Review Article

Microspheres As A Novel Drug Delivery System - A Review

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Received: 16-04-2022; **Revised:** 15-06-2022; **Accepted:** 22-06-2022; **Published on:** 15-07-2022.

ABSTRACT

Controlled drug delivery system can conquer the issues of conventional drug therapy and gives better therapeutic efficacy of a drug. The microspheres are one of the novel drug delivery system which can be given as an effective therapeutic alternative to conventional or immediate release single-unit dosage forms. Microspheres are spherical free flowing powder having particle size less than 200µm, consisting of synthetic polymers and proteins which are biodegradable in nature. Microsphere improves bioavailability, reduces the side effects, improves stability, decreases dose frequency and targets the drug to specific site at predetermined rate. The different types of microspheres are bioadhesive, floating, radioactive, polymeric and biodegradable microspheres. In future microspheres will track down the focal spot in novel drug delivery conveyance, especially in diagnostics, genetic materials, targeted and effective drug delivery.

Keywords: Microsphere, Types of microsphere, Methods of preparation, Characterization of Microsphere, Application of Microspheres.

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DOI: 10.47583/ijpsrr.2022.v75i01.027

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v75i01.027

INTRODUCTION

Novel drug delivery system delivers a therapeutic substance to the target site in a well-controlled and sustained model.[1] Microspheres or microparticles are defined as a free-flowing spherical particles consisting of polymer matrix and drug. They consist of proteins or synthetic polymers which are biodegradable in nature having a particle size less than 200µm.[2]

Microspheres can be referred as small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres can also be called as microparticles. Microspheres had been explored significantly for their use in the subject of drug transport and various polymers had been utilized for the formulation of the microspheres, which in turn have been assessed for distinctive purposes. Eventually the whole dose and few adverse reactions can be decreased due to the fact that a steady plasma concentration is maintained.[3]

Microspheres are of two types; Microcapsules and Micromatrices. Microcapsules are those in which entrapped substance is surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersed throughout the microsphere matrix.[1]

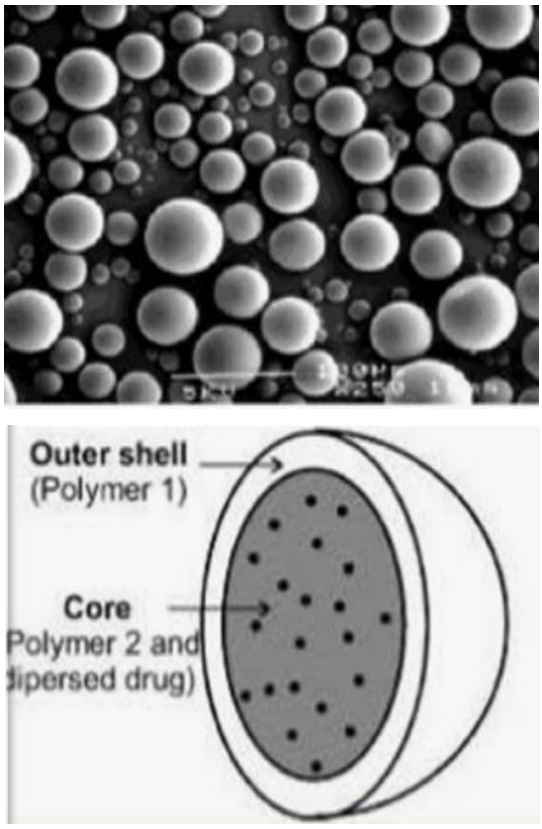

Figure 1: Microspheres[4]

Advantages of Microspheres[5,6]

1. Decreased size of microsphere contributes increased surface area thereby increases the potency of the poorly soluble material.
2. Dose frequency and adverse effects can be reduced.
3. Increased patient compliance.

4. Drug packaged with polymer prevent drug from enzymatic cleavage therefore the drug can be protected from various enzymes.
5. Enhances bioavailability.
6. Gastric irritation can be reduced.
7. Biological half-life can be enhanced.
8. First pass metabolism can be reduced.
9. Unpleasant odour and taste of the drug can be masked.

Disadvantages of microspheres[6]

1. Reproducibility is less.
2. The cost of materials and processing is high compared to conventional preparations.
3. Change in process variables such as change in temperature, pH, solvent addition and evaporation/agitation may influence the stability of core particles.
4. The fate of polymer matrix and additives.

Materials used in the formulation of microsphere[7]

Microspheres are usually made of polymers, they are classified as follows.

- Synthetic Polymers
- Natural polymers

A. Synthetic polymers are of two types

a) Non-biodegradable polymers

Eg- Acrolein, Polymethylmethacrylate (PMMA), Epoxy polymers, Glycidyl methacrylate

b) Biodegradable polymers

Eg- Glycolides and their co polymers, Poly alkyl cyano acrylates, Poly anhydrides and lactides.

B. Natural polymers – These are obtained from different sources such as proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Collagen and gelatin

Carbohydrates: Agarose, Carrageenan, Starch, chitosan, Chemically modified carbohydrates: Poly dextran, Poly starch[9]

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
   I. Biodegradable polymeric microspheres
   II. Synthetic polymeric microspheres

1. Bioadhesive microspheres[8]

Sticking of drug to the membrane by using the water-soluble property of the water-soluble polymers is called adhesion. Sticking or adhesion of drug delivery system to the mucosal membrane such as buccal, nasal, ocular, rectal etc can be termed as bioadhesion. This type of microsphere provides prolonged residence time at the target site and provide better therapeutic action.

2. Magnetic microspheres[9]

This type of delivery system localizes drug to the target site. In this type of delivery system, a drug or therapeutic radioisotope bound to a magnetic component is injected in the systemic circulation, which is then stopped with powerful magnetic field in the disease/target site. Magnetic microspheres are molecular particles which are small enough to move across capillaries without creating an esophageal occlusion(<4µm) but are extremely sensitive (ferromagnetic) to be trapped in micro-vessels and drawn by a magnetic field through neighbouring tissues. Here larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug.

There are different kind of magnetic microsphere. They are

- Therapeutic microsphere- They are used to target anticancer agents to liver tumors. This helps in tumor cell eradiation without harming the nearby cells.
- Diagnostic microsphere- They are 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[10]

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[11,12]

Radio embolization therapy microspheres sized 10-30nm are of larger than the diameter of the capillary bed when they come across. They are injected in the arteries that lead 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. Here radioactivity is not released from

microsphere but acts within a radioisotope in typical distance. The different types of radioactive microspheres are α emitters, β emitters and ϒ emitters.

5. Polymeric microspheres[13]

Polymeric microspheres can be classified as biodegradable polymeric microsphere and synthetic polymeric microspheres

i. Biodegradable polymeric microspheres

Natural polymers such as starch are used as they are biodegradable, biocompatible and also bioadhesive in nature. Biodegradable polymers prolong the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium resulting in gel formation. The rate and extent of drug release are controlled by concentration of polymer and the release pattern a sustained manner. This type of microspheres shows prolonged residence time at the site of application.

ii. Synthetic polymeric microspheres

Synthetic polymeric microspheres are widely used in clinical application, moreover they are 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 they tend to migrate away from the injection site and lead to potential risk, embolism and further organ damage.

Table 1: List of drugs given as microspheres[14]

S.no	Drug	Category	Polymer	Method
1	Fluorouracil	Anticancer	Glutaraldehyde	Dry in oil
2	Aceclofenac	NSAID	Eudragit	Dissolving drug in polymer
3	Gentamycin	Antibiotic	PLGA	Double emulsion
4	Diclofencac	Antiinflammatory	Sodium alginate	Gelation method
5	Insulin	Antidiabetic	Chitosan	Cross-linking
6	Furosemide	Diuretics	Chitosan	Cross-linking

METHOD OF PREPARATION

The choice of technique depends upon the nature of polymer as well as nature of drug and the duration of therapy. The most important physical and chemical factors that may be controlled in microsphere manufacture are

- The particle size requirement
- Molecular weight of polymer
- Polymer to drug ratio
- Stability problem
- Reproducibility
- Total mass of drug and polymer
- Dispersibility in aqueous vehicle

TECHNIQUES FOR MICROSPHERE PREPARATION

1. Solvent evaporation
2. Single emulsion technique
3. Double emulsion technique
4. Phase separation coacervation technique
5. Spray drying and spray congealing
6. Solvent extraction
7. Quassi-emulsion solvent diffusion

1. Solvent evaporation[15]

Solvent evaporation is carried out in a manufacturing vehicle phase. The microcapsule coating is first dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. In a coating polymer solution, a core material to be microencapsulated is dissolved or dispersed. To obtain acceptable size microcapsule, agitation is performed so that the core material mixture is dispersed in the liquid manufacturing vehicle phase. If necessary, the mixture is heated to evaporate the solvent. If the core material is dissolved in the coating polymer, matrix-type microcapsules are formed. The core material may be either water soluble or water insoluble material. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.

2. Single emulsion technique[16]

The microparticulate carriers of natural polymers i.e. those of proteins and carbohydrates can be prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium such as oil. In the next step, cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross-linking agents used are glutaraldehyde, formaldehyde, acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredients to

chemicals if added at the time of preparation. It is then subjected to centrifugation, washing and separation. The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, drug loading, drug release and bio performance of the final multiparticulate product.

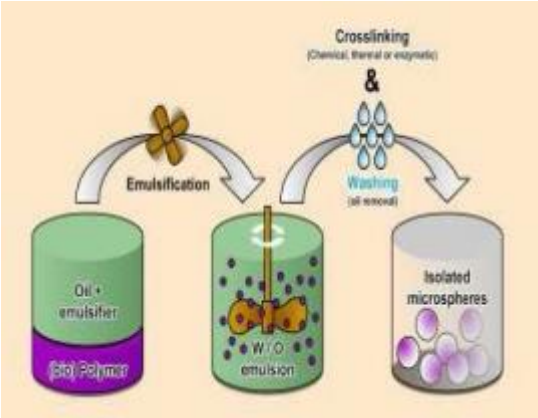

Figure 2: Microspheres by Single Emulsion Technique

3. Double emulsion technique[17]

Double emulsion method of microsphere involves the formation of the multiple emulsion or double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase generally consists of the polymer solution that eventually encapsulates protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the sonication before addition to the aqueous solution of the polyvinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to a solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drug like luteinizing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using method of double emulsion solvent evaporation/extraction.

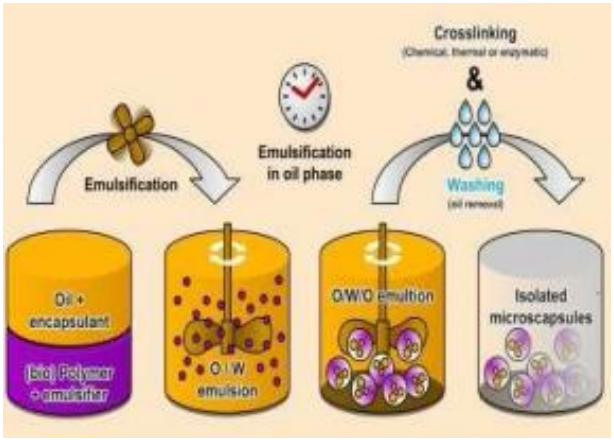

Figure 3: Microspheres by Double Emulsion Technique

4. Phase separation coacervation technique[18]

This technique is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called coacervates. In this process, the drug particles are dispersed in a polymer solution and an incompatible polymer is added which makes the first polymer to phase separate and engulf the drug particles. In order to avoid agglomeration stirring should be done.

5. Spray Drying and spray congealing[19]

These processes 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, two processes are named spray drying and spray congealing respectively. In spray drying, the polymer is dissolved in a volatile organic solvent such as dichloromethane, acetone etc. The drug in solid form is dispersed in the polymer solution with high-speed homogenization. This dispersion is then subjected to atomization in a stream of hot air. The atomization leads to the formation of small droplets or the fine mist from which the solvent evaporates instantaneously leading to the formation of the microspheres in a size range 1-100µm. Microparticles are separated from the hot air with the help of cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of this process is feasibility of operation under aseptic conditions.

6. Solvent extraction[20]

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.

7. Quassi emulsion solvent diffusion[21]

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.

CHARACTERIZATION OF MICROSPHERE[22]

1. Particle size and shape

The microparticles are visualized by microscopic method using calibrated optical micrometer. The most widely used procedure for microparticular visualisation are standard

light microscopy (LM) and Scanning electron microscopy (SEM).

LM provides a control over coating parameters in double walled microspheres. SEM provides higher resolution when compared to LM. The Samples can be analysed through SEM. The sample are scanned in parallel lines using a centered electron beam. Microspheres are placed on a sample holder for SEM characterization followed by coating with a conductive metal like platinum or zirconium using a sputter coater. The sample is scanned with a fine electron beam. The surface properties of the sample are obtained from the secondary electrons leaked from the sample surface.

2. Electron spectroscopy for chemical analysis

The electron spectroscopy for chemical analysis (ESCA) is used to determine the surface chemistry of the microspheres. It is also used for the determination of the atomic composition of the surface. The surface degradation of the biodegradable microspheres can be determined using the ESCA spectra.

3. Attenuated total reflectance Fourier Transform Infrared Spectroscopy

FT-IR is used for the determination of degradation of the polymeric matrix of the carrier system. The microspheres' surface is examined by measuring alternating total reflectance (ATR). The ATR-FTIR gives information about surface composition of the microspheres depending upon manufacturing procedures and conditions.

4. Density determination

The density of the microspheres is measured by using multi volume pychnometer. Accurately weighed sample in a cup is kept into the multi volume pychnometer. Helium is introduced at a constant pressure in the chamber and is allowed to expand. This expansion will result in lowering of pressure within the chamber. Two consecutive readings of decrease in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier can be determined.

5. Isoelectric point

Electrophoretic mobility of microspheres can be measured using micro electrophoresis from which the isoelectric point is determined. The electrophoretic mobility is related to the surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.

6. Determination of percentage yield

The percentage yield is determined by calculating the measured amount of the product and the polymers used in the formulation of the microspheres and the overall sum of microspheres produced.

7. Drug content

The mixture is kept aside to allow the particles to sediment and then wash. Transfer 1ml of the filterate into volumetric flask, and the volume is made up with 0.1N NaOH. Drug is measured spectrophotometrically after the optimum dilution.

8. Determination of drug loading

Drug loading is the amount of drug loaded per unit nanoparticle weight, indicating the percentage of nanoparticle weight which is attached to the encapsulated product. Drug loading (%) can be determined by the total amount of drug entrapped, divided by the total weight of nanoparticles. In the delivery of drugs, yield is given as a percentage which represents the amount of drug delivered per quantity.

9. Capture efficiency or entrapment efficiency

The capture efficiency of the microspheres or the percent entrapment is determined by allowing washed microspheres to lyse. The lysate is then subjected for determination of active constituents as per monograph requirement. The percent encapsulation efficiency can be calculated using following equation

% Entrapment = Actual content/Theoretical content x 100

PHARMACEUTICAL APPLICATION OF MICROSPHERES

1) Microspheres in vaccine delivery[23]

The prerequisite of a vaccine is safety toward the microbes and its toxic components. An ideal vaccine should fulfil the need of effectiveness, protection, affordability in application and cost. The aspect of safety and avoidance of adverse effects is complicated. The aspect of safety and the extent of the production of antibody responses are closely linked to mode of application. Biodegradable delivery system for vaccines which are provided by parenteral route may resolve the shortcoming of this same conventional vaccines. The involvement in parenteral (subcutaneous, intramuscular, intradermal) carrier exists even though those who offer significant advantages which includes;

1. Modulation of antigen release
2. Improved antigenicity
3. Stabilization of antigens

2) Microspheres in Gene delivery[21,22]

Genotype drug delivery includes viral vectors, non-ionic liposomes, polycation complexes, and microcapsules technologies. Viral vectors are important for genotype delivery even though those who are extremely efficient and also have a wide variety of cell goals. Even so, if used in vivo they trigger immune system and thereby pathogenic effects. To resolve the problems of viral vectors, non-viral delivery systems have been introduced for gene therapy. The advantages of non-viral delivery system are ease of preparation, cell / tissue targeting, reduced immune system, unrestricted plasmid size, as well as large-scale replicable manufacture. Polymers are used as a transporter of DNA for gene delivery applications.

3) Oral drug delivery[23]

The potential of polymer matrix containing diazepam through oral drug delivery has been evaluated through rabbits. Studies showed that even a film consisting of a 1:0.5 drug-polymer combination may have been an effective dosage form which is comparable to commercial tablet formulations.

4) Transdermal drug delivery[24]

Polymer are having good film-forming characteristics. The release profile from the system is impacted by the membrane thickness as well as crosslinking of a film. Chitosan-alginate polyelectrolyte structure has been prepared in-situ in beads and microspheres for potential uses in packaging, controlled release systems and surgical instruments. Polymer gel beads are highly biocompatible vehicle for chemotherapy of inflammatory cytokines for medications like prednisolone that also showed prolonged release action enhancing treatment effectiveness. The amount of drug release was found to be depend on the characteristics of cell wall used. A mixture of chitosan membrane and chitosan hydrogel containing lidocaine hydrochloride, a local anaesthetic is a great comprehensive process for controlled drug release and release kinetics.

5) Targeting by Using Micro Particulate Carriers[25]

The concept of targeting is a well-established concept, which is gaining huge attention in present days. The efficiency of drug depends on availability and ability to interact with binding site. Generally, pellets technique is established that can be formulated by utilising extrusion / spheronization technique e.g. microcrystalline cellulose (MCC) and chitosan.

6) Monoclonal Antibodies[25,26]

Monoclonal antibodies targeting microspheres are physiologically immunomicrospheres. Monoclonal antibodies are highly precise compounds and can be utilized to target microspheres loaded bioactive molecules to target sites. Monoclonal antibodies can be attached to microspheres by one of the following methods;

a. Non-specific adsorption
b. Specific adsorption
c. Direct coupling
d. Coupling via reagent

8) Other applications

Microspheres are utilized for membrane technology developed for mass spectrometry, cell biology, cell biology, Fluorescent connected Immuno-Sorbent Assay. Yttrium can used for standard treatment of hepatocellular carcinoma Applications of microencapsulation in other industry sectors are numerous. Carbonless copying paper, photosensitive paper, microencapsulated fragrances such as "scent-strips" (also known as "snap-n-burst") and microencapsulated aromas ("scratch-n-sniff"') are the well-known microencapsulated products. Scratch-n-sniff are used in children's literature and in the development of nutrition and cosmetics fragrance advertising. Microcapsules also are extensively included as diagnostic tests, for example, temperature-sensitive microcapsules for temperature dependent visual detection of cancer. In the biotech industry, microcapsules microbial cells are used for the manufacture of recombinant and proteins.[27]

CONCLUSION

The present review article suggests that microspheres are better drug delivery system and can resolve problems associated with conventional dosage form. Microspheres play a central and significant role in novel drug delivery system particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted, specific, and effective in vitro delivery, and supplements as miniature versions of diseased organs and tissues in the body. Microspheres provide a number of advantages over existing technology. Microsphere formulation shows more potency and is having more effectiveness in *in-vivo* drug delivery system and also, they are found to be effective carriers for the novel drug delivery system.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.