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Review Article

A Review on Microspheres: Novel Approach in Drug Delivery System

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ABSTRACT

Microspheres are spherical, free-flowing particles ranging in size from 1 to 1000 micrometers and are widely utilized in drug delivery systems due to their controlled and sustained release properties. These systems offer significant advantages, including enhanced bioavailability, reduced dosing frequency, targeted delivery, and improved patient compliance. Microspheres can be fabricated using a variety of biodegradable and biocompatible polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers (PLGA), as well as natural polymers like gelatin and chitosan. This review provides a comprehensive overview of the types, preparation methods, and evaluation parameters of microspheres. Techniques such as solvent evaporation, spray drying, and phase separation are discussed alongside methods for assessing particle size, morphology, encapsulation efficiency, in vitro drug release, and biocompatibility. The potential of microspheres in various therapeutic areas, including cancer, diabetes, and vaccine delivery, highlights their versatility and relevance in modern pharmaceutical research. Despite current challenges in scale-up and regulatory approval, microspheres remain a promising platform for the development of advanced drug delivery systems

INTRODUCTION

To improve a medicine's therapeutic efficacy and get around some issues with traditional therapy, a controlled drug delivery system is employed. It becomes essential to get the drug to the target tissue in the ideal quantity within the ideal time frame in order to achieve optimum therapeutic efficiency with the least degree of toxicity and adverse effects. A medicinal ingredient can be delivered to the target site using a variety of methods in a prolonged controlled release form.[1] Various drug delivery and drug targeting methods are now being developed to reduce drug degradation and loss, avoid unwanted side effects, and maximize drug bioavailability and the percentage of the medication accumulated in the necessary zone. Soluble polymers, microparticles composed of insoluble or biodegradable natural and synthetic polymers, cells, cell ghosts,

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lipoproteins, liposomes, and micelles are examples of drug carriers.
By conjugating the carriers with particular antibodies against particular distinctive elements of the area of interest, the carriers can be designed to be slowly degradable, stimuli-reactive (such as pH- or temperature-sensitive), and even targeted. Using microspheres as medication carriers is one such strategy. Microspheres are tiny particles (between one and a thousand micrometers in size) that are used as medication and therapeutic agent carriers. They are made of proteins or artificial polymers that are biodegradable. A monolithic spherical structure with the medication or therapeutic agent dispersed throughout the matrix or as a dispersion of particles is referred to as a microsphere [2]

Different Types of Methods for Preparation of Microspheres

1.Single Emulsion Technique [3]

The micro particulate carriers of natural polymers i.e., those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium e.g., oil. In the second step of preparation cross-linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical crosslinkers. The chemical cross linking agent used include gluteraldehyde, formaldehyde, terephthaloyl chloride, diacid chloride, etc. Croslinking by heat is carried out by adding the dispersion, to previously heated oil. Heat denaturation is however, not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation. denaturation is however, not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation.

2) Double Emulsion Technique [4,5]

Involves creating multiple emulsions or type w/o/w double emulsions, and it works well with water-soluble medications, proteins, peptides, and vaccines. Both synthetic and natural polymers can be employed using this technique. A lipophilic organic continuous phase disperses the aqueous protein solution. The active ingredients may be present in this protein solution. The polymer solution that ultimately envelopes the protein in the dispersed aqueous phase often makes up the continuous phase. After that, the primary emulsion is homogenized or sonicated before being added to the polyvinyl alcohol (PVA) aqueous solution. As a result, the double emulsion is created. The solvent is subsequently removed from the emulsion using either the solvent extraction technique or solvent evaporation. The emulsion is kept at a lower pressure or stirred to allow the organic phase to evaporate in order to accomplish the solvent evaporation. In the latter scenario, a considerable amount of water—with or without a surfactant—is mixed with the emulsion, and the organic phase diffuses out. Filtration and washing are next used to obtain the solid microspheres. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist; vaccines, proteins/peptides and conventional molecule are successfully incorporated in to the microspheres using the method of double emulsion solvent evaporation/extraction.

3.Spray Drying and Congealing Technique [6]

The drying of the polymer and drug mist in the air is the foundation of the spray drying and spray congealing processes. The two procedures are called spray drying and spray congealing,

respectively, depending on whether the solvent is removed or the solution is cooled. First, the polymer is dissolved in an appropriate volatile organic solvent, like acetone, dichloromethane, etc. Following high-speed homogenization, the solid medication is subsequently distributed throughout the polymer solution. After that, a stream of heated air atomizes this dispersion. The atomization process creates tiny droplets or a fine mist, from which the solvent evaporates to generate microspheres that range in size from 1 to 100 µm. The heated air is separated from the microparticles.

4) Polymerization Technique

Interfacial Polymerization [7]

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed; one is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet.

Normal Polymerization (8)

Uses methods such as micellar, emulsion, bulk, and suspension precipitation polymerization. A monomer and initiator are heated to start the polymerization process in bulk polymerization. The addition of an initiator speeds up the rate of reaction. During the polymerization process, a drug is added. The polymer so obtained is fragmented to microspheres.

Suspension Polymerization

Suspension polymerization is also called as bead/pearl polymerization. Carried out by heating the monomer or mixture of monomers with active principles (drug) as droplets dispersion in a continuous phase. The droplets may also contain an initiator & other additives. The emulsion polymerization differs from the suspension polymerization as due to presence of initiator in the aqueous phase, which later on diffuses to the surface of the micelles or the emulsion globules. The suspension & emulsion polymerization can be carried out at lower temperature since continuous external phase is normally water through which heat can easily dissipate

5.Solvent Extraction[9]

Solvent evaporation has been extensively used for the preparation of PLA and PLGA microspheres which contain various drugs. Several variables are identified that can significantly affect microspheric characteristics, such as solubility of drug, internal morphology, type of solvent, diffusion rate, temperature, polymer composition, viscosity, and drug loading. The efficacy of this method relies on the effective entrapment of the active substance into the particles, and therefore this procedure is particularly efficient with drugs that are either insoluble or partially soluble in the liquid medium.

6.Quassi Emulsion Solvent Diffusion[10]

Quasi-emulsion solvent diffusion method is used for the manufacturing of the controlled release microspheres of drugs with acrylic polymers. Microsponges can be manufactured by this method by using external phase which contains distilled water and polyvinyl alcohol. Internal phase consists of the drug, ethanol and polymers. Firstly, the internal phase is heated at 60ºC and added to

the external phase in the room temperature. The mixture is stirred continuously for 2 hours. Then the mixture can be filtered for separation of the microsponges.

Types Of Microspheres

Microspheres are classified into different types. They are of following

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

1. Bio adhesive Microspheres [11]

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.

2. Magnetic Microspheres[12]

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.

3. Floating microspheres[13]

In floating type, 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, and the system is found to be floating on gastric contents and decrease gastric residence and increases fluctuation in plasma concentration. Moreover, it also reduces chances of dose dumping. It produces prolonged effect and so reduces dosing frequencies.

4. Radioactive microspheres[14,15]

Treatment with radio embolization When they appear, microspheres that are 10–30 nm in diameter are greater than the capillary bed's diameter. Under all of these circumstances, radioactive microspheres give a high dosage of radiation to the targeted locations without harming the healthy surrounding tissues because they are injected into the arteries that flow to the tumor of interest. Here, radioactivity acts within a radioisotope at a normal distance rather than being expelled from a microsphere. There are three different kinds of radioactive microspheres: α, β, and ϒ emitters.

5. Polymeric microspheres[16,17]

Polymeric Microspheres - The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric

microspheres and Synthetic polymeric microspheres.

A- 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 rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner.

B-Synthetic Polymeric Microspheres - The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc.

Ideal characteristics of microspheres:[18]

➤ The ability to incorporate reasonably high concentrations of the drug.

➤ Stability of the preparation after synthesis with a clinically acceptable shelf life.

➤ Controlled particle size and dispersability in aqueous vehicles for injection.

➤ Release of active reagent with a good control over a wide time scale.

➤ Biocompatibility with a controllable biodegradability.

➤ Susceptibility to chemical modification.

Advantages of Microspheres: [19,20]

1. Particle size reduction for enhancing solubility of the poorly soluble drug.
2. Provide constant and prolonged therapeutic effect.
3. Provide constant drug concentration in blood thereby increasing patent compliance,
4. Decrease dose and toxicity.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
6. Reduce the dosing frequency and thereby improve the patient compliance
7. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
8. Microsphere morphology allows a controllable variability in degradation and drug release.
9. Convert liquid to solid form & to mask the bitter taste.
10. Protects the GIT from irritant effects of the drug.
11. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
12. Controlled release delivery biodegradable microspheres are used to control drug release rates. There by decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Evaluation Parameters of Microspheres:

1.Particle Size and Morphology [20]

Drug release rate, biodistribution, and cellular absorption are all impacted by microsphere size. To evaluate size and shape, methods like Dynamic Light Scattering (DLS) and Scanning Electron Microscopy (SEM) are used.

Relevance: While larger particles might be better suited for oral or depot systems, smaller particles have a larger surface area and are better suited for intravenous or pulmonary delivery.2

2. Drug Loading and Encapsulation Efficiency [21]

This metric is crucial for dose accuracy since it establishes the amount of drug entrapped.

Techniques: HPLC and UV-Vis spectrophotometry.

Importance: Effective encapsulation lowers expenses while enhancing treatment outcomes.

3. In Vitro Drug Release[22]

Release studies simulate the drug diffusion from microspheres under physiological conditions.

Methods: Dialysis, USP apparatus.

Purpose: Helps in predicting in vivo performance and choosing appropriate release kinetics.

4. Zeta Potential (Surface Charge) [23]

Zeta potential indicates the stability of microspheres in suspension and their interaction with biological membranes.

Technique: Laser Doppler Anemometry.

Significance: Affects aggregation behavior and cellular uptake.

5. Biodegradability and Stability [24]

Evaluation under physiological pH and enzymatic conditions helps assess degradation profile.

Relevance: Critical for drug delivery longevity and safety.

6. Biocompatibility and Cytotoxicity [25]

Biocompatibility is essential for clinical translation, evaluated using in vitro assays (MTT, hemolysis) and in vivo studies

CONCLUSION

Microspheres have emerged as a promising and versatile drug delivery system, offering controlled release, targeted delivery, enhanced bioavailability, and patient compliance. Their ability to encapsulate a wide range of therapeutic agents—including peptides, proteins, and small molecules—makes them ideal for diverse applications across pharmaceuticals, biotechnology, and diagnostics. Various natural and synthetic polymers are used to fabricate microspheres, each influencing characteristics such as degradation rate, drug release profile, and biocompatibility. The evaluation of microspheres, through parameters like particle size, encapsulation efficiency, in vitro release, surface charge, and biocompatibility, is crucial to ensure their effectiveness and safety. Ongoing advancements in polymer science, microencapsulation techniques, and nanotechnology are expected to further refine microsphere-based systems, making them more precise and responsive to physiological conditions.

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