Original Research Article

A Review on Microspheres: Preparation, Characterisation, Evaluation and Applications

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Abstract

Now a day the recent development in new drug delivery systems plays a vital role in pharmaceutical industries. The drug delivery practice has been modified in the last decades and even many advanced innovations happened in recent times. Newer drug delivery systems are largely influencing the current medical practice. The idea of targeted drug delivery is to concentrate the treatment in the target tissues while lowering the relative concentration of the drug in the non-target tissues. As a result, the medication is concentrated at the desired location. As a result, the medication has no effect on the tissues nearby. Therefore, by combining the drug with a carrier particle like microspheres, nanoparticles, liposomes, niosomes, etc. that regulates the release and absorption characteristics of the drug, carrier technology offers an intelligent way for drug delivery. Microspheres attracted a lot of interest for their sustained release as well as their ability to direct anti-cancer medications to the tumour. Microspheres will play a key role in novel drug delivery in the future by fusing together a variety of other strategies, especially in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, and efficient in vivo delivery, and supplements as miniature representations of diseased organs and tissues in the body.

Keywords: Microspheres, controlled release, Types of microspheres, Methods of preparation, Evaluation of microspheres, applications

Introduction

Microspheres are small, spherical particles usually made up of biodegradable and biocompatible polymers having the size ranging from 1 to 1000 μm and incorporating drugs and other bioactive within their core. Microspheres are of two types microcapsules and micromatrices. Micromatrices are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micropherere those in which entrapped substance is disperesed throughout the matrix. Microspheres are completely spherical and homogenous in size. They are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. The drug particles can be dispersed at the molecular or macroscale within a framework comprised of one or more miscible polymers is referred to as a microsphere and it is described as "monolithic spheres or therapeutic substances dispersed either as a molecular particle dispersion or a throughout the matrix." The two most popular varieties of polymer microspheres are made of polyethylene and polystyrene. The capacity of polystyrene microspheres to simplify processes like cell sorting and antibody precipitation makes them a common choice for biomedical applications. Polystyrene microspheres are useful for scientific studies in biology and medical researchbecause proteins and ligand binds to the substance firmly and easily. Drug release can be modified and delayed via microencapsulation. Due to its tiny particle size, it is broadly dispersed throughout the digestive tract, improving drug absorption and decreasing side effects. Drug manufacturing up in a specific area that irritates the gastrointestinal mucosa.[1-5]. To maintain drug release and lessen or eliminate gastrointestinal tract discomfort, oral microspheres have been used. Multiparticulate delivery techniques also disperse more evenly throughout the digestive system. Compared to single-unit dosage forms such polymeric matrix tablets with no disintegration, this leads to more consistent drug absorption and lessens local discomfort.

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It is also possible to prevent unwanted intestinal retention of the polymeric substance, which might happen when taking matrix tablets on a regular basis[6]. Drug release can be modified and delayed via microencapsulation. As a result of their small particle size, they are broadly dispersed throughout the digestive system, improving drug absorption and lowering side effects brought on by a localised build-up of irritating substances against the gastrointestinal mucosa[7].

Advantages of Microspheres

1. The therapeutic action of microspheres are constant and prolonged.
2. After particle size reduction poorly soluble medication becomes more soluble.
3. Reduce toxicity and dosage.
4. Improves patient compliance.
5. Protect the drug from enzymatic and photolytic cleavage so it is best for drug delivery of protein.
6. Provide constant drug concentration in blood.
7. Increase bioavailabilty and lessen the frequency or severity of side effects
8. Gaurds the drug irritating effect on GIT.
9. Regulate drug release rates, reduce toxicity and issue associated with repeated and injections.
10. Masking taste and odour.
11. Become less reactive to the environment outside in relation to the core.[8]

Disadvantages of Microspheres

1. The prices of the components and processing for the controlled release preparation are significantly greater.
2. Process conditions likechange in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core paticle.
3. Reproducibility is less.
4. Degradation of product due to heat, hydrolysis,oxidation, solar radiation or biological agents.
5. How polymer matrix decays and how it affects the environment.
6. What happens to polymer additives such fillers, stabilisers, antioxidants, and plasticizers.[9]

Materials used for the Formulation of Microspheres

Microspheres used usually are polymers. They are classified into two types:

1. Synthetic Polymers
2. Natural polymers

1. Synthetic polymers are divided into two types

(A) Non-biodegradable polymers

For examples: Poly methyl methacrylate acrolein (PMMA), Glycidyl methacrylate, Epoxy polymers

(B) Biodegradable polymers

For example: Lactides and Glycolides and their copolymers, Poly alkyl cyano acrylates, Polyanhydrides and Poly-ε-caprolactone (PCL)

2. Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

(A) Proteins: Albumin, Gelatin4 , and Collagen

(B) Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

(C) Chemically modified carbohydrates: Poly dextran, Poly starch.[9]

Types of Microspheres

S. No.	Types	Description	Application
1.	Bioadhesive microspheres	Prolong residence time	Nasal – Gentamycin
2.	Floating microspheres	Bulk density less than gastric fluids.	NSAIDS, antibiotics
3.	Radioactive microspheres	Delivers high radiation dose to targeted site.	Diagnostic: Liver, spleen
4.	Polymeric microspheres	Biodegradable and non biodegradable, swells in aqueous medium	Vaccines: Hepatitis, Local: Protien and hormones
5.	Magnetic microspheres	Localise the drug to the disease site	Chemotherapeutic agent to liver

Methods of Preparation

Microspheres can be prepared by following methods,

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

1. Spray Drying

The spray drying process involves the atomization of a solution, slurry, or emulsion containing one or more components of the desired product into droplets by spraying followed by the rapid evaporation of the sprayed droplets into solid powder by hot air at a certain temperature and pressure.[19]

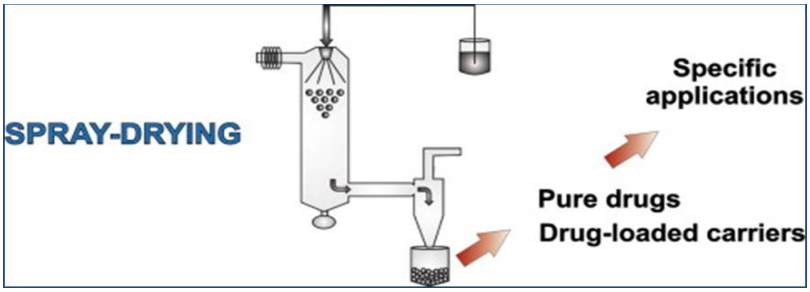

Fig 1: Spray drying technique [20]

2. Solvent Evaporation

In the solvent evaporation process, the polymer is dissolved in a suitable water immiscible solvent, and the medicament is dispersed or dissolved in this polymeric solution. The resultant solution or dispersion is then emulsified in an aqueous continuous phase to form discrete droplets. In order for the microspheres to form, the organic solvent must first diffuse into the aqueous phase and then evaporate at the water/air interface. As solvent evaporation occurs, the microspheres harden and free flowing microspheres can be obtained after suitable filtration and drying[21]

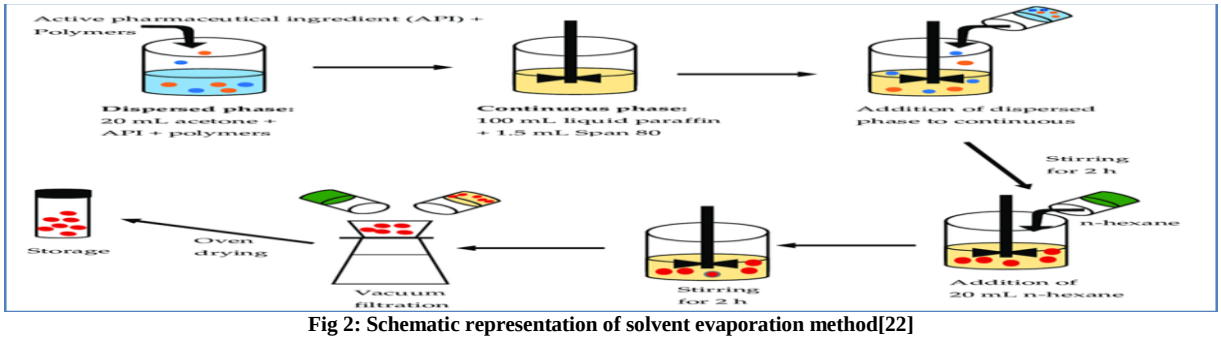

Fig 2: Schematic representation of solvent evaporation method[22]

3. Single Emulsion Technique

In this technique aqueous solution of polymer are dispersed in organic phase oil/chloroform with continuous stirring this process called as sonification. After this microsphere can be prepared by two ways, first heat denaturation and chemical crosslinking and centrifuge the product and washing or finally separation to produce microspheres[19].

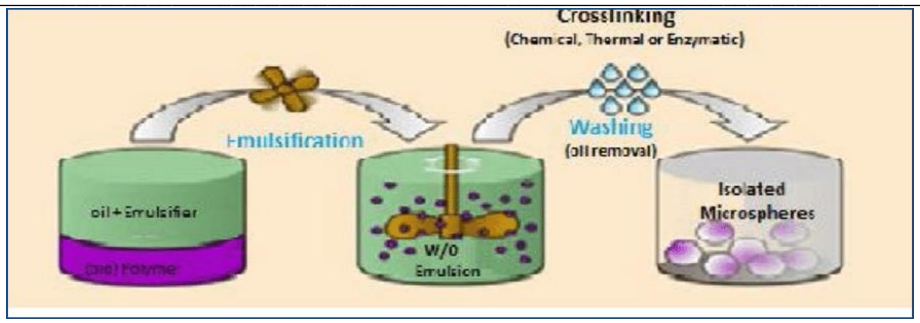

Fig 3: Single emulsion method[23]

4. Double Emulsion Technique

The ideal candidates for this method of microsphere preparation include water soluble medications, peptides, proteins, and vaccines. It involves the formation of multiple emulsions or double emulsions of type w/o/w. Both natural and synthetic polymers can be employed using this technique. The lipophilic organic continuous phase contains a dispersion of the aqueous protein solution. The active ingredients could be present in this protein solution[24].

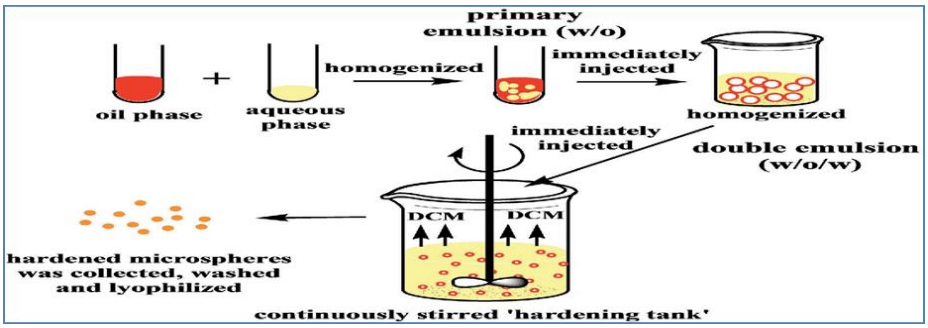

Fig 4: Double emulsion technique

5. Phase Separation Coacervation Technique

This method is based on the idea that when polymers become less soluble in organic phases, coacervates—a phase rich in polymers—become more likely to develop. This method involves dispersing drug particles in a polymer solution before adding an incompatible polymer to create the first polymer needed for phase separation[19]

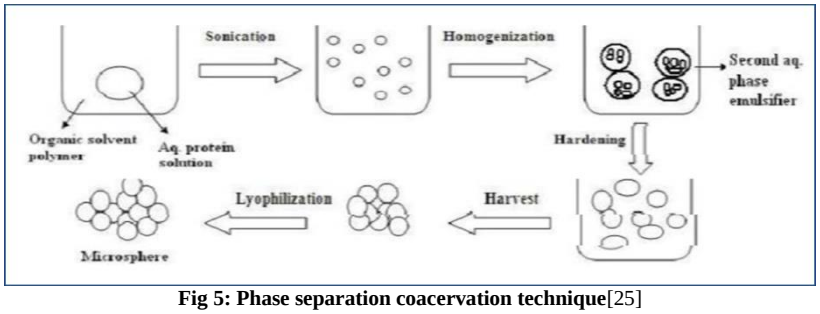

Fig 5: Phase separation coacervation technique[25]

6. Spray Drying and Spray Congealing

Although both techniques are based on the generation of droplets through atomization of a fluid, the mechanisms of MPs formation in spray drying and spray congealing are basically different, as centered on the evaporation of solvent and on the hardening of a molten material respectively[26].

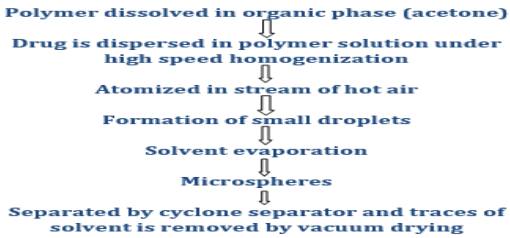

Fig 6: Spray drying and spray congealing

7. Solvent Extraction

Solvent extraction is the process in which a compound transfers from one solvent to another owing to the difference in solubility or distribution coefficient between these two immiscible (or slightly

soluble) solvents. Compared with other separation methods, it gives a better separation effect than chemical precipitation, and a higher degree of selectivity and faster mass transfer than the ion exchange method [19].

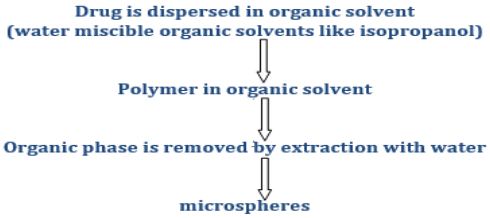

Fig 7: Solvent extraction

8. Quassi Emulsion Solvent Diffusion

QESD technique consists of the emulsification of organic solution of drug which is miscible with water and it also contains stabilizers. On shifting a temporary O/W emulsion into water, droplets solidify promptly as a result of the diffusion of the organic solvent out of the droplets to the external phase[27].

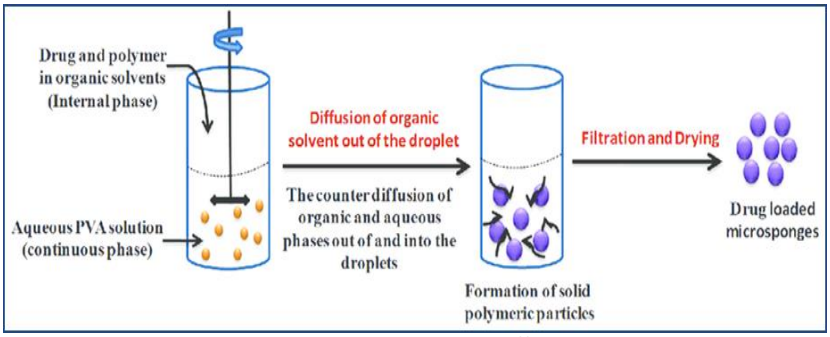

Fig 8: Quassi Emulsion solvent diffusion [28]

Percent yield of microsphere

Microspheres that had been completely dried were gathered and precisely weighed. The formula given was then used to obtain the percentage yield below.

%Yield = Mass of Microsphere / Total Weight of Medication Divided by 100

1. Optical microscopy

This method and an optical microscope were used to determine Particle size.(MeizerOPTIK).100 particles were calculated for the measurement under 450x (10x eyepiece and 45x objective). [29]

2. Scanning electron microscopy

SEM was used to evaluate the surface morphology. With the aid of double-sided tape, the microcapsules were placed directly on a sample of the SEM sluband, while operating under lower pressure, covered with gold film. [30]

3. Thermal analysis

Thermal analysis techniques routinely analyse these changes by Applying predetermined specimen atmospheres and pressures, as well as scheduled temperature variations for heating and cooling.Among the most frequently observed properties are the tiny fluctuations in gas evolution, thermal expansion or shrinkage, weight loss or gain, Young's modulus, and heat and enthalpy.[31]

4. Entrapment efficiency

Five milligrammes of the medication were present in crushed microspheres, combined with distilled water for three hours using an ultrasonic stirrer, filtered, and then subjected to UV-vis spectroscopy analysis. The proportion between theoretical and actual drug content determines the effectiveness of entrapment.[32]

5. Flow properties

The Hausner ratio, the resting angle of repose, and the Carr's compressibility index can all be used to analyse the flow properties.A volumetric cylinder was used to calculate the densities of the bulk and tapped materials[33].

6. Swelling index

Utilizing the following formula, the microsphere's swelling index was determined.

Swelling index = (mass of swollen microspheres–mass of dry microspheres / mass of dried microspheres) 100[34-35]

7. Drug content

Allowing the dust to settle before washing it away, the mixture needs to be set aside. A volumetric flask was filled with 1 mL of the filtrate, and the volume was then adjusted with 0.1 N NaOH. The drug was evaluated. Using spectrophotometry after the proper dilution[36].

8. Isoelectric point

Micro electrophores is equipment can be used to measure the isoelectric point by monitoring the electrophoretic mobility of microspheres. The time it takes for particles to move across a distance of 1 nm is used to compute the mean velocity at various pH values between 3 and 10[37]

Applications of Microspheres

Microspheres developed using polymer exhibits favourable biological behaviour such as bioadhesion, permeability-enhancing properties, and interesting physicochemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. e.g. Chitosan, Alginate, Gelatin[38-44]

1. Monoclonal Antibodies: Monoclonal antibodies or targeting microspheres are biologically immune microspheres. This type of targeting is used to achieve selective targeting to specific sites of the body organ. Monoclonal Antibodies are extremely specific molecules which bind to the specific part of the body system through which absorption takes place via

a. Non specific adsorption and specific adsorption

b. Direct coupling

c. Coupling via reagents[32-33, 36-38]

2. Gene Delivery: Microspheres could be a useful oral gene carrier be-cause of its adhesive and transport properties in the GI tract. e.g. Chitosan, Gelatin, viral vectors, cationic liposome, polycation complexes and Gene therapy with DNA plasmids and also delivery of insulin. It is also beneficial in vaccine delivery also as the prerequisite of a vaccine is protection against the microorganism or its toxic product. Biodegradable delivery system for vaccines that are given by Parenteral route may overcome the shortcoming of conventional

vaccines. Several parenteral vaccines have been encapsulated in biodegradable polymeric microspheres, including the tetanus and diphtheria Vaccine[39]

3.Imaging: Diameter of microspheres plays an important role in determining the imaging of targeted sites using already labelled microspheres having radio activity. The microspheres injected via IV route apart from the portal vein will usually become entrapped in the area of lungs. This phenomenon is specifically used for scintigraphic imaging of tumour masses in lungs using human serum albumin microspheres[39]

4. 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 to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make microspheres more suitable for oral drug delivery applications. e.g. Chitosan, Gelatin.

5. Nasal Drug Delivery: Polymer based drug delivery systems, such as micro-spheres, 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. e.g. Starch, Dextran, Albumin, Chitosan + Gelatin.40

6. 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 e.g. Gelatin, PLGA, Chitosan.

7. 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.

8. Gastrointestinal Drug Delivery: Polymer granules having internal cavities prepared by deacidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug e.g. Eudragit, Ethyl cellulose + Carbopol BSA, Gelatin.

9. Transdermal Drug Delivery: Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and thrombosis can be done.

13. Other Applications: Fluorescent microspheres can be used for membrane based technology flow cytometry, cell biology, fluorescent linked immunosorbent assay. Yttrium 90 can be used for primary treatment of carcinoma and also used for pre transplant management of HCC with promising results.

14. Colonic Drug Delivery: Polymer has been used for the specific delivery of insulin to the colon e.g. Chitosan.

15. 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 e.g. Chitosan, Gelatin, PLGA.

16. Targeting by Using Micro Particulate Carriers: The concept of targeting is a well established dogma, which is gaining full attention now a days. The response produced by the drug depends on its access and interaction with receptor usually pellets method is reported which can be prepared by using extrusion / Spheronization technology e.g. microcrystalline cellulose (MCC) and chitosan

Marketed Formulations of Microspheres

Marketed Name	Company Name	Disease	Drug
Mesacol tablet	Sunpharma	Ulcerative colitis	Mesalamine
Asacol	Win Medicare Pharma	Ulcerative colitis, Crohn's disease	Mesalamine
SAZO	Wallac India	Ulcerative colitis, Crohn's disease	Sulphasalazine
Intazide	Intas,India	Ulcerative colitis	Balsalazide
COLOSPA	Solvay, India	Irritable colon syndrome	Mabeverine
CYCLOMINOL	Neol India	Irritable colon syndrome	Dicyclomine
Decapeptyl	Ferring pharmaceuticals	Advanced prostate cancer	Triptorelin
Arestin	OraPharma	Periodontitis	Minocycline
Risperdal	Apollo	Schizophrenia	Respiridone
Nutropin	Genentech	Growth hormone deficiency	Somatropin

Conclusion

From this review, we could conclude that different types of preparation methods are being used for Microspheres as a drug delivery system for delivering the definite amount of medications in a controlled manner. It may include oral, targeted, sustained, topical, naso-pulmonary and various biotechnology applications such as gene therapy etc. The most widely used drug delivery method is microspheres because of their benefits of sustained and controlled release action, better stability, decreased dosing frequency, dissolving rate, and bioavailability. The spherical microspheres are used to deliver the medicine precisely to the target site and to keep the desired concentration at the place of interest without producing any unwanted side effects. The microspheres will play a significant and central role in novel drug delivery in the future by combining various other strategies, particularly in diagnostics, diseased cell sorting, gene & genetic materials, targeted, safe, effective & specific in vitro delivery & supplements as the miniature versions of the diseased tissues & organ in the body

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54. https://www.nutropin.com/

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