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MICROSPHERES AS DRUG CARRIERS FOR CONTROLLED DRUG DELIVERY: A REVIEW

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ABSTRACT: Microspheres play a very important role as particulate drug delivery system because of their small size and other efficient properties. Microspheres have been proved to be a suitable bridge to scale the distance over to formulate an effective dosage form, to simulate controlled drug release. Microspheres are characteristically free flowing solid powders, which consist of proteins or synthetic polymer, which are biodegradable in nature. Microspheres having particle size in range between 0.1-200 µm, can be delivered by several routes like oral, parentral, nasal, ophthalmic, transdermal, colonal etc. Various recent advancement in case of microspheres like mucoadhesive, hollow, floating, microballons, magnetic have been contributed to overcome the various problems that are associated with the use of microspheres, which includes site specific targeting and improved release kinetics. In future by combining various new strategies, microspheres will find a central place in novel drug delivery, particularly in diseased cell sorting, genetic materials, safe, targeting and effective drug delivery.

INTRODUCTION: Earlier patients have been using conventional dosage forms like Tablet, Capsule to treat the acute and chronic diseases, but these conventional dosage forms have to be taken several times in a day for maintaining the peak plasma level concentration. Hence to overcome these problems controlled release drug delivery system were developed. Controlled drug delivery system (Microspheres) releases the drug in controlled rate and overcome the problems of conventional drug delivery system and enhances the therapeutic efficacy of a given drug [1]. The main purpose of Controlled drug delivery system is to ensure optimum plasma drug concentration, thus enhancing efficacy, safety and bioavailability of drug with improved patient compliances [2].

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Controlled release refers to the use of drug delivery with the objective of releasing the drug into the patient at a predetermined rate or controlled rate at specific times or with specific release profile. With the problems like hygroscopicity of drug as in case of capsule and bioavailability problems associated with tablet, various advancements have been done to overcome the problems of conventional dosage form and microsphere is one of them [3-4].

Microsphere is small spherical particle having the particle size range 0.1-200µm, and made up of biodegradable and non-biodegradable material and can be injected by 18 or 20 number of needles [5-6]. Drug absorption and side effects due to the irritating drugs against the gastrointestinal mucosa is improved because of small particle size of microspheres which get widely distributed throughout the gastrointestinal tract [7].

Basically each particle is the mixture of drug that is dispersed in a polymer and release pattern of drug follow the first order process. The release of drug is controlled by dissolution or degradation of matrix.

Microsphere offers the Ball bearing effect due to their size & shape. Microspheres vary in quality, sphericity, uniformity of particle and particle size distribution. The appropriate microsphere needs to be chosen for each unique application. To control the drug administration, various opportunities are there for the preparation of microspheres.

It facilitates the accurate delivery of small amount of potent drugs and reduced drug concentration at the site other than the target site and protection of labile compound before and after the administration and prior to appearance at the site of action. By coupling the drug with carrier molecule we can change the behavior of drug *in-vivo*. The behavior of carrier molecule can affect the clearance kinetics, tissue metabolism & cellular interaction of drug. The exploitation of these changes in Pharmacodynamics may lead to enhanced therapeutic effect [8].

The goal of this controlled drug delivery system is to provide a therapeutic amount of drug at the required site promptly and after achieving therapeutic level, to maintain the desired drug concentration at the site of action [9].

Oral route is the most convenient and commonly employed route for most of the drugs. Some Drugs that are easily absorbed by the G.I.T. and having short $t_{1/2}$ are eliminated quickly from the blood circulation. Controlled Drug delivery System can avoid the problems of conventional drug delivery system by releasing the drug slowly into the G.I.T. and maintain a constant drug concentration in the serum for longer period of time [10].

The number and chemical diversity of drugs has increased, new and updated strategies are required to be developed for orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the drug in stomach and improve their bioavailability, have been developed[11].

Advantages of microspheres over conventional dosage forms: [12-13]

- Microspheres provide prolonged and constant therapeutic effect.
- Microspheres reduce the dosing frequency and therefore improve the patient compliance.
- Microspheres provide controlled, sustained and targeted delivery of the drug.
- Microspheres produce more reproducible drug absorption.
- 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.
- 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.
- Microspheres 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.

Limitations of microspheres: [15]

- Controlled release rate of microspheres may vary due to certain factors like intrinsic or extrinsic factors may be food, rate of transit through gut, mucin turnover rate etc.
- There are differences in release from one to another dosage form.

- Low drug loading is done in case of parentral microspheres.
- In case of parentral application of microspheres it is difficult to remove carrier completely from the body.
- Parental delivery of microspheres may interact or form complex with blood components.
- The release of formulation can be modified.
- Any loss of integrity in release pattern may cause potential toxicity.
- Controlled release dosage form cannot be crushed and chewed. Types of polymer used in the preparation of microspheres:

A number of different substances both Biodegradable and Non-biodegradable have been investigated for the preparation of microspheres. This includes polymer of Natural and Synthetic origin and also Semi synthetic polymers.

1. **Natural Polymer:** These polymers are obtained from different sources like Protein, Carbohydrate and chemically modified Carbohydrates [1, 10].

   i. **Protein:** Albumin, Gelatin, Collagen

   ii. **Carbohydrate:** Starch, Agarose, Carrageenans

   iii. **Chemically Modified Carbohydrate:** Poly acryl Dexron, Poly acryl Starch

2. **Synthetic Polymer:**

   i. Biodegradable Polymers: Polyanhydride, Polyalkyl cyano acrylates, Lactides and Glycolides and copolymer [10, 16].

   ii. Non-Biodegradable Polymers: Acrolein, Glycidyl Methacrylates, Epoxy Polymer etc[17].

Ideal characteristics of Carrier [15]:
Carrier provides longer duration of action to drug molecule.

1. It provides stability to the drug molecule.
2. It provides protection to drug.
3. It provides water solubility.
4. It provides sterilizability to drug.

Method of Preparation of microspheres:
The choice of method of preparation depends upon the nature of Drug, nature of Polymer and duration of therapy. There are several techniques to prepare microspheres:

1. Single Emulsion Technique:
i. Heat Stabilization Method
ii. Chemical Stabilization Method
iii. Ionic Chelation Method

2. Double Emulsion Technique

3. Polymerization Technique
i. Normal Phase (Bulk, Suspension, Emulsion)
ii. Interfacial Phase

4. Spray Drying Technique

5. Solvent extraction Technique

6. Phase separation Co-Acervation Technique

7. Solvent Evaporation Technique

1. Single Emulsion Technique:
Several Carbohydrates and Proteins are mainly prepared by this technique. In this technique, natural polymers are first dissolved in aqueous medium and then dispersed in non-aqueous medium (oil phase) followed with next step cross-linking of dispersed globule; which can be achieved by 2 methods: [15]

i. **By Heat**: Addition of dispersion into heated oil, but this method is not suitable for thermolabile drugs.

ii. **By Chemical Cross-linking Agent**: Using glutaryldehyde, formaldehyde, acid chloride etc. as cross-linking agent. 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 and separation [1, 10] (**Fig.1**).

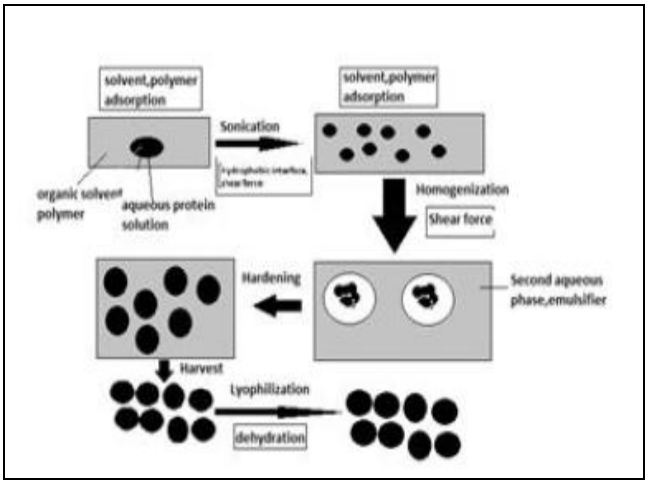

FIG.1: SINGLE EMULSION TECHNIQUE BY CHEMICAL CROSS-LINKING

2. Double Emulsion Technique: This method can be used with natural as well as synthetic polymer and is more suitable for water soluble drugs, peptides, proteins and vaccines. This method of microsphere preparation involves the formulation of multiple emulsions. In this technique, aqueous protein solution is dispersed in lipophillic organic continuous phase, which contain the active constituents. Continuous phase consist of polymer solution which encapsulates protein dispersed in aqueous phase. Then, primary emulsion is homogenized before addition to aqueous solution of PVA (Poly Vinyl Alcohol). Formation of double emulsion occurs and then emulsion is subjected to solvent removal either by solvent evaporation or solvent extraction[15, 18].

3. Polymerization Technique: Preparation of Microspheres by this method can be done by 2 types:

i. Normal Polymerization:

This type of Polymerization is done by using different techniques as bulk, suspension, precipitation, emulsion etc. In case of bulk, a monomer along with catalyst is heated to initiate Polymerization. Obtained Polymer is molded as Microspheres, and Drug loading may be done during the process of Polymerization. Bulk Polymerization has an advantage of formation of Pure Polymer. In case of suspension, heating of monomers or a mixture of monomers with active Drug as droplet dispersion in continuous aqueous phase. Suspension Polymerization is also known as Pearl/Bead Polymerization and done at low temperature. In case of emulsion polymerization, there is initiator present in aqueous phase, which later on diffuses at the surface of micelle [12, 16, 18].

ii. Interfacial Polymerization: It involves the reaction of various monomers at the interface between two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase [12, 15, 20].

4. Spray Drying Technique: In this technique, the polymer is dissolved in volatile organic solvent like dichloromethane, acetone etc. and then drug (solid form) is dispersed in polymer solution under high speed homogenization. Dispersion is then atomized in the hot air stream, and atomization lead to the formation of small droplets from which solvent evaporates instantaneously; leading to formation of microsphere in a size range of 1-100 µm. Prepared micro particles are separated by hot air by the help of cyclone separator and solvent traces is removed by vacuum drying (**Fig.2**).

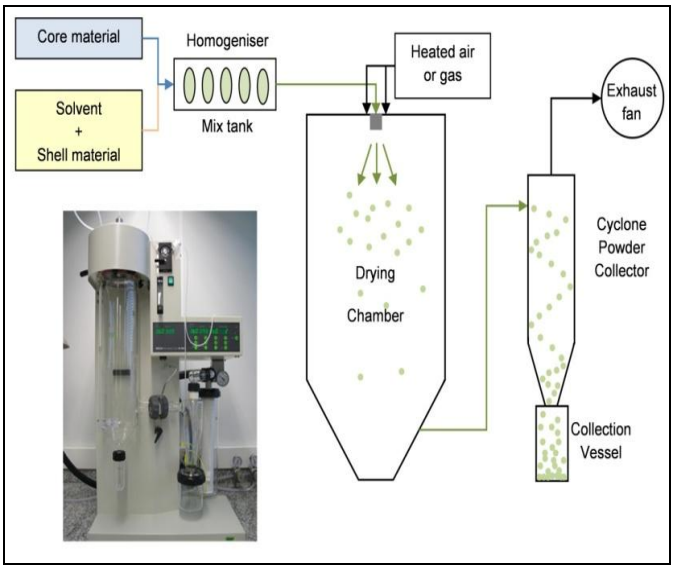

FIG.2: SPRAY DRYING TECHNIQUE

Principle:

1. Atomization: Liquid feed changed into fine droplets.

2. Mixing: It involves passing of hot gas stream through spray droplets which results in evaporation of liquid leaving dry particles.

3. Drying: Dry powder is separated from the gas stream and collected[19].

4. Solvent Extraction technique: In this technique, the contaminants are separated from solvent either by changing temperature or by pressure, by using a second solvent to take the first solvent out of the contaminant/solvent mixture, or by physical separation process.

5. Phase Separation Co-acervation Technique: It is a simple process of separation of a micro molecular solution into two immiscible liquid phases. The principle of coacervation involves decreasing solubility of polymer in organic phase to affect the formation of polymer rich phase called coacervates. In this method, formation of dispersion of drug particles in a solution of polymer and an incompatible polymer added to the system which makes first polymer to phase separate and engulf the drug particle [21, 22] (**Fig.3**).

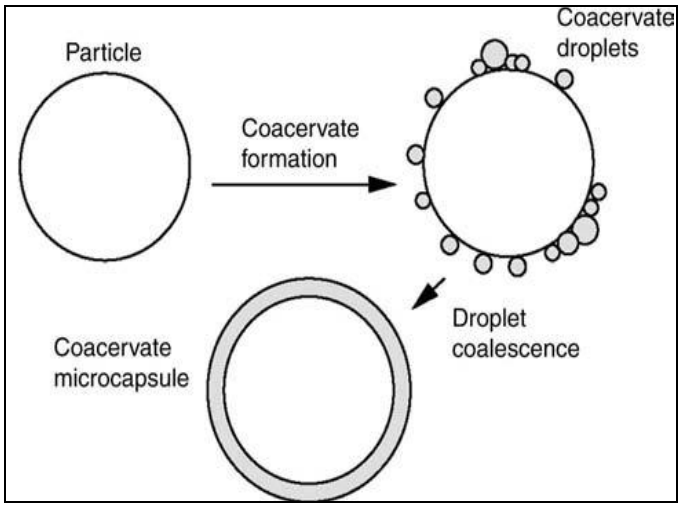

FIG.3: FORMATION OF COACERVATES AROUND THE CORE MATERIAL

7. Solvent Evaporation Technique: The polymer is dispersed in an organic solvent and the drug is either dissolved /dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing suitable additives (surfactants/polymer) to form oil in water emulsion. After the formation of emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the oil/water interphase of droplets, forming cavity [23, 24, 25] (**Fig. 4**).

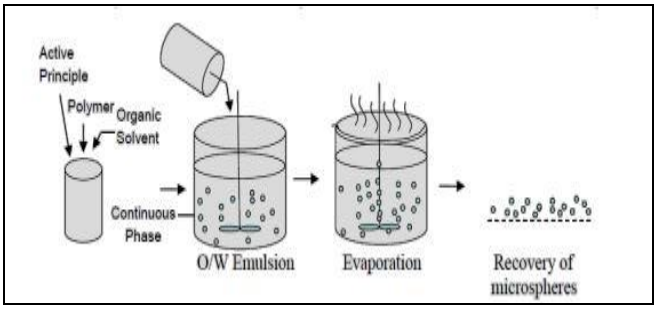

FIG.4: SOLVENT EVAPORATION TECHNIQUE

Physicochemical evaluation:

Particle Size and Shape: Particle size can be determined by optical microscopy with the help of calibrated eyepiece micrometer. The size of around 100 microspheres is measured and their average particle size is calculated [26, 27, 28].

$$D \text{ mean} = \sum n d / \sum n$$

Where, n = number of microspheres checked; d = Mean size

Density Determination:

The density of microspheres can be measured by using a multi volume pycnometer. 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 decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of microsphere carriers is determined [29].

Isoelectric Point: The isoelectric point can be measured by using micro electrophoresis apparatus by measuring electrophoretic mobility of microspheres. The mean velocity at different pH value from 3-10 is calculated by measuring the time of particle movement over a distance of 1nm [30].

Angle of Contact: The angle of repose Ø of microspheres, which measures the resistance to particle flow is calculated as

$$\tan \Theta = 2h/d$$

Where, 2h /d is the surface area of free standing height of microspheres heap that is formed after making microspheres flow from the glass funnel [31].

Electron Spectroscopy for Chemical Analysis:
The surface chemistry of microspheres can be determined by using electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of atomic composition of the surface. The spectra obtained using ESCA can be used to determine the surface degradation of biodegradable microspheres.

Fourier Transform Infrared Spectroscopy: Drug polymer interaction and degradation of microspheres can be assessed by FTIR [32-33].

Drug Entrapment Efficiency: Weighed amount of microsphere are taken and crushed. Then dissolved in buffer solution with the help of stirrer and filtered. The filtrate is assayed by UV spectrophotometer at particular wavelength by using calibration curve [34-35].

[Drug Entrapment efficiency = Actual weight of microspheres/Theoretical weight of drug and polymer × 100]

Percentage Yield: It is calculated as the weight of microspheres obtained from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100 [36-37].

Swelling Index: It is determined by measuring the extent of swelling of microspheres in a particular solvent. The equilibrium swelling degree of microspheres is determined by swelling of 5mg of dried microspheres poured in 5ml of buffer solution overnight in a measuring cylinder. It is calculated by given formula [38].

Swelling index = Mass of swollen microsphere – Mass of dried microspheres ×100 / Mass of dried microspheres.

***In-vitro* methods:**
This method allows the determination of release characteristics and permeability of a drug through membrane. *In-vitro* method is employed as a quality control procedure in pharmaceutical production and in product development etc. Sensible and reproducible release data derived from physically, chemically and hydro dynamically defined conditions are necessary.

Beaker Method: In this method Dosage form is made to adhere at the bottom of beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500ml and the stirrer speed from 60-300rpm [39-41].

Interface Diffusion Method: This method was developed by Dearden & Tomlinson. It consists of four compartments. Compartment A represents the oral cavity, and initially containing an appropriate concentration of drug in buffer. The compartment B representing the buccal membrane, containing 1-octanol, and compartment C representing body fluids, containing 0.2M HCl. The compartment D represents protein binding, also containing 1-octanol. Before use, the aqueous phase and 1-octanol are saturated with each other. Samples are withdrawn and returned to compartment A with a syringe [39].

Modified Keshary Chien Cell Method: It utilizes specialized laboratory designed apparatus. It comprises of a Keshary Chien cell containing distilled water (50ml) at 37°C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) is placed in a glass tube fitted with a 10# sieve at the bottom which reciprocates in the medium at 30 strokes per minute [42-43].

Dissolution Apparatus Method: Standard USP or BP dissolution apparatus have been used to study *in-vitro* release profiles using both rotating elements Paddle and basket. Dissolution medium used for the study varies from 100-500ml and speed of rotation from 50-100rpm [44-48].

***In-vivo* method:** Method for studying the permeability of intact mucosa comprises of technique that gives the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrate at their surface. The most widely used methods of *in-vivo* studies

include using animal models, buccal absorption tests.

Animal Models: It is used mainly for the screening of series of compounds, investigating the mechanisms and evaluating a set of formulations. Animal model such as dogs, rats, pigs and sheep etc. are reported. Generally the procedure involves anesthetizing the animal followed by administration of dosage form, withdrawing blood at different time intervals and analyzing [49].

Buccal Absorption test: It is most suitable and reliable method for measuring the extent of drug loss from human oral cavity for single and multi component mixtures of drugs. The test has been successfully used to investigate the relative importance of drug structure, contact time, initial drug concentration and pH of solution while drug is held in oral cavity. The test is carried to measure the kinetics of the drug absorption by swirling a 25 ml sample of the test solution for 15 min by human volunteers followed by the expulsion of the solution. The amount of the drug remaining in the expelled volume is then determined to assess the amount of drug absorbed [50].

***In-vitro/in-vivo* correlation:** Correlations between *in-vitro* dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "*in-vitro-in-vivo* correlation". Such correlations allow one to develop product specifications with availability.

Applications of microspheres:

In Vaccine Delivery: The prerequisite of a vaccine is protection against the microorganism or its toxic product. Biodegradable delivery system for vaccines that are given by Parentral route may overcome the shortcoming of conventional vaccines. Several parenteral vaccines have been encapsulated in biodegradable polymeric microspheres, including the tetanus and diphtheria vaccine[51].

Monoclonal Antibodies: Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is used to achieve selective targeting to specific sites. Monoclonal antibodies are extremely specific molecules. Maps can be attached to microspheres by any of following methods:

- Non specific adsorption and specific adsorption
- Direct coupling
- Coupling via reagent

Imaging: Particle size range of microspheres is an important factor in determining the imaging of particular sites using radio labeled microspheres. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of lungs. This phenomenon is exploited for scintigraphic imaging of tumor masses in lungs using labeled human serum albumin microspheres.

Topical Porous Microspheres: Micro sponges are porous microspheres having myriad of interconnected voids of particle size range 5-300µm. These micro sponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc. are used as the topical carries system [52].

Targeting Drug Delivery: The concept of targeting i.e. site specific drug is a well established dogma, which is gaining full attention. The therapeutic efficacy of drug relies on its access and specific interaction with its receptor[53].

Medical Application: [54]

- Release of proteins, peptides and hormones over the extended period of time.
- Passive targeting of leaky tumor vessels, active targeting of tumor cells, antigens, by intra arterial/ intravenous application.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used for various diagnostic tests for infectious disease like bacterial, viral and fungal.

Radioactive Application: Can be used for embolisation of liver and spleen tumors. Used for

radio synvectomy of arthritis joints, local radiotherapy, interactivity treatment, Imaging of liver, spleen, bone marrow, lung and even imaging of thrombus in deep vein thrombosis can be done [55].

Other Application: Fluorescent microspheres can be used for membrane based technology for flow cytometry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay [56]. Yttrium 90 can be used for primary treatment of hepatocellular carcinoma and also used for pre transplant management of HCC with promising results [57].

CONCLUSION: Microspheres are better choice of drug delivery system than many other types of drug delivery system. In future by combining various other strategies, microspheres will find the central and significant place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, specific and effective *in-vitro* delivery and supplements as miniature version of diseased organ and tissues in the body.

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