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MICROSPHERE: TYPES OF MICROSPHERE, METHOD OF PREPARATION AND APPLICATION ON BRIEF REVIEW

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ABSTRACT

Microspheres are small spherical particles, with diameters range 1 µm to 1000 µm. They are spherical free flowing particles with size less than 200 µm and consisting of proteins or synthetic polymers which are biodegradable in nature microsphere is basically a mixture of drug, dispersed in a polymer form with release occurs by 1st order process. Microspheres are two types; microcapsules and micromatrices in case Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall. And micromatrices in which entrapped substance is dispersed throughout the matrix. They are made from polymeric waxy or other protective materials such as natural, semi synthetic and synthetic polymers. The present review highlights various types of microspheres, different methods of preparation, its applications and also various parameters to evaluate their efficiency. Microspheres are various types like Bioadhesive microspheres, Magnetic microspheres, Floating microspheres, Radioactive microspheres, Polymeric microspheres, Biodegradable polymeric microspheres, Synthetic polymeric microspheres and are prepared by methods like Emulsion solvent evaporation method**,** Emulsion cross linking method**,** Ionic gelation method, Solvent Evaporation, Single emulsion technique, Double emulsion method, Phase separation coacervation technique, Spray drying and spray congealing, Solvent extraction. Microspheres have wide range of applications because of controlled and sustained release.

KEYWORDS: Microsphere, Types Of Microsphere, Method of preparation And Application.

INTRODUCTION

Microspheres are small spherical particles, with diameters range 1 μm to 1000 μm.[1] They are spherical free flowing particles with size less than 200 μm and consisting of proteins or synthetic polymers which are biodegradable in nature. It Can be injects by 18 or 20 number needle.[2] Microspheres are two types; microcapsules and micromatrices in case Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall. And micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles.[3] Microspheres can be manufactured from various natural and synthetic materials.[4] Microspheres play an important role to improve the bioavailability of conventional drugs, minimizing its side effects and also enhance the therapeutic efficacy of a given drug.[5,6]

Each particle of microsphere is basically a mixture of drug, dispersed in a polymer form with release occurs by 1st order process. Drug release is controlled by dissolution/degradation of matrix due its size and shapes, Microspheres offer a ball-bearing effect. Recent advances in polymer science and drug carrier technologies have promulgated the development of novel drug carriers such as bioadhesive microspheres that have boosted the use of "bioadhesion" in drug delivery.[7]

Floating microspheres are gastro-retentive drug delivery systems based upon the non-effervescent approach. Hollow microspheres are in strict sense and its spherical empty particles without core. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs[8] and magnetic microspheres use for target to tumors.

Microsphere Ideal characteristics properties[9, 10]

- The ability to incorporate reasonably high concentrations of the drug
- Stability of the preparation after synthesis with a clinically acceptable shelf life
- Biocompatibility with a controllable biodegradability
- Susceptibility to chemical modification
- Controlled particle size and dispersability in aqueous vehicles for injection

TYPES OF MICROSPHERE

Various types of microsphere show as in figure 1.

1. Bioadhesive microspheres

2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres

1. Bioadhesive Microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.[11, 12]

2. Magnetic Microspheres

This kind of delivery system is very much important which localizes 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 to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types are therapeutic magnetic microspheres and diagnostic microspheres.

(i) Therapeutic Magnetic Microspheres: It is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system.

(ii) Diagnostic Microspheres: It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.[13, 14]

3. Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces[15] chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.[16, 17]

4. Radioactive microspheres

Radio embolization therapy microspheres sized 10-30 nm are of larger than the diameter of the capillaries and gets tapped in first capillary bed when they come across. They are injected

in the arteries that leads them to tumour of interest so all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues.[3] It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.[18]

5. Polymeric Microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.[18]

(i) Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium , results gel formation. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment.[19]

(ii) Synthetic polymeric microspheres

Synthetic polymeric microspheres are widely used in clinical application[4], moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible but the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.[20]

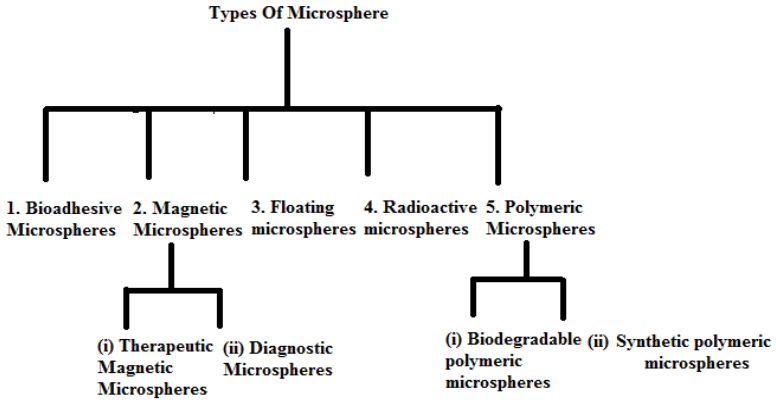

Figure 1:- Types of Microsphere

TYPES OF POLYMERS

Microsphere are used various polymers. They are classified into two types[21, 22] shown in figure 2:-

1. Synthetic polymers, **2.** Natural polymers

1. Synthetic polymers are further classified into two types.

A. Non-biodegradable polymers

- Poly methyl methacrylate (PMMA)
- Acrolein
- Glycidyl methacrylate
- Epoxy polymers

B. Biodegradable polymers[5, 6]

- Lactides, Glycolides & their co polymers
- Poly alkyl cyano Acrylates
- Poly anhydrides

2. Natural polymers obtained from different sources such as proteins, carbohydrates and chemically modified.carbohydrates.[7, 8]

(i) Proteins

3. Albumin
4. Gelatin9
5. Collagen

(ii) Carbohydrates

6. Agarose
7. Carrageenan
8. Chitosan10
9. Starch

(iii) Chemically modified carbohydrates

10. Poly dextran11
11. Poly starch

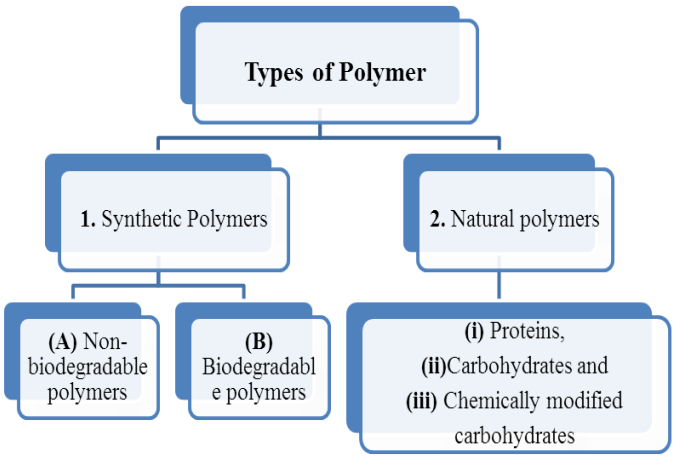

Fig - 2: Various Polymers role in development of Microspheres

ADVANTAGES OF MICROSPHERES[23, 24]

- Particle size reduction for enhancing solubility of the poorly soluble drug.
- Provide constant and prolonged duration of therapeutic effect.
- Better drug utilization will improve the bioavailability or decrease the incidence or intensity of dose related toxicity.
- Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery.
- Microsphere reduces the dosing frequency, constant drug concentration in blood there by improve the patient compliance.
- Microsphere morphology allows to controllable the variability in degradation and drug release.
- Microsphere is also converts liquid to solid form & to mask the bitter taste.
- Protects to the GIT from irritant effects of the drug.
- Biodegradable microspheres have the advantage over the large polymer implants in that case they do not require surgical procedures for implantation and removal.

LIMITATION

Microsphere contains some of the disadvantages were found to be as follows[23, 5]

- The modified release from the formulations.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- Differences in the release rate from one dose to another.

- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed.
- The costs of the materials and processing of the controlled release preparation are higher than those of standard formulations.
- The fate of polymer matrix and its effect on the environment and also less Reproducibility
- The environmental impact of the degradation products of the polymer matrix process in resulting to heat, hydrolysis, oxidation, solar radiation or biological agents.

METHODS OF PREPARATION

The preparation of microspheres should satisfy certain criteria. These include.[25, 26]

- The ability to incorporate reasonably high concentrations of the drug.
- Release of active agent with a good control over a wide time scale.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersibility in aqueous vehicles for injection.
- Biocompatibility with a controllable biodegradability.
- Susceptibility to chemical modification.

TYPES OF METHOD OF PREPARATION

Microsphere preparation method can be represents as in figure 3:

- Spray drying and spray congealing method
- Polymerization method
- Phase separation coacervation method
- Multiple emulsion method
- Emulsion solvent evaporation method
- Emulsion cross linking method
- Ionic gelation method

1. Spray drying and spray congealing method

Methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively.[27] The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. One of the major advantages

of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins.[28]

2. Emulsion solvent evaporation method

Method used the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0 .2% sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs.[28]

3. Multiple emulsion method

Oral controlled release drug delivery of various drugs was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The the primary emulsion was then reemulsified in aqueous medium. Under optimised condition discrete microspheres were formed during this phase.[29]

4. Emulsion cross linking method

In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 400C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 oC, results in w/o emulsion then further stirring is done for 10 min at 150C. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80 at 370 C for 10 min to block unreacted glutaraldehyde example such as Gelatin A microspheres.[29]

5. Ionic gelation method

Alginate/chitosan particulate system for Nateglinide release was prepared using this technique. Different % (w/v) of Nateglinide was added to 2% (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added dropwise to a solution containing Ca2+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 6 hrs & 24 hr for internal

gellification followed by filteration for separation. The complete release was obtained at pH 7.4 but the drug did not release in acidic pH.[29]

6. Phase separation coacervation method

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 which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates.[30]

7. Polymerization method

The polymerization methods conventionally used for preparing the microspheres are mainly classified as[31, 32]:

(i) Normal polymerization andInterfacial polymerization.

These are both are carried out in liquid phase. Normal polymerization can used in different method as bulk, suspension, precipitation, emulsion and micellar polymerization methods.

It is carried out by heating the monomer or composition of monomers as droplets dispersion in a continuous aqueous phase. Droplets may also contain an initiator and other additives.

And interfacial polymerization is the reaction of various monomers at the interface between the two immiscible liquids to form a film of polymer that essentially envelops the dispersed phase.

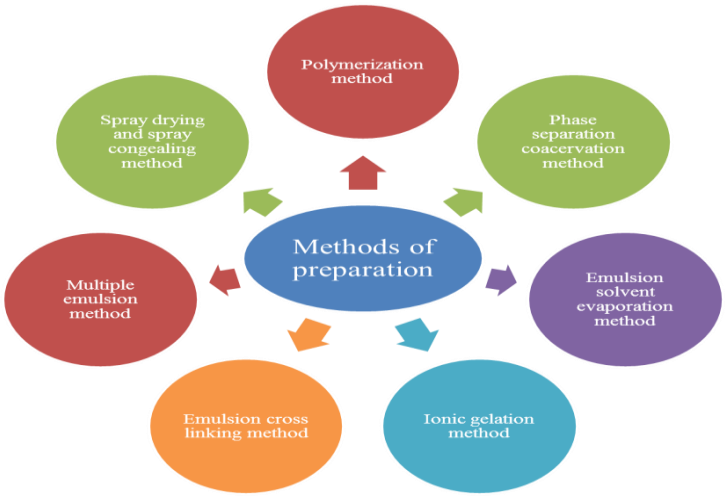

Figure 3: Various method of preparation in Microsphere

APPLICATION OF MICROSPHERES IN PHARMACEUTICAL INDUSTRY[33, 10]

1. Ophthalmic Drug Delivery
2. Oral drug delivery
3. Gene delivery
4. Nasal drug delivery
5. Intratumoral and local drug delivery
6. Buccal drug delivery
7. Gastrointestinal drug delivery
8. Transdermal drug delivery
9. Colonic drug delivery
10. Vaginal drug delivery
11. Targeting by using microparticulate carriers

1. Ophthalmic Drug Delivery

Microspheres developed using polymer contains various favorable biological behavior such as bioadhesion, permeability-enhancing properties and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Example as Chitosan, Alginate, Gelatin.

2. Oral drug delivery

The ability of microspheres containing polymer to form films permit its use in the formulation of film dosage forms, as an alternative it is also used to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the basic primary amine groups ($-NH_2$)

which make it microspheres more suitable for oral drug delivery applications. Eg. Chitosan, Gelatin.

3. Gene delivery

Microspheres could be a useful oral gene carrier due its adhesive and transport properties in the GI tract. Eg. Chitosan, Gelatin, viral vectors, cationic liposomes, polycation complexes.

4. Nasal drug delivery

Polymer based drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Eg. Starch, Dextran, Albumin.

5. Intratumoral and local drug delivery

In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films are fabricated. Mixture of drug has promising potential for use in controlled delivery in the oral cavity. Eg. Gelatin, PLGA, Chitosan and PCL.

6. Buccal drug delivery

Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Chitosan, Sodium alginate.

7. Gastrointestinal drug delivery

Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug. eg. Eudragit, Ethyl cellulose+Carbopol BSA, Gelatin.

8. Transdermal drug delivery

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Eg. Chitosan, Alginate, PLGA.

9. Colonic drug delivery

Polymer has been used for the specific delivery of insulin to the colon. Eg. Chitosan.

10. Vaginal drug delivery

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely used for the treatment of mycotic infections of the genitourinary tract. Eg. Chitosan, Gelatin, PLGA.

11. Targeting by using microparticulate carriers

Pellets are prepared with polymer by using the extrusion spheronization technology. Eg. Chitosan, Microcrystalline cellulose.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Microspheres by ionotropic gelation technique promises to be potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. 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.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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