WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 5, 198-217. Review Article ISSN 2277–7105

MAGNETIC MICROSPHERES: PIONEERING ADVANCEMENTS IN PRECISION DRUG DELIVERY AND BEYOND

Reinhard David*, Ganesh N. S., J. Adlin Jino Nesalin and Vineeth Chandy

Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru, Karnataka, India.

Article Received on
07 January 2025,

Revised on 27 Jan. 2025,
Accepted on 17 Feb. 2025

DOI: 10.20959/wjpr20255-35671

***Corresponding Author**
Reinhard David
Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru, Karnataka, India.

ABSTRACT

Magnetic drug delivery is an innovative approach that involves attaching a drug to a biocompatible, magnetically responsive component, encapsulated in a biodegradable polymeric matrix. This method allows for precise targeting of therapeutic agents to specific sites within the body through the application of a high-gradient magnetic field, leading to improved therapeutic outcomes and reduced side effects. Targeted magnetic systems include magnetic microspheres, liposomes, nanoparticles, resealed erythrocytes, and emulsions, with microspheres typically ranging in size from 1 to 1000 µm. These magnetic polymer microspheres consist of polymeric shells that prevent particle aggregation and magnetic cores (e.g., iron oxide, nickel, cobalt) that generate the magnetic response, facilitating targeted drug delivery. The polymeric shell not only protects the drug from degradation but also enhances its efficacy and minimizes toxicity. Magnetic particles can carry therapeutic drugs or radioisotopes, which are directed to the targeted area via an external magnetic field, resulting in higher concentrations at the disease site compared to traditional drug administration. Additionally, these particles are biocompatible, non-toxic, and show significant accumulation in target tissues. Various synthesis methods for these particles, such as continuous solvent evaporation, phase separation emulsion polymerization, crosslinking, and sonochemical methods, have been explored. This drug delivery system offers new opportunities in RNA and DNA separation, cell isolation, and environmental monitoring, demonstrating a promising avenue for improved bioanalysis and therapeutic applications.

KEYWORDS: Magnetic microspheres, targeted drug delivery, controlled release, magnetite,

phagocytosis.

INTRODUCTION

Magnetic drug delivery is a promising technique in which a drug is attached to a small, biocompatible magnetically responsive component, then encapsulated in a biodegradable polymeric matrix. A stable, pharmacologically active formulation is created and injected into the bloodstream. By applying a high-gradient magnetic field, the drug particles are pulled to the target site, allowing for precise delivery and improved therapeutic outcomes.

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.[1]

Small particles with a diameter in the micrometre range (1-1000 µm) are known as microspheres. Typically, magnetic polymer microspheres consist of polymeric shells that provide positive functional groups and prevent particle aggregation, and magnetic cores that exhibit a significant magnetic response. Large doses of medication can be substituted with smaller doses that are magnetically directed to specific locations. In addition, medications inside the sphere are shielded from deterioration while being transported. These medications don't damage delicate organs like bone marrow since they are targeted rather than absorbed through the bloodstream. The target site is the direction of a magnet that is externally positioned. The magnet can be housed in apparatus that resembles an open magnetic resonance imaging scanner, or it can be a permanent magnet in the shape of a rod of any length.[2]

Targeted magnetic particles typically consist of a polymer shell around a magnetic core. The magnetic agent, which can be iron oxide (magnetite; Fe3O4), nickel, cobalt, neodymium, iron, iron-boron, or samarium-cobalt, is present as microscopic magnetic nanoparticles that make up the core. The magnetic properties are the result of this delivery system component. Encircling the magnetic core is a polymer shell that can decrease toxicity, increase drug efficacy, and shield the medication from deterioration. Polymers and a magnetic entity are integrated with therapeutic medicines.[3]

Magnetic drug delivery using particulate carriers is a highly effective method for targeting a drug to a specific disease site. In this approach, a drug or therapeutic radioisotope is attached

to a magnetic compound, which is then injected into a patient's bloodstream. A strong magnetic field is applied to guide the particles to the targeted area.[4]

Research has shown that drugs can reach disease areas at much higher concentrations several times more compared to traditional free drug administration. Additionally, these particles are considered nontoxic, biocompatible, injectable, and tend to accumulate in target tissues at high levels.[3]

TYPES OF MAGNETIC MICROSPHERES

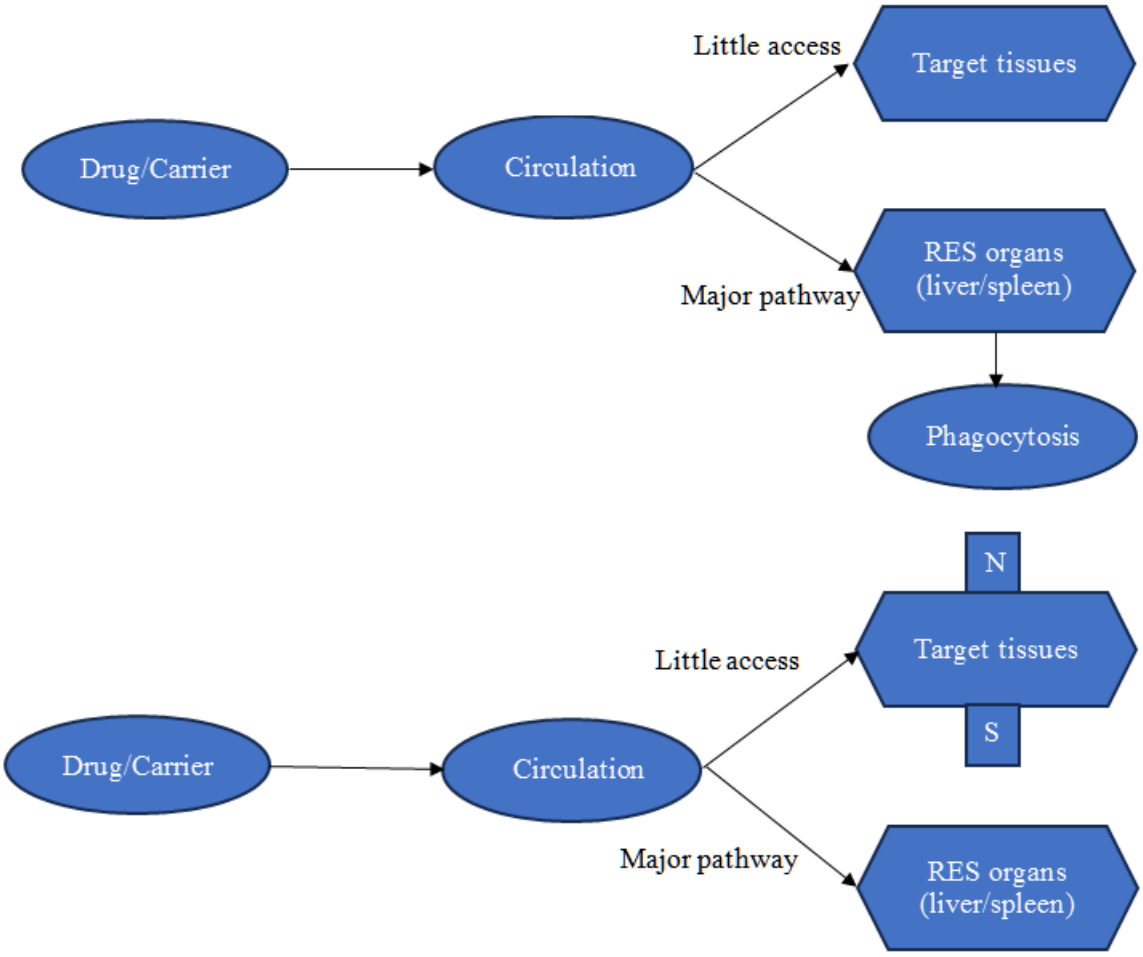
Magnetic carriers generate a magnetic response when exposed to a magnetic field, due to the materials incorporated into magnetic microspheres, such as chitosan, dextran, and others.[5] The different types of magnetic microspheres include:

I. Therapeutic Microspheres: These are used to deliver chemotherapeutic agents directly to liver tumours. This system can also be used to target drugs like proteins and peptides.[6]

II. Diagnostic Microspheres: These are employed for imaging liver metastases and for differentiating bowel loops from other abdominal structures by forming nanosized particles of superparamagnetic iron oxides.[7]

PRINCIPLE OF MAGNETIC TARGETING

Drug targeting is a specialized method of drug delivery that directs the medication to its intended site of action or absorption, such as a specific cell, organ, or tissue.[8] The goal of this targeted approach is to enhance drug delivery efficiency while minimizing toxicity and side effects. The magnetic drug transport method relies on the concept of encapsulating the drug in magnetic microspheres or attaching it to their surface. When the magnetic carrier is administered intravenously, it accumulates in the area exposed to the magnetic field, often enhanced by magnetic aggregation. This accumulation allows for the drug to be delivered directly to the target site. The effectiveness of this accumulation depends on factors such as particle size, surface characteristics, magnetic field strength, and blood flow rate.[9] The magnetic field aids in directing the carrier to the targeted area. This technique enables the delivery of high concentrations of chemotherapeutic agents to the target site, reducing the toxic effects on surrounding healthy tissues and the rest of the body. By using magnetic targeting, it’s possible to concentrate a large amount of drug at a localized disease site, leading to more effective treatment with minimal side effects.



Magnetite

Magnetic particles consist of one or more magnetic cores surrounded by a coating matrix made of materials like polymers, silica, or hydroxylapatite, which have terminal functional groups. The magnetic core is typically magnetite, an iron oxide that combines FeO and Fe_2O_3. This material, also known as ferrous ferrite, exhibits magnetic properties similar to pure iron. Magnetite particles are usually small and fine, and they've been applied in various medical fields, such as in transmission radiography, as a contrast agent for the gastrointestinal tract, for promoting clotting in arteriovenous malformations, as blood flow tracers, and in radionuclide angiography. Due to their small size, iron particles can navigate through tiny capillaries in the body.[10]

MECHANISM OF MAGNETIC MICROSPHERES

Drug release from microspheres occurs through different mechanisms

- A - Diffusion through water filled pores
- B - Diffusion through the polymer

- C - Osmotic pumping
- D - Hydrolysis/Erosion[11]

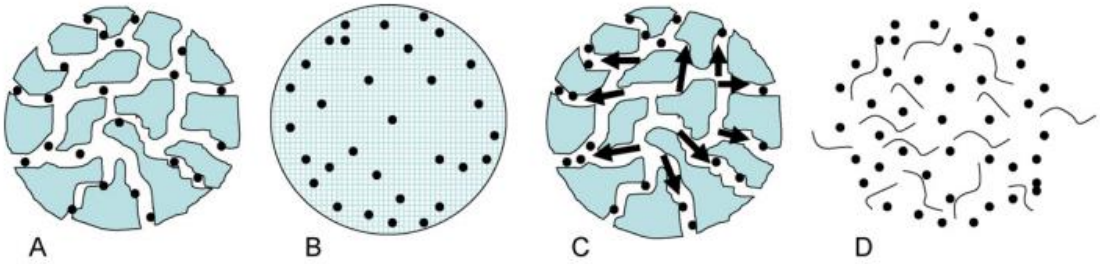


Figure 1: Different drug release mechanism from magnetic microspheres.

When the polymer is immersed in water or introduced in vivo, it rapidly absorbs water, with hydration occurring much faster than drug release.[12] The water absorbed into the polymer matrix creates pores, making water absorption a process that forms these pores. Initially, these pores are too small to allow drug transport, but as the number and size of the water-filled pores increase, they form a connected porous network that facilitates drug release.[13]

Hydrolysis, which involves the breaking of ester bonds and a subsequent decrease in molecular weight (M_w), begins immediately when the polymer comes into contact with water. This process generates acids that further accelerate the hydrolysis reaction.[14] This auto-catalytic effect causes heterogeneous degradation within PLGA matrices,[15] meaning that degradation occurs more rapidly at the center of the matrix compared to the surface. As the size of the drug delivery system (DDS) increases, the acid gradient becomes more pronounced, amplifying this effect.[16] However, heterogeneous degradation has also been observed in particles and films as small as 10 µm.[17] As M_w decreases, the polymer becomes less hydrophobic, and when Mw reaches 1100 Da, the oligomers become water-soluble.[18]

Erosion, which refers to the loss of polymer mass, begins when the degradation products of the polymer dissolve and diffuse into the release medium. PLGA typically undergoes bulk erosion rather than surface erosion, as it hydrates relatively quickly.[19] The dissolution of degradation products and the erosion process create pores. Initially small pores form through water absorption or polymer erosion, and as the polymer continues to interact with water, hydrolysis occurs. The acids produced locally catalyse further degradation, causing the polymer to dissolve within the pores, leading to additional erosion. Over time, small pores grow and eventually merge with neighbouring pores, resulting in fewer but larger pores.[20] In

some cases, pores may close.[21,22] This behaviour is related to the mobility of the polymer chains and their ability to rearrange.[23] **Figure:2** depicts the complex picture of physico-chemical processes taking place within PLGA matrices, leading to drug release.

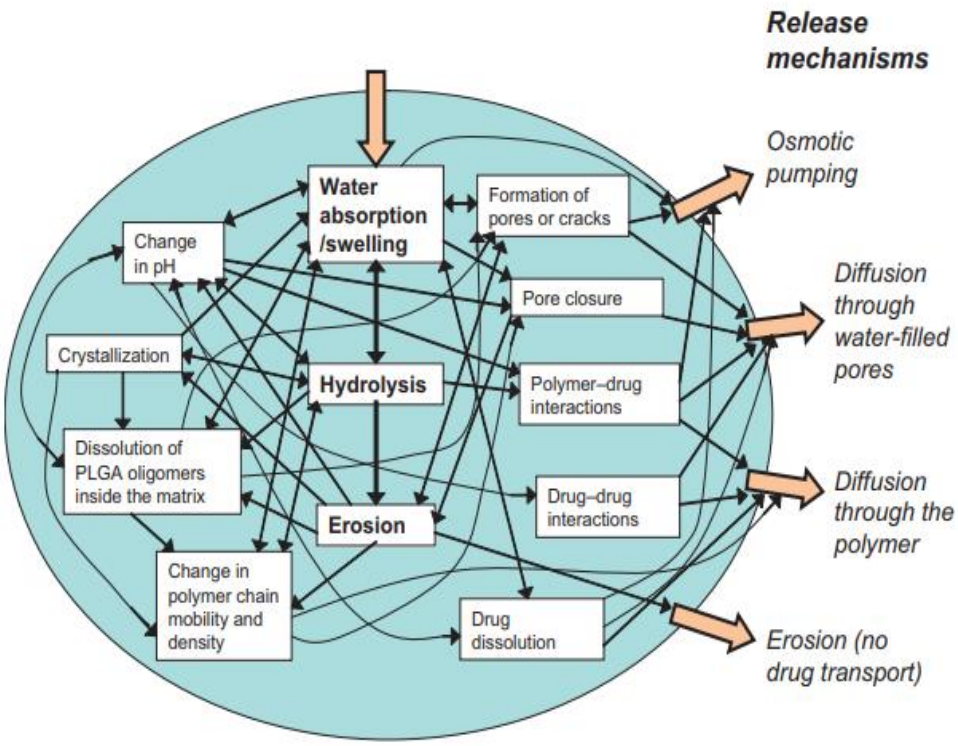


Figure 2: The complex picture of physicochemical processes taking place within PLGA matrices, leading to drug release. The influence of processes on drug release and on other processes is illustrated by arrows.

The dissolved polymer degradation products influence the system in several ways:

(i) As acids, they catalyse the hydrolysis process.

(ii) They act as plasticizers, which increases the rate of water absorption and reduces the polymer's resistance to transport.[24]

(iii) They raise the osmolality within the polymer matrix, which in turn enhances the force driving water absorption.

(iv) These degradation products are also capable of crystallizing, particularly when there are long sequences of the same monomer, such as glycolic, l-lactic, or d-lactic monomers.[25]

This crystallization can hinder water absorption, further degradation, and transport.[26]

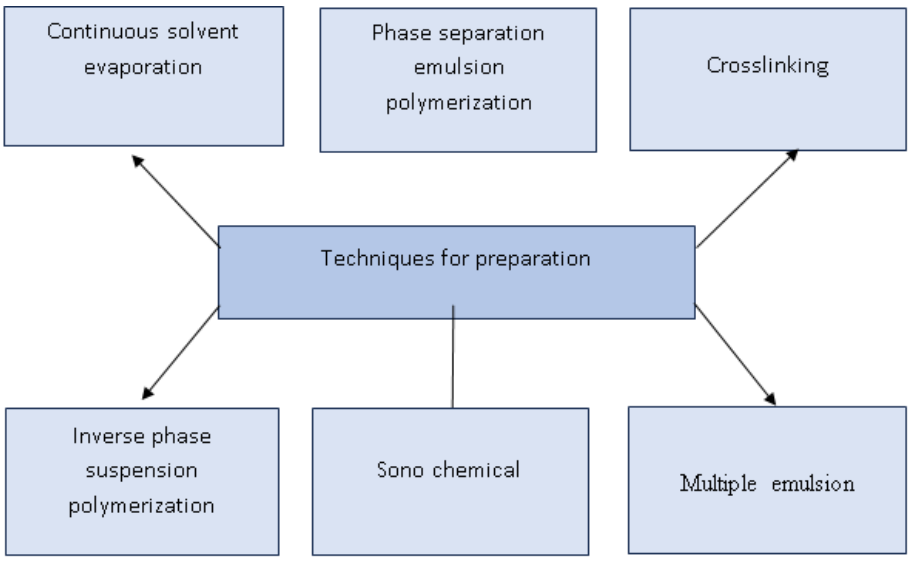
METHODS AND METHODOLOGY

When preparing microspheres, several essential criteria must be fulfilled

- The capacity to incorporate the drug at suitable concentrations.
- Stability of the formulation after synthesis, ensuring it maintains a clinically acceptable shelf life.
- The ability to control particle size and ensure easy dispersion in aqueous solutions for injection.
- Effective management of the release rate of the active ingredient over a prolonged period.
- Biocompatibility, along with predictable biodegradability, and the potential for chemical modifications.[27]

Criteria for selecting drugs for the formation of magnetic microspheres

- Magnetic microspheres are used when the drug is highly dangerous and should not circulate freely in the bloodstream.
- When the drug is very expensive and we cannot afford to lose any of it.
- When a selective regional effect is needed to achieve a localized therapeutic goal.
- When an alternative formulation is necessary to continue treatment for patients who need to temporarily stop systemic therapy due to life-threatening toxicity targeting specific organs.[1]



1. Continuous solvent evaporation method

In this method, the drug and polymer (carrier) are dissolved in a suitable volatile organic solvent. Magnetite (for magnetic microspheres) is then added to this solution while stirring to create a uniform suspension. This suspension is subsequently mixed with an immiscible auxiliary solution under vigorous stirring. The volatile organic solvent is slowly evaporated at

22-30°C to form microspheres. Afterward, the microspheres are centrifuged, freeze-dried, and stored at 4°C.[28] **Figure:3** indicates the different steps involved in continuous solvent method.

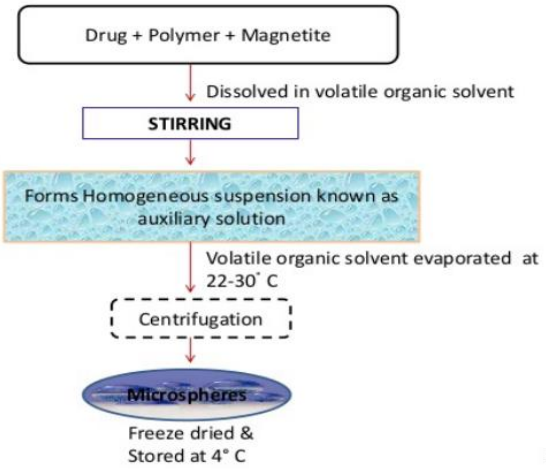


Figure 3: Continuous solvent evaporation method.

2. Phase separation emulsion polymerization

A brief aqueous solution of the polymer, drug, and magnetite is added to vegetable oil and emulsified using an emulsifying agent. The solution is stirred with a magnetic stirrer at 1,500 rpm for 2 minutes. The mixture is then stabilized by heating at 100-150°C. A cross-linking agent is added dropwise to the emulsion while stirring continuously. The magnetic microspheres form in the oil suspension and are then separated from the oil through washing. The final product is freeze-dried and stored at 4°C.[29] **Figure:4** indicates the synthesis of magnetic microspheres by phase separation emulsion polymerization.

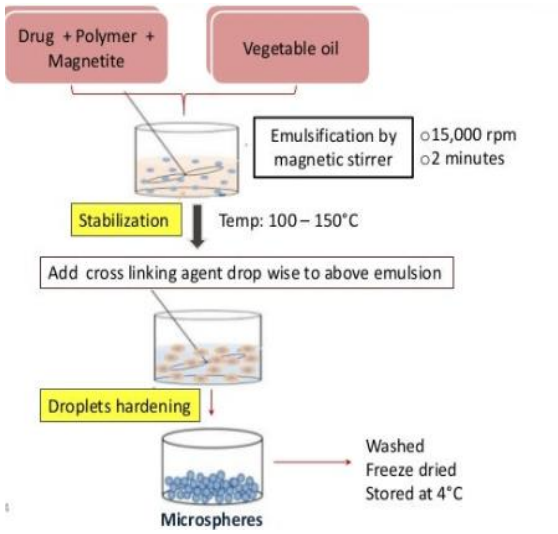


Figure 4: Phase separation emulsion polymerization.

3. Crosslinking method

The following reagents are used in the process

- Acetate buffer serves as the solvent for the chitosan polymer.
- Cross-linker: Glutaraldehyde.
- Medium: Sodium hydroxide solution.

Synthesis of magnetic fluid: A 35% (w/v) ferrous sulphate solution, a 54% (w/v) ferric chloride solution, and a 36% (w/v) sodium hydroxide solution are prepared using distilled water. The ferric and ferrous salts are then mixed, stirred, and heated. Once the temperature reaches 55°C, the alkaline solution is added. The mixture is stirred for 30 minutes, and then 5g of PEG-10000 is added. The temperature is raised to 80°C and maintained for another 30 minutes. The mixture is subsequently neutralized as it cools, completing the preparation of the magnetic fluid.

Next, a 1% (w/w) chitosan solution is prepared in acetate buffer at pH 4.5. The dissolved chitosan is then added dropwise to the magnetic fluid. The resulting chitosan magnetic microspheres are washed with deionized water and soaked in 1%, 3%, and 5% glutaraldehyde solutions for 2 hours before being washed again with deionized water.[30] **Figure:5** indicates the preparation of magnetic microspheres by crosslinking method.

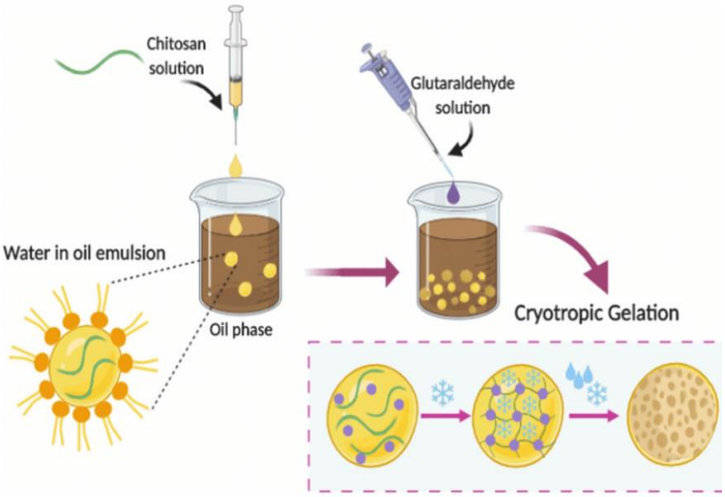


Figure 5: Crosslinking method.

4. Inverse Phase Suspension Polymerization

A 250mL three-neck flask fitted with a mechanical stirrer used for performing the reaction. Continuous phase includes: 100 mL of castor oil and 10 mL of span 80. Determined 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.[31] **Figure:6** indicates the synthesis of magnetic microspheres by inverse phase suspension polymerization method.

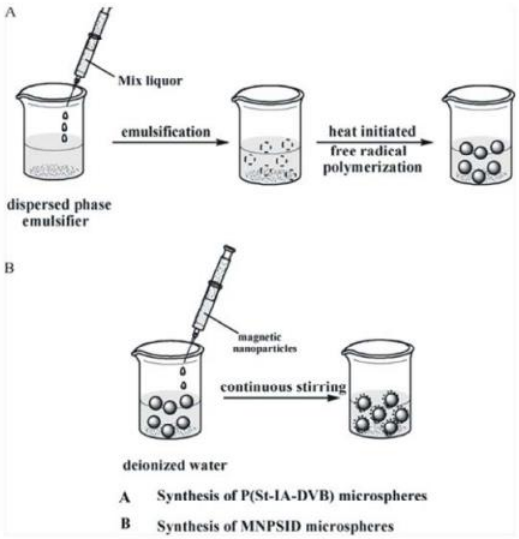


Figure 6: Inverse phase suspension polymerization method.

5. Sono chemical method

In this method, the microspheres are having iron oxide-filled and coated globular BSA. Here, the magnetic microspheres were prepared from BSA and iron pentacarbonyl or from BSA and iron acetate. Protein microspheres have a number of biomedical application, i.e., use as echo contrast agents for sonography. The microsphere was formed by two ways

(i) by heat denaturation at various temperatures or

(ii) by cross linking with carbonyl compounds in the ether phase.

Cross linking was completed as the microspheres are formed by chemically cross-linking cysteine residues of the protein with HO2 radical formed around a nonaqueous droplet. The chemical cross-linking is known to be responsible for the formation of the microspheres. This is due to the chemical ejects of the ultrasound radiation on an aqueous medium.[11] **Figure:7** indicates the steps involved in preparation of magnetic microspheres by sonochemical method.

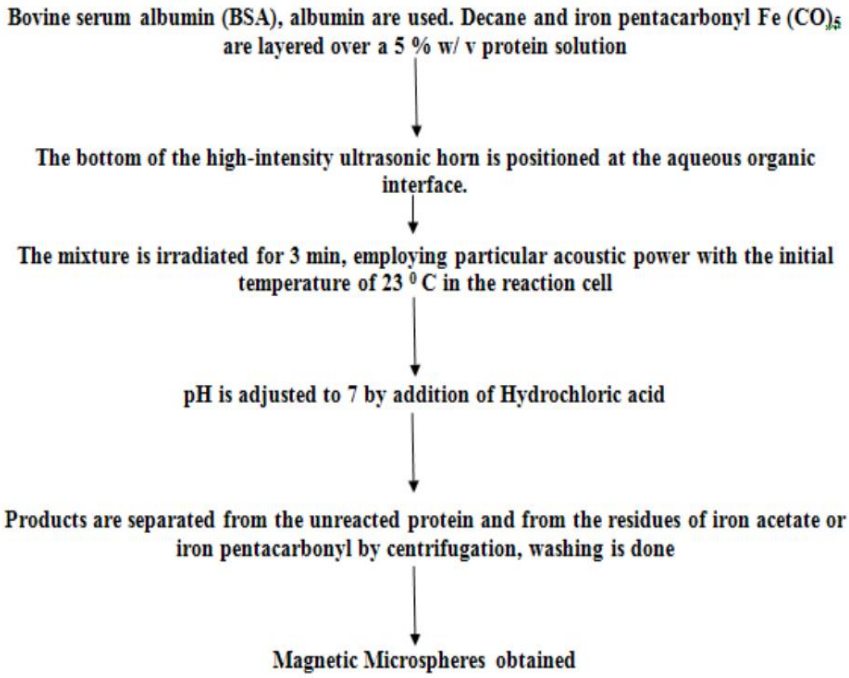


Figure 7: Sonochemical method.

5. Multiple emulsion method

In this method, researchers incorporate water-dispersible magnetite with a poly (acrylic acid)-poly (ethylene glycol) (PEG/PAA) coating into the inner water phase containing bovine serum albumin (BSA). A 0.2 ml solution of 1 mg/ml BSA is added to a 4 ml mixture of dichloromethane and ethyl acetate (EA) in a 3:1 ratio, which also contains 200 mg of poly (lactic-co-glycolic acid). A w/o emulsion is prepared using a homogenizer in an ice bath at 26,000 rpm for 2.5 minutes. Next, 15 ml of a 1% poly vinyl alcohol (PVA) solution is added directly to the primary emulsion and re-emulsified under the same conditions for another 2.5 minutes. The resulting w/o/w emulsion is then transferred to a beaker containing 85 ml of 1% PVA solution and stirred in a hood with an overhead propeller for 2 hours, allowing the solvent to evaporate. The solidified microspheres are collected by centrifugation at 2500 rpm for 10 minutes and washed three times with distilled water.[11] **Figure:8** indicates preparation of magnetic microspheres by multiple emulsion method.

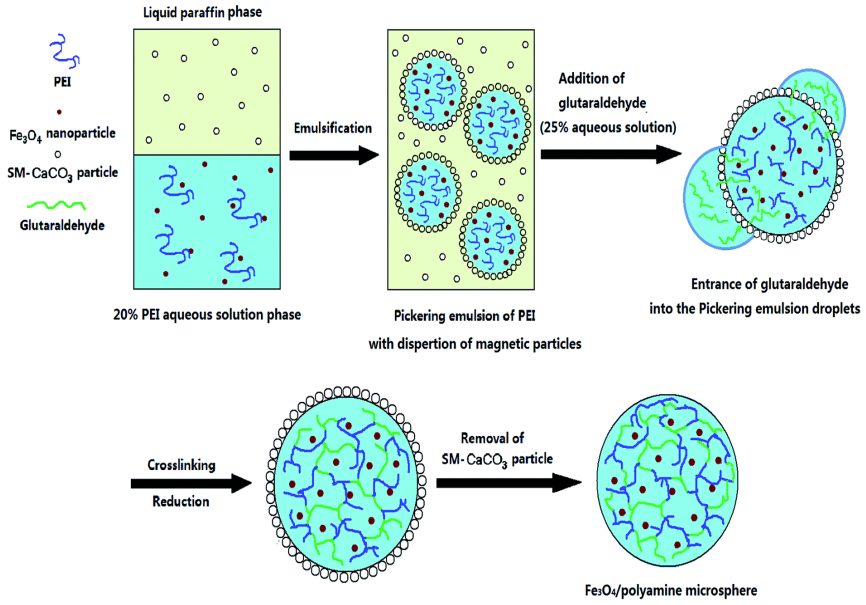


Figure 8: Multiple emulsion method.

Storage

Several precautions should be observed during the formation of microspheres

1. Microsphere suspensions should not be frozen, as freezing may lead to irreversible aggregation.
2. Cold storage (2-8°C) is recommended to prevent microbial growth. "Standard" (non-protein coated) microsphere suspensions do not contain antimicrobial agents.
3. All suspensions should be handled using aseptic techniques.
4. Continuous rolling (e.g., 3-5 revolutions per minute on a cell culture roller) is advised to maintain microspheres in suspension without creating foam, as foam may cause particle loss due to bead entrapment.
5. If continuous rolling is not feasible, the particles should be thoroughly resuspended before use. Higher-speed rolling (30-60 revolutions per minute for 2-4 hours) is effective for resuspending settled material.
6. The rolling speed should be adjusted to effectively resuspend the beads without generating foam.[32]

CHARACTERIZATION OF MAGNETIC MICROSPHERES

1. Particle size and size distribution

The particle size of the microspheres is determined using an optical microscope with a calibrated ocular micrometre. A total of 100 particles are measured, and the average size is calculated based on these measurements.

2. Surface characterization

Surface characteristics can be analysed using

a. High-resolution microscopy

b. Scanning electron microscopy

c. Scanning tunnelling microscopy.

3. Surface charge analysis

Surface charge can be analysed by

a. Micro electrophoresis

b. Laser doppler anemometry.

4. Density

a. Tapped density

Tapped density is determined by accurately weighing the microspheres, pouring them into a measuring cylinder, and tapping the cylinder 100 times from a fixed height to determine the tapped volume. Tapped density is then calculated.

$$Tapped\ Density\ =\ Weight\ of\ powder\ /\ Tapped\ volume\ of\ powder$$

b. Bulk Density

Bulk density is determined by weighing the microspheres and measuring their bulk volume.

$$Bulk\ Density\ =\ Weight\ of\ powder\ /\ Bulk\ volume\ of\ powder$$

5. Flow Properties

Flow properties are measured in the following ways

a. Angle of Repose

The angle of repose refers to the angle formed between a static heap of particles and the horizontal. The flow properties of microspheres can be evaluated using the fixed funnel flow method to calculate the angle of repose.

$$\tan\theta\ =\ h\ /\ r$$

$$\theta\ =\ \tan^{-1}(h\ /\ r)$$

b. Hausner Ratio

This ratio is calculated from the tapped and bulk densities.

$$Hausner\ Ratio\ =\ Tapped\ density\ /\ Bulk\ density$$

6. Hardness

Hardness refers to the force required to break a microsphere. It can be measured using the Monsanto hardness apparatus.

$$Hardness = Final\ reading - Initial\ reading$$

7. Friability

Friability is determined using a Roche Friabilator.

$$\%\ Friability = (Initial\ weight - Final\ weight) / Initial\ weight \times 100$$

8. Surface Area

Surface area can be measured using suitable techniques.

9. Porosity

Porosity refers to the void spaces within the microspheres.

10. Drug Content

Drug content is analysed to determine the amount of active drug in the microspheres.

11. Drug Release Profiles

Drug release profiles describe the release pattern of the drug from the microspheres over time.[32]

EVALUATION OF MAGNETIC MICROSPHERES

1. IR spectroscopic studies

The IR spectra of the free drug and the microspheres were analysed. The matching peaks corresponding.

To the functional groups albumin features (such as BSA, egg albumin and human serum albumin confirm that the polymer and preparation method have not affected the drug's stability.

2. Thin layer chromatographic (TLC) studies

The TLC method was used to assess the drug stability in the prepared microspheres. The Rf values of the microspheres were compared with those of pure drug, indicating the constancy of the drug.

3. Surface topography by SEM

Scanning electron microscopy (SEM) was used to examine the surface morphology of the microspheres, revealing details such as their shape and size.

4. Particle size distribution of prepared microspheres

The particle size of the microspheres was measured using optical microscopy with a calibrated stage micrometre and random samples from each formulation were selected for measurement.

5. Drug entrapment capacity

The effectiveness of drug entrapment for each batch was calculated as the percentage of drug entrapment using the following formula

$$\%\ Entrapment = (Actual\ content / Theoretical\ content) \times 100$$ [35]

6. Drug release profile

***In-Vitro* Methods**

Experimental methods are essential for assessing the release characteristics and permeability of a drug through membranes. Several *in-vitro* and *in-vivo* techniques have been developed for this purpose. *In-vitro* drug release studies are commonly used for quality control in pharmaceutical production and product development. Standard USP or BP dissolution apparatus are utilized to study the *in-vitro* release profiles, employing both rotating elements such as paddles and baskets. The dissolution medium typically ranges from 100 to 500 ml, with rotation speeds varying from 50 to 100 rpm.

***In-vivo* methods**

The most frequently used *in-vivo* methods include

A) Animal Models

Animal models are primarily employed for screening series of test compounds, exploring the mechanisms and efficacy of permeation enhancers, and evaluating different formulations. Numerous animal models are reported in the literature, through *in-vivo* studies are less common. Animals such as dogs, rats, rabbits, cats, hamsters, pigs and sheep are typically used. The standard procedure involves anesthetizing the animal and administering the dosage form. In rats, the oesophagus may be ligated to limit absorption to the oral mucosa only. Blood samples are collected at various time points for analysis.

B) Buccal absorption test

The buccal absorption test, developed by Beckette and Triggs in 1967, is a simple and reliable method to measure drug loss from the human oral cavity for both single and multi-component drug mixtures. This test has been successfully used to investigate the impact of drug structure, contact time, initial drug concentration and the pH of the solution while the drug remains in the oral cavity.[35]

APPLICATIONS OF MAGNETIC MICROSPHERES

1. Enzyme immobilisation

In 1973, magnetic carriers were first used for enzyme immobilization. Free enzymes were immobilized onto the surface or porous walls of magnetic carriers through physical adsorption or covalent bonding. Compared to other immobilization carriers, magnetic carriers offer several advantages: (1) Immobilized enzymes can be easily separated from the reactants or products. (2) The movement of immobilized enzymes can be controlled using external magnetic fields, significantly enhancing catalytic efficiency. (3) Enzyme-catalysed reactions can be continuously monitored and controlled within a bioreactor using a magnetic field, which helps reduce enzyme consumption.

2. Target drugs

Targeted drugs are designed to deliver medication specifically to pathological tissues by exploiting the pH sensitivity, thermal sensitivity, and magnetism of drug carriers. Drug delivery can be categorized into passive and active methods. Passive drug delivery relies on changes in the hydrophilic and hydrophobic properties of the carrier surface and the size of the carriers. Active drug delivery, on the other hand, directs drugs to the targeted pathological areas using external magnetic fields and the specific affinity of coupled ligands. This approach not only minimizes potential toxic side effects but also reduces the amount of drug needed.

3. RNA and DNA separation

DNA and RNA separation using magnetic carriers can be classified into two types: non-specialized separation and specialized separation. In non-specialized separation, DNA or RNA precipitates out of the solution and attaches to the surface of magnetic carriers in the presence of high salt concentrations and hydrophilic organic agents like polyethylene glycol. Magnetic silica carriers are frequently employed in this process.

4. Cell isolation

Magnetic carriers used for cell isolation rely on affinity principles. An antibody is attached to the surface of magnetic carriers, forming immunomagnetic beads (IMBs). When exposed to an external magnetic field, these beads bind to antigens on the surface of target cells, allowing for cell isolation. This method offers several advantages, including simplicity, speed, high purity, and good activity of the isolated cells.[34]

Applications in other fields

1. Catalyst field

Zhang et al developed a superparamagnetic spheroidal c-Al2O3 catalyst carrier using oil moulding.[35] Chang et al created a magnetic nano-sized solid acid catalyst by combining magnetic materials with solid acid.[36]

2. Environmental monitoring and bio-analysis

Yang et al detected hydrazine concentrations as low as 0.1 µg/L in water using magnetic microspheres.[37] Yu et al quickly identified coliform bacteria in food and environmental water samples by employing magnetic carriers in fluorescent immuno-electrochemical analysis.[38] Takafuji successfully removed metal ions from water through the use of magnetic microspheres.[39]

CONCLUSION

In conclusion, magnetic microspheres have emerged as a transformative technology in precision drug delivery, offering substantial improvements in targeted treatment and therapeutic outcomes. By utilizing the magnetic properties of these microspheres, drugs can be effectively directed to specific sites within the body, reducing systemic side effects and enhancing therapeutic efficacy. The incorporation of biocompatible and biodegradable polymeric matrices not only protects the drugs from degradation but also ensures their stability during transport. Beyond drug delivery, magnetic microspheres demonstrate significant potential in applications such as RNA and DNA separation, cell isolation, and environmental monitoring. As ongoing research and development in this field advance, magnetic microspheres are poised to play a critical role in the future of personalized medicine, enabling more precise, effective, and safer treatments across a wide range of medical conditions.

REFERENCE

1. Kakar S, Jain A, Singh R. Magnetic Microspheres: A Novel Targeting Delivery System. FABAD J. Pharm. Sci., 2017 Jul 1; 42(3): 209-23.
2. Sharma DI, Sharma AB. Magnetic microsphere an emerging drug delivery system. Asian J. Pharm. Clin. Res., 2017; 10(6): 54.
3. Enriquez GG, Rizvi SA, D'Souza MJ, Do DP. Formulation and evaluation of drug-loaded targeted magnetic microspheres for cancer therapy. Int J Nanomedicine, 2013 Apr 10; 1393-402.
4. Chandna A, Batra D, Kakar S, Singh R. A review on target drug delivery: magnetic microspheres. J. Acute Dis., 2013 Jan 1; 2(3): 189-95.
5. Li SP, Kowarski CR, Feld KM, Grim WM. Recent advances in microencapsulation technology and equipment. Drug Dev., 1988 Jan 1; 14(2-3): 353-76.
6. Kutmalge MD, Ratnaparkhi MP, Wattamwar MM, Chaudhari SP. A review on microsphere. PSM, 2014 Apr 2; 5.
7. Shanthi NC, Gupta R, Mahato KA. Traditional and emerging applications of microspheres: A review. Int. J. Pharm. Res., 2010; 2(1): 675-81.
8. Vidyavati S, Koppisetti, Sahiti B. Magnetically modulated drug delivery systems. IJDDR, 2010 Jan-March; 3(1): 260-266.
9. Shaikh Siraj, GJ Khan, Patel Huzaifa, Wedachchhiya Sufiyan, Shaoor Ahmad, Sanjay Padvi. Magnetic microspheres as novel expansion in multiparticulate drug delivery system. World J. Pharm. Res., 2016; 5(1): 337-346.
10. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery. New Delhi: CBC Publisher & Distributors, 2004; 459-63.
11. Fredenberg S, Wahlgren M, Reslow M, Axelsson A. The mechanisms of drug release in poly (lactic-co-glycolic acid)-based drug delivery systems—A review. Int. J. Pharm, 2011 Aug 30; 415(1-2): 34-52.
12. Batycky RP, Hanes J, Langer R, Edwards DA. A theoretical model of erosion and macromolecular drug release from biodegrading microspheres. J. Pharm. Sci., 1997 Dec 1; 86(12): 1464-77.
13. Mochizuki A, Niikawa T, Omura I, Yamashita S. Controlled release of argatroban from PLA film—Effect of hydroxyl esters as additives on enhancement of drug release. J. Appl. Polym. Sci., 2008 Jun 5; 108(5): 3353-60.
14. Shenderova A, Burke TG, Schwendeman SP. The acidic microclimate in poly (lactide-co-glycolide) microspheres stabilizes camptothecins. Pharm. Res., 1999 Feb; 16: 241-8.

15. Li S, McCarthy S. Further investigations on the hydrolytic degradation of poly (DL-lactide). Biomaterials, 1999 Jan 1; 20(1): 35-44.
16. Dunne M, Corrigan OI, Ramtoola Z. Influence of particle size and dissolution conditions on the degradation properties of polylactide-co-glycolide particles. Biomaterials, 2000 Aug 1; 21(16): 1659-68.
17. Lu L, Garcia CA, Mikos AG. In vitro degradation of thin poly (DL-lactic-co-glycolic acid) films. Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials, 1999 Aug; 46(2): 236-44.
18. Park TG. Degradation of poly (D, L-lactic acid) microspheres: effect of molecular weight. JCR., 1994 May 1; 30(2): 161-73.
19. Chen X, Ooi CP, Lye WS, Lim TH. Sustained release of ganciclovir from poly (lactide-co-glycolide) microspheres. J. Microencapsul., 2005 Sep 1; 22(6): 621-31.
20. Batycky RP, Hanes J, Langer R, Edwards DA. A theoretical model of erosion and macromolecular drug release from biodegrading microspheres. J. Pharm. Sci., 1997 Dec 1; 86(12): 1464-77.
21. Fredenberg S, Wahlgren M, Reslow M, Axelsson A. Pore formation and pore closure in poly (D, L-lactide-co-glycolide) films. Journal of controlled release, 2011 Mar 10; 150(2): 142-9.
22. Kang J, Schwendeman SP. Pore closing and opening in biodegradable polymers and their effect on the controlled release of proteins. Molecular pharmaceutics, 2007 Feb 5; 4(1): 104-18.
23. Yamaguchi Y, Takenaga M, Kitagawa A, Ogawa Y, Mizushima Y, Igarashi R. Insulin-loaded biodegradable PLGA microcapsules: initial burst release controlled by hydrophilic additives. JCR, 2002 Jun 17; 81(3): 235-49.
24. Mauduit J, Bukh N, Vert M. Gentamycin/poly (lactic acid) blends aimed at sustained release local antibiotic therapy administered per-operatively. II. The case of gentamycin sulfate in high molecular weight poly (dl-lactic acid) and poly (l-lactic acid). JCR., 1993 Mar 1; 23(3): 221-30.
25. Schliecker G, Schmidt C, Fuchs S, Wombacher R, Kissel T. Hydrolytic degradation of poly (lactide-co-glycolide) films: effect of oligomers on degradation rate and crystallinity. Int. J. Pharm., 2003 Nov 6; 266(1-2): 39-49.
26. Li S. Hydrolytic degradation characteristics of aliphatic polyesters derived from lactic and glycolic acids. Journal of Biomedical Materials Research: An Official Journal of The

Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials, 1999; 48(3): 342-53.

27. Shi W, Ching YC, Chuah CH. Preparation of aerogel beads and microspheres based on chitosan and cellulose for drug delivery: A review. Int. J. Biol. Macromol., 2021 Feb 15; 170: 751-67.
28. Lachman LA, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Mumbai, India: Varghese Publishing House, 2002; 414-5.
29. Satinder Kakar SK, Ramandeep Singh RS. Preparation of magnetic microspheres of mesalamine by phase separation emulsion polymerisation technique. Afr. J. Pharmacy Pharmacol., 2014; 8(9): 246-58.
30. Nasra MK, Mohamed MM, Elblbesy MA, Hefney BA. Preparation of biocompatible magnetic microspheres with chitosan. JBNB., 2011 Apr 29; 2(02): 193.
31. Vidya KP, Gopinath E, Nesalin JA, Chandy V. Unveiling the potential of microsponges: Enhancing oral bioavailability. WJBPHS, 2024; 17(2): 405-14.
32. Morino T, Kawai N, Ito A, Kobayashi T, Yasui T. Novel nano-thermal ablation therapy using functionalized heat-generating nanoparticles for solid cancer treatment. WJCOR, 2023 Feb 4; 29-46.
33. Chan LW, Heng PW. Effects of poly (vinylpyrrolidone) and ethylcellulose on alginate microspheres prepared by emulsification. J. Microencapsul, 1998 Jan 1; 15(4): 409-20.
34. Zhang B, Xing J, Liu H. Preparation and application of magnetic microsphere carriers. Frontiers of Chemical Engineering in China., 2007 Feb; 1: 96-101.
35. Zhang G D, Shan G B, Meng X K, An Z T, Jia G H, Liu H Z. Effects of thermal treatment in solvents on properties of magnetic spheroidal c-A12O3 catalyst carrier. Chinese J Catal., 2003; 24(11): 839–44.
36. Chang Z, Guo C X, Li F, Duan X. Preparation and characterization of the novel magnetic nano-size solid acid catalyst. Acta Chim. Sin., 2002; 60(2): 298–304.
37. Yang M, Li H L. Determination of trace hydrazine by differential pulse voltammetry using magnetic microspheres. Talanta, 2001; 55: 479–484.
38. Yu H. Developing an immunomagnetic separation-fluorescent immunoassay (IMS-FIA) for rapid and high throughput analysis of environmental water. Anal. Chim. Acta, 1998; 376: 77–8.
39. Takafuji M, Ide S, Ihara H, Xu Z H. Preparation of poly(1- vinylimidazole)-grafted magnetic nanoparticles and their application for removal of metal ions. Chem Mater, 2004; 16: 1977–1983.