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MAGNETIC MICROSPHERES AS NOVEL EXPANSION IN MULTIPARTICULATE DRUG DELIVERY SYSTEM

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ABSTRACT

Main objective of targeted drug delivery is selective and effective availability of active pharmaceutical ingredients into the target site at therapeutic concentrations. Various approaches are used for drug targeting using single as well as multiparticulate. Recentally in multiparticulate Magnetic microspheres is novel approach used for drug targeting. Microspheres are better choice of drug delivery system than many other types because it is having the advantage of detection of bimolecular interactions and better patient compliance. Magnetically targeted drug delivery by microspheres is an efficient method of delivering drugs to localized disease sites. Magnetic microspheres hold great promises for reaching the goal of controlled and site specific drug delivery. Magnetic microspheres as an alternative to traditional radiation method which uses highly penetrating radiations that is absorbed throughout the body. Magnetic drug delivery is a novel approach to delivery drug using engineered 'smart' micro carriers which appears to overcome a number of limitations facing current methods of delivering medicines. The drug and a suitable ferrofluid are formulated into a pharmaceutically stable formulation which is usually injected through the artery that supplies the target organ or tumor in the presence of an external magnetic field. This review focus on various aspects of the magnetic microspheres like mechanism, benefits, fabrication &various applications of magnetic microspheres.

KEYWORDS: Drug delivery, Magnetic microspheres, Targeted drug delivery, Magnet, Dosage form.

INTRODUCTION

Drug delivery systems aims to deliver the drug at a rate directed by the needs of the body during the period of treatment, and target the activity entity to the site of action. Its use is limited by toxicity and side effects.

The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. While a variety of devices have been used for controlled release drug delivery, biodegradable polymer microspheres are one of the most common types and hold several advantages. There are a number carriers Microspheres, nanoparticles, liposomes and others for which optimized technologies are under development to enhance the performance of products that have already been delivered with some success via that route and modulates the release and absorption characteristics of the drugs particularly those drugs which have shorter biological half-life.[1]

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 1000 µm.. microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of detection of bimolecular interactions and better patient compliance.. Magnetic microspheres as an alternative to traditional radiation methods which use highly penetrating radiation that is absorbed throughout the body. Its use is limited by toxicity and side effects. Magnetic radioactive microspheres are applied in methods similar to non-radioactive spheres.[2]

By using magnetic microsphere small amounts of drug targeted magnetically to localized sites can replace large doses of drug that, using traditional administration methods, freely circulate in the blood and hit the target site in a generalized way only. Also, drugs within the sphere are protected from breaking down during transport and, because they are targeted instead of distributed in blood, don't harm some sensitive organs such as bone marrow.[3]

How magnetic microsphere works

A drug is encapsulated in a magnetic compound; injected into patient's blood stream & then stopped with a powerful magnetic field in the target area. A magnet, placed outside the body, is directed to the target site. The magnet can be a rod-shaped permanent magnet of any size or

can be contained in equipment that looks like an open magnetic resonance imaging scanner. The loaded microspheres are introduced into a blood vessel, and in as little as half an hour, they gather at the target site to emit radiation that kills surrounding cancer cells. The therapeutic action usually a couple of days or weeks, depending on the material used.

When the magnetic carrier is intravenously administered, the accumulation takes place within area to which the magnetic field is applied & often augmented by magnetic agglomeration. The accumulation of the carrier at the target site allows them to deliver the drug locally.[4]

Benefits of magnetic microsphere

- Large freely circulating drug is converted in small amount of magnetically targeted drug.
- Increased duration of action of drug using magnetic microsphere
- First pass effect can be avoided by using magnetic microsphere
- This technique helps in reduction in the dose & side effects of the drug
- Improved protein and peptide drug delivery
- They enable controlled released of drug.
- Reduced toxicity.
- Ability to bind and release high concentration of drug
- Patient adherence to therapy is good.
- Simple Method of fabrication.
- Can be injected into the body hypodermic needle
- Localise drug at disease site.
- Controlled & predictable drug release achieved by using magnetic microsphere.[5,6,7]

Ferrofluid in magnetic microsphere

Ferrofluid plays important role in magnetic microsphere. Ferrofluid, is a colloidal suspension of single-domain magnetic particles, with dimensions of about 10 nm, dispersed in a liquid carrier. Theit are two ferrofluid surfaceed ferrofluid if coating is surfactant molecule and magnetic ferrofliud if it is an electric shell.[8]

Formulation aspects of magnetic microsphere

Selection of drugs in magnetic microspheres drug targeting

a) The drug is so dangerous or labile that we cannot allow it to circulate freely in the blood stream.

b) Requires a selective, regional effect to meet localized therapeutic objective

c) Drugs which are much expensive, that we cannot afford to waste 99.9% of it.[9,10]

Polymers used in magnetic microsphere

Biodegredable, non biodegradable natural, synthetic polymerslike poly alkyl cynoacrylate, albumin, gelatin, starch and other polymers are used for magnetic microsphere preparation.[11,12]

Formulation factors considered during manufacturing magnetic microspheres

a) Stability issues

b) Non toxicity of products.

c) Particle size of microsphere

d) Reproducibility of method & result

e) Effect of process on drug.[13,14]

Methods of fabrication of magnetic microsphere.

1. Continuous solvent evaporation

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

2. Phase separation emulsion polymerization

Homogenous aqueous suspension is prepared by adding albumin water-soluble drug and agent with magnetite in appropriate quantity of water (if magnetic microspheres). This aqueous suspension is then emulsified in the presence of suitable emulsifying agent to form spheres in emulsion. This aqueous proteineous sphere thus formed in the emulsion are stabilized either by heating at 100-150 °C or by adding hydrophobic cross linking agents like formaldehyde, glutraldehyde or 2-3 butadiene, microspheres thus produced are centrifuged out and washed either in ether or some other appropriate organic solvent to remove excess of oil. Microspheres are freeze dried and stored at 4 °C.

4. Multiple emulsion method

First w/o emulsion was prepared using a homogenizer .Water dispersible magnetite with a PEG/PAA coating was added to the BSA. Then multiple emulsion prepared.

5. Cross linking method

Reagents used: Acetate buffer–used as solvent for the chitosan polymer; Glutraldehyde-used as the cross-linker; Sodium hydroxide solution-used as medium. Synthesis of magnetic fluid.

6. Alkaline co precipitation method.[15,16,17]

Alkaline co precipitation method is unique technique used for preparation of magnetic microsphere.

In vitro-In vivo Characterization of Magnetic Microspheres.

1. Determination of percent yield: Dried Magnetic microspheres is to be collected and to be weighed accurately. The percentage yield is then to be calculated using the below mentionedformula.

Percentage yield=Practical yield/Theoritical yield X 100.

2. Particle size analysis: Separation of the microspheres into various size fractions can bedetermined by using a mechanical sieve shaker. A series of five standard stainless steel sieves is to be arranged in the order of decreasing aperture size. Few grams of drug loaded microspheres is to be placed on the upper-most sieve. The sieves has to be shaken for a period of about 10 min, and then the particles on the screen is to be weighed.

3. **Micrometric properties:** microspheres is to be characterized for their variousmicrometric properties such as bulk density, tapped density, bulkiness, cars index and angleof repose.

4. Bulk Density: It is determined by pouring accurately weighed microspheres in measuring cylinder and thus determining its bulk volume.

5. Tapped Density: Accurately weighed microspheres is to be poured in a well driedmeasuring cylinder and tapped 100 times from a constant height to determine the tappedvolume and finally tapped density is to be calculated.

6. Carr's Index: Carr's index is determined from the values of bulk and tapped density whichhelps to determine the compressibility between the particles.

7. Hausner's Ratio: It is determined from the ratios of tapped density and bulk density.

8. Angle of Repose: It is the maximum possible angle that a static heap of particles make with the horizontal. The flow properties of microspheres can be determined by fixed funnel flow method, which issued to calculate angle of repose.

9. Determination of drug loading and encapsulation efficiency: Drug-loaded microspheres is to be digested with 10 ml of water at room temperature for 12 h. The solution is then to befiltered and analyzed. The drug loading in microspheres is estimatedby using the formula:L = (Qm/Wm) × 100

Where, L is the percentage loading of microspheres, Qm the quantity of drug present in Wmg of microspheres.

10. ***In vitro*** **methods**: In-vitro release studies can be performed according to USP XXII type Idissolution apparatus at suitable pH conditions. The temperature should be maintained at 37 ±0.5°C and the rotation speed of 100 rpm. Then, few ml of sample was withdrawn at varioustime intervals and replenished with an equal volume of fresh dissolution media. The drugcontent in the sample was analyzed spectrophotometrically at specific wavelength.

11. Stability studies: By keeping the microspheres in screw capped glass container and stored them at following conditions: Ambient humid condition Room temperature (27 +/- 2oC), Oven temperature (40 +/- 2oC),Refrigerator (50oC - 80oC) It was carried out of a 60 days and the drug content of the microsphere was analyzed.

12. Interreaction study: By, TLC/FTIR/DSC

13. Other studies: Surface area, Porosity, Hardness & friability, Drug content, Drug release profiles are also studied.

14. In vivo studies[**18**,19,20]

Limitations of Magnetic microsphere

- Deposition of fraction of magnetite in targeted tissue is the major limitations of Magnetic microsphere.
- Magnetic targeting is an expensive, technical approach and requires specialized manufacture and quality control system.

- It needs specialized magnet for targeting, advanced techniques for monitoring, and trained personnel to perform procedures.
- Magnets must have relatively constant gradients, in order to avoid focal over dosing with toxic drug.[21,22]

Applications of magnetic microspheres in various filed

1. Magnetic microsphere carriers used in following sector of biomedicine and bioengineering, biological and biomedical developments and trends such as enzyme immobilization, cell isolation, protein purification, and target drugs.
2. Magnetic microsphere carriers used in tumor targeting
3. Magnetic microsphere applied for bacteria detection.
4. Magnetic vehicles are very attractive for delivery of therapeutic agents.
5. Drug discovery, molecular targeting, DNA analysis, proteomics, and understanding the pathways of cell cycle regulation.
6. In Contraceptive drug delivery Magnetic microsphere are used.[23,24]

Storage condition of Magnetic microsphere

Magnetic microsphere should be stored at cold temprature.It should not be frozen.[25]

CONCLUSION

Targeted Drug delivery is mainly used to aid the drug molecule to reach preferably at desired site. Magnetic Microsphere is efficient & novel approach of drug targeting & these are used for localizing the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses towards a magnetic field from incorporated materials magnetic microspheres. Magnetic Microsphere has been investigated for targeted drug delivery especially magnetic targeted chemotherapy due to their better tumor targeting. The magnetic targeted chemotherapy has better tumor& other drug targeting, therapeutic efficacy & lower toxicity. Thus above review concludes that Magnetic Microsphere is novel expansion in multiparticulate drug delivery.

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