Research Article

A Comprehensive Review of Microspheres: Fundamentals, Classifications, Preparation Techniques, Evaluation Parameters and Therapeutic Applications in Modern Drug Delivery Systems

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ABSTRACT

Microspheres have become important drug delivery system because they provide controlled and targeted release of drugs. These are tiny particles which are prepared from synthetic or natural polymers and particle size ranging from 1-1000 µm. Various preparation techniques such as single emulsion, double emulsion, solvent evaporation, spray drying, ionic gelation, phase separation, solvent extraction and polymerization are used to design microspheres according to the physiochemical properties of different drugs. Their quality is assessed by several parameters such as particle size, morphology, swelling index, density, ATR-FTIR analysis and in-vitro drug release studies. Microspheres have wide range of applications. This review serves as a valuable resource for pharmaceutical scientists, researchers, and healthcare professionals involved in novel drug delivery system development and clinical applications.

Keywords: Microspheres, solvent evaporation, morphology, swelling index, targeted release.

INTRODUCTION

- The pharmaceutical industry has witnessed remarkable in drug delivery technologies, with microspheres emerging as one of the most promising and versatile platforms for controlled drug administration. Microspheres, defined as spherical particles ranging from 1 to 1000 micrometres in diameter, represent a sophisticated approach to addressing fundamental challenges in traditional drug therapy, including poor bioavailability, frequent dosing requirements, systemic toxicity, and patient non-compliance.
- The concept of microencapsulation and controlled release was introduced in 1960s, when researchers first recognized the potential of polymer-based systems for modulating drug release kinetics. However, modern microsphere technology represents years of research by pharmaceutical scientists, materials engineers, and biomedical researchers. The evolution from simple matrix systems to sophisticated, stimulus-responsive microspheres demonstrate the remarkable progress made in this field.
- Microspheres have several benefits compared to conventional dosage forms, including the ability to protect labile drugs from degradation, provide sustained drug release for a longer time, improve targeted delivery to specific tissues or cells, and reduce dosing frequency while minimizing side effects. These characteristics microspheres particularly valuable for treating chronic conditions, delivering protein and peptide drugs, and providing sustained release formulations for various therapeutic applications.
- The versatility of microsphere technology is evidenced by the diverse range of materials available for their construction, including natural polymers such as albumin, gelatin , and chitosan, as well as synthetic polymers like poly (lactic-co-glycolic acid) (PLGA), poly (lactic acid) (PLA), and various other biodegradable and non-biodegradable materials. This material diversity helps the design of microspheres with tailored properties to satisfy particular therapeutic requirements [1].

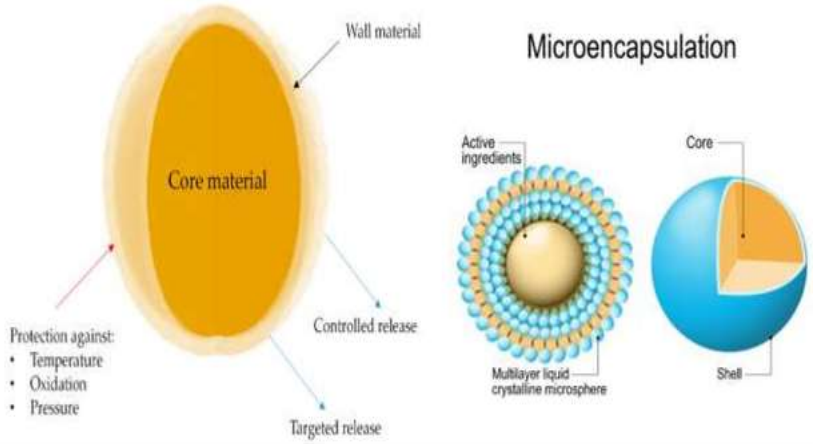


Fig 1. Structure Of Microsphere. [5]

CLASSIFICATION OF MICROSPHERES:

1. Bio-adhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres

i) Biodegradable polymeric microspheres

ii) Synthetic polymeric microspheres

1. Bio-adhesive microspheres:

Adhesion can be defined as the sticking of the drug to the membrane by using the sticking property of the water-soluble polymers. Adhesion of drug delivery devices to the membrane of mucous such as buccal, ocular, rectal, nasal etc. is called as Bio-adhesion. These types of microspheres exhibit a prolonged residence time at the application site causing intimate contact with the absorption site and giving better therapeutic action. [5]

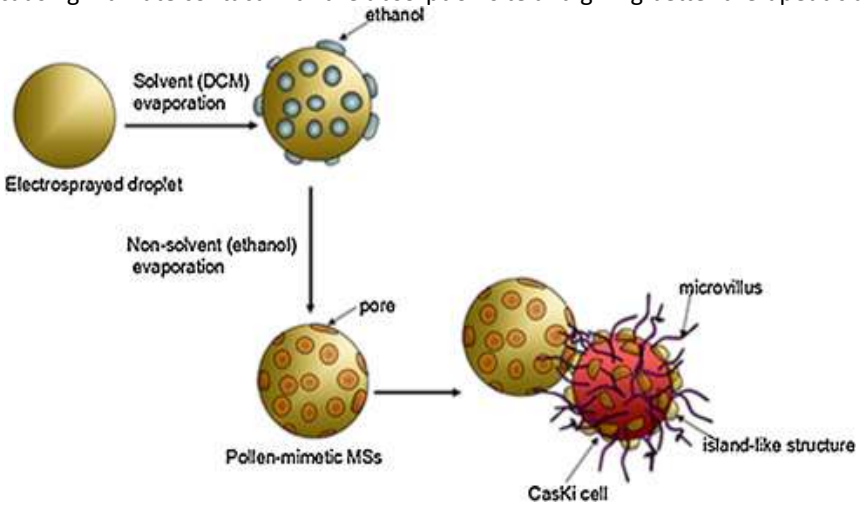


Fig 2. Bio-adhesive microspheres [5]

2. **Magnetic microspheres**:

Magnetic microsphere are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion but are (ferromagnetic) to be captured in micro vessels. This type of delivery system is very much important which localizes the drug to the disease site. The larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. The different type is Therapeutic and magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. [12]

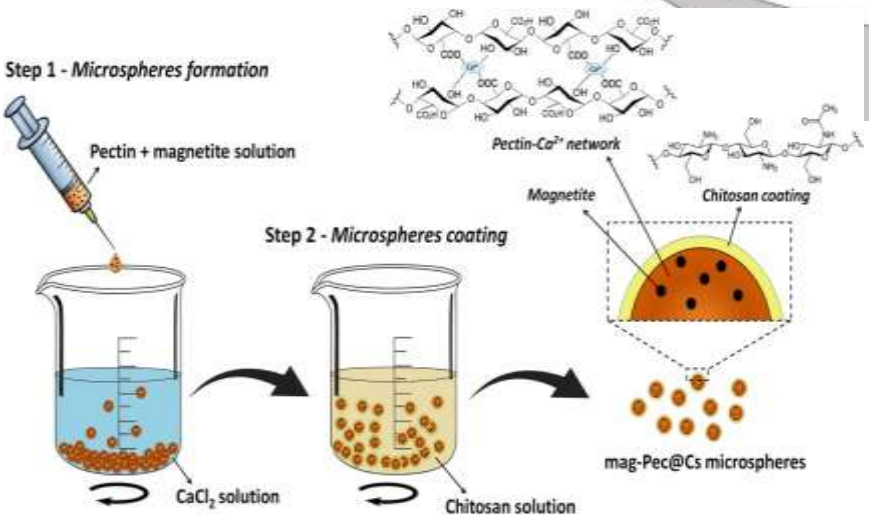


Fig 3. Magnetic microspheres.[5]

3. Floating microspheres:
The volume of floating microspheres is less than the liquid in the stomach without affecting the digestive system. The drug is slowly released to where it is needed. It also reduces the risk of accidents and disposable drug products.[6]

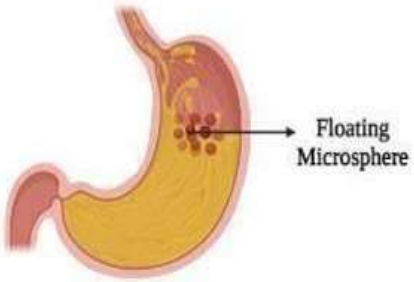


Fig 4. Floating microspheres. [5]

4. **Radioactive microspheres**:
These microspheres are used in Radioembolization therapy in which microspheres having sizes 10-30 nm are larger than capillaries. They are injected into arteries which leads to tumours of interest. These radioactive microspheres deliver high radiation doses to targeted areas without any damage to the normal tissues. Different types of radioactive microspheres are being used such as α emitters, β emitters, γ emitters. [5]

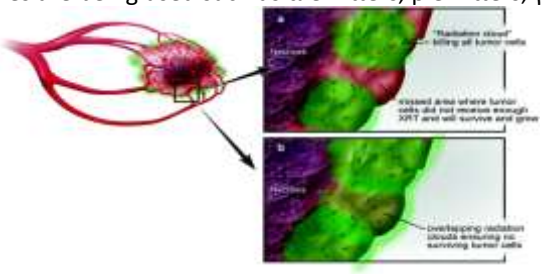


Fig 5. Radioactive microspheres.[6]

5. **Polymeric microspheres**:
The different types of polymeric microspheres classified as

i. **Biodegradable polymeric microspheres**:
Natural polymers such as starch are considered biodegradable, biocompatible, and naturally bio adhesive. These polymers cause gel formation by prolonging their contact time with the mucosa due to their swelling properties in aqueous media.

ii. **Synthetic polymeric microspheres**:

Synthetic polymer microspheres are widely used in medicine and are also used as containers, containers, embolization materials and drug carriers, etc. They can also be used and have been proven to be safe and biocompatible. Displacement of the injection and risk of embolism and other organ damage. [6]

MICROSPHERES TECHNIQUES:

1) Single emulsion technique:

Microparticulate carriers of natural polymers like proteins and carbohydrates is feasible with single emulsion technique. After dissolving in an aqueous medium, the natural polymers proceed to a non-aqueous medium, such as oil. Then undergo heating or chemical cross-linking agents can be used to cross connect dispersed globule in following phase. Cross linking chemicals like formaldehyde and glutaraldehyde. Then followed by centrifugation and preparation is cleaned and separated. [2]

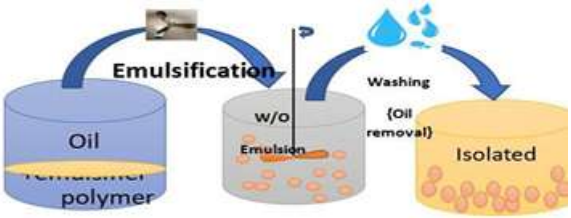


Fig 6. Single emulsion technique.[2]



Fig 7. Single Emulsion Method.[3]

2) Double emulsion technique:

The double emulsion technique (W/0/W) technique is commonly used for water-soluble drugs like proteins, peptides and vaccines. In the double emulsion technique, the drug solution is first emulsified into a polymer containing organic phase to form emulsion called primary emulsion. This primary emulsion is then dispersed into an aqueous phase containing polyvinyl alcohol to produce double emulsion. The organic solvent is removed by evaporation or extraction resulting in hardened polymeric microspheres. [2]

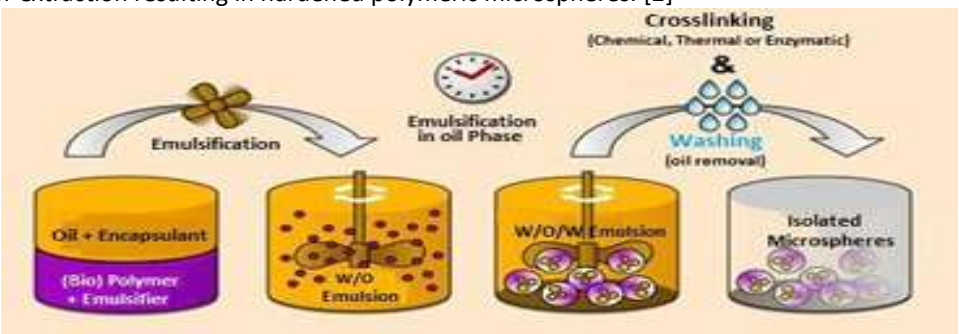


Fig 8. Double emulsion technique [2]

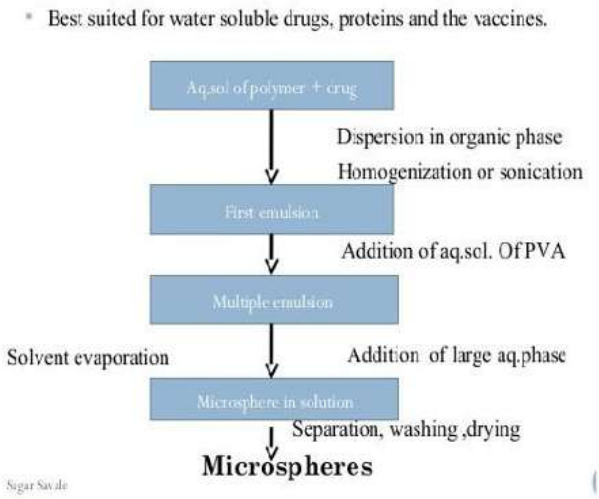


Fig 9. Double emulsion technique.[12]

3) Solvent evaporation:

In the solvent evaporation method, the process is carried out in the liquid manufacturing stage of the vehicle. The coating polymer is dissolved in a volatile solvent that is compatible with the vehicle phase and the core material is dispersed in the polymer solution. To obtain the required size of microcapsules, continuous agitation is required so that the core material is dispersed in liquid manufacturing vehicle. [7] The dispersion is then heated to evaporate the solvent, allowing the polymer to solidify around the core material. [8] If the core material is dissolved in the polymer solution, a matrix- a form of microcapsules is formed.[9]

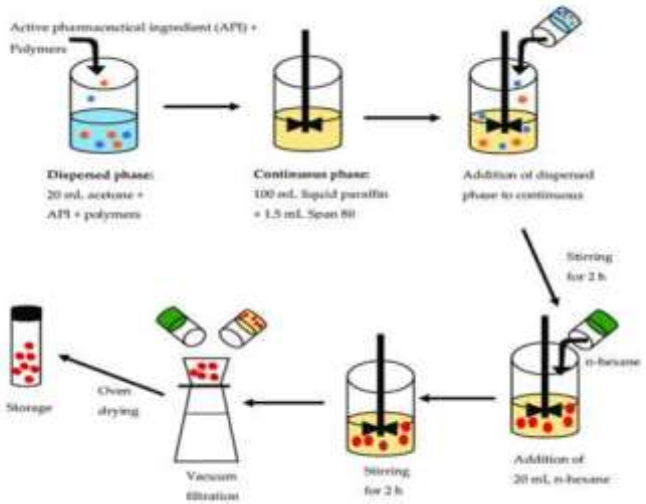


Fig 10. Solvent evaporation. [7]

4) **Spray drying and spray congealing:**

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 process are named spray drying and spray congealing respectively. In spray drying, the polymer is dissolved in a volatile organic solvent such as dichloromethane or acetone etc. [8] Polymeric solution is used to rapidly homogenize and distribute the medication.[2] The solvent rapidly evaporates to generate microspheres which the size ranges from 1–100 µm and collected using cyclone separator and dried.[7] In spray congealing, microspheres are formed by cooling the sprayed molten material instead of evaporating the solvent. [12]

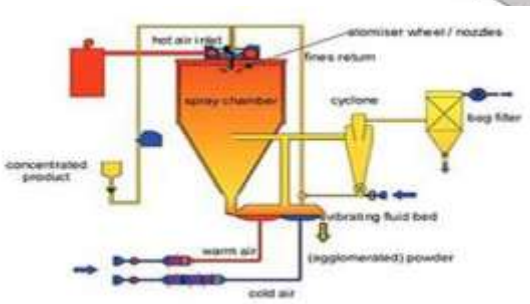


Fig 11. Spray drying and spray congealing. [6]

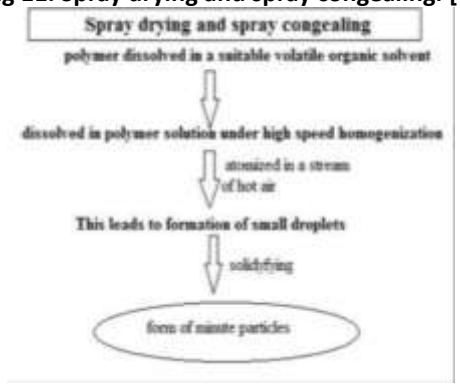


Fig 12. Spray drying and spray congealing.[7]

5) Quassi emulsion solvent diffusion:

A Quasi-emulsion solvent diffusion method is used to prepare the controlled release microspheres of drugs with acrylic polymers. [14] The internal phase contains drug, polymer and ethanol. External phase consists of distilled water and polyvinyl alcohol (PVA). The heated internal phase is added to the external phase with continuous stirring for about 2 hours. Then it is filtered for separation of the microsponges.[3]

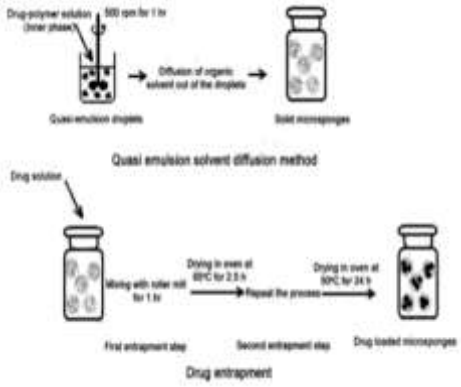


Fig 13. Quassi emulsion solvent diffusion. [12]

6) **Phase separation Cocervation method :**

This technology mainly prepares hydrophilic substances such as peptides and proteins with water. [4] The principle is based on reducing the solubility of polymers in the organic phase and creating a polymer-rich phase called coacervate. In this method, drug particles are dispersed in a solution of polymer and an incompatible polymer is added to the system which makes the first polymer for the phase separation.[5]

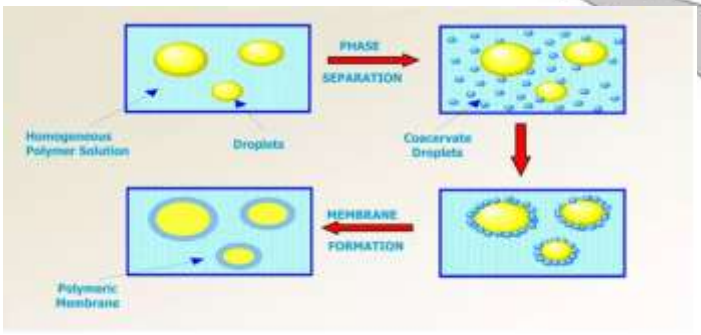


Fig 14. Phase separation Cocervation method. [4]

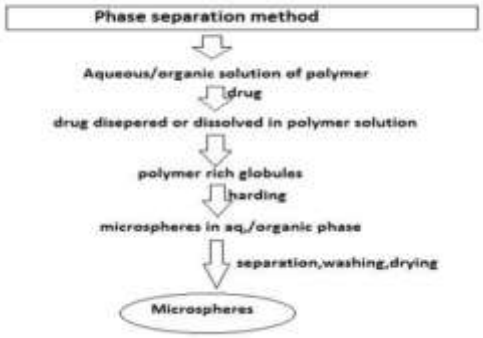


Fig 15. Phase separation Cocervation method.[7]

7) Solvent extraction:

This method is used for the preparation of microparticles by removing the organic solvent through extraction. A water-miscible solvent such as isopropanol is used and the organic phase is extracted with water resulting in rapid hardening of microspheres.The drug may be added directly to the polymer solution. The rate of solvent removal by extraction method depends on the temperature of water, emulsion-to-water ratio and the polymer's solubility.[14]

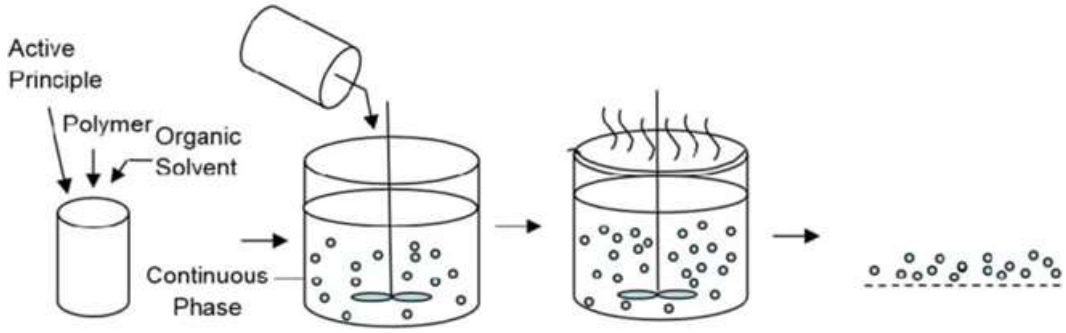


Fig 16. Solvent extraction. [2]

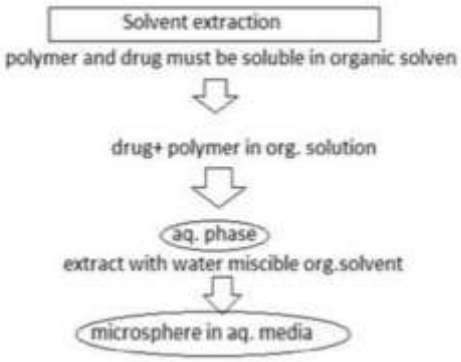


Fig 17. Solvent extraction. [7]

8) Ionic Gelation Method:

This technique is used for preparing the Alginate/chitosan particulate system for different drugs in controlled release. [5] Different % (w/v) of drugs get added to aqueous solution of sodium alginate. To get the complete solution stirring is continued and after that, it is added dropwise to a solution containing Ca+ and chitosan solution in acetic acid. Microspheres formed by this will be kept in the original solution for 6 hrs & 24 hrs for internal gellification followed by filtration for separation. The complete release will be obtained at pH 7.4 but the drug did not release in acidic pH. [12]

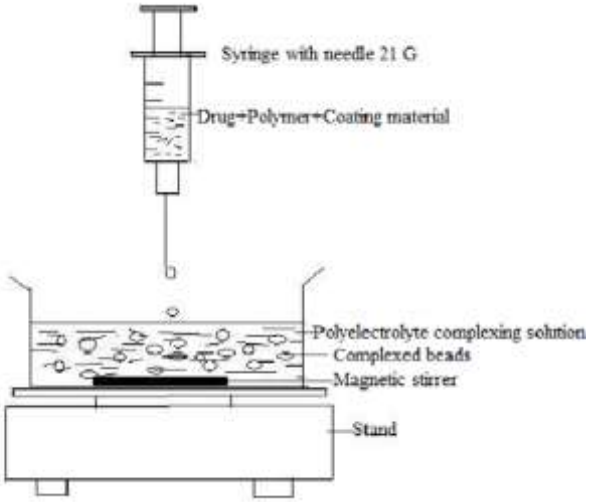


Fig 18. Ionic Gelation Method. [12]

9) Polymerization method

1. Normal polymerization:

It is carried out by using different techniques such as bulk, suspension, precipitation, emulsion and micellar polymeriztion methods. In bulk polymerization, monomers are polymerized with an initiator to form pure polymers. Polymer so obtained may be moulded as microspheres. Suspension polymerization forms polymer beads in an aqueous phase while emulsion polymerization uses an initiator present in the aqueous phase to produce microspheres. [13]

2. Interfacial polymerization:

The process of interfacial polymerization comprises the reaction of monomers at the interface between the two immiscible liquids resulting in formation a film of polymer that essentially encapsulates the dispersed phase. [11]

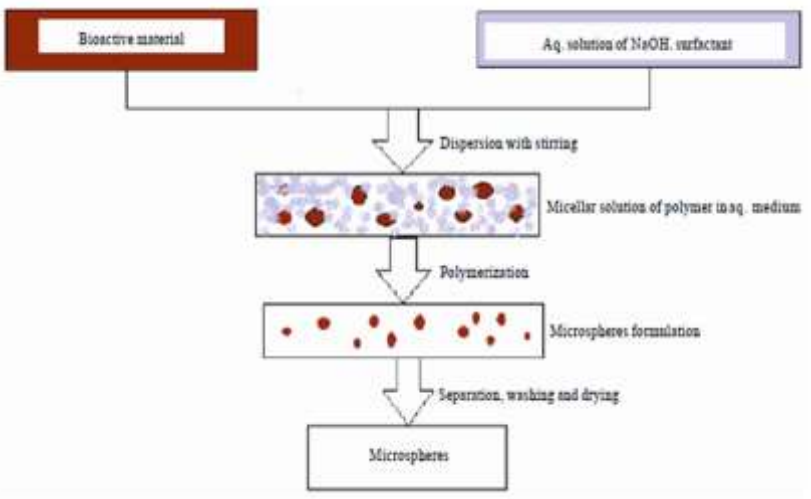


Fig 19. Interfacial polymerization. [11]

10) **Emulsion cross linking method**

In emulsion cross-linking method, the drug is dissolved in a heated aqueous gelation solution and added dropwise to liquid paraffin under stirring results in water-in-oil emulsion. The formed microspheres are washed with acetone and isopropyl alcohol which then air dried and cross-linked with glutaraldehyde. Finally glycine solution containing Tween 80 is added to neutralize any unreacted glutaraldehyde.[15]

EVALUATION OF MICROSPHERES:

1) **Particle size and shape**:

Particle size to visualize microparticles is conventional light
microscopy (LM) and scanning electron microscopy (SEM). Both can be used to
determine the shape and outer structure of microparticles LM provides a control over coating parameters in the case of double-walled microspheres. SEM provides higher resolution in contrast to the LM. [12]

2) **Electron spectroscopy for chemical analysis**:

The surface chemistry of microspheres can be determined by using
electron spectroscopy for chemical analysis, which provides the determination of the atomic composition of the surface. ESCA can be used to determine the surface degradation of biodegradable microspheres. [11]

3) **Density determination**:

Multi-volume pycnometer is used to determine the density of a microsphere. An accurately weighed sample in a cup is placed into the multi-volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of the reduction in pressure at different initial pressures are noted. From two pressure readings, the volume and hence the density of the microsphere carrier is determined. [12]

4) **Isoelectric point**:

Microelectrophoresis equipment can be used to measure theisoelectric point by monitoring the electrophoretic mobility ofmicrospheres. The time it takes for particles to move across aof 1 nm is used to compute the mean velocity atvarious pH values between 3 and 10. [7]

5) **ATR-FTIR**:

The polymeric matrix degradation is assessed using FT-IR. ATR (attenuated total reflectance) is mainly used to measure the surfaces of microspheres. Infrared spectra of the sample's surface material were mostly obtained by many reflections of the IR beam that passed through the ATR cell. ATR-FTIR analysis yields surface composition information about the microspheres based on circumstances and production processes. [4

6) **Swelling index**:

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. The swelling index of the microsphere was calculated by using the formula, Swelling index= (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) 100. [12

7) **In-vitro methods**:

This approach determines a drug's membrane permeability and release qualities. The in vitro approach is used in product development, pharmaceutical manufacturing, and other areas as a quality control procedure. It is essential to have sensible and repeatable release data that are generated from settings that are chemically, physically, and hydrodynamically characterized. [4]

PHARMACEUTICAL APPLICATIONS:

1) **Microspheres in gene delivery**:

They are few examples of gene delivery uses microspheres are viral vectors, non-ionic liposomes and microcapsule technology for genotype drug delivery method. While viral vectors are highly effective and have a broad range of cell targeting and crucial for genotype delivery, and they cause harmful effects by activating the immune system. Non-viral gene therapy delivery techniques have developed to address the viral vectors and it have some benefits like DNA is transported by polymers in gene delivery applications, reduces cell targeting, unrestricted plasmid size. [2]

2) **Oral drug delivery**:

The drug can be administered more easily and conveniently by the oral route and it has greater patient compliance rate. Oral route of administration widely used for variety of medicinal compounds. Mainly oral route improves drug solubility and drug permeability, drug delivery by microspheres shows prolonged release of medication improves patient compliance. [2]

3) **Microspheres in vaccine delivery**:

An ideal vaccine must meet the following criteria: effectiveness, safety, ease of use, and cost. Biodegradable vaccine delivery systems for vaccines administered through the parenteral route may be able to overcome the limitations of conventional vaccines.

- Improved antigenicity by adjuvant action
- Modulation of antigen release
- Stabilization of antigen. [9]

4) **Targeting using micro particulate carriers**:

The concept of targeting, i.e. site specific drug delivery is a well established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is enter to drug action mediated by use of a carrier system. [11]

5) **Monoclonal antibodies**:

Microspheres are biologically immunospheres that are targeted by monoclonal antibodies and it can be used to target areas with microspheres it contains bioactive chemicals. There are several ways to attach monoclonal antibodies to microspheres. Non-specific adsorption, specific adsorption, direct coupling, coupling via agent. [2]

CONCLUSION

Microspheres have established themselves as indispensable components of modern pharmaceutical technology, revolutionizing drug delivery across diverse therapeutic areas. The concept of microsphere drug delivery systems offers certain advantages over the conventional drug delivery systems such as controlled and sustained delivery. Appropriate evaluation methods ensure the quality, stability and performances of microspheres before clinical application. Sustained investment in research and development, coupled with regulatory support and industry collaboration, microspheres will remain at the forefront of pharmaceutical innovation for years to come.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

All authors contributed to the literature review, collection of relevant information, manuscript preparation, and final approval of the manuscript.

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