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Review Article

MAGNETIC MICROSPHERES: A LATEST APPROACH IN NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Magnetic microspheres are at the forefront of the rapidly developing field of pharmaceutical technology with several potential applications in drug delivery, clinical medicine and research as well as in other varied sciences. Due to their unique size-dependent properties, magnetic microspheres offer the possibility to develop new therapeutics. The ability to incorporate drugs into carriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Hence, magnetic microspheres hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers. This review presents a broad treatment of magnetic microspheres discussing their advantages, limitations and their possible remedies. Different production methods which are suitable for large scale production and applications of magnetic microspheres are described. Appropriate analytical techniques for characterization of magnetic microspheres like Photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry are highlighted. Aspects of magnetic microspheres route of administration and their biodistribution are also incorporated. If appropriately investigated, magnetic microspheres may open new vistas in therapy of complex diseases.

Key Words: Emulsion-Solvent evaporation technique, Electromagnet, Magnetic microspheres, Magnetometry, Magnetically modulated drug delivery systems.

INTRODUCTION

The term Magnetic Microsphere is small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm (1 mm)). Magnetic microspheres are sometimes referred to as micro particles. These are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm[1,2].

Magnetically targeted drug delivery system (MT-DDS) will be a promising way, which involves binding a drug to a small biocompatible magnetically active component, entrapped in the biodegradable polymeric matrix and formulating in to a pharmacologically active stable formulation, which is injected into the blood stream and using a high-gradient magnetic field to pull them out of suspension in the target region. Magnetic microspheres will be formulated with an intension to produce a depot near the target organ, by placing a suitable magnet near it. From the depot, drug will be released slowly & carried to the target organ through blood. By localizing the drug carrier near the target organ, unwanted distribution of drug to non target organ can be avoided. This approach will localize the drug only at target site & minimize the drug-induced toxicity. For example Vimal M et al. prepared Diclofenac sodium-containing ethyl cellulose micro particles were prepared by the Emulsion-solvent evaporation method with a view for use in the application of magnetic carrier technology[3].

Polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid magnetic microspheres have numerous applications depending on what material they are constructed of and what size they are[1]:

Polyethylene microspheres[2]

Polystyrene microspheres[2]

1. Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immune precipitation. Proteins and ligands adsorb onto polystyrene readily and permanently, which makes polystyrene microspheres suitable for medical research and biological laboratory experiments.
2. Polyethylene microspheres are commonly used as permanent or temporary filler. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials. High sphericity of polyethylene microspheres, as well as availability of colored and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, microscopy techniques, health sciences, process troubleshooting and numerous research applications. Charged polyethylene microspheres are also used in electronic paper digital displays.

Glass microspheres are primarily used as a filler and volumizer for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology.

Magnetic microspheres vary widely in quality, sphericity, uniformity, particle size and particle size distribution. The appropriate microsphere needs to be chosen for each unique application.

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion but are (ferromagnetic) to be captured in micro vessels (Fig 1). Dragged in to the adjacent tissues by magnetic fields of 0.5-0.8 teals (T).[3]

Mechanism wise basic difference with non Magnetic Microspheres

The use of magnetic force for site-specific drug delivery by using albumin microspheres containing magnetite appears to be a promising strategy. Significant improvements in response can be incorporated and obtained with magnetic albumin microspheres delivery system compared with conventional and nonmagnetic microspheres drug regimens.[3]

In the presence of a
suitable magnetic field, the microspheres are internalized by the endothelial cells of the target tissue in healthy as well as

tumors bearing animals. The magnetically carried microspheres and liposomes were employed to selectively transport the curare like drugs (pyrocurine, diadonium) to the muscles of one of the limbs of the cat. The use of magnetic microspheres produced no changes in systemic arterial blood pressure, local blood flow, EEG, or ECG. The method also diminished the respiratory depression produced by the curare like substances when they are routinely used for body muscle relaxation. Administration of drug containing magnetic microspheres was shown to increase the relative drug exposure to both tail target segment and liver. Advantages of the super paramagnetic particles are easy re suspension, large surface area, slow sedimentation and uniform distribution of the particles in the suspension media. Once magnetized, the particles behave like small permanent magnets, so that they form aggregates or lattice due to magnetic interaction. Advantages of ferromagnetic particles are very strong magnetic properties and therefore the fast separation with an external magnetic field even in viscous media. Ferromagnetic particles are generally recommended for the separation of DNA/RNA (SiMAG/MP-DNA), whereas super paramagnetic particles are more suitable for all other applications[4-6].

Selection of Drugs

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

a. The drug is so dangerous or labile that we cannot allow it to circulate freely in the blood stream.
b. The agent is so expensive, that we cannot afford to waste 99.9% of it.
c. Requires a selective, regional effect to meet localized therapeutic objective.
d. 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.

ADVANTAGES OF MAGNETIC MICROSPHERES[3]

1. Increased duration of action.
2. First pass effect can be avoided.
3. Improved protein and peptide drug delivery.
4. They enable controlled release of drug. Ex: narcotic, antagonist, steroid hormones.
5. Less side effects and increased therapeutic effect.
6. Reduce toxicity.
7. Ability to bind and release high concentration of drugs.
8. Patient compliance is good.
9. Method of preparations is simple.
10. Can be injected into the body using hypodermic needle.

DISADVANTAGES OF MAGNETIC MICROSPHERES[3]

1. Removal once injected is difficult.
2. Sometimes non-uniformity to drug content may result while preparation.
3. Unknown toxicity of beads.

MATERIALS USE

Materials used in the preparation of magnetic microspheres are described in the Table 1.

In case of non-biodegradable drug carriers, when administered parenterally, the carrier remaining in the body after the drug is completely released poses possibility of carrier toxicity over a long period of time.

Bio degradable carriers which degrade in the body to non-toxic degradation products do not pose the problem of carrier toxicity and are more suited for parenteral applications.[2]

Synthetic polymers

Poly alkyl cyano acrylates is a potential drug carrier for parenteral as well as other ophthalmic, oral preparations. Poly lactic acid is a suitable carrier for sustained release of narcotic antagonist, anti cancer agents such as cisplatin, cyclo phosphamide, and doxorubicin.[10]

Sustained release preparations for anti malarial drug as well as for many other drugs have been formulated by using of co-polymer of poly lactic acid and poly glycolic acid.[11]

Poly anhydride microspheres (40µm) have been investigated to extend the precorneal residence time for ocular delivery.[12]

Poly adipic anhydride is used to encapsulate timolol maleate for ocular delivery. Poly acrolein microspheres are functional type of microspheres. They do not require any activation step since the surfacial free CHO groups over the poly acrolein can react with NH2 group of protein to form Schiff's base.[13]

Natural polymers

Albumin[7] is a widely distributed natural protein. It is considered as a potential carrier of drug or proteins (for either their site specific localization or their local application into anatomical discrete sites). It is being widely used for the targeted drug for the targeted drug delivery to the tumor cells.

Gelatin[8] microspheres can be used as efficient carrier system capable of delivering the drug or biological response modifiers such as interferon to phagocytes.

Starch[9] belongs to carbohydrate class. It consists of principle glucopyranose unit, which on hydrolysis yields D-glucose. It being a poly saccharine consists of a large number of free OH groups. By means of these free OH groups a large number of active ingredients can be incorporated within as well as active on surface of microspheres.

Chitosan[14] is a deacylated product of chitin. The effect of chitosan has been considered because of its charge. It is insoluble at neutral and alkaline Ph values, but forms salts with inorganic and organic salts. Upon dissolution, the amino groups of chitosan get protonated, and the resultant polymer becomes positively charged.

METHODS OF PREPARATION

The magnetic microsphere can be prepared by using several techniques but the choice of the technique mainly depends on the nature of the polymer used, the drug, the intended use and the duration of therapy. The method of preparation and its choice are equivocally determined by some formulation and technology related factors as maintain below[15]:

1) The particle size requirement.
2) The drug or the protein should be adversely affected by the process.
3) Reproducibility of the release profile and the method.
4) No stability problem.
5) There should be nontoxic product.

There is mainly 2 method of magnetic microsphere preparation[14-17].

1. Phase separation emulsion polymerization.
2. Continuous solvent evaporation.

Phase separation Coacervation technique

Phase separation method is specially designed for preparing the reservoir type of the system to encapsulate water soluble drugs. Ex: peptide, proteins.

In matrix type device, the drug is soluble in the polymer phase.

Some of the preparations are of matrix type particularly, when the drug is hydrophobic in nature. Ex: steroids.

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system (magnetic fluid) which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer.

In this technique the polymer is first dissolved in a suitable solvent and then drug is dispersed by making its aqueous solution.

Phase separation is then accomplished by changing the solution condition by using any of the method mentioned.

- Salt addition
- Non-solvent addition
- Addition of in-compatible polymer
- Change in p^H

Solvent evaporation

Solvent evaporation method is used for the preparation of micro particles, involves removal of the organic phase by extraction of the organic solvent.

Ex: The method involves water miscible organic solvents such as isopropanol.

Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution.

The rate of solvent removal by extraction method depends on-

i) Temperature of water
ii) Ratio of emulsion volume to the water
iii) Suability profile of the polymer**.**

CHARACTERIZATION PROPERTIES OF MICROSP - HERES[2, 18-28]

1] Particle size analysis
2] Scanning electron microscopy (SEM) study
3] Flow properties
4] Thermal analysis
5] Determination of percentage yield
6] Drug content
7] Determination of drug loading
8] Incorporation efficiency of microspheres
9] Determination of solubility
10] Dissolution studies of microspheres

1] Particle size analysis

Particle size of recrystallized sample, pure samples, spays dried microspheres were determined by microscopic method using calibrated ocular micrometer.

A microscopically image analysis technique for determination of particle size was applied. The morphology and particle sizes were determined in a Digital microscope equipped with a 1/3"CCD camera imaging accessory

The microspheres were dispersed on a microscope slide. A microscopically field was scanned by video camera. The images of the scanned field are analyzed by the software.

2] Scanning electron microscopy (SEM) study

The morphology of microspheres was examined by scanning election microscopy. A small amount of powder was spread on an aluminum stub, which was placed latter gold sputtering in san SEM chamber.

Photographs were taken at an acceleration voltages of 20 KV electron beam. Obtained photograph to identify and confirm spherical nature and Surface topography of the crystals.

3] Flow properties

Flow properties of the microspheres were evaluated by determining the angle of repose and the compressibility index.

a) The angle of repose of microsphere and commercial crystals was measured by fixed funnel method.

Static angle of repose was measured according to the fixed funnel and free standing cone method of Banker and Anderson.

A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip at a given height (1 cm), H, above graph paper placed on a flat horizontal surface. The microspheres were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel.

Thus, the R being the radius of the base of the microspheres conical pile:

$\tan \theta = H/ R$

or

$\theta = \tan\text{-}1 (H/ R)$

Where θ = the angle of repose

b) Compressibility index (I):

Carr's index was determined from powder volumes at the initial stage and after 1250 tapings to constant volume.

Compressibility index (I) values of the microspheres were determined by measuring the initial volume (V0) and the final volume (V) after subjecting to 100 tapping in a graduated measuring cylinder using the equation.

$I = [1- (V/V0)] \times 100$

Apparent particle densities of microsphere were measured using a Pycnometer.

4] Thermal analysis

Differential scanning calorimeter (DSC)

DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on differential scanning calorimeter (DSC DuPont 9900) with a thermal analyzer.

Differential scanning calorimeter (DSC) was performed on ketoprofen and ketoprofen loaded microspheres. DSC measurement were done on a Mettle Toledo DSC 822c C/ min over a temperature range of 30 to 30000 C under an inert atmosphere flushed with nitrogen at a rate of 20 ml/min.

5] Determination of percentage yield

The yield of microspheres was determined by the formula,

$$\%Yield = \frac{\text{Total Weight of Microspheres}}{\text{Total Weight of Raw Material}} \times 100$$

The percentage yield of each formulation was determined according to the total recoverable final weight of microsphere and the total original weight of Indomethacin.

6] Drug content

Microspheres in a particular quantity were dissolving in a solvent and at specified λ max of drug. The drug content of Microspheres is estimated.

Microspheres (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, samples were measured at particular λ max value of drug. Drug content was determined from standard plot.

7] Determination of drug loading

The drug loading was determined by UV-Visible spectrophotometer. The microspheres were stirred with 100 ml particular solution as dissolution media (pH 7.40 phosphate buffer) for 2hr. The drug concentration will be determine at particular λ max value of drug after suitable dilution. The readings were taken in triplicate.

$$\text{Drug loading (\%)} = \frac{\text{M actual}}{\text{Weighed quantity of powder of microspheres}} \times 100$$

8] Incorporation efficiency of microspheres

$$\text{Incorporation efficiency (\%)} = \frac{\text{M actual}}{\text{M theoretical}} \times 100$$

Where,

M actual is the actual drug content in weighed quantity of powder of microspheres &

M theoretical is the theoretical amount of drug in microspheres calculated from the quantity added in the fabrication process.

9] Determination of solubility

The solubility of particular drug microspheres in specific solution as microspheres or microcapsule to be soluble in that particular environment (water and pH 7.4 phosphate buffers) was determined by taking excess quantity of microspheres in 50 ml to screw-capped glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatman filter paper No.1 and drug concentration was being determined at particular λ max value of drug.

10] Dissolution studies of microspheres[29-32]

The dissolution of microspheres is determined by using USP dissolution apparatus XXIV Type II. Dissolution medium was 900 ml 7.4 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method at specified λ max of particular drug. The readings were taken in triplicate.

APPLICATIONS

Applications of magnetic microspheres are as follows[32]

1. Magnetic microsphere carriers have wide application in the field of bio medicine, bioengineering, biological and biomedical developments.
2. It is used in enzyme immobilization, cell isolation, protein purification and targeted drugs.
3. Drug discovery, molecular targeting, and undergoing the path way of cell cycle regulation.
4. High throughput DNA isolation. (Magnetic bead purification of labeled DNA fragments for high-throughput capillary electrophoresis sequencing.)
5. Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
6. Magnetic fluid hyperthermia.(Presentation of a new magnetic field therapy system for the treatment of human solid tumors)
7. It is used as chemotherapeutic agent.(Loco regional Cancer Treatment)
8. Magnetic vehicles are used for delivery of therapeutic agent as they can be targeted to specific location in the body through the application of magnetic field.

Table: 1 Material used in Magnetic Microspheres

Materials used	Types	Examples
Synthetic Polymers	a. Non-biodegradable polymers	Poly methyl methacrylate (PMMA)[4], Acrolein[5], Glycidyl methacrylate,
	b. Biodegradable polymers	Epoxy polymers Lactides, Glycolides & their co polymers[6], Poly alkyl cyano acrylates, Poly anhydrides
Natural polymers	a. Proteins	Albumin[7], Gelatin7[8], and Collagen
	b. Carbohydrates	Agarose, Carrageenan, Chitosan, Starch[9]
	c. Chemically modified carbohydrates	Poly dextran, Poly starch

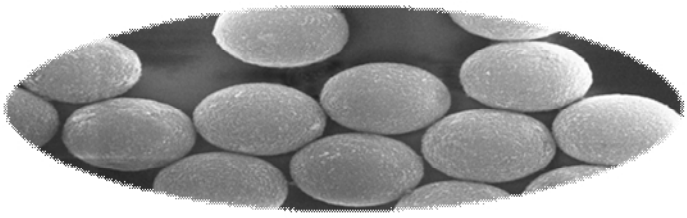

Figure 1: Magnetic Microspheres

CONCLUSION

In the early days of the 20th century, Paul Ehrlich envisioned his magic bullet concept- the idea that drugs reach the right site in the body, at the right time, at right concentration. It should not exert side effects, neither on its way to the therapeutic target, nor at the target site, nor during the clearance process. The magnetic microspheres have the potential to achieve, at least partially, these broad objectives. Apart from these, the regular objective of controlled drug delivery is aptly achieved with magnetic microspheres. They are relatively young drug delivery systems, having received primary attention from the early 1990s and future holds great promise for its systematic investigation and exploitation. We can expect many patented dosage forms in the form of magnetic microspheres in the future.

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