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Review Article

Novel Drug Delivery System Microsphere: A Review

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Abstract: The concept of targeted drug delivery is designed to attempt to concentrate the drug in the tissues of interest while reducing the relative concentration of the drug in the remaining tissues. As a result, the drug is localized to the targeted site. Therefore, the surrounding tissues are not affected by the drug. Therefore, carrier technology provides an intelligent approach to drug delivery by coupling drugs to carrier particles such as microspheres, nanoparticles, liposomes, niosomes, etc., modulating the release and absorption characteristics drug revenue. Microspheres are typically free-flowing powders made of proteins or synthetic polymers that are biodegradable in nature and ideally have a particle size of less than 200 µm. It is a reliable way to deliver drugs to the target site with specificity, if altered, and to maintain the desired concentration at the site of interest without side effects. Microspheres have received a great deal of attention not only for sustained release but also for targeting anti-cancer drugs to tumors. In the future, by combining various strategies, microspheres will occupy a central place in the delivery of new drugs, especially in the classification of diseased cells, diagnostics, genes and genetic material, safe, targeted and effective in vivo delivery and supplements in miniature versions of diseased organs and tissues in the body.

Keywords: Microspheres, Types of microspheres, Formulation and characterization of microspheres& applications.

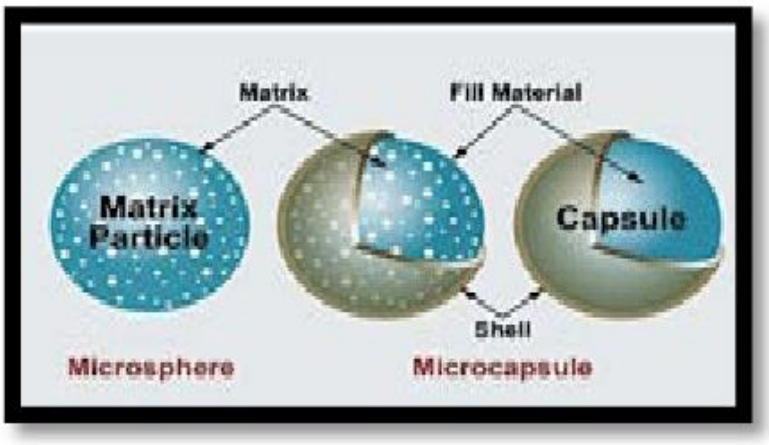
INTRODUCTION

Novel Drug Delivery System

Between the 1940s and 1960s, the concept of microencapsulation technology began as an alternative way to deliver drugs. In the continued search for a more sophisticated system, in the 1980s polymer/membrane technology became known at the forefront. In addition, site-specific targeting and delivery can be achieved with absolute precision by attaching bioactive molecules to liposomes, biopolymers, implants, monoclonal antibodies, and carriers of different particles (eg, nanoparticles and microspheres, etc.).The most desirable and convenient method of drug administration is the oral route because it is easy to administer. However, in many cases, oral administration is not desirable if the drug undergoes significant first-pass degradation in the liver. Therefore, the lack of systemic absorption through the gastrointestinal tract has led to the search for alternative routes of drug delivery such as parenteral, intramuscular, subcutaneous, and intranasal and transdermal. Traditional oral drug administration usually does not result in a significant increase in drug concentration. This often reaches toxic levels, and after a relatively short period of time at therapeutic levels, drug levels eventually drop until re-administration. To achieve maximum therapeutic effect, the drug must be delivered to the target tissue in the optimal amount for the required period, with little toxicity and minimal side effects. Targeted drug delivery, sometimes referred to as smart drug delivery, is a method of delivering a drug to a patient by increasing the drug concentration in a particular part of the bodies compared to other. The goal of a targeted drug delivery system is to stretch, localize, and target lesion tissue and protect drug interactions with. The conventional drug delivery system is the absorption of the drug through the biological membrane, and the targeted release system is the reduction in the frequency of dosing taken by the patient, resulting in a more consistent effect of the drug, a reduction in the side effects of the drug. , And reduced

fluctuations in circulating drug levels. The disadvantages of this system are its high cost, which makes it difficult to increase productivity and limits its ability to adjust dosages. There are various types of vehicles used in targeted drug delivery systems, including: The ideal drug delivery vehicle should be non-toxic, biocompatible, non-immunogenic, and biodegradable.

Microspheres are small spherical particles with a diameter in the micron range, typically 1 µm to 1000 µm (1 mm). Microspheres are sometimes called fine particles. They are free-flowing spherical particles made from synthetic proteins or polymers. Microspheres are free-flowing powders made from proteins or synthetic polymers, which are inherently biodegradable. They are made of polymers, waxes, or other protective materials. H. Biodegradable synthetic polymers and denatured natural products such as starch, gum, proteins, fats and waxes. Natural macromolecules include albumin and gelatin. Synthetic polymers include polylactic acid and polyglycolic acid. Microspheres are small and have a large surface area to volume ratio. At the lower end of their size range, they have colloidal properties. The interfacial properties of microspheres are very important and often determine their activity [1].



Microsphere

Microspheres (MS), that are emulsion cells or solid dispersed in a continuous phase, were applied in numerous industries consisting of foods, cosmetics and pharmaceuticals, etc. Using the traditional techniques of emulsion production, the emulsions (or MS) produced are commonly extensively polydispersed over a huge range. It is believed that surfactants play a very important role in the emulsification process. Surfactants reduce interfacial tension and promote emulsion formation. It is presumed that the surfactant stabilizes the emulsion by generating a repulsive force between the droplets [2]. Microspheres are small spherical particles with a diameter in the micron range, typically 1 µm to 1000 µm (1 mm). Microspheres are sometimes called fine particles. They are made of polymers, waxes, or other protective materials. H. Biodegradable synthetic polymers and denatured natural products such as starch, gum, proteins, fats and waxes. Natural macromolecules include albumin and gelatin. Synthetic polymers include polylactic acid and polyglycolic acid. Microspheres are small and have a large surface area to volume ratio. At the lower end of their size range, they have colloidal properties. The interfacial properties of microspheres are very important and often determine their activity [3]. Basically, each particle is a mixture of a drug dispersed in a polymer, and the drug release pattern follows a first order process. The release of the drug is controlled by dissolution or degradation of the substrate. Microspheres provide a ball bearing effect due to their size and shape. Microspheres differ in quality, sphericity, particle uniformity and particle size distribution. You must choose the right microsphere for each unique application. There are many possibilities for fabricating microspheres to control drug administration. Facilitates accurate delivery of small amounts of potent drugs, reduces drug concentrations at sites other than the target site, and protects labile compounds before and after administration and before appearing at the site of action. By binding drugs to carrier molecules, we can change how drugs work in vivo. The behavior of carrier molecules can influence clearance kinetics, tissue metabolism, and cellular drug interactions. The use of these changes in pharmacodynamics may increase the effectiveness of treatment [4]. The purpose of this controlled drug delivery system is to immediately ensure that the amount of therapeutic amount is immediately and reached the treatment level, and maintain the desired drug concentration in the action area [5]. Oral route is convenient and usually occupied route for most drugs. Some medicines that are easily absorbed in G.I.T. having short t1 / 2 are quickly removed from blood circulation. Managed drug delivery systems can avoid problems with existing drug delivery systems, and slowly emit drugs of G.I.T. Maintain a constant concentration in serum for a longer time.

Various advantages and disadvantage of Microsphere are as follows [6, 7]:

ADVANTAGES	DISADVANTAGES
• Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. • Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug. • Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor. • The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo. • Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly. • Blood flow determination. • Microspheres provide freedom from drug and recipients incompatibilities especially with buffer. • Microspheres reduce dose dumping. • Microspheres provide the protection of drugs against environment. • Microspheres also mask the taste and odor. • A microsphere avoids the first pass metabolism. • Microspheres can be easily injected in body because of their small and spherical size. • Microspheres enhance the biological half-life and also improve the bioavailability. • Microspheres also reduce the chances of G.I. irritation • Drug discharge in stomach is hindered and that's why local unwanted effects are reduced. • In case of microspheres, better therapeutic effect for short half-life of drugs can be achieved.	• Drug gets difficult to remove after injected. • Sometime non-uniformity of drug content may result while preparation.

Limitations of microspheres [8]

- The controlled release rate of microspheres can vary due to certain factors such as internal or external factors be it food, intestinal transit rate, mucin turnover rate etc.
- There is variation in release from one dosage form to another.
- Low drug intake is done in case of extra-gastrointestinal microspheres.
- In the case of parenteral administration of microspheres, it is difficult to completely remove the carrier from the body.
- Parenteral use of microspheres may interact or form complexes with blood components. Formula release may vary.
- Any loss of integrity in the release sample could lead to potential toxicity.

Materials used in formulation of Microspheres [9-10]

Microspheres used generally are polymers. They are classified into two types.

1. Synthetic Polymers
2. Natural polymers

Synthetic Polymers	Natural polymers
• Non-biodegradable polymers : Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers • Biodegradable polymers: Lactides, Glycolides & their co polymers Poly alkyl cyano Acrylates, Poly anhydrides.	• **Proteins:** Albumin, Gelatin, Collagen. • **Carbohydrates:** Agarose, Carrageen an, Chitosan, Starch. • **Chemically modified carbohydrates:** Poly dextran, Poly starch.

Formulation of Microsphere

Preparation of microspheres should satisfy certain criteria:-

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

Single Emulsion Technique

The micro particulate carriers of natural polymers 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 like oil. Next 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 cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, di acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation.

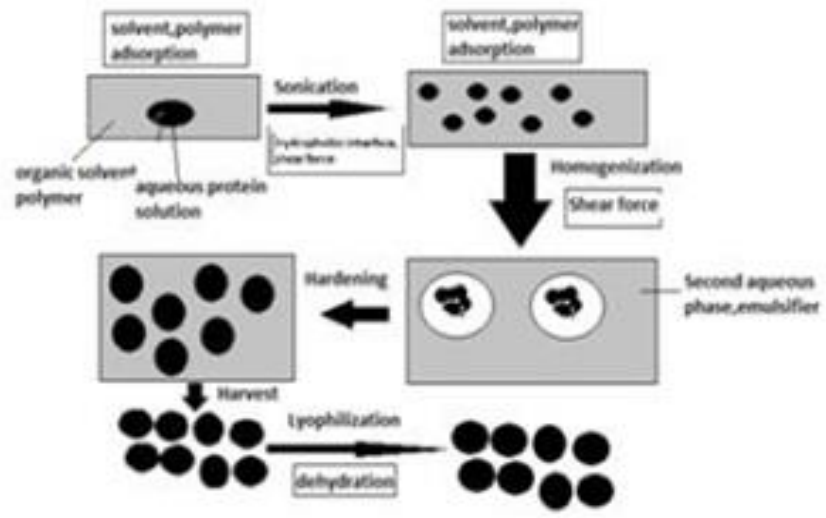


Fig-1: Single emulsion technique by chemical cross-linking

Double Emulsion Technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to 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 is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction.

Polymerization Techniques

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

I. Normal polymerization
II. II. Interfacial polymerization.

Both are carried out in liquid phase. Normal polymerization: It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be molded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers. Interfacial polymerization: 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.

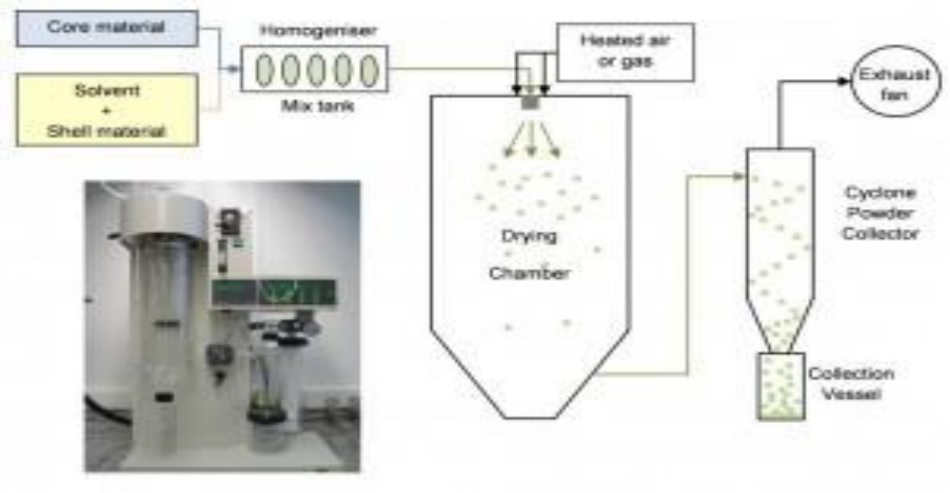


Fig-2: Spray drying technique

Phase Separation Coacervation Technique

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. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.

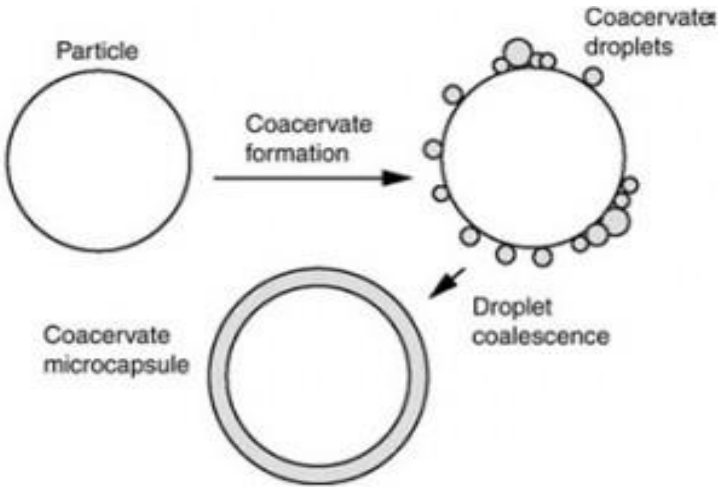


Fig-3: Formation of coacervates around the core material

Spray Drying and Spray Congealing

These 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. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 µm. Micro-particles are separated from the hot air by means of the cyclone separator while the

traces of solvent are removed by vacuum drying. 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. Thiamine mononitrate14 and sulpha-ethylthiadizole15 are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous micro-particles.

Solvent Evaporation

Solvent evaporation method is used for the preparation of micro-particles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer [11].

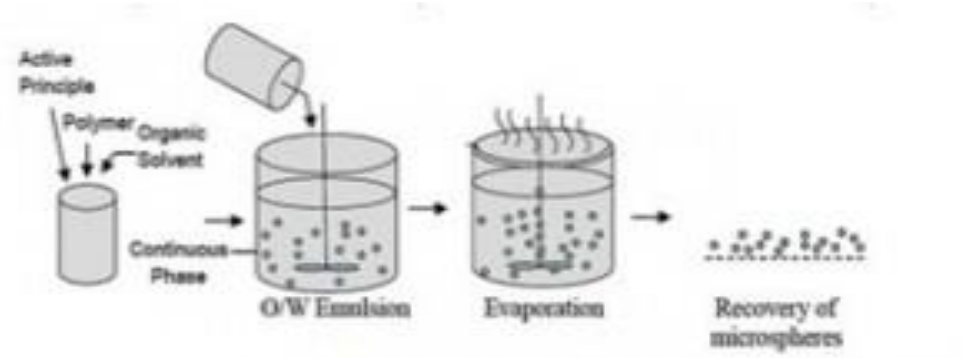


Fig-4: Solvent evaporation technique

Characterization

Characterization of the micro particle carrier is an important phenomenon, helping to design suitable carriers for the delivery of proteins, drugs or antigens. These microspheres have different microstructures. These microstructures determine the release and stability of the carrier [12].

- Particle size and shape determination.
- Electron spectroscopy for chemical analysis
- Attenuated total reflectance Fourier-Transform Infrared Spectroscopy
- Density determination.
- Capture efficiency

Applications of Microspheres

Novel applications for microspheres are discovered every day, below are now a few [13-20]

- **Ophthalmic Drug Delivery:** Microspheres designed with polymers exhibit favorable biological properties such as bio-adhesion, permeation enhancing properties and interesting physicochemical properties, making them unique materials for the creation of ophthalmic drug delivery vehicles such as chitosan, alginate, and gelatin.
- **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.
- **Gene Delivery:** Microspheres can be useful oral gene carriers due to their adhesion and transport properties in the gastrointestinal tract. For example, Chitosan, gelatin, viral vectors, cationic liposomes, polycationic complexes.
- **Nasal Drug Delivery:** Polymer-based drug delivery systems such as microspheres, liposomes, and gels have been shown to increase bioavailability and residence time of drugs through

the nasal route by having good bioadhesive properties and easily swelling upon contact with the nasal mucosa. e.g. Starch, Dextran, Albumin, Chitosan+ Gelatin.

- **Intratumoral and Local Drug Delivery:** A polymeric film is created to deliver paclitaxel to the tumor site at a therapeutically appropriate concentration. The mixture of drugs has promising potential for use in the controlled delivery of to the oral cavity. e.g. Gelatin, Chitosan.
- **Buccal Drug Delivery:** Polymers are excellent polymers for buccal delivery as they have mucosal/bioadhesive properties and can act as absorption enhancers (eg chitosan, sodium alginate).
- **Gastrointestinal Drug Delivery:** Internal cavities have prepared in polymer via a de- acidification through added to acidic and neutral media are found buoyant and provided a controlled release of the drug e.g. Eudragit, Gelatin.
- **Transdermal drug delivery:** Polymer having good film-forming properties. The drug release from the devices is pretentious by the membrane thickness and cross-linking of the film. e.g. Chitosan, Alginate.
- **Colonic drug delivery:** Polymer has been used for the precise delivery of insulin into the colon. e.g. Chitosan.

CONCLUSION

This review focuses on recent advances in microsphere formulation, characterization, and applications. In the future, by combining other substances, the microspheres will find the central location and the meaning of providing new drugs, especially the classification of disease cells, diagnosis, genes and raw genetic, safe delivery with additional efficiency. Several microencapsulated pharmaceutical products are currently marketed, such as aspirin, theophylline and its derivatives, vitamins, pancrelipase, antihypertensives, potassium chloride, progesterone, and combinations of oral contraceptives. Microencapsulated KCL is used to prevent gastrointestinal complications associated with potassium chloride. The dispersibility of the microcapsules and controlled release of ions minimizes the possibility that high local salt concentrations can lead to ulceration, bleeding or perforation. Microspheres have also been found to have potential applications as injectable or inhaled products. They have emerged as an exciting new platform for biologists to apply these techniques to the study of biomolecular interactions and cellular processes.

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