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A Review on Microspheres: Method of Preparation and Evaluation

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ABSTRACT

The microsphere is spherical microparticles and is used where consistent and predictable particle surface area is important. A microsphere has a unique polymeric membrane encasing a centrally located drug in it. Microsphere drug delivery system has gained enormous attention not only for prolonged-release but also due to its wide range of application as it covers targeting the drug to a particular site to imaging and helping the diagnostic features. Today by combining various other strategies, microspheres have found the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body. This review compiles various types of microspheres, polymers used, different preparation methods, Factors influencing, various parameters to evaluate their efficiency, its applications, and also some Recent Advancements in Microspheres.

INTRODUCTION:

Microspheres are small spherical Particles, with a diameter in the micrometer Range (typically 1 micrometre to1000) micrometer Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres, and ceramic microspheres are commercially available Solid and Hollow microspheres Vary widely in Density and therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are. Polyethylene and polystyrene microspheres are the two most common types of polymer microspheres. Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate Procedures such as Cell sorting and immune Precipitations.

DEFINITION

Microparticles are defined as the polymeric entities falling in the range of 1- 1000 micrometer, covering two types of forms as follows:

Microcapsules: micrometric Reservoir system.

Microspheres: micrometric matrix system.

- Types of drug delivery system are:

a) Liposome

b) Niosome

c) Nanoparticle

d) Microsphere

- **HISTORY**

Between the 1940s and 1960s, the concept of chemical microencapsulation Technology began as an alternative means of delivering the drug. In continued quest for the more refined system in the 1980s Polymer/membrane came to be known at the forefront.

- **ADVANTAGES OF MICROSPHERES**

• They provide protection before after administration for the unstable drug.

• They reduced concentration of drug at site Other than the tissue or the target organ.

• Decreases dose and toxicity.

• Particle size reduction for enhancing solubility of poorly soluble drugs.

• Provide Constanta and Prolonged therapeutic effect.

• Reduced gastric irritation.

• Improve bioavailability

• Enhanced biological half-life.

- **DISADVANTAGES OF MICROSPHERES**

• Dosage forms of this kind should not be crushed or chewed.

• Low drug loading (maximum of 50%) for controlled release parental.

• Once injected it is difficult to remove the carrier completely from the body in case of toxic effect.

• Parental delivery of microspheres may interact or form complexes with the blood component.

• Differences in the release rate from one dose to another.

• Controlled release formulations generally contain a higher drug Load and thus any loss of integrity of the release characteristics of the dosage form may lead to dumping of dose, result in failure of the therapy and produce potential toxicity.

- **TYPES OF MICROSPHERE**

1. Bioadhesive microspheres:

Adhesion can be defined as sticking the drug to the membrane by using the sticking property of the water-soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal, etc. can be termed as bio adhesion. The term “bio

adhesion" describes materials that bind to biological substrates, such as mucosal members. Adhesion of Bioadhesive drug delivery devices to the mucosal tissue offer the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and combination with a controlled release of the drug also improved patient compliance by reducing the frequency of administration. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanospheres, liposomes, nanoparticles, etc., which modulates the release and absorption of the drug.

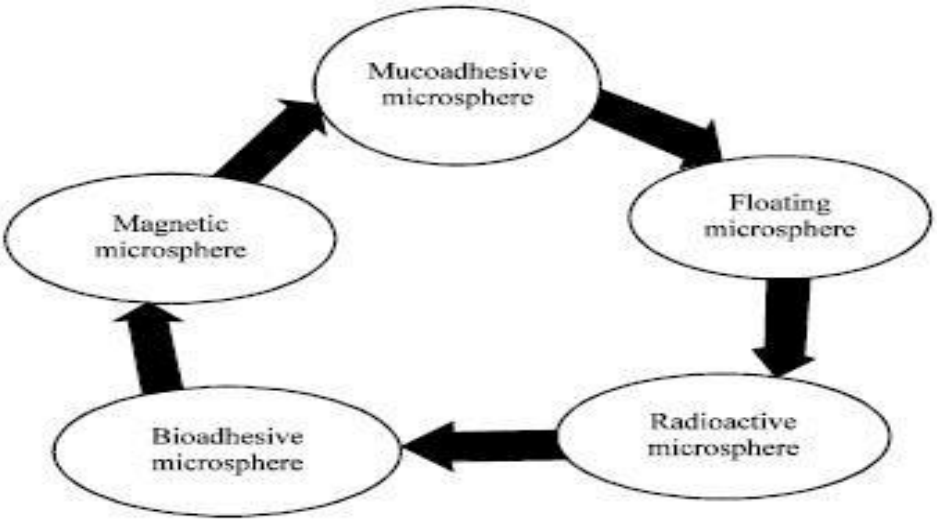


Figure No. 1: Bioadhesive microspheres

2. Magnetic microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. This larger amount of freely circulating drug can be replaced by a smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran, etc.4 The different types are Therapeutic magnetic microspheres are used to Deliver chemotherapeutic agents to the liver tumor. Drugs like proteins and peptides can also be targeted through this system of Diagnostic microspheres.6 Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere or conjugated on the surface of the microsphere The accumulation of the carrier at the target site allows them to deliver the drug locally.

3. Floating microspheres

In floating types, the bulk density is less than the gastric fluid and so remains buoyant in the stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate if the system is floating on gastric content, which increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces a prolonged therapeutic effect. Drug (ketoprofen) is given through this form.

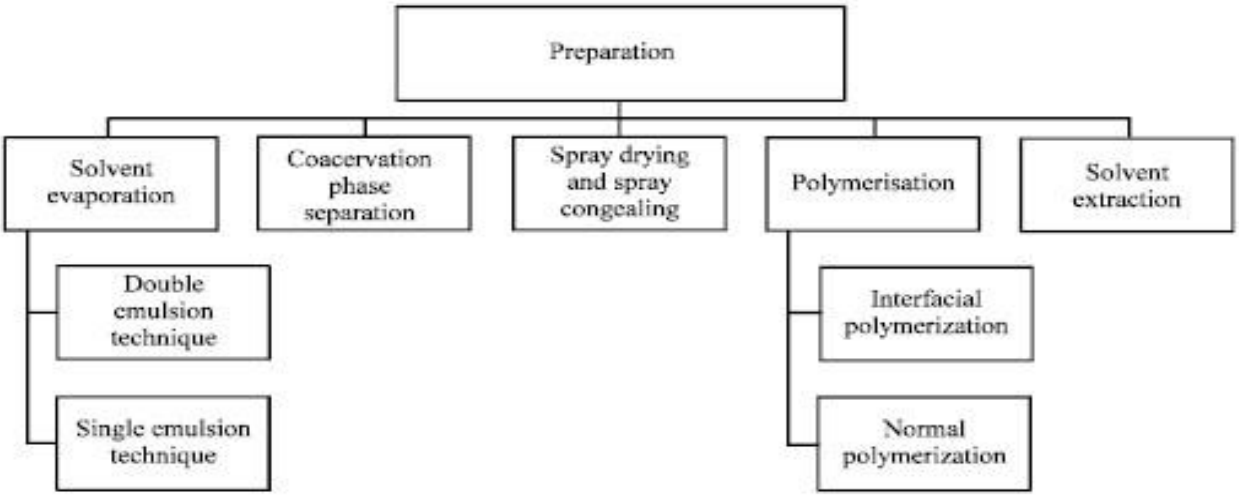
4. Radioactive microspheres

Radio demobilization therapy microspheres sized 10-30 nm are larger than capillaries and get tapped in the first capillary bed when they come across. They are injected into the arteries that lead to the tumor of interest. So these radioactive microspheres deliver a high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from the drug delivery system, as radioactivity is not released from microspheres but acts from within a radioisotope typical distance and the different So these radioactive microspheres deliver a high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from the drug delivery system, as radioactivity is not rulemakings of radioactive microspheres are α emitters, β emitters, γ emitters.

5. Mucoadhesive microspheres

Mucoadhesive microspheres which are 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of entirelyysive properties to microspheres has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions, and antibodies, etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in the eye, nasal cavity, urinary, and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.

❖ **Method of preparation of microspheres**



❖ **Solvent evaporation method:**

• Single emulsion technique

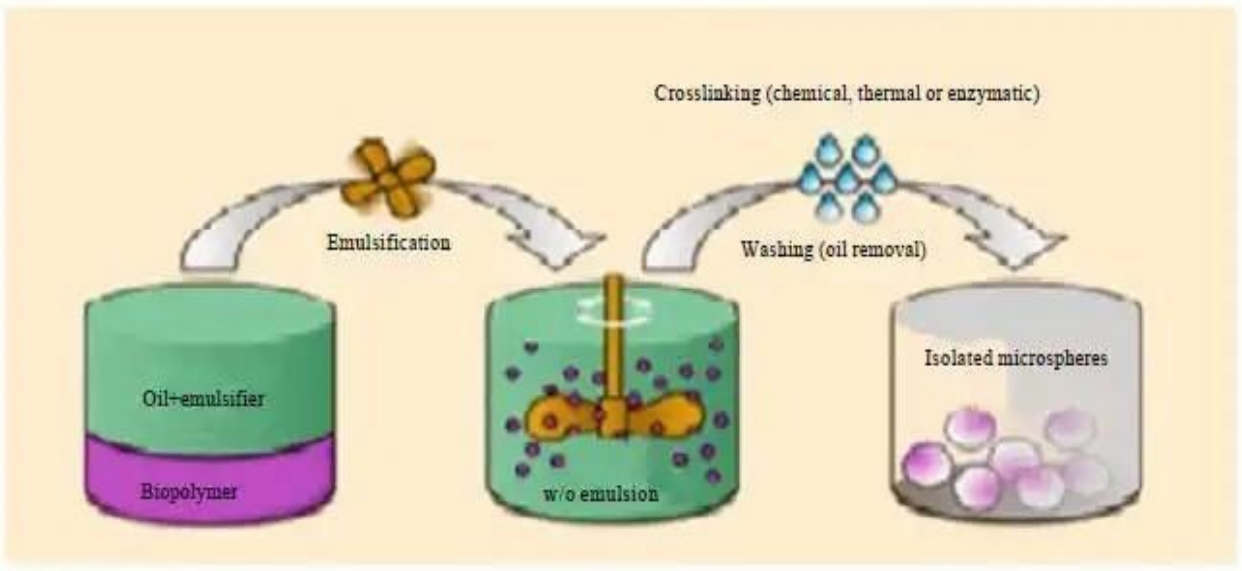


Figure No. 2: Single emulsion technique

The microparticulate carriers of natural polymers which are proteins and carbohydrates are prepared by a single emulsion technique. The natural polymers are dissolved/dispersed in an aqueous medium followed by dispersion in the non-aqueous medium e.g., oil. In the next step, cross-linking of the dispersed globule is carried out either using heat or by using chemical cross-linkers. The chemical cross-linking agents used lauraldehyde, formaldehyde, terephthalate chloride, diacid chloride (Vyas and Khar, 2010; Trivedi et al., 2008).

Crosslinking by heat is affected by adding the dispersion to previously heated oil. Heat denaturation is not suitable for the thermolabile drugs while the 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 (Schugens et al., 1994).

- **Double emulsion technique**

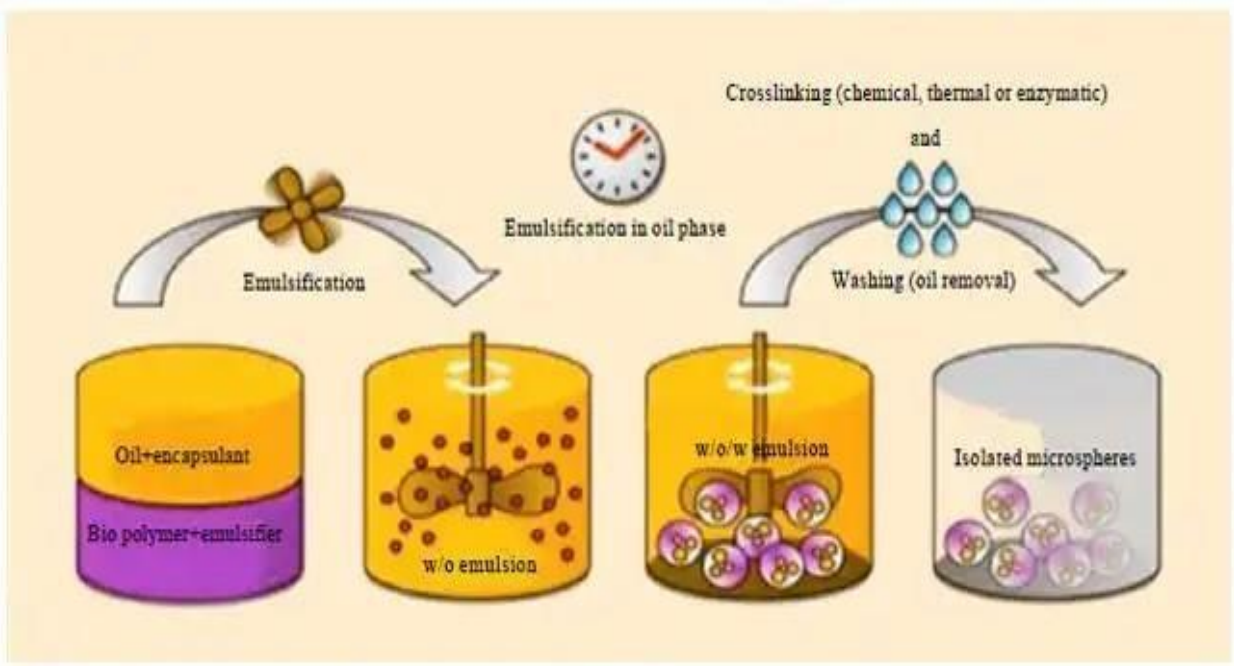


Figure No. 3: Double emulsion technique

This process consumes the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to the water-soluble drugs, peptides, proteins, and vaccines (Fig. 8). The aqueous protein solution is dispersed in a lipophilic organic continuous phase which is generally consisted of a polymer solution that eventually encapsulates protein contained in the dispersed aqueous phase. The primary emulsion is then subjected to homogenization before addition to an aqueous solution of PVA. This results in the formation of double emulsion which is then subjected to solvent removal by solvent evaporation maintaining the emulsion at reduced pressure or by stirring so that the organic phase evaporates out. Examples are hydrophilic drugs like LHRH agonists, vaccines, and proteins.

- **Coacervation phase separation method**

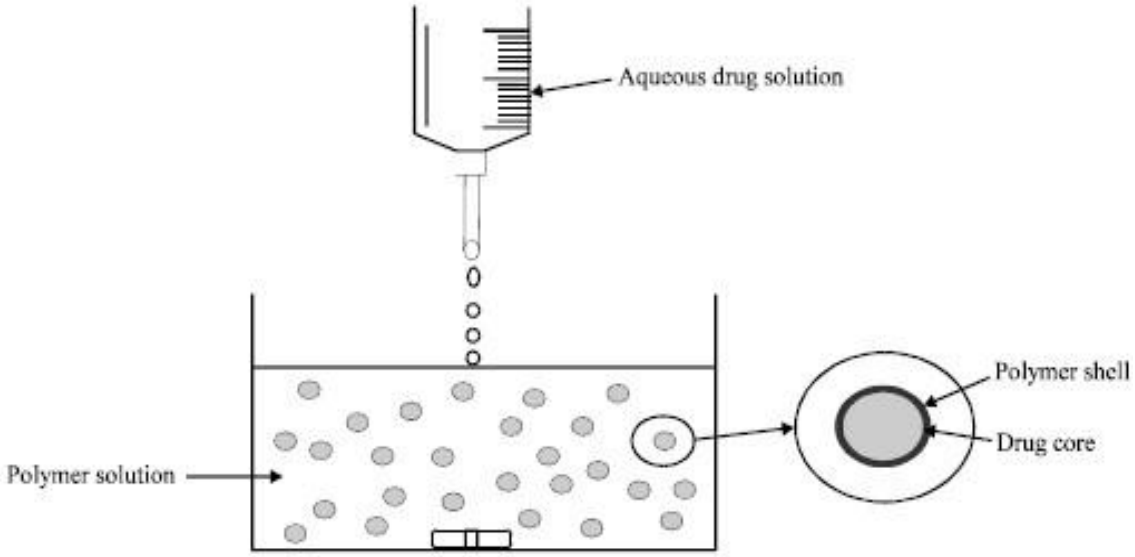


Figure No. 4: Coacervation phase separation method

This method is used to prepare the reservoir type of the system to encapsulate water-soluble drugs like peptides, proteins, matrix type particularly. When the drug is hydrophobic e.g., steroids. In a matrix-type device, the drug or the protein is soluble in the polymer phase. The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer-rich phase called the concordats. The coacervation can be brought about by the addition of the third component to the system which results in the formation of the two phases, one i.e., supernatant, depleted of the polymer. In this technique, the polymer is first dissolved in a suitable solvent and then the drug is dispersed by making its aqueous solution, if hydrophilic or dissolved in the polymer solution itself, if hydrophobic.

- **Spray drying and spray congealing:**

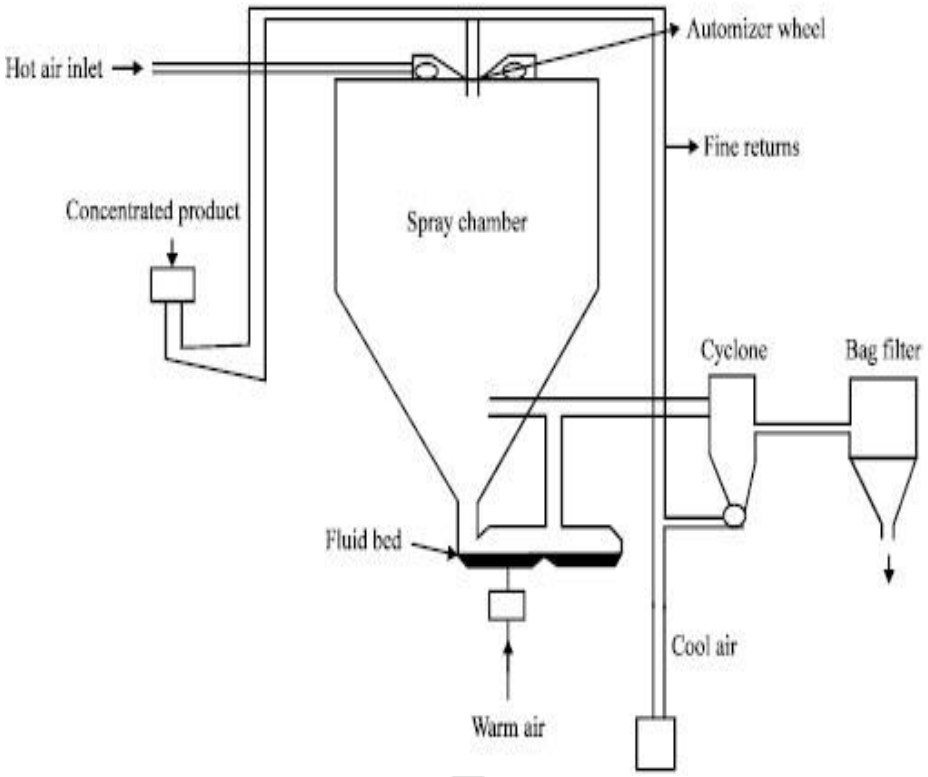


Figure No. 5: Spray drying and spray congealing

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, 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 to the formation of the microspheres in a size range of 1-100 µm. Microparticles are separated from the hot air using the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is the feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillin's. Thiamine mononitrate and sylph ethylthiadiazole are encapsulated in the mixture of mono and triglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however, leads to the formation of porous microparticles.

- **Polymerization techniques:**

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

1) 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 is also referred to 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 other additives. Emulsion polymerization differs from suspension polymerization due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has the advantage of the formation of pure polymer.

2) 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.

- **Solvent extraction :**

The solvent evaporation method is used for the preparation of microparticles, involving the removal of the organic phase by extraction of the organic solvent. The method involves water-miscible organic solvents such as is propanol. Organic phases were removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves the direct addition of the drug or protein to polymer organic solution.

The rate of solvent removal by extraction method depends on the temperature of the water, the ratio of emulsion volume to the water, and the solubility profile of the Polymer.

- **Evaluation of Microspheres:**

➢ **Micro metrics Properties (Particle Size and Shape):**

The most widely used procedures to visualize micro-particles are conventional light microscopy (LM), Particle size analyzers, and scanning electron microscopy (SEM).

➢ **Electron Spectroscopy for Chemical Analysis:**

The surface chemistry of the microspheres can be determined using electron spectroscopy for chemical analysis (ESCA).

➢ **Drug Entrapment Efficiency:**

The aim is to calculate the total entrapment of drugs in the microspheres. It can be calculated by calculated using the following equation, Entrapment = Actual content/Theoretical content X100

➢ **Density Determination:**

The density of the microspheres can be measured by using a multi-volume cyclometer.

➢ **Isoelectric Point:**

The micro electrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined.

➢ **The angle of Contact:**

The angle of contact is measured to determine the wetting property of a microparticulate carrier.

➢ ***In-vitro* Methods:**

Release studies for a different type of microspheres are carried out by using different suitable dissolution media, by using Dissolution apparatus used in IP/USP / BP).

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