

Magnetic Microspheres: A Novel Targeting Delivery System

Satinder KAKAR^{*°}, Anurekha JAIN^{*}, Ramandeep SINGH^{**}

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Manyetik Mikroküreler: Yeni Bir Hedefleme Taşıyıcı Sistem

SUMMARY

Magnetic microspheres comprises the novel drug delivery systems. The major advantage is that reticuloendothelial clearance can be minimized and drug can reach the target site of action thus producing maximum efficacy and minimum side effects. Various techniques for preparation of magnetic microsphere, evaluation, application, marketed preparations are discussed in the paper.

Keywords: Magnetic, reticuloendothelial, supramolecular, particles, target, novel, delivery

ÖZET

Manyetik mikroküreler yeni ilaç taşıyıcı sistemlerini içerir. En büyük avantajları retiküloendotelial açıklığın en aza indirgenmesi ve ilacın hedef etki alanına ulaşabilmesi, böylece maksimum etkinlik ve minimum yan etki yaratmasıdır. Makalede manyetik mikrokürenin hazırlanması için çeşitli teknikler, değerlendirme, uygulama, piyasadaki müstahzarlar tartışılacaktır.

Anahtar kelimeler: Manyetik, retiküloendotelial, supramoleküler, partikül, hedefleme, yenilik, taşıyıcı

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Introduction

Magnetic microspheres are the supramolecular particles that are small enough to circulate through the capillaries but are sufficiently susceptible to be captured in microvessels by applying magnetic fields of 0.4 T-0.8 T. Targeted drug deliveries can be done by two modes i.e. magnetic drug delivery and non magnetic drug delivery. Magnetic drug delivery by various novel carriers is an excellent method in which a drug is directly delivered to the diseased location/area. nonmagnetic drug delivery systems such as nanoparticles, microspheres and microparticles etc are successfully utilized for drug targeting but donot show a satisfactory site specificity and are rapidly cleared off by RES (reticuloendothelial system) (Widder et al. 1987). Magnetic polymer microspheres are usually composed of magnetic cores to ensure a strong magnetic response and polymeric shells to protect from particle aggregation. These microspheres exhibit features such as small and proper size, different shapes, and various functional groups on the surface. They have therefore received much attention in recent years for wide potential applications such as immobilization of enzymes, protein separations, and various drug delivery processes. Thus magnetism plays an important role in living beings metabolism. For example, the haemoglobin is an iron complex present in blood and is magnetic in nature. Magnetite, Fe_3O_4 , is a biocompatible structure and it has a cubic inverse spinal structure with oxygen forming a FCC closed packing and therefore it is one of the most commonly used biomaterials for biological and medical applications from cell separation and drug delivery to hyperthermia (Alexiou et al. 2001). Magnetically drug delivery is a excellent way, in which a drug is binded to a small biocompatible magnetically active component, entrapped in the biodegradable polymeric matrix and pharmacologically active stable formulation is formulated, which is injected into the stream of blood and a high-gradient magnetic field is used to pull them out of suspension in the target region. Controlled drug release and further biodegradation are important for developing successful formulations. Mechanisms which involves Potential release are :

- Desorption of surface-bound /adsorbed drugs
- Diffusion through the carrier matrix
- carrier wall diffusion
- Carrier matrix erosion; and
- Combination of erosion /diffusion process (Alagusundaram M et al. 2009).

Principle of magnetic targeting

1. A drug or therapeutic radioisotope is encap-

sulated in a magnetic compound; injected into patient's blood stream & powerful magnetic field in the target area is applied to stop it

2. Depending on the type of drug, it is then slowly released from magnetic, thus it reduces the loss of drug as freely circulating in body (Aggarwal A et al. 2012).

Figure 1,2 and 3 shows the drug targeting principle

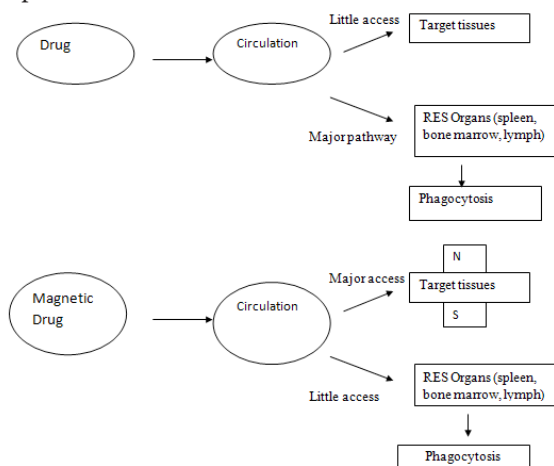


Fig 1: Drug targeting via magnetic and non magnetic systems

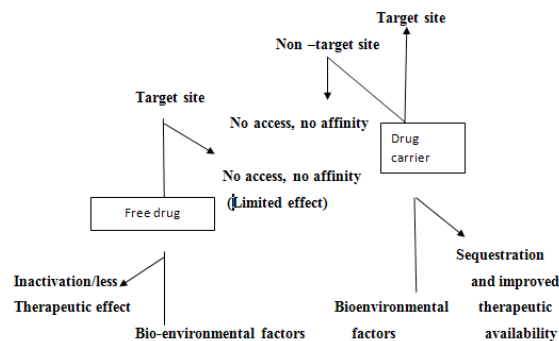


Fig 2: Rationale of drug targeting

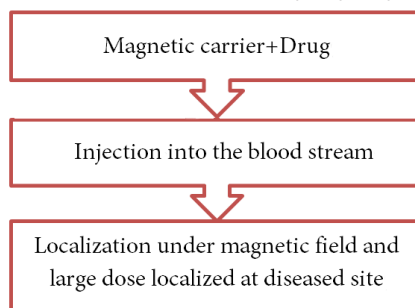


Fig 3: Mechanism of drug targeting

History of magnetic carriers

Table 1 shows the history of magnetic carriers

Table 1: History of Magnetic Carriers

Year	Scientist	Discovery
1956	Gilchrist	published a seminar paper in 1956 on the selective inductive heating of lymph nodes after injection of 20-100 nm sized magnetite particles into the lymph nodes near surgically removed cancer(Cleveland, 2004).
1960	Freeman, Arott, Watson	Transport of fine magnetic particles carrying radioactive materials or drugs through the vascular system with their subsequent focusing at localized parts of the body using magnetic fields (Freeman MW et al.1960)
1962	Meyers and co workers	Demonstrated the magnetic focusing of intra-arterially injected 1 to 3 µm radioactive iron (⁵⁹ Fe) particles in dogs(Meyers PH et al.1963; Meyers PH,1966).
1971	Nakamura et al	Reported the localized capture of magnetic particles introduced into the blood circulation of both rats and dogs (Nakamura T,1971).
1983	Ovadia et al	pointed out that typical magnetic carriers are essentially saturated at 4000 Gauss (0.4 T) and that the magnitude of the field gradient then governs their focusing. This was consistent with their observation of the focusing of magnetic carriers at the edges of their magnet pole piece where the field gradients were highest, a phenomenon they referred to as the “edging effect.” Targeting an area with the face of a simple magnet could result in focusing of magnetic drug carriers more strongly to cells adjacent to the target. They proposed that the edge effect could be used to target specific areas by careful orientation and positioning of the magnet (Ovadia H,1983).
1984	Ishii et al	described some <i>in vitro</i> studies using submicron magnetic liposome drug carriers(Ishii et al.1984).
1991	Goodwin et al	observed extravasation of magnetic carriers (iron/carbon particles of diameter 0.5 to 5 µm, with 95% < 3 µm) in targeted areas of the liver in pigs. This, they claimed, was a mechanism for retention of the carriers at the targeted site after the removal of the magnetic field. The same carriers carrying doxorubicin were later used for a study of intravesical magnetic targeting of the bladder wall in healthy pigs using an externally applied neodymium-iron-boron (NdFeB) magnet (0.5 T). (Goodwin S et al. 1999; Goodwin SC et al.2001).
1997	Lübbe and co-workers	carried out the first Phase I clinical trial of magnetically targeted nanoparticles to deliver the anti-cancer drug 4'-epidoxorubicin to advanced solid tumors in 14 patients (Lubbe AS et al. 1983; Lubbe AS et al. 1996).

Magnetic modulated systems

Targeted systems are classified as follows:

1. Magnetic microspheres
2. Magnetic liposomes
3. Magnetic nanoparticles

4. Magnetic resealed erythrocytes

5. Magnetic emulsions (Lubbe AS et al.1996)

Table 2 shows various systems along with their methods of preparation and evidence for them by scientists in past

Table 2:Various magnetic modulated systems

System	Methods of preparation	Evidence for effectiveness
Magnetic microspheres	Phase separation emulsion polymerization Continuous solvent evaporation	Gupta and Hung suggests that in presence of magnetic field, microspheres demonstrated 16 fold increase in the maximum drug concentration, 6 fold increase in drug exposure and 6 fold increase in the drug targeting efficiency to rat tail target segments (Margolis LB et al. 1983)
Magnetic nanoparticles	Co- precipitation, sol-gel method, hydrothermal method, Thermal decomposition, Electrochemical deposition, polyol method, Sono- chemical method, Bio mimetic synthesis	Using an external magnetic field, Mikhaylov et al. showed that ferri- liposomes with SPION clusters encapsulated inside liposomes were able to reach tumor tissue in an immune competent tumor-bearing FVB/N mouse model (G.Mikhaylov et al. 2011)
Magnetic liposomes	Fusion method, Mechanical method	Magnetic liposomes containing doxorubicin were intravenously administered to osteosarcoma-bearing hamsters. When the tumour-implanted limb was placed between two poles of a 0.4 Tesla magnet, the application of the field for 60 minutes resulted in a fourfold increase in drug concentration in the tumour. In the same osteosarcoma model in which the magnet was implanted into the tumour, magnetic liposomes loaded with adriamycin demonstrated better accumulation in tumour vasculature and resulted in enhanced tumour -growth inhibition (Kubo T et al. 2001; Nobuto, H et al. 2004) .
Magnetic resealed erythrocytes	Presswell technique	.Local thrombosis in animal arteries was prevented by means of magnetic targeting of aspirin loaded red cell was studied (Flores GA et al. 2002)
Magnetic emulsions	Emulsion polymerisation technique	Akimoto and Morimoto prepared magnetic emulsion by utilizing ethyl oleate based magnetic fluid as the dispersed phase, casein solution as the continuous phase and anticancer agent, methyl CCNU trapped in the oily dispersed phase as active chemotherapeutic agent. Magnetic emulsion appears to have potential in conferring site specificity to certain chemotherapeutic agent (Dailey JP et al. 1999)

Criteria for selection of drugs for formation of Magnetic microspheres

1. Magnetic microspheres are prepared when the drug is so dangerous that we cannot allow it to circulate freely into the blood stream.
2. When the agent is so expensive and we cannot afford to waste it.
3. Requires a selective regional effect to meet localized therapeutic objective.
4. Requires an alternative formulation essential to continue treatment in patients whose systemic therapy must be temporarily discontinued due to life threatening toxicity directed at selective organs.

Methods of preparation of magnetic microspheres

1. Phase separation emulsion polymerization
2. Continuous solvent evaporation
3. Emulsion solvent extraction method
4. Low temperature hydrothermal method
5. Sonochemical method
6. Chemical precipitation method
7. Suspension polymerization method
8. Swelling and penetration method
9. Photopolymerisation method
10. Emulsion solvent evaporation technique
11. Vapour deposition technique
12. Alkaline co-precipitation method
13. Multiple emulsion method
14. Crosslinking method
15. Inverse phase suspension polymerization method

Phase separation emulsion polymerization

Various steps for preparation of magnetic microspheres via phase separation emulsion polymerization are shown in figure 4. (Ishida M et al. 1983; Salim Md et al. 2010)

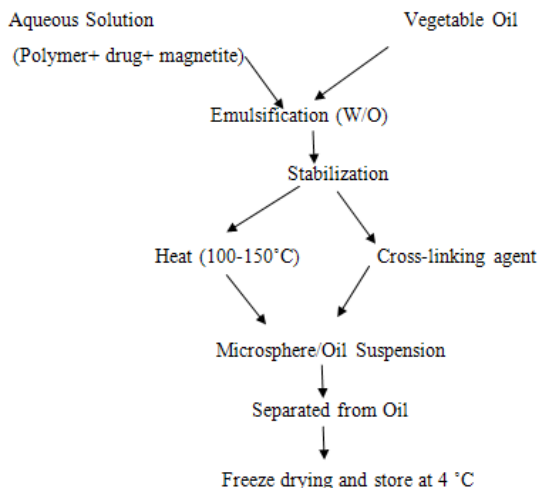
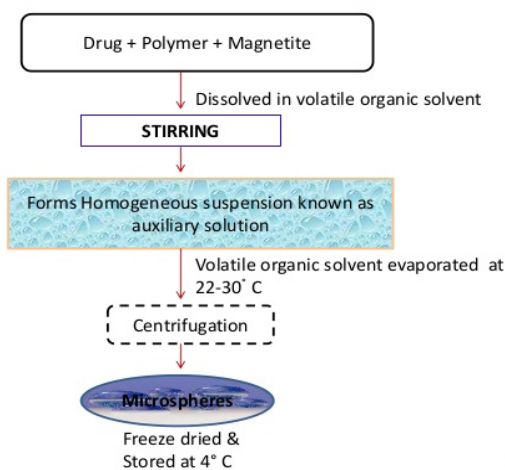


Fig 4: Process for Phase separation emulsion polymerization method

Continuous solvent evaporation method

Various steps for preparation of magnetic microspheres via Continuous solvent evaporation method are shown in figure 5. (Lachman LA et al. 2002)

I. Continuous solvent evaporation method



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Fig 5: Process for continuous solvent evaporation method

Co-precipitation of inorganic salt

Various steps for preparation of magnetic microspheres via Co-precipitation of inorganic salt are shown in figure 6, 7. (Zhang BO et al. 2007).

Preparation of silica coated magnetic carriers

Silicate hydrolysis

Sol-gel method

Hydrolyzation of sodium silicate by adjusting pH values and condensing silica onto the magnetic particles

Method is simple and easy to perform

Fig 6: Preparation of carriers by silicate hydrolysis

Multiple emulsion method

Various steps for preparation of magnetic microspheres via Multiple emulsion method are shown in figure 8 (Jian Yang et al .2007).

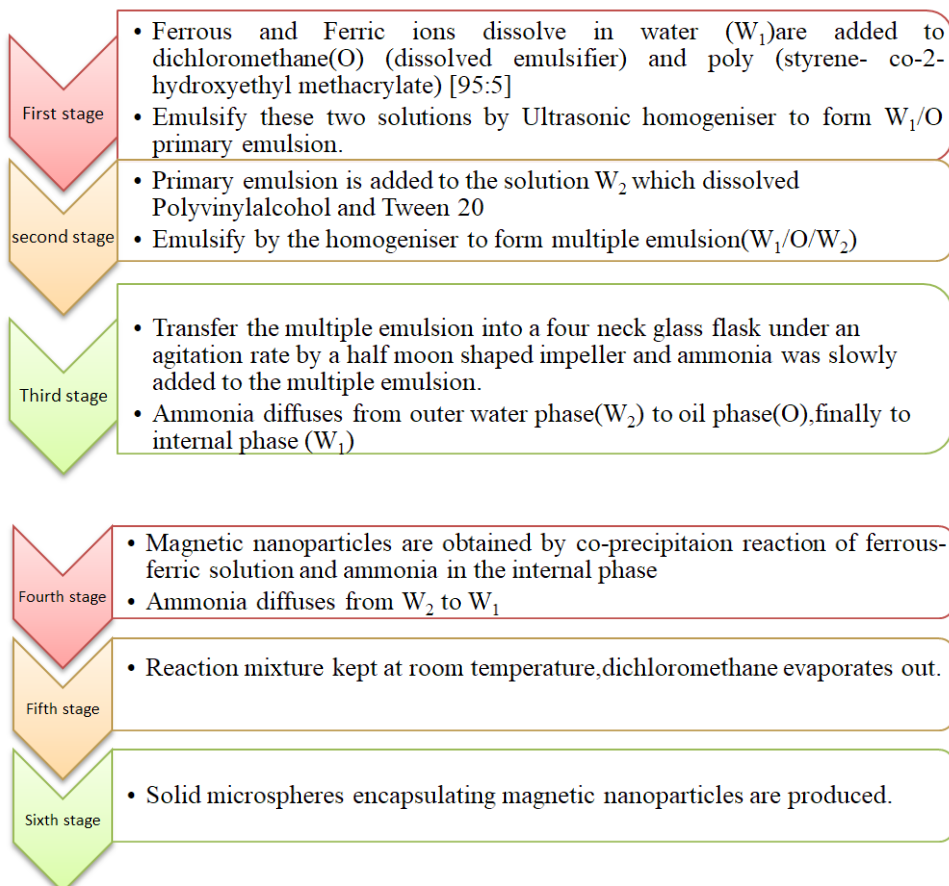


Fig 8: Preparation of magnetic microspheres via multiple emulsion method Low temperature hydrothermal method

Disperse magnetic particles in the solution of intetraethyl orthosilicate(TEOS)

TEOS was hydrolysed under alkali and condensed onto the surface of magnetic particles

Fig 7: Preparation of magnetic carriers by Sol-gel method

Various steps for preparation of magnetic microspheres via low temperature hydrothermal method are shown in figure 9 (Wei Jiang et al. 2013).

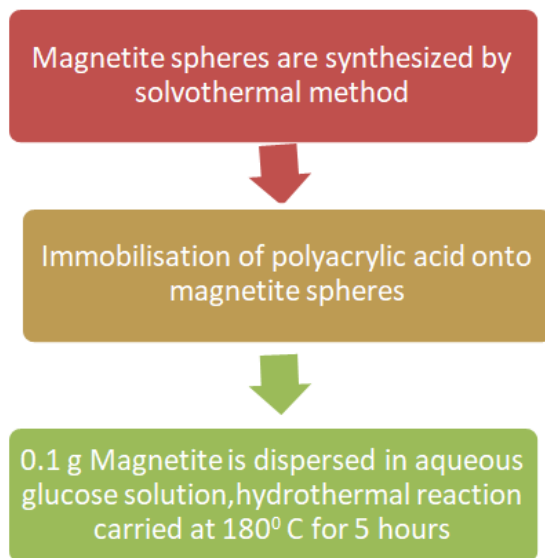


Fig 9: Low temperature hydrothermal method

Sonochemical method

Various steps for preparation of magnetic microspheres via Sonochemical method are shown in figure 10 (Avivi S et al. 2001).

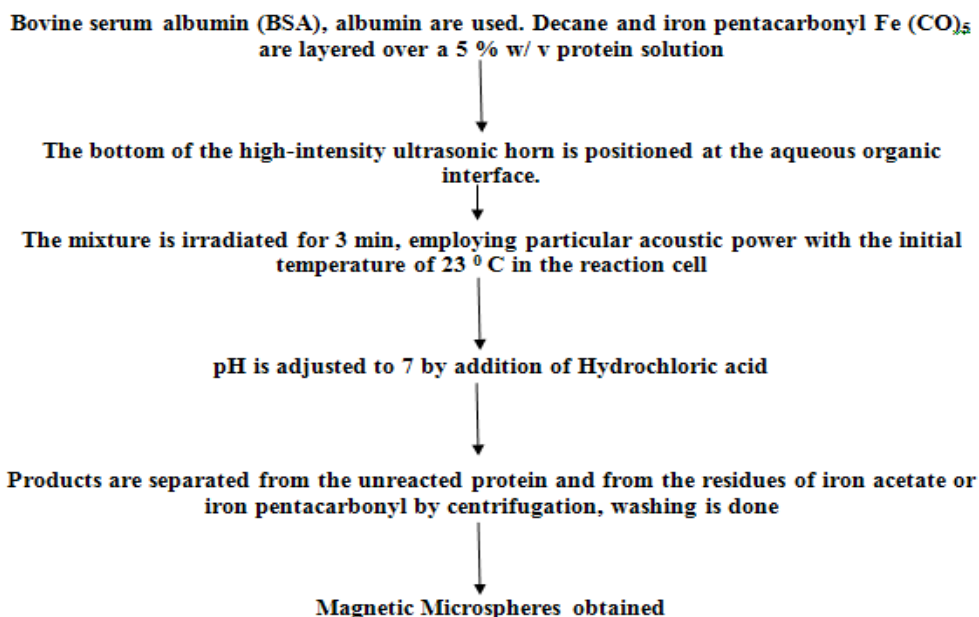


Fig 10: Sonochemical method

Emulsion polymerization method

Various steps for preparation of magnetic microspheres via Emulsion polymerization method are shown in figure 11 (E Pollert et al. 2006).

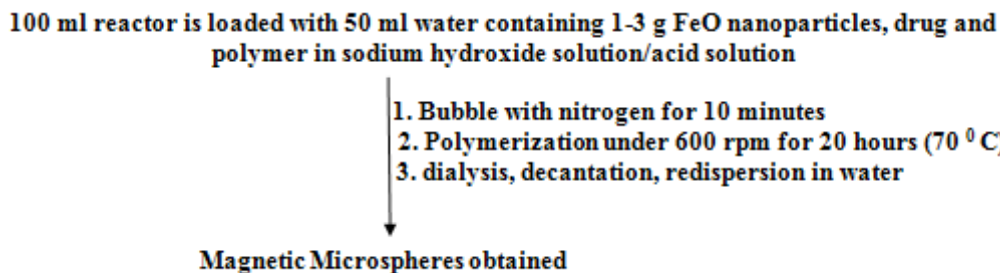


Fig 11: Emulsion polymerization method

Chemical precipitation method

1. Polymer is added to aqueous solution of sodium hydroxide depending on its solubility.
2. Fe⁺² and Fe⁺³(in molar ratio 1:2) are dissolved in water and are added drop wise under continuous stirring at 25°C.
3. Hybrid material is separated by applying magnetic field and washed several times with water and then in ethanol
4. Dry at 50° C to obtain magnetic microspheres for 24 hours
5. Magnetic microspheres are dispersed in minimum quantity of ultra-pure water and drug is added.
6. Finally dry at 40° C for 6 hours. (Carmen Mariana Chifiruc et al. 2012).

Suspension polymerization method

1. Porous hydrophilic magnetic microspheres are prepared by suspension polymerization. a saturated sodium chloride aqueous solution (50 ml) with the stabilizer soluble starch (2% of the total weight of the aqueous solution) as aqueous continuous phase is used, dropping a few methylene blue. The organic phase contained monomers GMA (glycidyl methacrylate), and VAc crosslinker EGDMA(ethylene glycol dimethacrylate (EGDMA) and vinyl acetate (VAc)), OA-Fe₃O₄(oleic acid coated) and n-heptane as the porogen.
2. The organic phase is placed overnight and vibrated with ultrasonic for 1 h, then initiator AIBN (azobisisobutyronitrile) is added before using.
3. Suspension polymerization is carried out in a 100 ml three-necked flask fitted with a nitrogen inlet, refluxing condenser and mechanical stirrer, the three-necked flask is placed in a water bath, stirred at 450 rpm under a nitrogen atmosphere.
4. The suspension polymerization is carried out at 50 .8°C for 1 h, 60.8°C for 2 h and then for 6 h at 75.8°C. After the reaction, the magnetic copolymer microspheres are isolated by magnetic decantation, and washed with heated distilled water several times, then are extracted in acetone for 48 h.
5. After that, the microspheres were alcoholysed

in 5% NaOH–methanol solution at room temperature for 12 h (Lei YL et al. 2001).

Swelling and penetration method

1. PS (non porous polystyrene) particles are mixed with NMP (Styrene, N-methyl-2-pyrrolidone)/ water solution in a specific v/v NMP-to-water ratio.
2. SDS (sodium dodecyl Sulfate) is added to the NMP/water solution. The NMP/water mixture with PS spheres is left soaking for 24 h at room temperature while stirring (125 rpm).
3. Subsequently, the superparamagnetic nanoparticles dispersion is added to the mixture of PS sphere and NMP/ water solution at 30°C while shaking (at 140 rpm) for 1– 5 days to allow the magnetic nanoparticles to penetrate into the interior of the PS particles.
4. Afterwards, the polymer particles were separated from the solution by centrifugation.
5. Finally, particles were sequentially washed three times with methanol, three times with deionized water, and vacuum dried at room temperature for 1–2 days to yield the magnetic polymer microspheres. (T.H. Chung et al. 2008).

Vapour deposition technique

Vapour deposition technique is shown in figure 12 below:

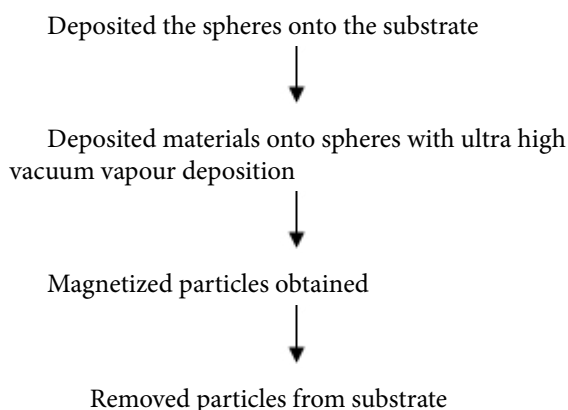


Fig 12: Schematic four-step process for fabrication of uniform magnetic particles that can be used as Magnetically Modulated Optical Nanoprobes

Which production method is preferred for the preparation of the microparticles?

Production method depends on the type of drug used. Literature survey is done in order to find out which method is most compatible with our drug.

The most common methods used are Continuous solvent evaporation method and Phase separation emulsion polymerization method.

Phase separation may occur in case of Phase separation emulsion polymerization which is its major disadvantage thus Continuous solvent evaporation method is preferred over it.

FACTORS AFFECTING RATE OF DRUG DELIVERY

I. Amount and rate of drug delivery via magnetic microspheres can be regulated by changing size of microspheres, drug content, and content of magnetite and drug release of carrier.

- The size of microsphere is related to the drug content directly

- solubility characteristics of the drug and method of preparation of microspheres affects the drug content

- Hydration state of microspheres affect drug release rate from the carrier

II. The retention of microspheres at the target sites is governed by the magnetic content and magnitude of applied field. If magnetic content is higher in microspheres, smaller magnetic fields are sufficient for effective retention of microspheres at targeted sites. But in case of excessive magnetite in the microspheres the effective space available for drug in the microspheres is reduced appreciably. So balance between drug and magnetite content of microspheres is needed in order to design an efficient therapeutic system (Chopra KS et al. 1994).

Various drugs which have been formulated as magnetic microspheres are shown in table 3.

Table 3:List of drugs,polymer,use and their respective methods for which Magnetic microspheres have been formulated

Drug	Polymer	Use	Method	Reference
Amphoterecin B	Albumin	Treatment of leishmaniasis	Spray drying	(Sánchez-Brunete JA, 2004)
Aztreonam	Dextran	Antimicrobial activity	Continuous solvent evaporation	(Kang et al. 1987).
Adriamycin	Albumin	Cytotoxic effect on tumour cells	Heat stabilized protein methods	(Tao K et al., 1999).
Alpha chymotrypsin	Titanium oxide	hydrolysis of N-acetyl-L-tyrosine ethyl ester	Immobilization techniques	(Izmailov AF, 2000).
Aclarubicin	Gelatin	Intravascular tumour targeting	Water in oil emulsion polymerisation	(Kang et al. 1987).
Mesalamine	Chitosan, Eudragit, Ethylcellulose	Ulcerative colitis	Phase separation emulsion polymerisation	(Satinder Kakar et al. 2014).
dexamethasone	Albumin	Lymphocytic tumors	Modified phase separation emulsion technique	(Sussan et al.1996).
azithromycin	Dextran	Potentiator effect on antimicrobial activity against S.aureus and Paeruginosa reference strains	Continuous solvent evaporation	(Grumzesce et al. 2012).
Diclofenac sodium	Gelatin	Reduced joint swelling	Emulsification and cross linking	(Saravanan M et al. 2008).
Oxanzazole	Chitosan	Cancer therapy	Solvent evaporation	(Hassan, EE,1992).
Vancomycin	Starch	Cytotoxic effect on cancer cells	Continuous solvent evaporation	(AM Grumzesce, 2012).
α- chymotrypsin	Titanium oxide	hydrolysis of N-acetyl-L-tyrosine ethyl ester	Immobilisation techniques	(Izmailov AF, 2000).
Penicillin	Dextran	Potentiator effect on antimicrobial activity	Continuous solvent evaporation	(Kang Choon Lee,1987)
Methotrexate	Polyethylene glycol	Anticancer activity	Methotrexate reaction with amino-terminated magnetic microspheres	(Devineni, D,1995)
Doxorubicin	Albumin	Anticancer activity	Crosslinking techniques	(Kenneth, Widder, 1979).
Cisplatin	Albumin	Anticancer activity	Phase separation emulsion polymerization	(Vyas MB 2012).
Sulforaphane	Bovine serum albumin	Cancer treatment	Spray drying	(Gerald G Enriquez, 2013)

Insulin	Feridex	diabetes	Invasive method	(Vijayaganapathy Vaithilingam,2016)
Etoposide	Poly-(caprolactone)	Anticancer activity	Continuous solvent evaporation	(Vankayalu Devendiran Sundar, 2014)
Boron specific chelating substances	poly (glycidylmethacrylate)	In treatment of boron contaminated water	Dispersion polymerisation	(D Yin, 2016)
6-thioguanine	Poly(lactic acid-polyethylene glycol copolyester)	anticancer	Continuous solvent evaporation	(Kakar and Singh, 2014)
Ofloxacin	Dextran	Antimicrobial activity	Continuous solvent evaporation	(Kang Choon Lee, 1987)
Rifampicin	Dextran	Antimicrobial activity	Continuous solvent evaporation	(Kang Choon Lee, 1987)
Oxacyclin	Dextran	Antimicrobial activity	Continuous solvent evaporation	(Kang Choon Lee, 1987)
Clindamycin	Dextran	Antimicrobial activity	Continuous solvent evaporation	(AM Grumezescu, 2012)
5-Fluorouracil	Bovine serum albumin	Treatment of hepatomas	Emulsion, heat stabilization technique	(Tao K,1999)
Piperacillin	Dextran	Antimicrobial activity	Continuous solvent evaporation	(Kang Choon Lee, 1987)
Cephalosporins	Chitosan	Antibacterial activity	Solvent evaporation	(Carmen Mariana Chifruic,2012).

Patents which are related to Magnetic microspheres are discussed in table 4.

Table 4: Patents related to magnetic microspheres

Patent number	Filing date	Publication date	Applicant	Title
US4452773	Apr 5,1982	June 5,1984	Canadian patents and development ltd	Magnetic iron-dextran microspheres(Canadian patents and development ltd,1984)
US5032381	Dec 20,1988	July 16,1991	Tropix, Inc	Chemiluminescence based static and flow cytometry (Tropix.,1991)
US5091206	May 30,1989	Feb 25,1992	Baxter diagnosis Inc	Process for producing magnetically responsive particles(Baxter diagnosis Inc)
US5283079	Dec 14,1989	Feb 1,1994	Baxter diagnosis Inc	Process to make magnetically responsive fluorescent polymer particles(Baxter diagnosis Inc)
US5855790	Feb 7,1995	Jan 5,1999	Selective Environmental Technologies, Inc.	Magnetic particles, a method for the preparation thereof and their use in the purification of solutions(Selective Environmental Technologies, Inc,1999)
WO1997020214A1	Nov 28,1996	June 5,1997	The Minister Of Agriculture, Fisheries and Food In her Britannic Majesty's Government Of The United Kingdom Of Great Britain and Northern Ireland	Extraction and labelling of biological materials with magnetic and fluorescent beads or liposomes(US Patent,1997)
US20030186465	Nov 27,2001	Oct 2,2003	Kraus Robert H	Apparatus used in identification, sorting and collection methods using magnetic microspheres and magnetic microsphere kits(Kraus Robert H,2003)
US 20090092837 A1	Mar 20,2007	Apr 9,2009	Andreas Axen, Eva Holmgren,Nils Norrman, Tobias E. Soderman	Magnetic beads(Andreas Axen,2009)
US8564776B2	Oct 12,2010	Oct 23,2013	Stevens W. Graves, Robert C. Habbersett	System and method for measuring particles in a sample stream of a flow cytometer using a low power laser source (Stevens W. Graves,2013)

Applications of magnetic microspheres

1. Magnetic microspheres in labelling and separation of cells

Magnetic and fluorescent properties of Probe (cell surface) containing iron-containing polymeric microspheres tagged with dyes which are fluorescent in nature and coupled chemically to antibodies or lectins have been used in the magnetic separation of red blood cells and in the identification of immunoglobulin receptors and wheat germ agglutinin (WGA) receptors present on lymphocytes and Hela cells by SEM and fluorescent microscopy (RS Molday,1977).

2. Magnetic microspheres have widespread application in bioengineering, biomedicine, trends such as enzyme immobilization (Lea T,1985).

3. Deoxyribonucleic (DNA) research and genetic exploration

DNA makes each species different and unique. Nucleic acid isolation by means of magnetic beads is a good method of extracting DNA for analysis and genetic exploration. (Cax X,1977).

4. Magnetically induced Hyperthermia for treatment of cancer.

Reduction of viability of cancer cells on treatment of organs with heat to a 42–46 °C is termed as hyperthermia. It is based on the fact that tumor cells are more sensitive to temperature than normal cells. In hyperthermia a heat delivery system is established, such that the tumor cells are inactivated while normal ones are unaffected. (Burns MA,1985).

5. Human cholangiocarcinoma xenografts

Cholangiocarcinoma, is a malignant disease affecting the biliary tract, and the incidence ratio of

male to female is 1.46:1. Treatment includes mainly operation, and combined chemotherapy and radiation. But it is very difficult to diagnose it in early stages. the outcome of operation can be unsatisfactory, and the survival rate is very low. Single or combined application of chemotherapeutic drugs is usually less than 30% successful in the clinic. The targeting drug with magnetic microspheres to treat human cholangiocarcinoma xenografts is a novel technique for it+ (Deore BV et al. 2009)

6. Delivery of chemotherapeutic drugs to liver tumors

Lubbe *et al* performed the first clinical cancer therapy trial using magnetic microspheres in Germany for the treatment of advanced solid cancer in 14 patients. The phase I study showed the low toxicity of the method and the accumulation of the Magnetic Microspheres in the target area. MRI measurements were carried out which showed that more than 50% of the Magnetic Microspheres were ended up in the liver. This was likely due to the particles' small size and low magnetic susceptibility which limited the ability to hold them at the target organ. (Kobayashi H, 1991; Matsunaga TJ, 1991; Lubbe et al. 1996)

7. Bioassays

Drug, hormone, vitamins etc, are tested for determining their activity by testing its potency on a living organism, and are measured in comparison to recognized standards. Magnetic beads provide high levels of chemical and physical stability for calculating changes of selected particles within a sample. (Mittag TW, 2000)

Market Products

Marketed products are discussed below in table 5.

Table 5: Marketed products

Name	Advantages	Applications
NanoLink™ Streptavidin Magnetic Beads 0.8 μm	1. Highest Biotin Binding 2. Fast (<2 min) Response Time 3. Versatile nature	Magnetic Beads are suited for generating single-stranded PCR templates that can increase hybridization efficiency to complementary probes by removal of the unbiotinylated, competing PCR strand (Fowler DM et al.2010)
AbraMag™ Magnetic beads	1.Superior binding capacity 2.Superior yield 3.Equal or superior purity of target analyte 4.Small size, irregular surface but non-porous particles mean high	The AbraMag Genomic DNA Magnetic Beads Kit is designed to extract and purify genomic DNA from tissues and bacteria (gram-positive and -negative) (Ahmed S,1980)
SPHERO™ carboxyl ferro-magnetic particles	Demagnetized and remagnetised easily and reproducibly	These are designed to study mechanotransduction across the cell surface by binding to cell surface receptors and applying mechanical stress directly to the receptor (Jolley ME,1984)
SPHERO™ amino ferro-magnetic particles	Demagnetized and remagnetised easily and reproducibly	These are designed to study mechanotransduction across the cell surface by binding to cell surface receptors and applying mechanical stress directly to the receptor(Jolley ME,1984)

SPHERO™ fluorescent carboxy ferromagnetic particles	Demagnetized and remagnetised easily and reproducibly	These are designed to study mechanotransduction across the cell surface by binding to cell surface receptors and applying mechanical stress directly to the receptor((Jolley ME,1984)
SPHERO™ polystyrene magnetic particles	Magnetic Particles are spherical in shape, and paramagnetic in nature. They are also very uniform in size.	The SPHERO™ Magnetic Particles can be used for cell separation, affinity purification, DNA probe assays, magnetic particle EIA, etc(Jolley ME,1984)
Ethylene/acrylic acid copolymer-209	EA-209/MT-100T is an odorless, fine white powder by Kobo products Inc	This product is composed of Ethylene/Acrylic Acid Copolymer, Titanium Dioxide, Alumina, and Aluminum Stearate. It is used as a component in cosmetic and personal care products, specifically combinations and complexes of UV Pigments(https://www.ulprospector.com/en/asia/PersonalCare/Detail/4727/207784/EA-209-MT-100T .)
Flo- beads SE-3107A(soft beads A)	This pressed powder formulation contains Kobo's Magnesium Myristate-treated pigments and fillers.	These treated products provide a great feel and even application, while improving the adherence of the pressed powder to the skin, resulting in long-wear(www.ulprospector.com/en/asia/PersonalCare/Detail/4727/596884/)
TOSPEARL® 3000 A	Tospearl Microspheres are a series of mono-dispersed, micro-fine spherical cross-linked siloxane particles. All of these T resins provide an exceptional feel to skin when incorporated into a variety of cosmetic formulations.	This newest member of the Tospearl Microspheres family has a slightly broader particle size distribution(http://www.momentive.com/products/showtechnicaldatasheet.aspx?id=14455)
TOSPEARL® 1110A	This property increases the lubricity effect created by the spherical nature of Tospearl Microspheres	Tospearl 1110A microsphere is the most effective grade for reducing powder agglomeration (http://www.momentive.com/products/showtechnicaldatasheet.aspx?id=14455)
TOSPEARL® 120 A	Tospearl 120A microsphere has the smallest average particle size (2.0 µm).	It is particularly useful for sebum absorption in addition to sensory benefits(http://www.momentive.com/products/showtechnicaldatasheet.aspx?id=14455)
TOSPEARL® 145 A	Tospearl 145A microsphere has the narrowest particle size distribution.	It is particularly useful if sensory in a cosmetic formulation is the highest priority(http://www.momentive.com/products/showtechnicaldatasheet.aspx?id=14455)
TOSPEARL® 2000B	With particles (on average) almost as small as Tospearl 145A microsphere	Tospearl 2000B microsphere offers a sensational feel in combination with the other benefits T (http://www.momentive.com/products/showtechnicaldatasheet.aspx?id=14455)
BPD-800	This product is composed of HDI/Trimethylol Hexyllactone Crosspolymer and Silica.	Microspheres offer a ball-bearing effect which will impart finished products with an elegant silky texture, increased payoff, and enhanced slip which promotes better blendability on the skin (https://www.ulprospector.com/en/na/PersonalCare/Detail/4671/207680/BPD-800)
BPD-500	It is a fine white to pale yellow powder with a characteristic odor. This product is composed of HDI/Trimethylol Hexyllactone Crosspolymer and Silica.	Microspheres offer a ball-bearing effect which will impart finished products with an elegant silky texture, increased payoff, and enhanced slip which promotes better blendability on the skin. (https://www.ulprospector.com/en/na/PersonalCare/Detail/4671/207677/BPD-500)

Evaluation of magnetic microsphere

1. Compatibility study between drug and polymer

The IR spectra of the free drug and the microspheres are recorded. The identical peaks corresponding to the functional groups and polymer features confirm that neither the polymer nor the method of preparation has affected the drug stability. It can also be done by Thin layer chromatography. The Rf values of the prepared microspheres can be compared with the Rf value of the pure drug.

2. Particle size analysis

Particle size are determined by microscopy method such as by ocular micrometer. It is also done by scanning electron microscopy

3. Flow properties

Flow properties such as tapped density, bulk density are noted and Carr's index is calculated to determine the nature of flow.

4. Drug content and Drug entrapment efficiency

Efficiency of drug entrapment is calculated as percentage drug entrapment. Theoretical drug content can be determined by assuming that the entire drug present in the polymer solution used gets entrapped in microspheres and no loss occurs in the preparation of microspheres.

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

5. Effect of pH on magnetic microspheres

Equilibrated Swelling Rate of the microspheres is measured by immersing dry and known weight of microspheres into buffer solution with different pH data for 1 hour at room temperature. Microspheres are then removed from the buffer solution and weighed.

ESR is calculated by formula W_e/W_d , where W_e is the weight of the solution in equilibrated swollen microspheres at each predetermined buffer solution with different pH data.

The Swelling Rate, $(W_s+W_d)/W_d$, is defined as the ratio of total weight of water in swollen microspheres to the weight of the dried microspheres, where W_s is the weight of adsorbed water and W_d is the weight of the microspheres at dry state (Le B et al.2001; Vyas SP, 2004)

6. In vitro release studies

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. Drug release is calculated at different time intervals (Fricker J, 2001)

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 so more researches, 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.

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