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A Review on Magnetic Microsphere

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Abstract: 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 200 µm. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

Keywords: Magnetic, Microspheres, Tissues

1. Introduction

Microsphere can be defined as the particles that flow freely end are encapsulated spherical particle that have size between 125p-130p and can be suspended in a vehicle that can be aqueous and other organic or inorganic vehicles. There shape can be spherical and resembling spherical. Some approaches revealed that microspheres are those drugs that deliver their action on target site with a probable concentration on a desired interest. There are consisting of synthetic polymers or proteins size between 1-1000µm. They are not only prolonged release drugs but also control release drugs. [1].

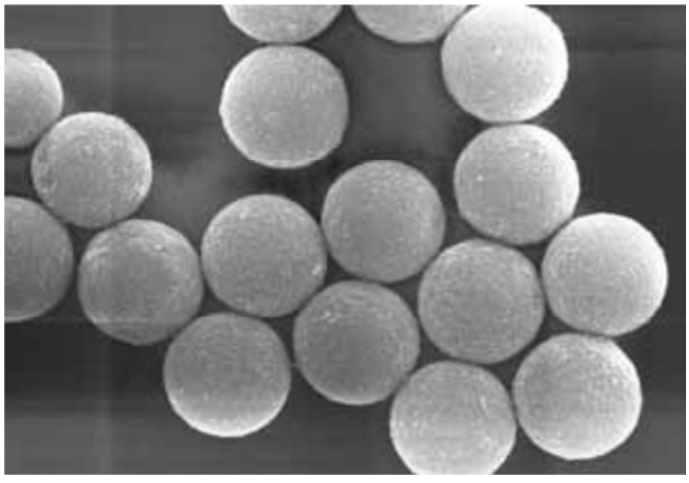

Figure 1. *Microspheres.*

The types of microsphere that are used today are of two types microcapsules and micromatrices that can be defined as the one which is entrapped by distinct capsule wall is called microcapsule and the one which entrapped substance is dispersed through out the microsphere matrix is called micrometrics. [2].

These are multiparticulate drugs that deliver there action with improved stability, bioavailability with predetermined rate. These delivery system have more advantages as that of conventional dosages form that include reduced toxicity, improved efficacy etc. Microsphere can also be classified as magnetic microspheres, floating microspheres, polymeric microspheres, bioadhesive microspheres, radio active microspheres, biodegradable microspheres, synthetic microspheres. The main motive of research was to formulate, characterize and evaluate the probable action of the targeted microsphere [3].

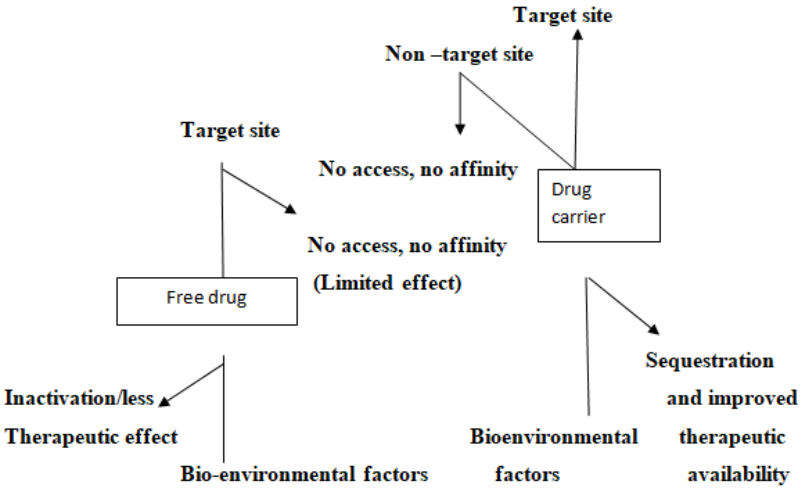

Figure 2. *Mechanism of magnetic drug targeting.*

1.1. Advantages of Magnetic Microspheres

1. Increased bioavailability
2. Reduced toxicity
3. Targeted drug delivery
4. Controlled drug delivery
5. Reduced side effects
6. Minimized drug degradation
7. Biocompatibility
8. Controlled delivery of drugs
9. Ease of surface modification
10. Confers local effect
11. Duration of action is increased
12. Protein delivery is increased
13. Peptide delivery is also increased
14. Binding ability with receptor is high
15. Release of drug is high
16. Increased therapeutic value
17. Preparation method is easy
18. Better patient compliance
19. Site specific drug delivery
20. Increased efficacy
21. Bitter taste and smell can be masked
22. Physical stability can be improved
23. Stabilization of gastric enzyme
24. Improved floatability
25. Improved dispersability
26. Reduced dose size.
27. Dose frequency is minimized.
28. Reduced irritation of gastric area.
29. Due to spherical and small size, injection of drug is easy.
30. Large freely circulating drug is converted in small amount of magnetically targeted drug.
31. Increased duration of action of drug using magnetic microsphere
32. First pass effect can be avoided by using magnetic microsphere
33. This technique helps in reduction in the dose & side effects of the drug
34. They enable controlled released of drug.
35. Ability to bind and release high concentration of drug
36. Patient adherence to therapy is good.
37. Simple Method of fabrication.
38. Can be injected into the body hypodermic needle
39. Localise drug at disease site.
40. Controlled & predictable drug release achieved by using magnetic microsphere. [4, 5]

1.2. Disadvantages of Magnetic Microspheres

1. Drug targeting is limited only to superficial tissues of skin like skin, superficial tumor and joints etc.
2. Toxicity of magnetic beads can occur.
3. In liver and RES regions, unknown localization of drug can seen.
4. Dangerous effect of self flocculation of magnetic particles can be seen.
5. At the site of catheterization, thrombosis can occur
6. Magnetic targeting is very expensive

7. It requires specialized technical approach
8. It is only employed for severe diseases.
9. Removal is difficult, once injected
10. During preparation, non-uniformity of drug can occur
11. Due to intrinsic and extrinsic factors, sustained release can vary
12. Rate of drug from one dosage form to that of another is different.
13. Failure of therapy can occur from dumping of dose
14. Interaction and formation of complexes with blood components can occur due to parental delivery.
15. This type of dosage form cannot be crushed or chewed. [6]

1.3. Methods of Preparation of Magnetic Microsphere

Selection of Drugs

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

1. The drug is so dangerous or labile that we cannot allow it to circulate freely in the blood stream.
2. The agent is so expensive, that we cannot afford to waste 99.9% of it. Requires a selective, regional effect to meet localized therapeutic objective. Requires an alternative formulation essential to continue treatment in patient whose systemic therapy must be temporarily discontinued due to life threatening toxicity directed at selective organs.

Methods

Continuous Solvent Evaporation Method

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 centrifuged then freeze dried and stored at 4°C.

Phase Separation Emulsion Polymerization Method

Homogenous aqueous suspension is prepared by adding albumin water-soluble drug and agent with magnetite in 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 proteinaceous 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 [7].

Multiple Emulsion Method

Water dispersible magnetite with a PEG/PAA coating was added to the BSA containing inner water phase. 0.2 mL of a 1 mg/mL BSA solution added to a 4 mL mixture of DCM and EA at a ratio of 3 to 1 containing 200 mg of PLGA (first w/o emulsion was prepared using a homogenizer (Polytron PT10-35; Kinematica, Luzern, Switzerland) in an ice bath at 26 000r/min for 2.5 min). Fifteen mL of a 1% PVA solution poured directly into the primary emulsion using the same homogenizer under the same conditions for another 2.5 min. W/o/w emulsion immediately poured into a beaker containing 85 mL of 1% PVA solution and stirred in a hood under an overhead Propeller for 2 h, allowing the solvent to evaporate. Solidified microspheres harvested by centrifugation at 2500 r/min for 10 min and washed with distilled water three times (Figure 2).

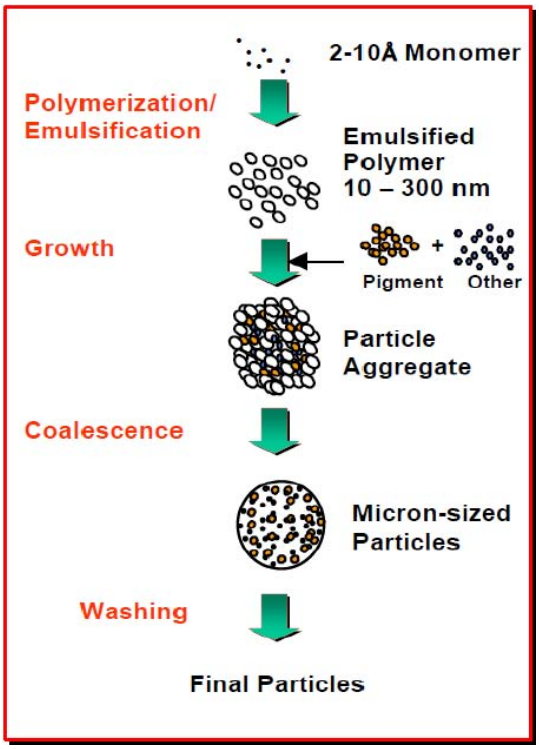

Figure 3. *Preparation of microspheres by multiple emulsion method.*

Cross Linking Method

Reagents Used

Acetate buffer–used as solvent for the chitosan polymer; Glutraldehyde-used as the cross-linker; Sodium solution-used as medium. Synthesis of magnetic fluid: A 35% (w/v) ferrous sulfate solution, 54% (w/v) ferric chloride solution and 36% (w/v) sodium hydroxide solution were prepared using distilled water. Then the ferric salt and ferrous salt were mixed, stirred and heated. When the temperature reached 55°C, the alkaline solution was added. The mixture was stirred for 30 min and then 5 of polyethylene glycol-10000 (PEG- 10000) was added. The temperature was raised to 80°C and maintained for 30min. The mixture was then neutralized while cooling and the magnetic fluid was prepared. 1% (w/w) chitosan was dissolved in acetate buffer at pH 4.5. The dissolved chitosan was added drop wise on the magnetic fluid. Formed chitosan magnetic microspheres were washed with deionized water and soaked in 1, 3 and 5 mol% glutraldehyde solution for 2 h and then washed with deionized water [8].

Alkaline Co-Precipitation Method

Treat poly (acrylic acid–divinylbenzene) microspheres with dilute aqueous NaOH solution (0.5 M) for hours at suitable temperature to transform the carboxylic acid groups to sodium carboxylates and then washed thoroughly with water to remove the excess NaOH till neutral pH. Purged the microsphere suspension with nitrogen for 30 min. To this suspension add an aqueous solution of $FeCl_3$ and $FeCl_2$ that had been purged with nitrogen. Stirred the mixture overnight under nitrogen atmosphere for ion exchange. The resulting microspheres were washed repeatedly with water under nitrogen atmosphere to remove excess iron salts. Added drop wise aqueous NaOH solution (3M) to a suspension of the microsphere taken up with iron ions under nitrogen atmosphere to adjust the pH value to be > 12. The mixture was then heated to 60°C and kept for another 2 h. The resulting magnetic microsphere were suspended in an aqueous HCL solution (0.1M) to transform the –COONa to COOH and then washed thoroughly with water to netral pH, dried under vaccum at 50°C overnight giving magnetic microsphere.

Inverse Phase Suspension Polymerization Method

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 (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 (Figure 3) [9]

Sonochemical Method

The microspheres composed of iron oxide-filled and coated globular bovine serum albumin (BSA). The magnetic microspheres were prepared from BSA and iron penta carbonyl, or from BSA and iron acetate application, i.e. use as echo contrast agents for sonography. The microsphere were formed by either heat naturation at various temperatures, or by cross linking with carbonyl compounds in the ether phase. Cross linking was done as: the microspheres are formed by chemically cross-linking cysteine residues of the protein with HO_2 radical formed around a non-aqueous droplet. The chemical cross-linking is responsible for the formation chemical ejects of the ultrasound radiation on an aqueousmedium. Two sonochemical methods for the fabrication of iron oxide nanoparticles were (i) Water as the solvent and (ii) Decalin as solvent. Decane and iron pentacarbonyl $Fe(CO)_5$ (7.43U1034 M) were layered over a 5% w/v protein solution. The bottom of the high-intensity ultrasonic horn was positioned at the aqueous organic interface. The mixture was irradiated for 3 min, employing a power of W150 W/ 32cm with the initial temperature of 23°C in the reaction cell. The pH was adjusted to 7.0 by adding HCl. This procedure was performed again with an aqueous solution of iron acetate, Fe $(CH_3CO_2)_2$ 95% (Sigma) (7.66U1033 M). After the synthesis, the products were separated from the unreacted protein and from the residues of iron acetate or iron pentacarbonyl by centrifugation (1000 r/min for 5 min). The magnetic microspheres were washed a few times with sufficient volumes of water to remove the residues of the precursors [10].

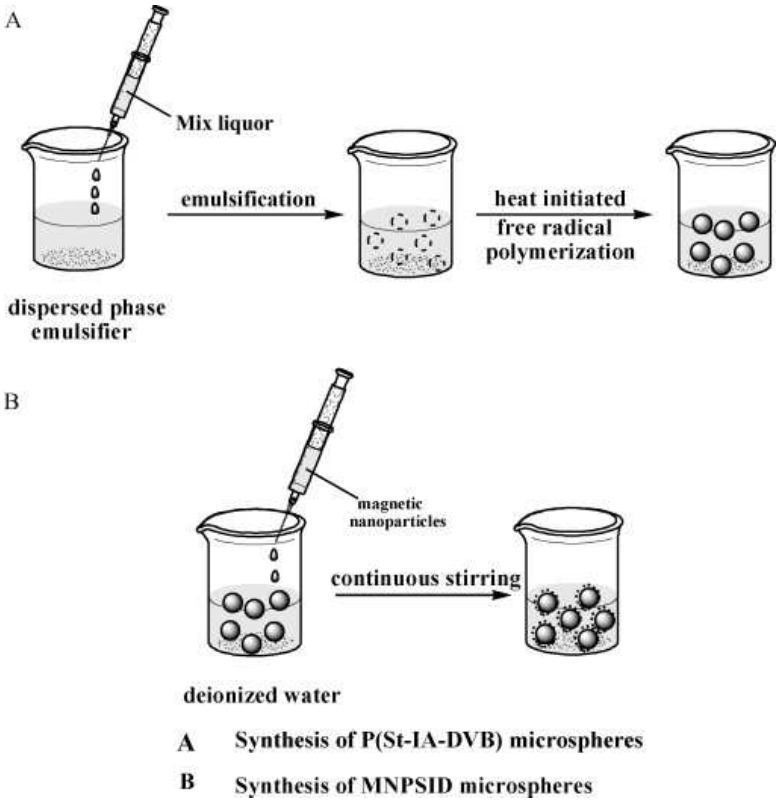

Figure 4. *Synthesis of P(St-IA-DVB) microspheres and MNPSID.*

Swelling and Penetration Method:

For swelling of polymer micro particles, 0.25 g of PS (Micron-size polystyrene) p 2 articles was mixed with 35 mL of a NMP/water solution in a specific v/v NMP (N-methyl-2-pyrrolidone)-to-water ratio. In later preparations of magnetic microspheres, SDS (Sodium dodecyl sulfate) was added to the NMP/water solution. Whenever SDS was used, 0.025 g of SDS were added to each NMP/water solution. The NMP/water mixture with PS spheres was left soaking for 24 h at room temperature while stirring. 2.5 mL of the superparamagnetic nanoparticle dispersion (24 mg/mL or other specified concentration) was added to the mixture of PS sphere and NMP/water solution at 30°C while shaking (at 140 r/min) for 1-5 days to allow the magnetic nanoparticles to penetrate into the interior of the PS particles. Afterwards, the polymer particles were separated from the solution by centrifugation. Finally, particles were sequentially washed with methanol, deionized water and vacuum dried at room temperature for 1-2 days to yield the magnetic polymer microspheres [11].

Low-temperature Hydrothermal Method

0.1g FeO was dispersed in the aqueous glucose solution without additives, the hydrothermal reaction catalyzed only by Fe_3O_4 was kept at 180°C for 5 h [12-14].

2. Conclusion

In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body. Microsphere drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development. The Microsphere offers a variety of opportunities such as protection and masking, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. This approach facilitates accurate delivery of small quantities of potent drugs; reduced drug concentrations at sites other than the target organ or tissue; and protection of labile compounds before and after administration and prior to appearance at the site of action. In future by combining various other approaches, Microsphere technique will find the vital place in novel drug delivery system.

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