), wide range of chemotherapeutic agent would be covered by CSE technique, due to availability of organic solvent with varying polarity. For phase separation emulsion polymerisation (PSEP), a narrow range of chemotherapeutic agents can be incorporated into microspheres by PSEP because this process required aqueous solubility of the agent to be incorporated into the microspheres is an essential prerequisite for this technique.

10. Characterization of magnetic microspheres

(1) Particle size & size distribution: a) Sieving; b)

Microscopy; c) Coulter counter analysis; d) Laser diffraction analysis.

(2) Surface characterization: a) High-resolution microscopy; b) Scanning electron microscopy; c) Scanning tunneling microscopy.

(3) Surface charge analysis: a) Micro electrophoresis; b) Laser Doppler anemometry.

(4) Density: a) Bulk density [Bulk density (ϱb) (g/cm^3) = M/Vb. Where, M = mass of powder taken, Vb = bulk volume]; b) Tapped density [Tapped density (ϱt) (g/cm^3) = M/Vt. Where, M = weight of sample powder, Vt = tapped volume].

(5) Flow properties: a) Angle of repose [Angle of Repose, θ = tan-1 h / r (Table 3)]; b) Hausner ratio [Hausner ratio = ϱt/ϱb. Where, ϱt = tapped density, ϱb = bulk density].

(6) Drug release profiles: a) *In vitro*; b) *In vivo*.

(7) Surface area

(8) Porosity

(9) Hardness & friability

(10) Drug content

(11) Drug release profiles[29].

Table 3
Flow properties (as per USP30-NF25 specifications).

S. No.	Angle of repose	Carr's index (%)	Hausner ratio	Flow character
1.	25-30	<10	1.00-1.11	Excellent
2.	31-35	11-15	1.12-1.18	Good
3.	36-40	16-20	1.19-1.25	Fair
4.	41-45	21-25	1.26-1.34	Passable
5.	46-55	26-31	1.35-1.45	Poor
6.	56-65	32-37	1.46-1.59	Very Poor
7.	>66	38	>1.60	Very Very Poor

11. Evaluation

11.1. Interaction study by TLC/ FTIR

11.1.1. IR Spectroscopic studies

The IR spectra of the free drug and the microspheres were recorded. The identical peaks corresponding to the functional groups and albumin (BSA, Egg albumin, Human serum albumin) features confirm that neither the polymer nor the method of preparation has affected the drug stability.

11.1.2. Thin layer chromatographic studies

The drug stability in the prepared microspheres can also be tested by the TLC method. The Rf values of the prepared microspheres can be compared with the Rf value of the pure drug. The values indicate the drug stability.

11.2. Surface topography by scanning electron microscopy (SEM)

SEM of the microspheres shows the surface morphology of the microspheres like their shape and size.

11.3. Particle size distribution of prepared microspheres

The size of the prepared microspheres can be measured by the optical microscopy method using a calibrated stage micrometer for randomly selected samples of all the formulations.

11.4. Drug entrapment capacity

Efficiency of drug entrapment for each batch can be calculated in terms of percentage drug entrapment (PDE). Theoretical drug content can be determined by calculation assuming that the entire drug present in the polymer solution used gets entrapped in microspheres and no loss occurs at any stage of preparation of microspheres.

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

11.5. In vitro release dtudies

In-vitro release studies can be performed according to USP XXII type I dissolution apparatus at suitable pH conditions. The temperature should be maintained at (37±0.5) °C and the rotation speed of 100 r/min. Then 5 mL of sample should be withdrawn at various time intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample can be analyzed spectrophotometrically at specific wavelength (nm).

11.5.1. Effect of pH on magnetic microspheres

Measurement of pH sensitive behavior 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 1 h 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. The SR, (Ws + Wd)/Wd, is defined as the ratio of total weight of water in swollen microspheres to the weight of the dried microspheres, where Ws is the weight of adsorbed water and Wd is the weight of the microspheres at dry state[30].

11.5.2. In vitro drug release rate

In vitro drug release rate determined by the following methods: (i) Dialysis method; (ii) Continuous column electron method; (iii) Dialysis method.

The albumin microspheres were taken in a funnel; 3 mL of phosphate buffer (7.3) was added. The mouth of the funnel was covered with cellophane paper and fastened to rubber band. The funnel was then inverted into a beaker containing 50 mL of phosphate buffer 7.3. 2.5 mL aliquots were withdrawn every half an hour and replaced with 2.5 mL of fresh buffer. Aliquots were withdrawn over a period

of 10 h. The buffer in china dish was continuously stirred using a magnetic stirrer. The buffer was maintained at 37 °C.

11.5.3. Continuous column elution method

A continuous flow system similar to that described by Chien was used. Microspheres were immobilized on a column containing a fixed weight of glass wall (3.5 g) as support material and kept at 37 °C. They were subject to at intervals of half an hour. The amount of drug eluted was estimated.

11.6. Determination of solubility

The solubility of particular microspheres in specific solution as microspheres or microcapsules to be soluble in that particular environment (water or phosphate buffers of pH 7.4) can be determined by taking excess quantity of microspheres in 50 mL vials filled with water. Shaked the vials on a magnetic stirrer. Filtered the solution through Whatmann paper no.1 and drug concentration determined at particular λ max value for the particular drug.

11.7. Solid state by DSC/XRD

This test is done by an X-Ray diffractometer to find out the solid state of the drug, polymer and drug-polymer mixture and also to find out the solid state of the drug in the prepared albumin microspheres. The characterization of the micro particulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier[31,32].

12. Advantages of magnetic microspheres

(1) Incorporation of magnetically responsive materials into microspheres makes them susceptible to applied magnetic field, so that they are concentrated to the target site by application of magnetic field externally to that site. Due to this, rapid clearance of these microspheres by RES is prevented.

(2) Difference occurs maximally in capillary network so efficient delivery of drug to diseased tissue is achieved.

(3) Microspheres can transit into extra vascular space creating an extra vascular depot of drug for sustained release of drug within the targeted areas.

(4) Increase of tumor targeting microspheres can be internalized by tumor 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.

(5) Controlled and predictable rate of drug release with smaller doses of drug can be achieved.

(6) 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.

(7) Avoidance of acute toxicity directed against endothelium and normal parenchyma cell, controlled release within target tissue for intervals of 30 min to 30 h. as desired, adaptable to any part of body.

13. Disadvantages of magnetic microspheres

(1) One of the major limitations of this system is the drug cannot be targeted to deep-seated organism in the body. This approach is confined to the targeting of drugs to the superficial tissues like skin, superficial tumors or the joints.

(2) Thrombosis at the site of catheterization.

(3) The unknown toxicity of magnetic beads.

(4) The possible unwanted localization of the product in the liver and the regions of RES and the dangerous effect of self-flocculation of the magnetic particles causing vascular obstruction to vital organs in the body[33].

14. 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[34].

15. Literature of drugs used in magnetic microspheres along with their polymers

Table 4 shows drugs along with their polymers used in preparation of magnetic microspheres.

16. Marketed products

Various preparations of magnetic microspheres are available which are characterized by their INCI names, size, oil abs, refractive index and density shown in Table 5.

17. Applications of magnetic microspheres

Magnetic microspheres have wide range of applications. Various applications have been listed in Table 6.

Table 4
Drugs and polymers used in preparation of magnetic microspheres.

S. No.	Drug	Polymer
1.	Dexamethasone	Albumin
2.	Indomethacin	Methylmethacrylate
3.	Oxantrazole	Chitosan
4.	Diclofenac sodium	Ethyl cellulose
5.	5-Fluorouracil	Eudragit L100, Eudragit S100, Eudragit P4135F and Methylcellulose
6.	Doxorubicin	Poly (N-isopropylacrylamide)
7.	Candida rugosa lipase	Glycidyl methacrylate, ethylene glycol dimethacrylate and vinyl acetate
8.	(Carboxymethyl)dextran	Glycidyl methacrylate
9.	Dexamethasone sodium phosphate	Human serum albumin
10.	Silicon (IV) phthalocyanine derivative	Polyhydroxybutyrate-co-valerate (PHBHV) and poly(ecaprolactone) (PCL)
11.	5-fluorouracil	Chitosan
12.	Poly-l-lysine methotrexate	Polyglutaraldehyde
13.	Derivative of cyclophosphamide, Asta Z,	Albumin
14.	Nimesulide	Polyvinyl alcohol,poly lactic acid
15.	Ganciclovir	Poly (d,L-lactide-co-glycolide (PLGA)
16.	Verapamil hydrochloride	Gelatin A and Chitosan
17.	Cyclosporine A	Poly(dl-lactide-co-glycolide)
18.	Methotrexate	Calcium pectinate
19.	Pilocarpine nitrate	Egg albumin
20.	Doxorubicin	Poly(acrylic acid)
21.	Tamarind gum	Chitosan
22.	Lysozyme	Tris(hydroxymethyl)aminomethane
23.	Monoclonal anibodies	Polystyrene
24.	Cyclosporine	Poly(caprolactone)
25.	Metronidazole	Gelatin
26.	Lectin	Human serum albumin and polystyrene
27.	Doxorubicin loaded folate	Poly(N-isopropylacrylamide)

Table 5
Marketed formulations

S. No.	Trade name	INCI name	Size (μ m)	Oil abs (g/g)	Refractive index	Density (g/in^3)
1.	EA-209	Ethylene/acrylic acid copolymer	10.0	0.60	1.51	2.6
2.	Flo- beads SE-3107A(soft beads A)	Ethylene /Methacrylate copolymer	11.0	0.62	1.49	3.1
3.	Flo-beads SE-3207 B(Soft beads B)	Ethylene/Methacrylate copolymer	11.6	0.62	1.49	3.9
4.	BPD-800	HDl/trimethylol hexyllactyl cross polymer (AND silica)	6.5	0.63	1.52	6.4
5.	BPD-500	HDl/trimethylol hexyllactyl cross polymer (AND silica)	12.0	0.65	1.52	9.5
6.	BPD-500T	HDl/PPG/Polycaprolactone cross polymer (AND silica)	13.5	0.58	1.52	8.2
7.	BPA-500	Polymethyl methacrylate	10.0	0.55	1.49	5.2
8.	BPA-500X	Methyl methacrylate crosspolymer	7.0	0.58	1.49	6.7
9.	MSP-822	Polymethyl methacrylate	7.0	0.55	1.49	6.2
10.	MSP-825	Methyl methacrylate crosspolymer	8.0	0.57	1.49	6.7
11.	MSP-930	Methyl methacrylate crosspolymer	11.0	2.00	1.49	5.0
12.	SUNPMMA-H	Methyl methacrylate crosspolymer	11.7	0.65	1.49	NA
13.	TR-1	NYLON-6	13.0	1.12	1.53	4.0
14.	TR-2	NYLON-6	20.0	1.41	1.53	3.5
15.	POMP-605	NYLON-6	6.0	1.70	1.53	3.3
16.	POMP-610	NYLON-6	11.0	1.80	1.53	2.8
17.	SP-10	NYLON-12	10.0	0.60	1.53	6.2
18.	SP-10L	NYLON-12	10.0	0.62	1.53	5.2
19.	SP-500	NYLON-12	5.0	0.60	1.53	4.7
20.	CL-2080	Polyethylene	12.0	0.60	1.51	4.0
21.	TOSPEARL® 1110A	Polymethylsilsesqui oxane	11.0	0.50	1.41	4.5
22.	TOSPEARL® 120A	Polymethylsilsesqui oxane	1.2	0.57	1.41	6.5
23.	TOSPEARL® 145A	Polymethylsilsesquioxane	4.5	0.55	1.41	8.2
24.	TOSPEARL® 2000B	Polymethylsilsesquioxane	5.0	0.54	1.41	8.5
25.	TOSPEARL® 3000 A	Polymethylsilsesquioxane	5.0	0.54	1.41	7.0

Table 6
Applications of magnetic microspheres.

S. No.	Application	Drugs/Carriers presently in current investigation	Reference
1.	Tumor targeting	Mitoxantrone, Paclitaxel	[35]
2.	Radioembolisation of liver and spleen tumors	186re/188re-glass Microspheres	[36]
3.	Magnetic control of pharmacokinetic parameters	Insulin	[37]
4.	Magnetic bioseparation	Dynabeads, used in isolation of mRNA, genomic DNA and proteins	[38]
5.	Changing the timing and/or extent of drug absorption in stomach or intestines	Diclofenac sodium	[39]
6.	Radiosynovectomy of arthritis joints	35s-colloid, microspheres,169er.citrate	[40]
7.	Hyperthermia for treatment of cancer	Cisplastin, Paclitaxel	[41]
8.	Detection of metastases in non-enlarged lymph nodes	Supramagnetic iron oxide	[42]
9.	Labeled sandwich immunoassay	Fluorogenic compound, AttoPhos(visual color generating compound)	[43]
10.	DNA detection (Figure 10)	Dynabeads	[44]
11.	Bacteria detection	Streptavidin coated magnetic beads	[45]
12.	Cell separation in microfluidics channel	Dynabeads for separation of , proteins, nucleic acids, antigens and antibodies) or cells (e.g., blood cells, stems cells or bacteria)	[46]
13.	Cell surface markers for the detection and localization of antigens and lectin receptors	separation of red blood cells (RBC) and lymphoid cells	[47]
14.	Isolation and functionality of cancer cells (eukaryotic cells)	Dynabeads for breast cancer cells	[48]
15.	Immunoprecipitation (isolation of various proteins)	Dynabeads for liposaccharide binding proteins	[49]
16.	Isolation of cell compartments of eukaryotic cells	Dynabeads for Golgi bodies,endosomal vesicles	[49]
17.	Removal of anti sperm antibodies and sperm cells	Goat anti-human immunoglobulin	[50]
18.	T8 depletion in allogenic transplantation	dynabeads for bone marrow	[50]
19.	Magnetic separation of poly (A) mRNA	Homogenization by mixture of guanidium thiocyanate and phenol-chloroform	[51]
20.	Magneto capture protein interaction assays (Figure 11)	Ni-NTA (nitriloacetic acid) tagged magnetic agarose beads have been used for versatile magneto capture assays using 6xHis-tagged proteins	[52]
21.	Drug targeting	Elemental iron particles and activated carbon. Magnetic targeted carriers (1-2 μm in size) can adsorb and desorbs pharmaceutical agents such as doxorubicin (DOX)	[53]
22.	Contraceptive drug delivery	Drug delivery is designed responsive to the changes in steroid secretion during menstrual cycle	[29]

18. Conclusion

Magnetism seems to be a 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. They are relatively young drug delivery systems, having received attention from the early 1990s. In the early days of twentieth century, Paul Ehrlich envisioned his MAGIC BULLET CONCEPT-the idea that drugs reach the right site in the body, at the right time, at right concentration. 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 microspheres have the potential for these objectives. 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 drug delivery system. 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.

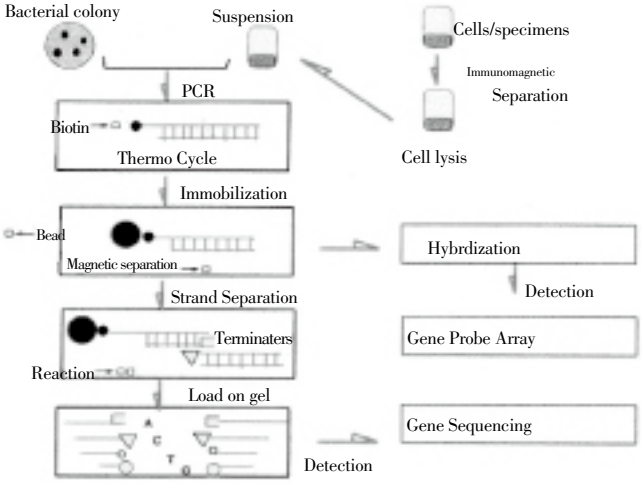

Figure 10. Concept of DNA detection system use of magnetic separation-based sample processing and solid phase sequencing technologies.

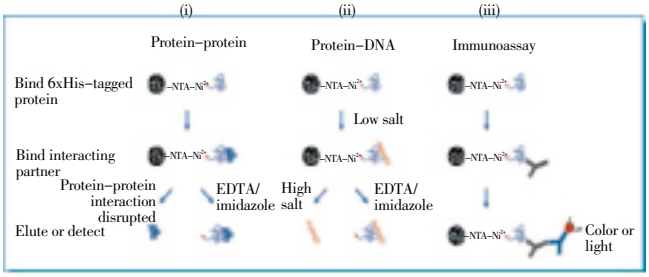

Figure 11. Magnetocapture protein interaction assays.

Conflict of interest statement

We declare that we have no conflict of interest.

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