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Review Article

MAGNETIC MICROSPHERES AS A TARGETED DRUG DELIVERY SYSTEM: AN OVERVIEW

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ABSTRACT

Magnetic microspheres as an alternative to traditional radiation methods which use highly penetrating radiation that is absorbed throughout the body. The *in-vivo* targeting of tumors with magnetic microspheres is currently realized through the application of external non-uniform magnetic fields generated by rare-earth permanent magnets or electromagnets. Magnetically controlled drug targeting is one of the various possible ways of drug targeting. There has been keen interest in the development of a magnetically target drug delivery system. These drug delivery systems aims 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. Its use is limited by toxicity and side effects. The aim of the specific targeting is to enhance the efficiency of drug delivery & at the same time to reduce the toxicity & side effects. This paper gives an overview of the mechanism, benefits, drawbacks, preparation and applications of magnetic microspheres.

Keywords: Magnetic microspheres, Targeted drug delivery, Magnet, Review.

INTRODUCTION

There are a number carriers Microspheres, nanoparticles, liposomes and others for which optimized technologies are under development to a) enhance the performance of products that have already been delivered with some success via that route and b) modulates the release and absorption characteristics of the drugs particularly those drugs which have shorter biological half life. Dosage forms that can precisely control the release rates and target drugs to a specific body site have created enormous impact on the formulation and development of novel drug delivery systems [1, 2]. 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.

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While a variety of devices have been used for controlled release drug delivery, biodegradable polymer microspheres are one of the most common types and hold several advantages. Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time [3]. Magnetite offers great potential for advancements in electronics, optoelectronics, magnetic storage, biomedical, ferrofluid, separation and magnetically guided drug carriers for targeting the therapy [4].

Small amounts of drug targeted magnetically to localized sites can replace large doses of drug that, using traditional administration methods, freely circulate in the blood and hit the target site in a generalized way only. Also, drugs within the sphere are protected from breaking down during transport and, because they are targeted instead of distributed in blood, don't harm some sensitive organs such as bone marrow. 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 [5, 6]

For applications requiring *in vivo* magnetic targeting, for example, magnetic drug delivery, the magnetic carriers must have a proper size range (i.e. between 200 nm and 3 mm) and high magnetizations to enable technically feasible external magnetic guidance within the vasculature. In these applications the microspheres (i.e. 1–2 mm) would be more advantageous than nanospheres in terms of better targeting and easier capture [7-11].

MECHANISM OF TARGETING BY MAGNET

The aim of the specific targeting is to enhance the efficiency of drug delivery & at the same time to reduce the toxicity & side effects. Magnetic drug transport technique is based on the fact 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, the accumulation takes place within area to which the magnetic field is applied & 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

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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 [12].(Figure 1)

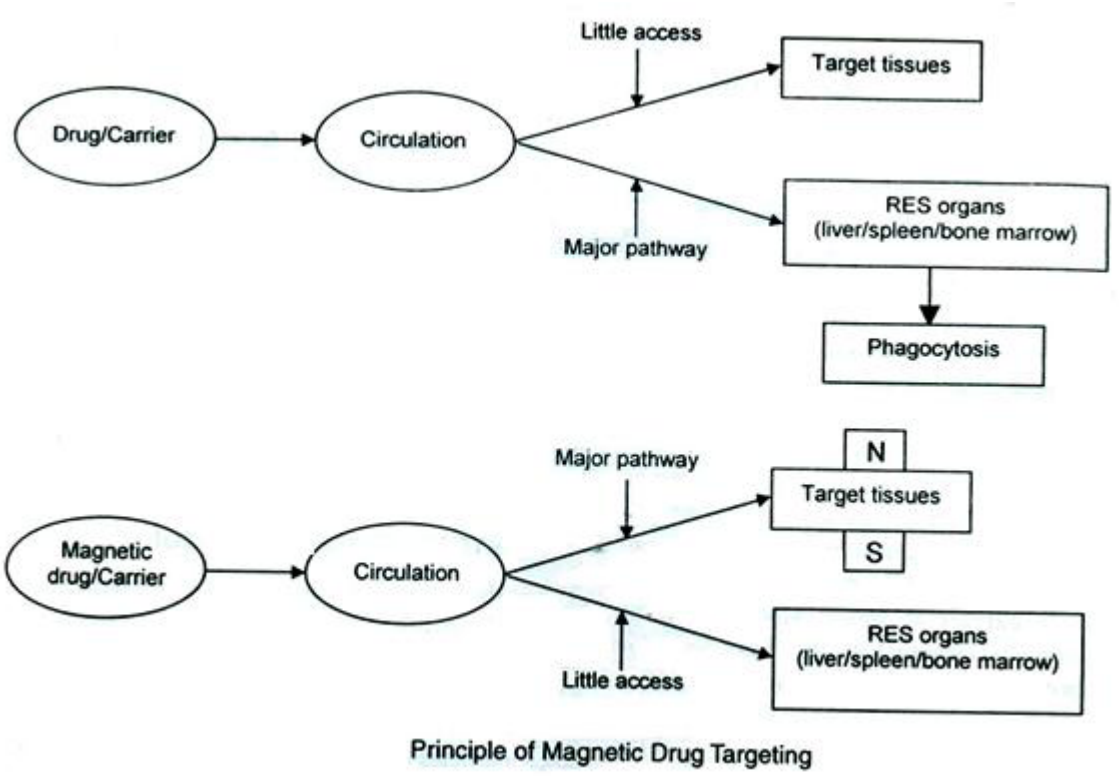

Figure 1 Principles of Magnetic Drug Targeting

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**.**

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).

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Figure 2-Super Paramagnetic Particles under the influence of external Magnetic field [13].

Figure-3 Super Paramagnetic Particles in absence of an external magnetic field, monodisperse Particle distribution

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. (Figure 4 & 5) Ferromagnetic particles are generally recommended for the separation of DNA/RNA(SiMAG/MP-DNA)[14].

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Figure-4 Ferromagnetic particles under the influence of an external magnetic field

Figure-5 Ferromagnetic Particles in absence of an external Magnetic field

Preparation of Magnetite Magnetite from a-FeOOH (goethite) or FeO

The nitrogen gas was flushed through a 500 ml, two-necked round-bottom flask fitted with a condenser. The flask was charged with 8.9g (0.1mol) ofgoethite, 9.94g (0.05mol) of$FeCl_2.4H_2O$ along with 250 ml deionized water and then 50 ml of 2M NaOH was added whilestirring vigorously. The reaction mixture was heated to reflux for 12h.During the transformation of the pH, its pH fell from14 (orange) in to 8–9 (black precipitates) particles were washed with distilled water, filtered and dried under vacuum at room temperature [15,16].

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Table-1 Materials used in magnetic Microspheres [17]

Material used	Types	Examples
Synthetic Polymers	a)Biodegradable b)Non biodegradable	Glycolides, Epoxy polymers, polyanhydrides, Lactides Polymethylmetharylate, Acrolein, Glycidyl methacrylate
Natural Polymers	a)Proteins b)Carbohydrates c)Chemically modified carbohydrates	Albumin, Gelatin, Collagen Agarose, Starch, Chitosan Polydextran, Polystarch

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 so dangerous or labile that we cannot allow it to circulate freely in the blood stream.
- The agent is so expensive, that we can not afford to waste 99.9% of it.
- 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[18]

METHODS

CONTINUOUS SOLVENT EVAPORATION

Polymer encapsulated microspheres are synthesized on the basis of a Continuous solvent evaporation technique. A solution of polymer, drug and magnetite should be added to the volatile organic solvent, which forms Auxiliary solution on stirring. The resulting solution should be homogenized at stirring temperature (22-30^{o}C). The magnetic microspheres will be formed in the suspension and should be separated by centrifugation. The product should be Freeze dried & stored at 4°C.

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

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ice bath at 26,000 rpm 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 2500 rpm for 10 min and washed with distilled water three times [19, 20] (Figure-6).

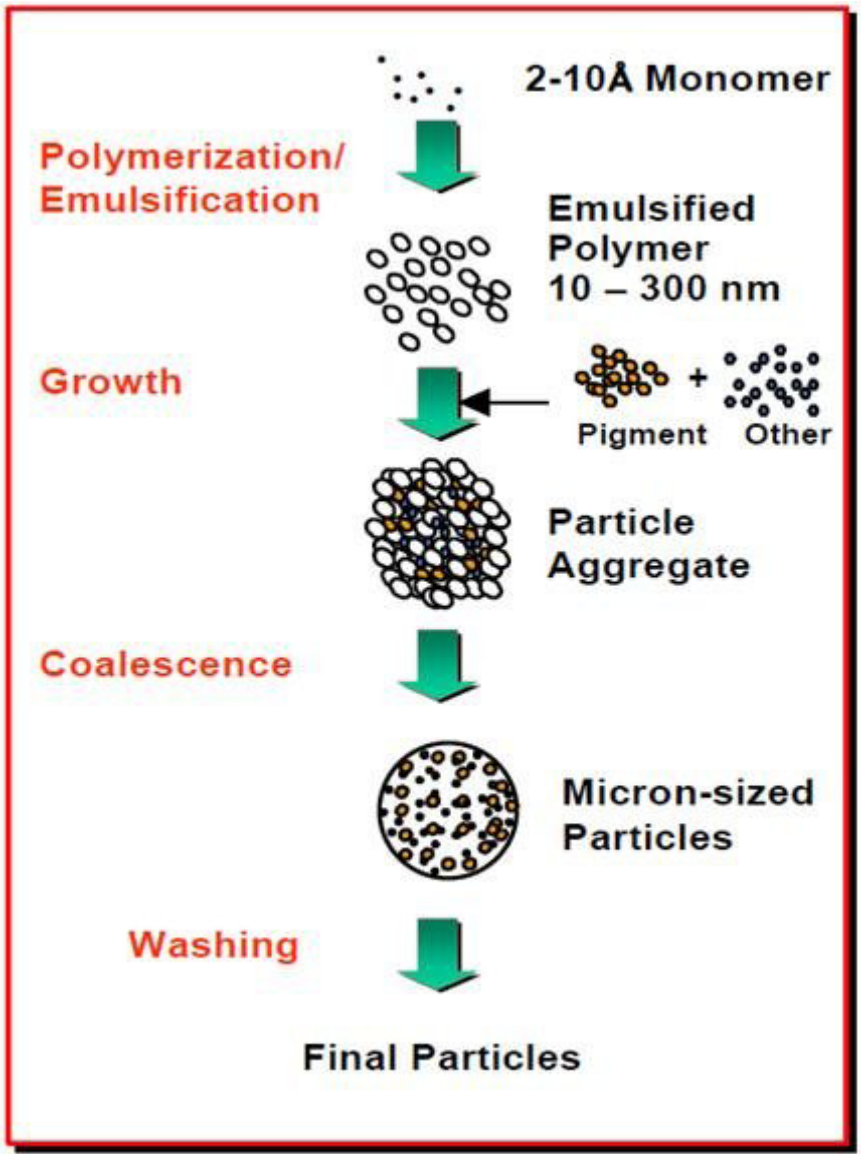

Figure-6 Microsphere preparation by Multiple Emulsion Method

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Phase separation emulsion polymerization

Polymer encapsulated microspheres are synthesized based on a modified Phase separation emulsion polymerization technique. Briefly aqueous solution of polymer, drug and magnetite should be added to the vegetable oil and emulsified using a magnetic stirrer at 1,500 rpm for 2 minutes. The resultant should be stabilized by heating at the temperature (100-150 °C). Then cross linking agent should be injected drop wise into the resultant emulsion under continuous stirring. The magnetic microspheres will be formed in the Oil suspension and then should be separated from oil by washing procedures. The product should be Freeze dried & stored at 4°C [21].

Other Methods

Inverse Phase Suspension Polymerization

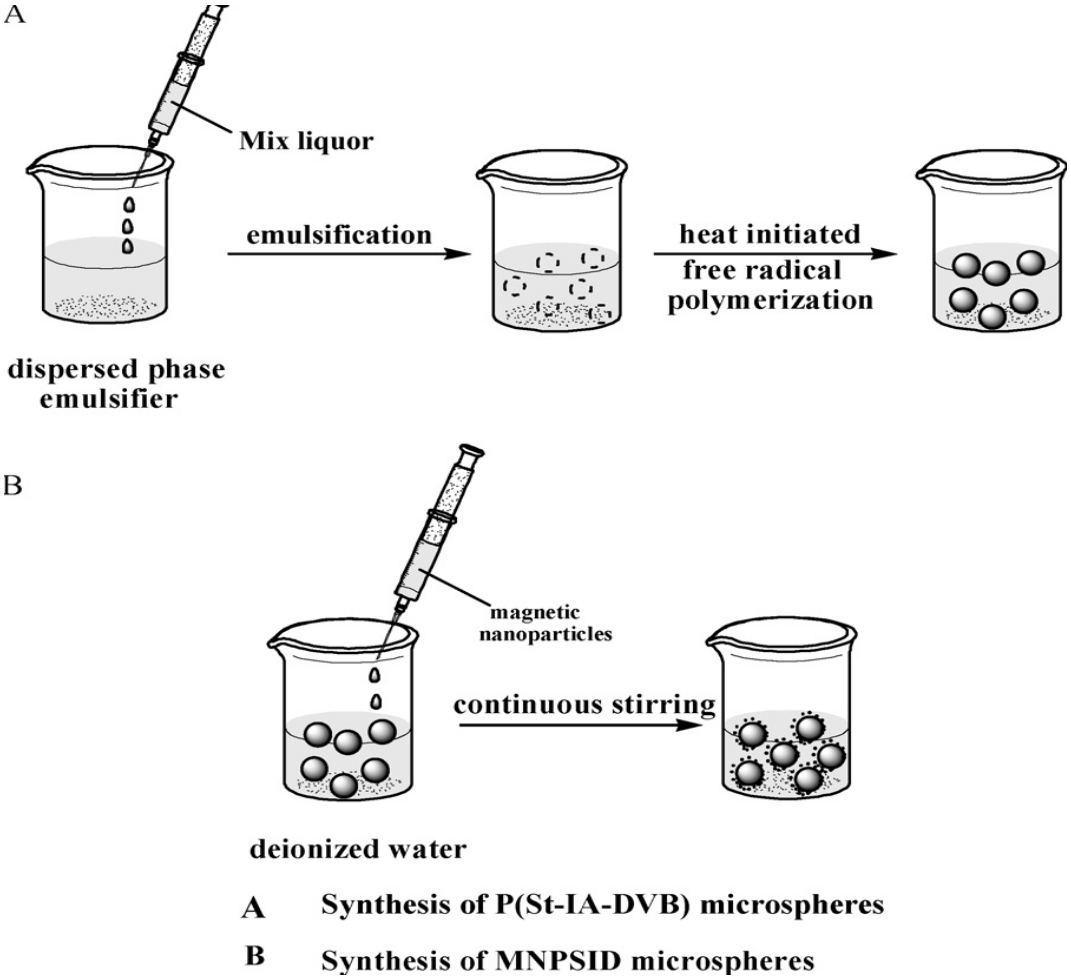

Figure – 7 Schematic illustration of synthesis of P (St-IA-DVB) microspheres and MNPSID microspheres, respectively P (St-IA-DVB) microspheres=P (styrene-itaconic acid divinylbenzene) microspheres, MNPSID=magnetic nanoparticles coated P (styrene-itaconic acid-divinylbenzene) microspheres.

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Materials

Styrene (St) and divinylbenzene (DVB) washed with 10% NaOH aqueous solution to remove the inhibitors. N,N_-Methylene-bisacrylamide(BIS), itaconic acid (IA),ammonium persulfate (98%)(APS) all of analytic grades.

Preparation of blank P (St-IA-DVB) Microspheres

The inverse-phase suspension polymerization method was employed to prepare microspheres. The reaction was performed in a 250 ml three-neck flask fitted with a mechanical stirrer. The continuous phase comprised of 100 ml of castor oil and 10 ml of span 80. A determined amount of IA, St, DVB and BIS were dissolved completely in DMSO, and the organic phase was added drop wisely into the flask, with 70 ◦C heating using an oil bath. Then the initiator of APS was added drop wisely with syringe. The reaction proceeded for 8 h with continuous stirring. The resulting microspheres were separated by centrifugation. The centrifuged microspheres were washed firstly with diethyl ether, followed by deionized water at least three times. After 3 times purification, the microspheres were lyophilized (Figure-7).

Preparation of Magnetic Nanoparticles coated P (St-IA-DVB) Microspheres (MNPSID Microspheres)

10 mg of blank microspheres were dispersed in 50 ml deionized water with continuous stirring. 50 µl of Fe_3O_4 nanoparticles were added drop wisely in 2 ml deionized water with ultrasonic dispersion. After that they were blended and dispersed completely in the water. The reaction kept up for 4 h, and the product was washed with excess deionized water three times and centrifuged. The obtained MNPSID microspheres were freeze dried, and then kept in 4 ˚C before use [22].

EMULSION SOLVENT EXTRACTION METHOD

Preparation of PLGA and PLA Microspheres

To prepare oleic acid and PLA-coated MMS, up to a total of 250mg of polymer and magnetite were combined into the methylene chloride phase. For the preparation of PLA-coated magnetite, the exact amount of PLA needed for further MMS preparation was used to coat the particles (i.e., the ferrofluid made was used directly to make MMS and no additional polymer was added based on 30%w/w magnetite loading). Higher loading up to 60% was attempted, however, it seemed that beyond 40% of magnetite, there was not enough PLA present to completely coat the magnetite and the particles would agglomerate. To prepare MMS containingW-40, the aqueous ferrofluid was directly added as the inner water phase to make the first w/o emulsion. $FeCl_2$.$4H_2O$ (0.6g, 0.30 mmol) and $FeCl_3$. 6H2O (1.4g, 0.52mmol) were dissolved in 10mLof degassed distilled H_2O andNH_4OH (2.4 ml, 29%) added with fast stirring. The flask was heated to 75˚C for 30min and then cooled to room temperature. The particles were magnetically filtered and washed with H_2O (2–3 times).The Ph of the solution was basic (9–10) before and neutral after the wash. The suspension of the particles

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in 5ml water was heated to 50ºC in a closed vial for 5min.PLA (1.4g) dissolved in 5mL of CH_2Cl_2 was added to this mixture with stirring. All particles moved from the aqueous to the organic phase. Water was decanted and the ferrofluid transferred to a dry vial [23].

Preparation of Magnetic Microspheres From Water-In-Oil Emulsion Stabilized By Block Copolymer Dispersant:

The preparation involved first the dispersion of an aqueous phase, containing magnetite nanoparticles and a water-soluble homopolymer, 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 homopolymer. 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 dispersibility to the spheres and to enable biomolecule immobilization [24].

Microwave-assisted Preparation of Magnetic Albumin Microspheres:

A new microwave-assisted method was used to prepare magnetic Fe_3O4 particles and magnetic bovine albumin microspheres (Fe_3O4 is combination of two oxides Fe_2O_3 and FeO).The microwave method produced smaller particles and is faster than traditional methods. The optimum conditions to prepare the Fe_3O_4 particles were three minutes at pH 13 and 80°C. Magnetic microspheres containing albumin were synthesized based on heating times and temperatures to form microspheres with different properties. For example, heating for 4min, at 160°C, yielded smaller sized microspheres (30 μm). Confirmed by FT-IR that iron oxide particles were encapsulated in biocompatible proteins, the thermal stability of the microspheres were determined by DSC and TG. The magnetic properties were determined by UV—VISIBLE Spectrophotometer and a Guoy magnetic balance. This microwave process could become a preferred method for the synthesis of magnetized protein microspheres

Synthesis of Amphiphilic Magnetic Microspheres By Dispersion Copolymerization of Styrene And Poly (Ethylene Oxide) Macro Monomer:

Amphiphilic magnetic microspheres ranging in diameter from 5 to 100 μm were prepared by dispersion copolymerization of styrene and poly (ethylene oxide) vinyl benzyl (PEO-VB) macro monomer (MPEO) in the presence of Fe_3O_4 magnetic fluid. The effects of various Polymerization parameters on the average particle size were systematically investigated. The average particle size was found to increase with increasing styrene concentration and initiator concentration. It also increased with decreasing stabilizer concentration and molecular weight of MPEO. The content of the hydroxyl groups localized in the microspheres ranged from 0.01 to 0.2 mmol /g [25].

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Characterization of Magnetic Microspheres

1) Particle size & size distribution
a) Sieving
b) Microscopy
c) Coulter counters 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
b) Tapped density
5) Flow Properties
a) Angle of repose
b) Hausner ratio
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 [26].

Evaluation of Magnetic Microspheres Interaction Study by TLC/ FTIR.

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.

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.

Surface topography by Scanning Electron Microscopy (SEM):

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

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.

Drug entrapment capacity:

Efficiency of drug entrapment for each batch can be calculated in terms of percentage drug entrapment (PDE) as per the following formula:
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. [27].

In vitro release studies:
In-vitro release studies can be performed according to USP XXII type I

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dissolution apparatus at suitable pH conditions. The temperature should be maintained at 37±0.5°C and the rotation speed of 100 rpm. 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) [28].

Advantages of Magnetic Microspheres:

1. Therapeutic responses in target organs at only one tenth of the free drug dose.

2. Controlled drug release within target tissues for intervals of 30 min to 30 hours, as desired.

3. Avoidance of acute drug toxicity directed against endothelium and normal parenchymal cells.

4. Adaptable to any part of the body.

Disadvantages of Magnetic Microspheres:

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

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

3. Magnets must have relatively constant gradients, in order to avoid focal over-dosing with toxic drugs.
4. A large fraction (40-60%) of the magnetite, which is entrapped in carriers, is deposited permanently in tissues [29].

Applications of Magnetic Microspheres:

1. 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.

2. 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.

3. Drug discovery, molecular targeting, DNA analysis, proteomics, and understanding the pathways of cell cycle regulation [30].

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Table-2 COMPARISON OF MAGNETIC AND NON MAGNETIC MICROSPHERES [31]

PROPERTY	MAGNETIC	NON MAGNETIC
SITE SPECIFICITY	well tolerated by the body, magnetic fields are believed to be harmless to biological systems and adaptable to any part of the body	Poor site specificity and are rapidly cleared off by RES
TEM features	Jagged edges seen by TEM which means that the magnetic nanoparticles are Embedded well by the microspheres' matrix material PLGA.	No jagged edges
Adaptability	Adaptable to any part of the body	Adaptable to less parts
Drug requirement	Locally congregating high concentrations of the drug at the diseased site thereby minimizing drug requirement and side effects.	More drug requirement than magnetic microspheres

Factors influencing the Properties of Microspheres:

1. Polymers commonly used to form microspheres
2. Choice of solvent

- should be able to dissolve the chosen polymer;
- poorly soluble in the continuous phase;
- High volatility and a low boiling point;
- Low toxicity.
- Alternative components (dispersed phase)
- Co-solvent:- organic solvents miscible with water such as methanol and ethanol.
- Porosity generator: increases degradation rate of polymer and improves drug release rate.
- E.g. Incorporating sephadex (cross-linked dextran gel) into insulin–pla microspheres
- Significantly increases microsphere porosity.

3. Continuous phase

a) Surfactant

- It reduces the surface tension of continuous phase.
- Avoids the coalescence and agglomeration of drops.
- Stabilizes the emulsion.

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- widely used stabilizers include:
- Non-ionic: partially hydrolyzed pva , methylcellulose , tween, span
- Anionic: sodium dodecyl sulphate (sds), sls
- Cationic: cetyl tri methyl ammonium bromide (ctab)

b) Alternative component:

- Antifoaming agent - foaming problem will disturb the formation of microspheres.
- Anti-foams of silicon and non-silicon constituents are used.

c) Impact of parameters and operating conditions on the properties of microspheres [32].

Table-3 Drugs encapsulated by Means of Magnetism and Magnetic Field

Sr. No.	Drug	Polymer
1	**Oxantrazole**	Chitosan
2	**Diclofenac sodium**	Ethyl cellulose
3	**5-Fluoro uracil**	Eudragit L100, Eudragit S100, Eudragit P4135F and Methylcellulose.
4	**Indomethacin**	Methylmethacrylate
5	**Doxorubicin**	Poly(N-isopropylacrylamide)
6	**Dexamethasone**	Albumin

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Table-4 Marketed products Polymeric Microspheres

Trade Name	INCI Name	Size(µm)	Oil abs(g/g)	Refractive index	Density(g/in ^{3})
EA-209	Ethylene/acrylic acid copolymer	10	0.60	1.51	2.6
Flo- beads SE-3107A(soft beads A)	Ethylene /Methacrylate copolymer	11	0.62	1.49	3.12
Flo-beads SE-3207 B(Soft beads B)	Ethylene/Methacrylate copolymer	11.6	0.62	1.49	3.9
BPD-800	HDl/trimethylol hexyllactyl crosspolymer (AND silica)	6.5	0.63	1.52	6.4
BPD-500	HDl/trimethylol hexyllactyl crosspolymer(AND silica)	12	0.65	1.52	9.5
BPD-500T	HDl/PPG/Polycaprolactone crosspolymer (AND silica)	13.5	0.58	1.52	8.2
BPA-500	Polymethyl Metharylate	10	0.55	1.49	5.2
BPA-500X	Methyl Methacrylate crosspolymer	7	0.58	1.49	6.7
MSP-822	Polymethyl Methacrylate	7	0.55	1.49	6.2
MSP-825	Methyl Methacrylate crosspolymer	8	0.57	1.49	6.7
MSP-930	Methyl Methacrylate crosspolymer	11	2.0	1.49	5.0
SUNPMMA-H	Methyl Methacrylate crosspolymer	11.7	0.65	1.49	NA
TR-1	NYLON-6	13	1.12	1.53	4.0
TR-2	NYLON-6	20	1.41	1.53	3.5
POMP-605	NYLON-6	6	1.7	1.53	3.28
POMP-610	NYLON-6	11	1.8	1.53	2.8
SP-10	NYLON-12	10	0.60	1.53	6.2
SP-10L	NYLON-12	10	0.62	1.53	5.2
SP-500	NYLON-12	5	0.60	1.53	4.7
CL-2080	POLYETHYLENE	12	0.60	1.51	4.0
TOSPEARL® 1110A	Polymethylsilsesquioxane	11	0.50	1.41	4.5
TOSPEARL® 120A	Polymethylsilsesquioxane	1.2	0.57	1.41	6.5
TOSPEARL® 145A	Polymethylsilsesquioxane	4.5	0.55	1.41	8.2
TOSPEARL® 2000B	Polymethylsilsesquioxane	5.0	0.54	1.41	8.5
TOSPEARL® 3000 A	Polymethylsilsesquioxane	5.0	0.54	1.41	7.0

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CONCLUSION

Targeted Drug delivery is an effective method to assist the drug molecule to reach preferably to the desired site. Over the years, Magnetic Microsphere have been investigated for targeted drug delivery especially magnetic targeted chemotherapy due to their better tumor targeting. Targeted Drug delivery is an effective method to assist the drug molecule to reach preferably to the desired site. The main advantage of this technique is the reduction in the dose & side effects of the drug. The magnetic targeted chemotherapy has better tumor targeting, therapeutic efficacy & 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 drug delivery system.

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