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Microspheres- Imperceptible Drug Delivery System

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Abstract : Microspheres are drug delivery systems which are prepared to get extended or controlled drug delivery to strengthen bioavailability, stability and target the drug to particular site at a predetermined rate. Microparticles are generally have the particle size range from 1–1000 µm size, serve as multiunit drug delivery systems with clear physiological and pharmacokinetic benefits in order to improve the effectiveness, tolerability, and patient compliance. It has been shown that it not only enhances the dissolution of poorly soluble drugs but also employ a remarkable effect on fat metabolism in the body. Microspheres can successfully increase the biological half-life and reduce the therapeutic dose of their drug, thereby reduce the adverse drug reaction. The present review provides detailed discussion of therapeutic feature of microsphere drug delivery including the advantages and disadvantages of microspheres, preparation of microspheres, carriers used, characterization, and applications of microspheres. Microspheres are one of the most promising targeted and effective drug deliveries. A microsphere has a drug located centrally within the particle, where it is closet within a single polymeric membrane. A Microspheres has its drug distribute throughout the particle i.e., the internal structure is a matrix of drug and polymeric excipients. It is the dependable 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 unpredictable effects.
Keywords : Microspheres, Types of microspheres, Method of preparation, polymer, drug release, Application.

Introduction

Microspheres are submicron size polymeric drug carrier systems in which the therapeutic agents have loaded core the polymeric matrix or encapsulated or physically absorbed or chemically coupled onto the surface. The dimension range of these colloidal particles is from 1-1000 micrometers. These particles are made up of core material, which is the drug and a coating material1. Microspheres are a novel drug delivery system. A well-considered controlled drug delivery system can overcome some of the problems of predictable therapy and enhance the therapeutic efficacy of a given drug2. Microspheres are small, insoluble spherical particles consisting of a polymer matrix. Microspheres are labeled with a variety of beta and delta emitting radionuclides

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such as a drug that is physically entrapped in the pore of microspheres or chemically conjugated to polymer matrix3. Microparticles, microspheres, and microcapsules are widely used components of multiparticulate drug delivery systems, offering both therapeutic and technological advantages. With well-defined physiological and pharmacokinetic benefits to improve the effectiveness, tolerability, and patient compliance4. Microspheres are characteristically free-flowing powders made up of proteins or synthetic polymers. Microspheres are sometimes referred to as microparticles. Microspheres can be made from various natural and synthetic materials. Microspheres play an important role to improve the bioavailability of conventional drugs and reduce side effects5. Microspheres containing tailored porosity exhibit greater surface area, lower mass density, superior cell attachment, cell proliferation, drug absorption, and drug release kinetics compared to bulk microspheres6.microspheres-based drug delivery systems have received considerable attention in present years[7]. (fig:1)

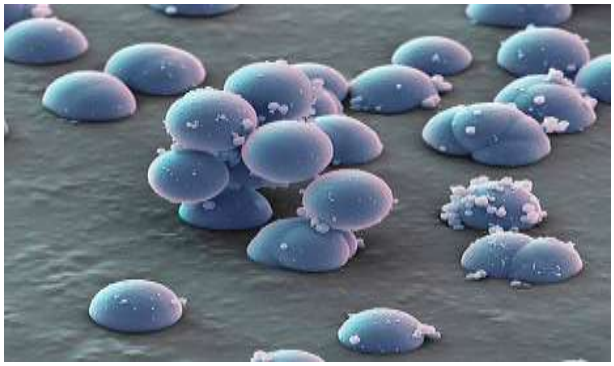

Fig:1: microspheres

Types of Microspheres:

1. **Bio Adhesive Microspheres:**Adhesion can be defined as adhering to a drug due to membrane by using the sticking property of the water-soluble polymers. Adhesion of the drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal can be termed as bio adhesion. These microspheres show a prolonged residence time at the site of application & cause intimate contact with the absorption site & produce better therapeutic action. ex HPMC, Carbopol- slower release of drug[8].

2. **Magnetic Microspheres:**Magnetite offers great potential for growth in electronics, optoelectronics, magnetic storage, biomedical, ferrofluid, separation, and magnetically guided drug carriers for targeting the therapy. Little amounts of drug targeted magnetically to localized sites can replace large doses of the drug that, using traditional administration methods. The different types of magnetic microspheres include therapeutic magnetic microspheres and diagnostic microspheres[9].

    a. **Therapeutic Magnetic Microspheres:**Therapeutic magnetic microspheres are utilized to deliver a chemotherapeutic agent to the liver tumor. Drugs such as proteins and peptides can also be targeted through this system.

    b. **Diagnostic Microspheres:**Diagnostic microspheres, used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nanosized particles supra magnetic iron oxides[10].

3. **Floating Microspheres:**Floating microspheres have been used to obtain the extended and uniform release of drugs in the stomach for the development of once-daily formulations. A controlled-release system designed to improve residence time in the stomach without contact with the mucosa11. Floating microspheres are low-density systems that have adequate buoyancy to float over the gastric content and remain in the stomach for an extended period while the system floats over the gastric content, the drug is released slowly at the desired rate which results in improved gastro-retention time and reduces fluctuation in plasma drug concentration. It is Despite tremendous advancement in drug delivery, the oral route remains the perfect route for the administration of a therapeutic agent[12]**.**

4. **Radioactive Microspheres:**Radioactive microspheres can be selectively targeted to various tumors without undue radiation to the nontumorous tissues. Radioactive microspheres have the advantage of delivering a high concentration of radioactivity to the target area without causing any damage to the local tissues and organs. Following administration, these microspheres get entrapped in the web of small blood vessels feeding a tumor and thus deliver the required concentration of radioactivity at the target site. The successful treatment range is up to 90 mm for alpha emitters, for beta emitters the range is not more than 12 mm and for gamma emitters, the range is up to several centimeters[13].

5. **Polymeric Microspheres:**Plenty of interest has been focused on polymer systems that show a phase transition in response to external stimuli such as temperature, pH, ionic strength, and electric potential because of their scientific or technological importance[14].The different types of polymeric microspheres can be categorized as follows and they are,

    a. **Biodegradable polymeric microspheres**: Biodegradable polymeric microspheres as injectable depots for protein and peptide drugs a biocompatible and biodegradable copolymer have been mostly used for delivering protein drugs15. Natural polymer like starch is used with the concept that they are biodegradable, bioadhesive, and also biocompatible. Biodegradable polymers prolong the residence time when contact with mucous membrane due to its high degree of swelling property with an aqueous medium, results in gel formation. The rate and extent of release of the drug are controlled by the concentration of polymer and the release pattern in a sustained manner. The main drawback in clinical use the drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.

    b. **Synthetic Polymeric Microspheres:**The synthetic polymeric microspheres are most widely used in clinical application, moreover, it is also used as a bulking agent, embolic particles, fillers, drug delivery vehicles, etc and proved to be safe and biocompatible. But the main disadvantage of these kinds of microspheres, tends to migrate away from the injection site and lead to potential risk, embolism, and further organ damage[16].

Materials used[17]

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres. These materials include polymers of natural and synthetic origin and also modified natural substances. Classification of polymers

1. Synthetic Polymers.
2. Natural polymers.

Synthetic Polymer:are divided into two types.

1. **Non- Biodegradable Polymers**: Poly methyl methacrylate (PMMA),Acrolein, Glycidyl methacrylate, Epoxy polymers.
2. **Biodegradable Polymers**: Lactides, Glycosides& their co polymers, Poly alkyl cyano Acrylates, Poly anhydrides.

Natural Polymers[18]:

These are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

1. **Proteins :**Albumin, Gelatine, and Collagen.
2. **Carbohydrates :**Agarose, Carrageenan, Chitosan, Starch.
3. **Chemically modifiedCarbohydrates :**Poly dextran, Poly starch.

Prerequisites for Ideal Microparticulate Carrier[19]

The material utilized for preparation of microparticulate should ideally full fill following prerequisites:

- Long duration of action.
- Control of content release.
- Increase of therapeutic efficiency.
- Protection of drug.
- Reduction of toxicity.
- Biocompatibility.
- Sterilizability.
- Relative bioavailability.
- Water solubility or dispersibility.
- Bioresorbability.
- Targetability.

Method of Preparation

The microspheres can be prepared by usingvarious techniques discussed in the following techniques.

Single Emulsion Technique

The microparticulate carriers of natural polymer that is those of proteins and carbohydrates are produced by a single emulsion technique. The natural polymer is dissolved or dispersed in an aqueous medium followed by dispersion in the non-aqueous medium e.g., oil. In the second step of preparation crosslinking of the dispersed globules is achieved. The crosslinking can be achieved either by utilizing heat is by using chemical crosslinkers. Crosslinking by heat is affected by adding the dispersion to previously heated oil. Heat denaturation is, however, not suitable for the thermolabile drug while the chemical crosslinking suffers disadvantages of excessive exposure of active ingredients to chemicals if added at the time of preparation[20].

Double Emulsion Technique

The double emulsion method of microspheres involves the formation of the multiple emulsion or the double emulsion type w/o/w and is best suited to the water-soluble drug, peptide, protein, and vaccines. This method can be used with both natural and synthetic polymers. The aqueous protein solution is spared in a lipophilic organic continuous phase. This protein solution may carry the active constituents. The continuous phase consisted of the polymer solution that eventually encapsulates the protein contained in the dispersed aqueous phase. The primary emulsion is subjected to homogenization or sonication before addition to the aqueous solution of the Polyvinyl alcohol. This result in the development of a double emulsion. The emulsion is then dominated to solvent removal either by solvent evaporation or solvent extraction process.

Polymerization Technique

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

I. Normal polymerization
II. Interfacial polymerization.

Normal Polymerization:

Normal polymerization proceeds and carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes.

In bulk polymerization, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate the polymerization. The polymer so produced may be molded as microspheres. Drug loading may be done throughout the process of polymerization.

Suspension polymerization is also mentioned as a bead or pearl polymerization. Here it is achieved by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also carry an initiator and other additives.

Emulsion polymerization varies from suspension polymerization due to the presence initiator in the aqueous phase, which later diffuses to the surface of micelles. has an advantage of the formation of pure polymers.

Interfacial Polymerization:

It involves the reaction of different monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this method two reacting monomers are employed, one of which dissolved in the continuous phase while the other being dispersed in a continuous phase. The continuous phase is commonly aqueous throughout which the second monomer is emulsified. The monomers present in either phase diffusion rapidly and polymerize rapidly at interphase.

The interfacial polymerization is not widely used in the preparation of the microparticles because of certain drawbacks, which are associated with the process such as:

- Toxicity associated with the unreacted monomer
- High permeability of the film
- High degradation of the drug during the polymerization
- Fragility of microcapsules
- Non-biodegradability of the microparticles[22].

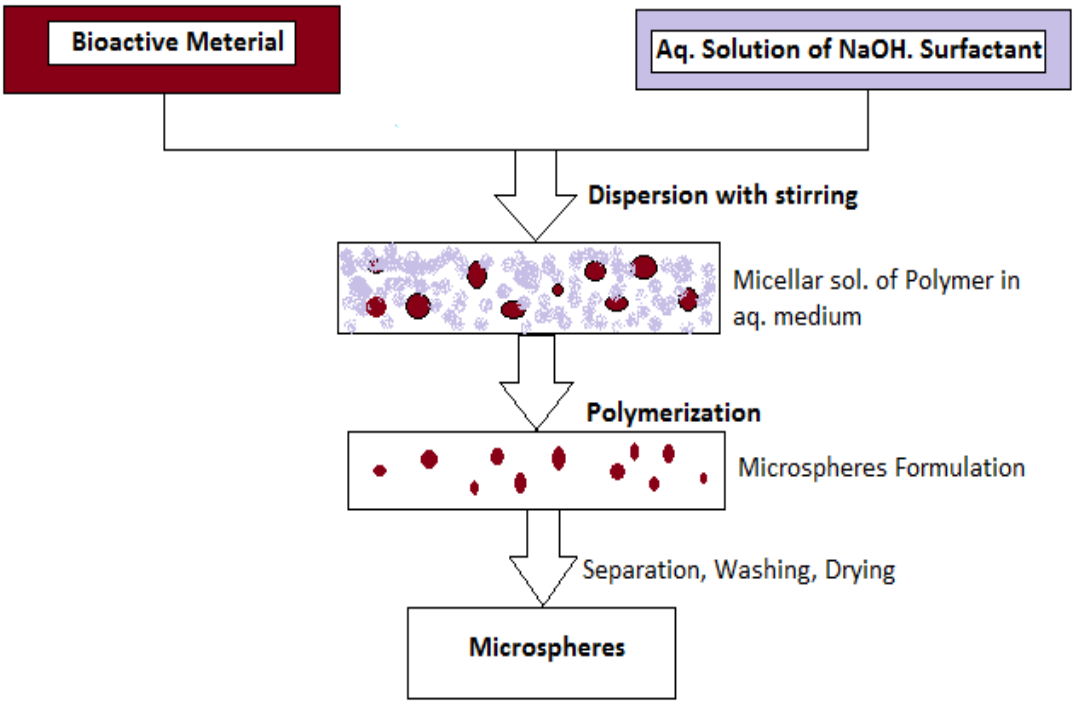

Fig 2: polymerization technique

Freeze drying Method

This methodology involves the freezing of the emulsion and the relative freezing points of the continuous and dispersed phases are important. The continuous phase solvent is normally organic and is removed by sublimation at low temperature and pressure. Finally, the dispersed phase solvent of the droplets is removed by sublimation, leaving polymer-drug particles[23]. (fig:3)

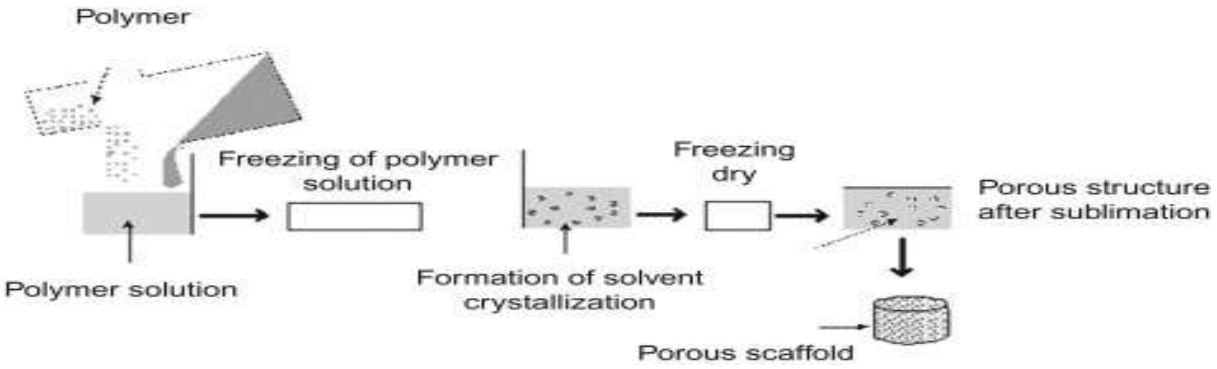

Fig 3: freeze drying method

Ionic Gelation Method

Alginate/chitosan particulate system for drug release was prepared using this technique Different % (w/v) of the drug was added to 2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added dropwise to a solution containing Ca2+ and chitosan solution in acetic acid. Microspheres that were formed were kept in original solution for 6 hrs& 24 hr for internal nullification followed by filtration for separation. The complete release was obtained at pH 7.4 but the drug did not release an acidic pH[24](fig:4).

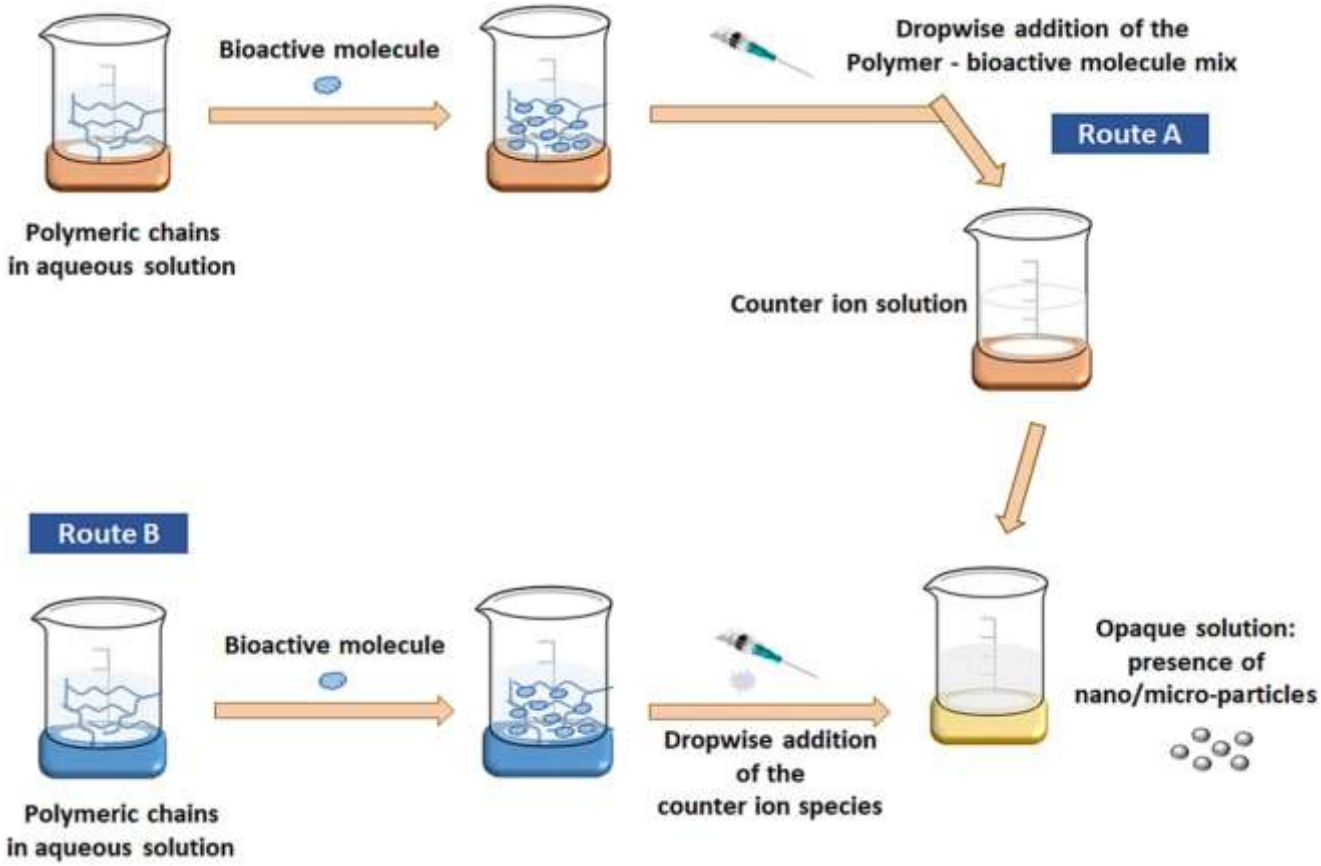

Fig:4: ionic gelation method

Phase Separation Coacervation Technique

This operation 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 coacervates. In this technique, the drug particles are dispersed in a solution of the polymer and the incompatible polymer is added to the system which makes the

first polymer to phase separate and engulf the drug particles. Insertion of non-solvent results in the solidification of polymer. Polylactic acid (PLA)microspheres have been made ready by this method by using butadiene as an 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 the aggregation of the formed particles. The aggregation must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerizes 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[25].

Solvent Extraction Method

In this method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. The method requires water miscible organic solvents such as isopropanol. Organic phase is separated by extraction with water. This process reduces the hardening time for the microspheres. One difference 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[26](fig:5).

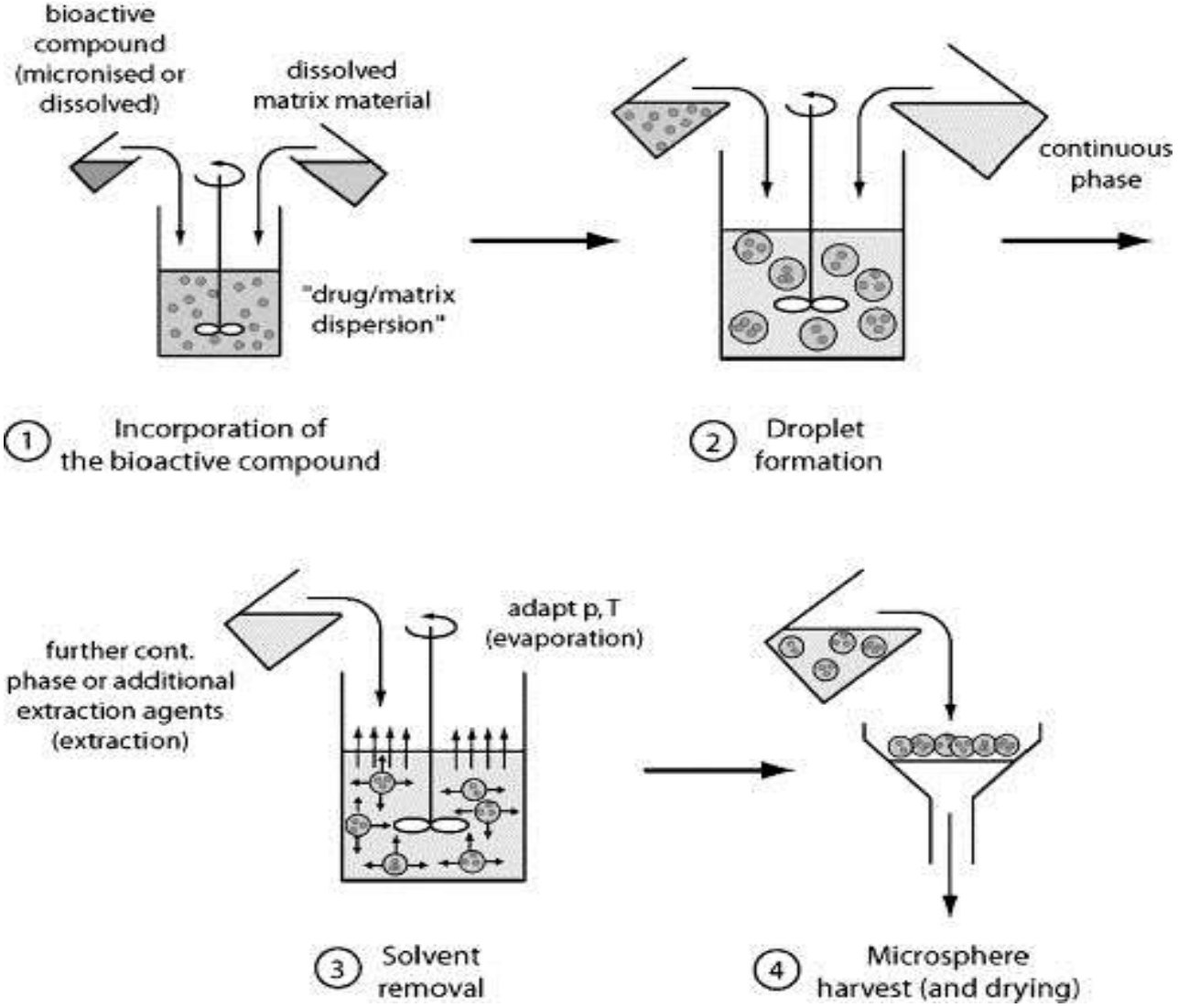

Fig 5 : Solvent extraction method

Characterization of Microspheres

The characterization of microparticulate carrier is an important phenomenon that helps to design a suitable carrier for the proteins, drug delivery. The microspheres have different microstructures, which depending on their method of preparation and condition during preparation. Several parameters are generally evaluated for the characterization of microspheres.

Particle Size and Shape

The most widely used procedure to visualize microparticles is conventional light microscopy and scanning electron microscopy. Both the technique can be used to determine the shape and the outer structure of microparticles nevertheless, they have a certain limitation when used for the analysis of the internal structure of such particle and distribution are determined by light microscopy, scanning electron microscopy, electron microscopy. The microspheres structure can be visualized before and after coating and the change can be measured microscopically.

Zeta Potential

Zeta potential is measured by adding a solution cell that contains two gold electrodes. When a voltage is applying to the electrode. The particles will be move towards the electrode with the opposite charge. A doppler technique is used to calculate the particle velocity as a function of voltage and the resulting particles were determined by zeta potential measurement.

Drug Content

The various batches of the microspheres were dominated for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in an adequate quantity of buffer and then filtered. The UV absorbance of the filtrate was measured using a UV spectrometer at particular nm[27].

Drug Entrapment Efficiency

Microspheres containing drug (5mg) are crushed and then dissolved in distilled water with the help ofultrasonic stirrer for 3 hrs, and filtered then assayed by UV-visible spectroscopy.

%Entrapment =actual content/Theoretical content x 100

Scanning Electron Microscope(SEM) Study

The surface morphology and particle size of microspheres are determined by Scanning Electron Microscopy. Dry microspheres are placed in a scanning electron microscope brass stub and coated with gold in an ion sputter. Picture of microspheres are taken by random scanning.

***In-vitro* Drug Release Study**

The drug release study is carried out using USP dissolution test apparatus paddle-type at 37 ± 0.5°C and 100 rpm using 900 ml of phosphate buffer pH 7.4, as dissolution medium for 8 h. Microsphere's equivalent to 10 mg of a drug are used for the test. 5ml of sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably, and analyzedSpectrophotometrically at suitable nm. An equal amount of fresh dissolution medium was replaced immediately after draw out of the test sample.

Kinetics of Drug Release

The analysis of the drug release mechanism from a pharmaceutical dosage form is an important but complex method and is practically evident in the case of mucoadhesive controlled release systems. As a model-dependent approach, the dissolution data were fitted to four popular release models as zero-order, first-order, Higuchi, and the Korsemeyer- Pappas equations. The order of drug release from the mucoadhesive

microspheres was reported by using zero-order kinetics or first orders kinetics. The mechanism of drug release from the mucoadhesive controlled release systems was studied by using the Higuchi equation and the Korsemeyer - Peppas equation

Stability Studies

By arrange the microspheres in screw capped glass container and stored them at following conditions:

1. Ambient humid condition
2. Room temperature (30^0C+/-20^0C)
3. Oven temperature (40^0C+/-20^0C)
4. Refrigerator (5^0C+/-3^0C)

It was carried out of 60 days and the drug content of the microsphere was analysed[28]**.**

Advantages of Microspheres[29]

1. Reduce the dosing frequency.
2. Improve the patient compliance.
3. It provides prolong therapeutic effects.
4. Duration of action is more.
5. Improve the bioavailability of drug.

Disadvantages[30]

Several of the disadvantages were found to be as follows

1. The costs of the materials and processing of the controlled release compound, are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its result on the environment
3. Reproducibility is less.
4. Process conditions like change in temperature, pH, solvent addition, and evaporation(or)agitation may control the stability of core particles to be encapsulated.
5. The environmental influence of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation, or biological agents.
6. Dosage forms of this category should not be crushed or chewed.
7.

Applications in Drug Delivery System[31,32]

- Ophthalmic Drug Delivery
- Gene delivery systems
- Intertumoral and local drug delivery
- Oral drug delivery
- Nasal drug delivery
- Buccal Drug Delivery
- Gastrointestinal Drug Delivery
- Transdermal Drug Delivery
- Monoclonal Antibodies
- Imaging
- Vaginal Drug Delivery
- Targeting by Using Micro Particulate Carriers

Conclusion

The present review article shows microspheres are a greater choice of drug delivery system than several other types of drug delivery systems**.** Specifically, in diseased cell sorting, diagnostic of a gene-targeted and beneficially in *In vivo* delivery.microspheres have great potentials being able to term poorly soluble,poorly

absorbed and labile biologically active substances in to promising deliverable substance they process greater stability when compared to liposomes so, microspheres will have an important role to play in the development of the medicinal field.

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