A: REVIEW OF ADVANCEMENT IN MICROSPHERES ON TARGET DRUG DELIVERY SYSTEM

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***Abstract*: Microspheres are the novel drug delivery system with several potential applications in site specific targeting and in varied sciences. Microspheres are spherical free flowing powder having a particle size ranging from 1-1000µm and consisting of natural or synthetic polymer. Due to its special size dependent characteristic, ability to incorporate drugs into carriers, lipid microspheres offers a possibility to developed new therapeutics. There are various techniques available for the formulation of microspheres and to release the drug in sustain and controlled manner at desired site of action. Microspheres received a greater attention in targeting and curing of many diseases because the ability of oral administration, improved half-life, improved therapeutic responses. This review discussing their aims, production procedure, advantages, and appropriate method for the characterization of micro particles like scanning electron microscopy, differential scanning calorimetric method.**

***Keywords*: Microspheres, Therapeutic response, Carriers, Polymers.**

INTRODUCTION:

Microparticles were firstly developed in 1990 and it considered being a promising drug carrier system especially for the incorporation of the active drug substance and to promote the sustained and controlled drug delivery (Pilaniya K et al., 2011). Microspheres are solid spherical in shape and size ranging from 1-1000µm and that can be suspended in suitable aqueous solvent system. This drug delivery system is preparing to obtained prolonged sustained or controlled drug delivery, to improves bioavailability, to enhance stability and to reduce toxic effects follows with target drug at specific site. Microspheres are also considered as microparticles. Microspheres are prepared mostly by two types of polymers especially natural polymer or synthetic polymer that assist in transportation of active compound. Ethyl cellulose and sodium alginate is natural polymer that obtained from the marine brown algae. This is biocompatible, biodegradable and non-toxic, and widely used in oral and topical formulation (Patel Balkrishnan et al., 2012**).** Microspheres have been proposed as a colloidal drug carrier for different administration routes such as oral, topical, ophthalmic, subcutaneous, and intramuscular and particularly for parenteral route of administration (Mishra Priyanka et al., 2012). Microsphere is an established technique that have been used to deliver various types of drugs which includes antigen, antibiotics, steroids, peptides and protein by either injection or through oral route. Biodegradable polymer microparticles, either microspheres or microcapsules are often used as a support for the delivery of bioactive compounds (Soni M.L et al., 2010). While triglyceride and cholesterol is synthetic polymer which shows detrimental effect on incorporating peptides and proteins during manufacturing of formulation. These polymers are biocompatible, biodegradable and non-toxic in nature (Pilaniya K et al., 2011). Microspheres vary widely in quality, sphericity, and uniformity of particle and particle size distribution. For each unique application appropriate microsphere is chosen. The ranges of techniques for the preparation of microsphere offers the variety of opportunity to control various aspect of drug administration and to facilitates the accurate delivery of small quantity of the potent drugs, and to avoid the unexpected concentration of drug at the site other than the target site. The behavior of the drug component can be manipulated according to need by coupling the drug to a carrier particle. The clearance kinetics, tissue distribution, metabolism and interaction of drug are strongly depending on the behavior of the carrier. The primary goal of drug delivery system is to obtain the therapeutic response with minimal side effect, that condition achievable by delivering drug at the specific site with pre-determined rate and over specified period of time in the body (Kataria Sahil et al., 2011). The oral drug delivery system is the most convenient route because of ease in administration and more patient compliance. To develop the oral doses form it is important to improve both the residence time as well as release of drug from the dosages forms (J.Josephine et al., 2011). Drugs that easily absorbed from gastric intestinal tract and having short half-life are eliminated faster from blood stream, to avoid this problem oral control drug delivery system develop as they release drug slowly and maintain constant drug concentration in serum for longer period of time that finally improves the bioavailability of drug. A well designed controlled drug delivery system overcome some of the problems related to usual therapy and enhance the maximum therapeutic efficacy, it become necessary to deliver the drug to target site in appropriate amount at right time to avoid the side effect and maximize the therapeutic effects (Kataria Sahil et al., 2011).There are numerous analytical techniques used for the characterization of microspheres are scanning electron microscopy technique, differential scanning calorimetric technique, photon correlation and Fourier transformed infrared spectroscopy (FTIR). This FTIR technique is used for the characterization of drug loaded formulation (T.S.keerthi et al., 2010). The *in-vitro* drug release was studied using rotator basket method which is described in the 5th edition of the European Pharmacopoeia with the help dissolution apparatus. The study carried out at 150 rpm in phosphate buffer solution of p^H 7.4 at 37^{0}C (Severine Jaspart et al., 2007).

ADVANTAGES

- Microspheres improve the absorption of poorly absorbed drug.
- Microspheres improve the bioavailability, reducing adverse effect, and showing constant target drug release.
- Microspheres improve the stability of drug, scale up and sterilized easily.
- Microspheres have high drug load and show constant and prolonged therapeutic effect.
- Microspheres can prepare on large scale with relatively at low cost.
- Incorporated active compound shows sustained drug release.
- Due to special size dependent character and spherical shape microspheres can be injected into the body. (Kaur D et al., 2012)

LIMITATIONS

- The release rate of drug may vary from dose form that depends upon the polymers used.
- Drug release profile may get altered by the presence of food or polymer coating that further affects the drug transient time.
- The cost of these formulations is too high in comparison to other conventional formulations.
- Product degradation either by environmental factors like: hydrolysis, oxidation, solar radiation, heat or on Changes in the integrity of formulations could affect the efficacy of doses forms and produce toxic effects. (B.Pavan kumar et al.,2011, Ojha Pari et al.,2014)

TYPES OF MICROSPHERES

Bio-adhesive microspheres
Biodegradable microspheres
Mucoadhesive microspheres
Magnetic microspheres
Radioactive microspheres
Hollow microspheres

- **Bio-adhesive microspheres:** Bio-adhesive microspheres are the drug delivery system which was having Mucoadhesives property to the mucosal membrane such as: buccal, ocular, nasal, rectal etc. It having adhesive property that prolonged the residence time of drug which assists in produces better therapeutic response with maximum bioavailability. (Namdev Abhishek et al., 2015)

- **Biodegradable microspheres:** Biodegradable microspheres are the drug delivery system which is widely used because of their biocompatible and biodegradable property. The incorporated drug released to the environment in a controlled manner either by leaching or by degradation of polymer matrix. This system forms gel when come in contact with aqueous medium because system having good swelling property. Due to unique property of system it prolonged the residence time and shows sustained release for attaining better patient compliance and to omit the frequent administration of drug. (Ojha Pari et al., 2014)

- **Mucoadhesives microspheres:** Mucoadhesives microspheres are formulated by the combination of drug with Mucoadhesives polymers. It is a complex process which involves wetting, adsorption, penetration, and drug release from polymer. When the system is in contact with mucous layer than get swell by the process of wetting. So drug starts to release and penetrate into the tissue and shows its therapeutic results. (Garg Ankita et al.,2012)
  Example: Preparation of Mucoadhesives microspheres using Verapamil HCl for sustained and controlled release to treat depressive disorder. This achieved by employing 2^3 factorial design method and solvent evaporation technique. The microsphere of size range 65.66 to 105.30µm was observed. The formulation shows good compatibility study with improved sustained drug release for more than 24 hours. (Senthil A et al.,2011)

- **Magnetic microspheres:** magnetic microspheres are the recently developed drug delivery system which localized the drug to the disease site. In this system the large amount of free circulating drug can be replaced by the smaller amount of magnetically targeted drug .in preparation of magnetic microspheres special materials used which response to magnetic field are chitosan and dextran etc. They are of two types.
  Therapeutic magnetic microspheres
  Diagnostic magnetic microspheres

- **Therapeutic magnetic microspheres:** This type is used for therapeutic purpose. It is used to treat liver tumor by delivery of chemotherapeutic agents. Drugs like proteins and peptide can also be targeted.

- **Diagnostic magnetic microspheres**: This is used for imaging liver metastasis and distinguish loop of bowel from other abdominal structure, forming Nano size particles with iron oxide. (Kadam N.R et al.,2015)

- **Radioactive microspheres:** Radio immobilization therapy microsphere sized ranged from 10-30 nm are than larger than the capillaries and gets trapped in first capillaries bed when they come across. It differs from drug delivery system as

radioactivity not released from microspheres. Radioactive microspheres deliver high radiation dose to the target tissue without effecting normal surrounding tissues'. They are injected to the arteries that lead tumors of interest. There are three types of radioactive microspheres are α emitter, β emitter, γ emitters. Which are used for diagnostic and therapeutic purpose. (Singh Chitra et al.,2013).
Example: Radioactive microspheres were prepared to treat various tumors and cancer by achieving controlled drug delivery at the specific site of action. (Sinha V.R. et al.,2004)

- **Hollow microspheres:** Hollow microspheres are also referred as micro balloons. In this system drug is loaded in their outer polymer shell this novel system were developed by emulsion-solvent diffusion method. The ethyl alcohol:dichloromethane solution of drug and acrylic polymer which is poured in to an agitated aqueous solution of PVA and its temperature were thermally controlled at 400C. The gas is generated by dispersing the droplet of polymer by evaporation of dichloromethane, which leads formation of cavity in microspheres that allows micro balloons to float continuously in the stomach over a prolonged period of time more than 12hours *in-vitro*. (Gholap S.B et al., 2010)

TECHNIQUES FOR PREPARATION OF MICROSPHERES:
Single emulsion technique.
Double emulsion technique.
Spray drying technique.
Solvent extraction technique.
Solvent evaporation technique.
Phase separation technique.

1. **Single emulsion techniques:** The single emulsion techniques works on the basis of two techniques.
Dissolve the natural polymer in an aqueous solution followed with the dispersion in non-aqueous solution.
Dispersed globules cross-linked either thermal cross-linking method, chemical cross-linking method or through ionic chelation method.

Procedure: Single emulsion techniques are used for the preparation of micro particulate carriers, which is used for the delivery of the drugs. In this technique natural polymer is dissolved in an aqueous solution followed with subsequent dispersion in non-aqueous solution like oil. The Cross-linking of the dispersed globules is performed either by thermal cross-linking method or by chemical cross-linking method. The cross-linking agents includes: glutaraldehyde, formaldehyde, acid chloride. The cross-linking can also be done by ionic chelation method (e.g. calcium chloride). The thermal cross-linking method is not best suitable for thermolabile drugs, while the demerits of chemical cross-linking method is excessive exposure of drugs to the chemicals, and the disadvantage associated with ionic chelation methods are chances of salt formation, counter ion formation, or chelation. (Shukla Priya et al.,2015)

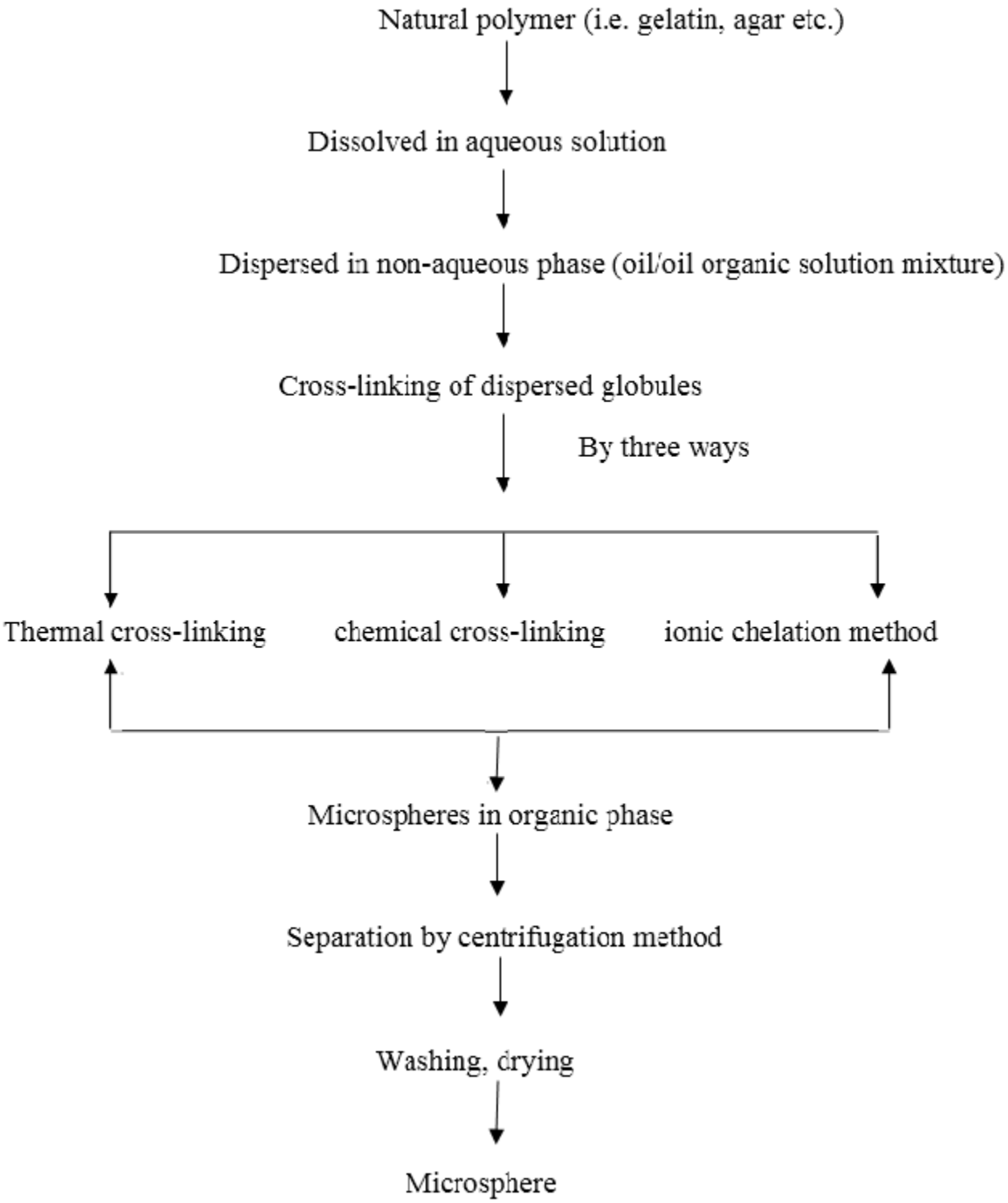

Fig 1: Schematic representation of Single Emulsion Method

2. Double emulsion Technique: This emulsion technique is also used for the preparation of multiple emulsions or double emulsion type w/o/w is best suitable for water soluble drugs, peptides, proteins and vaccines. Both kind of polymers either natural polymer or synthetic polymer can have been used. (Mahale Manisha M et al.,2019).

Principle: This method is quite suited for microspheres preparation. In this the aqueous solution is dispersed primarily in lipophilic organic continuous polymer phase along with drug. Which consist polymer solution that encapsulates protein contained in dispersed aqueous phase. Then the primary emulsion is subjected to homogenization/or sonication before addition to the aqueous solution of poly vinyl alcohol (PVA). This will form double emulsion. This emulsion is forwarded to solvent removal either by solvent evaporation method or through solvent extraction method at under reduced pressure. The numbers of water soluble drugs like luteinizing hormones (LH), vaccines, proteins, peptides are successfully incorporated into the microspheres. (Namdev Abhishek et al.,2015).

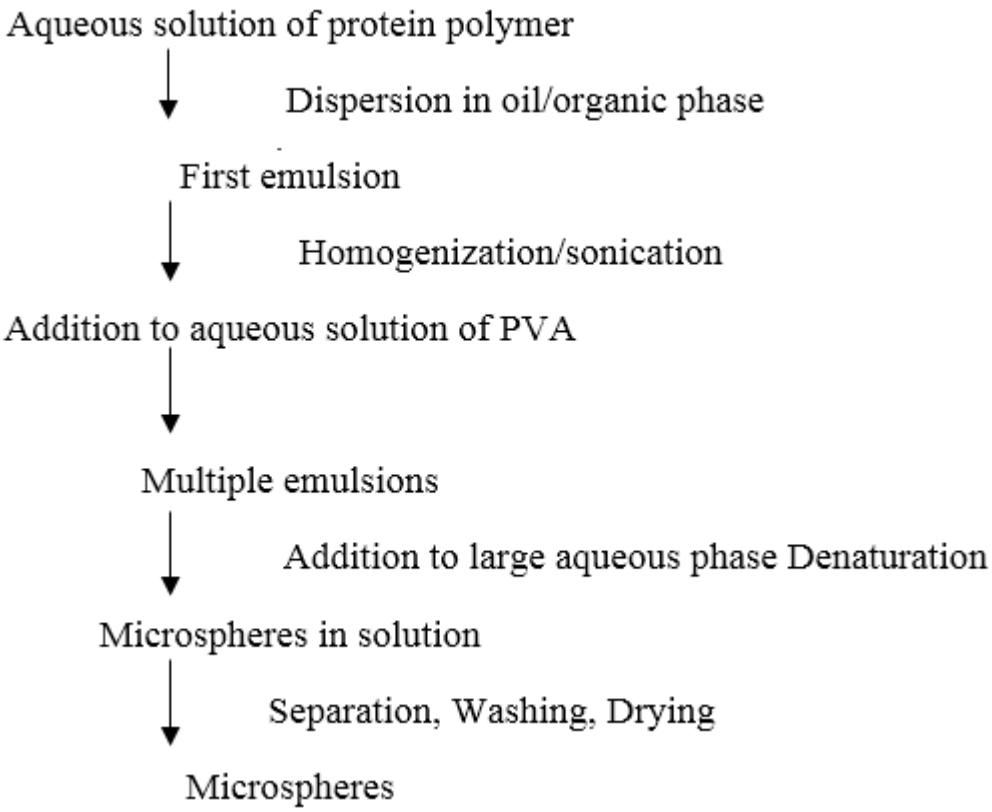

Fig 2: Schematic representation of Double Emulsion Method

3**. Spray Drying Technique:** The Spray drying technique based on the principle of atomization, mixing, and drying.
Atomization: It involves conversion of liquid feed material into fine solid droplets or mist.
Mixing: It involves the process which uniformly dissolve drug into the solvent system.
Drying: It is the process of removal of solvent from the microsphere and leads formation of dried microspheres. (Subrahmanyam C.V.S et al.,2009)
Procedure: In spray drying process the polymer is firstly dissolved in organic volatile solvent e.g. dichloromethane, acetone etc. then drug is dispersed in polymer solution under at high speed homogenization. This solution is atomized in stream of hot air. Which leads formation of small droplets or fine mist. The solvent evaporated instantaneously from the surface of fine mist and leading to the formation of microsphere of size ranging from 1-100µm. The cyclone separator is used for the separation of microparticles from the hot air, and the solvent is removed by means of vacuum drying and produce dried microsphere.
Advantages: Feasibility of operation under aseptic condition, rapid process, and formation of porous microparticles. (Alagusandaram M et al. ,2009)

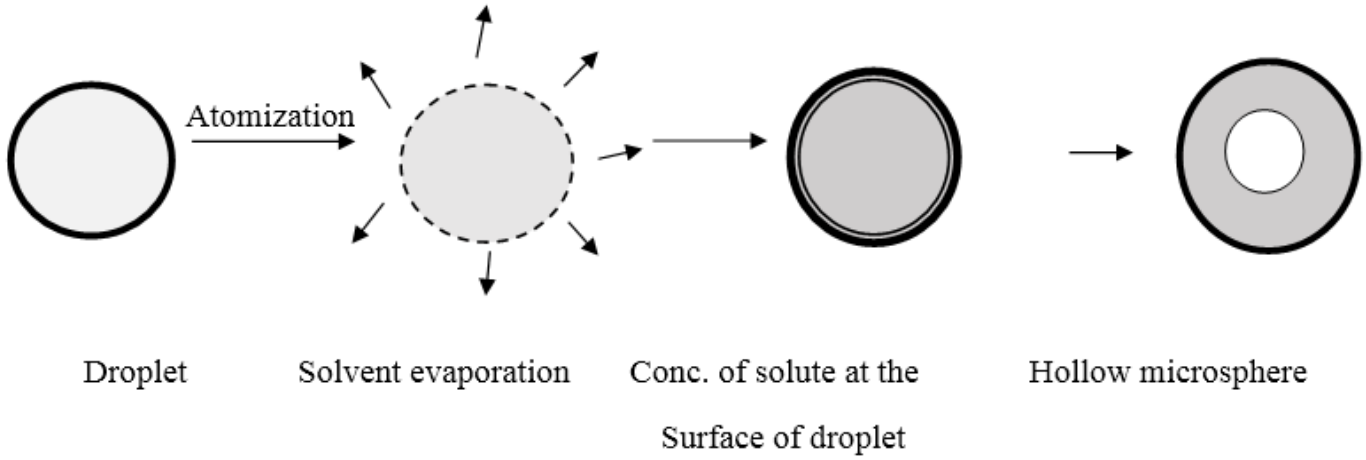

Fig 3: Schematic representation of formation of microspheres by Spray Drying Method

4. Solvent extraction method: This in the method used for the preparation of microsphere. In this process removal of organic phase by extraction of the organic solvent. The organic solvent which is used is water miscible i.e. isopropanol. Here organic phase removed by extraction with water. This process helpful in decreasing the hardening time of the microspheres. In this process drug

or protein are directly added to the polymer organic solution. The rate of solvent removal by extraction depends upon some factors like: the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer. (Singh Chitra et al.,2013)

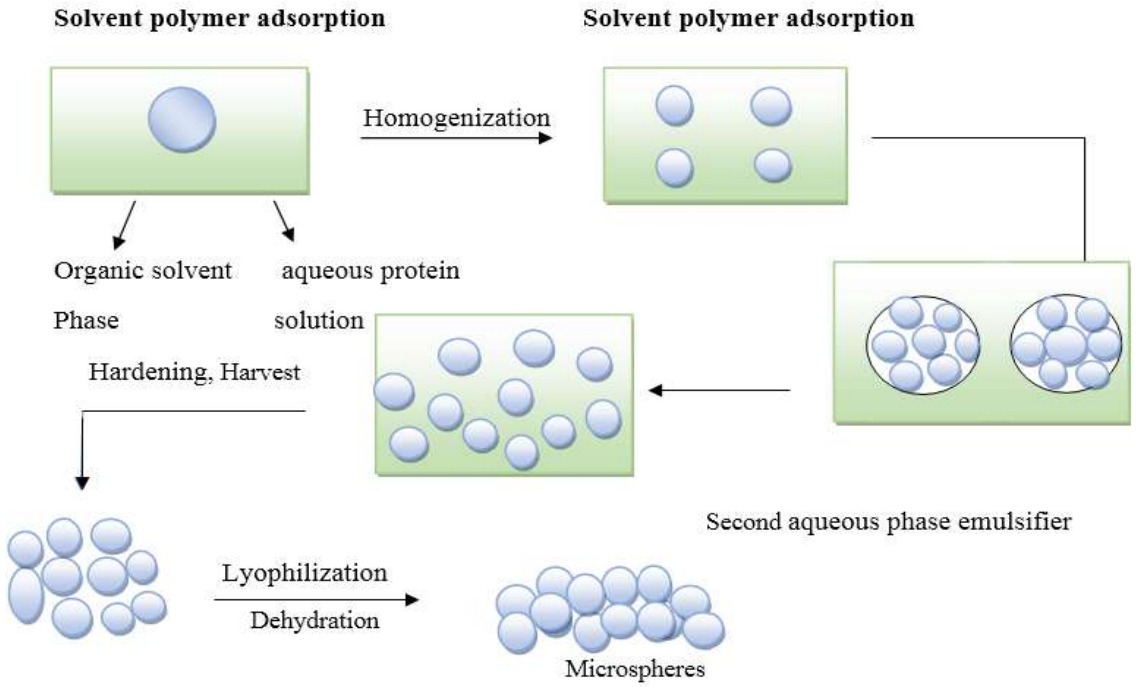

Fig 4: Schematic representation of microspheres prepared from Solvent Extraction Method

5. Solvent Evaporation Technique: This method is the being most popular and widely used than any other method, and having various advantages. This method requires mild conditions such as, ambient temperature, and stirring. The emulsion prepared by this method is more stable. (Basu S.K. et al.,2008)

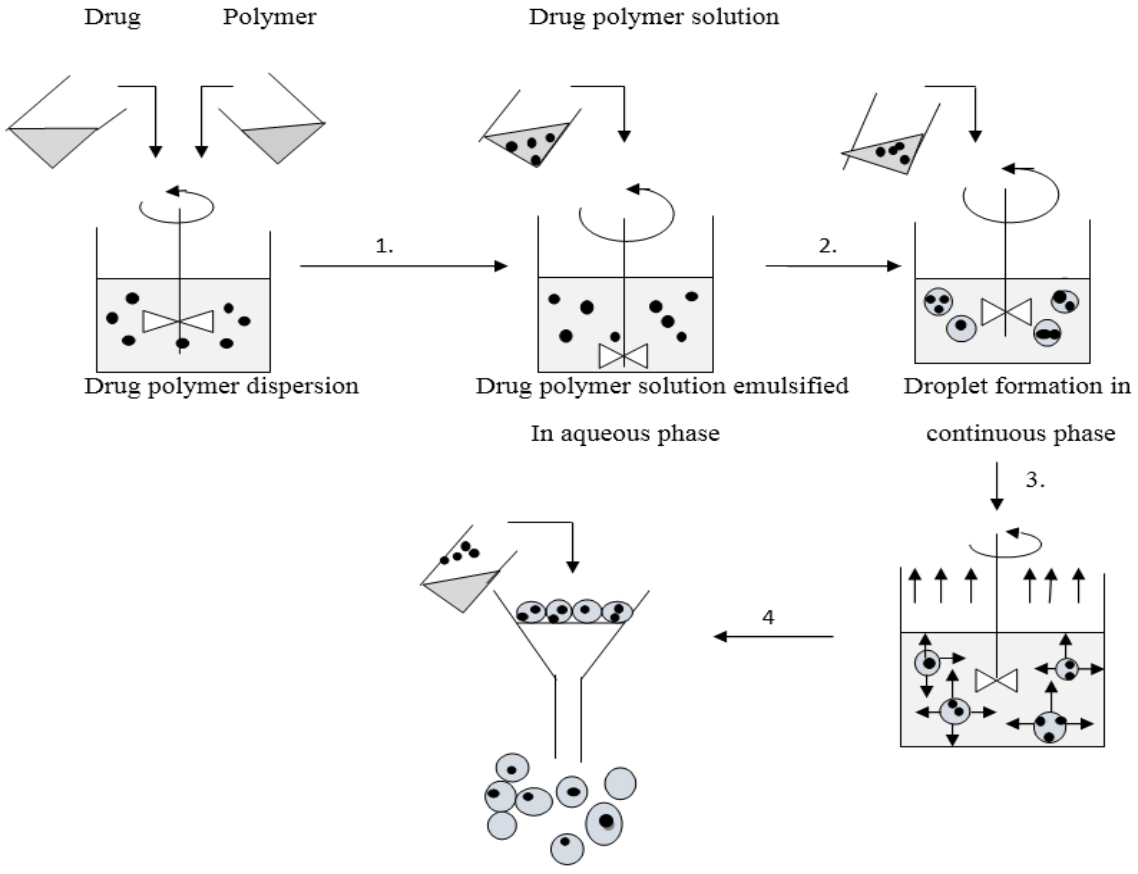

Fig 5: Schematic representation of microspheres formulated by Solvent Evaporation Method

Example: Preparation of microspheres of losartan potassium by using solvent evaporation technique intended to improve the oral bioavailability by means of varying the concentration of individual polymer like sodium alginate and distilled water is used as a solvent while liquid paraffin and span used as a continuous phase, and n-hexane or acetone for washing and hardening of microspheres. (T.S. keerthi et al.,2010)

Steps involved in preparation of microspheres is shown below:

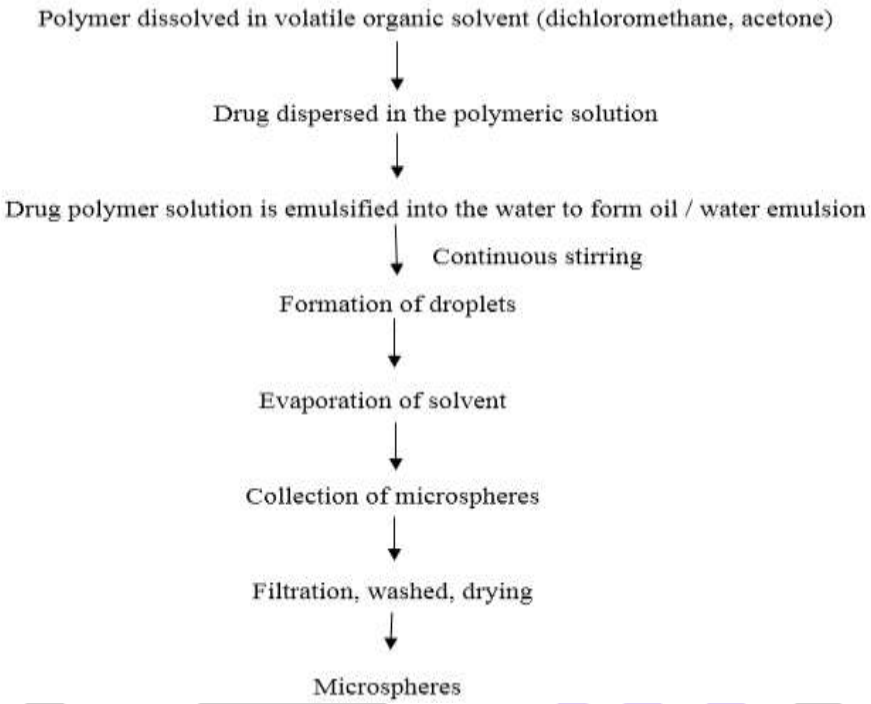

Fig 6: Schematic representation of microsphere by Solvent Evaporation Method

5. Phase separation coacervation technique: Coacervation is a technique in which the solubility of the polymer in organic phase is decreased which results decrease in the formation of polymer rich phase.

PROCEDURE: The formation of three phases' i.e. vehicle phase, core material phase, and coating material phase. Dispersion of drug solution in polymeric phase. Addition of incompatible polymer to achieve phase separation and to engulf the drug particles. Solidification of microspheres by addition of non-solvent. (Kaur D et al.,2012)

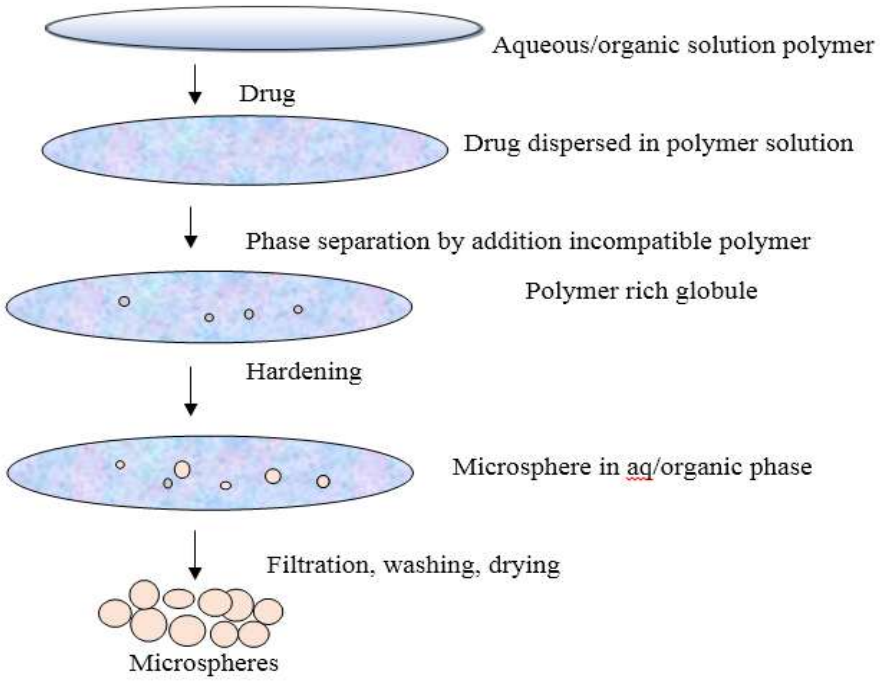

Fig7: Schematic representation of microsphere by phase separation coacervation Method

Application of microspheres:

- **Ocular delivery:** The potential of polymer exhibits favorable biological behavior such as: bioadhesion, unique physio-chemical property, with permeability enhancing property. All these property helps in designing of ocular drug delivery system to treat many diseases. The chitosan microsphere of acyclovir as a controlled release formulation for the treatment of ocular viral infection. The drug acyclovir shows first order kinetic release profile with non-fickian diffusion mechanism. The drug shows long term stability and better therapeutic effect *in-vivo*. On the other hand, chitosan loaded microsphere have greater application in ophthalmic drug delivery system for the management of glaucoma and conjunctiva because of Mucoadhesives property of chitosan which results in prolonged residence time of drug. (S.Selvaraj et al.,2011)
  Example: Formulation and evaluation of microspheres of losartan potassium using biodegradable natural polymer. Microspheres are prepared by solvent evaporation technique and the obtained microspheres ranges from 250-50µm. Formulation shows sustained drug release profile over the period of 12 hours. Preparation was found to be effective in management of hypertension. (T.S.Keerthi et al.,2010**)**

- **Pulmonary drug delivery system:** The polymer exhibits important role in pulmonary drug delivery system is because of its bio-adhesive property that improves the bioavailability as well as residence time of drug. In this relation microsphere formulation helps a lot. The microsphere of doxorubicin and paclitaxel loaded PLGA were prepared having mean diameter and mass median aerodynamic diameter 11.4±2.71µm and 3.52±0.82µm. The microsphere of this size range helps in aerolize the drug in lungs and shows better action in management of lungs metastases by sustained release from porous PLGA microsphere containing doxorubicin and paclitaxel. (Feng Tianshi et al.,2014)
  Example: Preparation and characterization of isoniazid loaded chitosan based microsphere for pulmonary delivery. The formulation exhibits good aerolization character. Sustained drug release was noted on addition of tripolyphosphate (TPP), which is used as a cross-linking agent. (Kundawala J. Aliasagar et al.,2011)

- **Vaginal drug delivery system:** The drug delivery by sustained or controlled manner with maximum bioavailability is the recent prospective. Microspheres have been recently developed to target the drug at the desired site with maximum bioavailability. The microspheres of econazole nitrate, which having anti-fungal activity has been prepared and targeted to treat vaginal infection. The polymer poloxmer were used that improves solubility and bioavailability of drug econazole nitrate. The poloxmer improves Mucoadhesives property of formulation and shows better release of drug in vaginal region with effective in cure of vaginal candidiasis. The econazole microspheres ranges from 100-335µm. **(**Beatric Albertini et al.,2009).

- **Nasal drug delivery system:** The polymer shows potential application in nasal drug delivery of pharmaceutically active compound. The nasal route considers the most prominent route for faster delivery and absorption of active compound with avoidance of first pass metabolism. The microspheres of fexofenadine HCl were recently formulated until the oral formulation available. The PEG 600 used as a polymer and microspheres of 20-30µm mean diameter were developed. The microsphere for nasal route having Mucoadhesives polymer which improves the residence time and bioavailability of drug that directly fasten the absorption of active compound. (Yeamin Hua et al., 2010)
  Example: Formulation of chitosan based microsphere of Verapamil HCl (VRP) for intranasal delivery. The particle size ranges from 20-50µm. The formulation shows improved bioavailability with effective drug performance. (Mamdoub Abdel Mouez et al., 2014)

- **Orthopedic drug delivery:** Orthopedic surgeries are performed more commonly today with the follow of high level of sterilization procedure but still complication arises related with orthopedic infection. The advancement in treatment of orthopedic diseases. The formulation of fusidic acid in poly (DL-lactic-co-glycolic acid) (PLGA) and poly [3-hydroxybutyric acid-co-3-hydroxyvaleric acid) (PHBV) microsphere for localized controlled drug release. The drug release from PLGA was observed slower in comparison to PHBV microsphere. The drug was found to be effective in treatment of orthopedic diseases. (Chiming Yang et al.,2009)

- **Colonic drug delivery:** Colonic drug delivery performed to improve bioavailability and providing therapeutic amount of drug with proper concentration at the desired site of action for the effective management of inflammatory bowel disease, crohns disease, ulcerative colitis and many more diseases by avoiding the wastage of drug in stomach. Formulation of microsphere of ketoprofen, which complexes with hydroxypropyl-β-cyclodextrin (HPβCyd) and chitosan. This complex improves solubility, drug release and drug permeation. All these factors contribute in the development of safe and power full drug delivery system for the site specific colon targeting. (F.Maestrelli et al.,2008)
  Example: Microspheres of measlamine was prepared following factorial design. Eudragit S-100 used as a coating material. Microsphere of 0.45µ was obtained, where drug releases by diffusion process. (Jain Vikas et al., 2011)

CHARACTERIZATION AND EVALUATION OF MICROSPHERES:

1. **Particle size and shape:** particle size visualization by conventional method is done by using light microscopy and scanning electron microscopy (SEM). Both the techniques helpful in determination of morphological shape and outer structure of microsphere. The sample were coated with Au/Pd using a vacuum evaporator and examined using a SEM at accelerated voltage of 20kV.

2. **Fourier transforms infrared spectroscopy:** FTIR study help in determining IR spectra of pure drug and excipient that were conducted on IR spectroscopy (Perkin Elmer). The sample were taken with KBr and then compressed into tablet. The drug KBr pellet were analyzed that will provide spectra (Kaurav Hemlata et al.,2012)

3. **Determination of Percentage yield:** The prepared microparticles firstly dried, then collect and weighed accurately. The actual weight of microparticles were divided by the total amount of all component which were used for the formulation of solid lipid microparticles (J.Josephine et al., 2011)

$$\text{Percentage yield} = \frac{\text{Mass of obtained microspheres X 100}}{\text{Mass of drug + Initial mass of polymer}}$$

4. **Drug loading:** Drug content of microspheres were determined on assayed spectrometrically (UV-1800 SHIMADZU) at the λmax of drug. Each formulation was filtered and analyzed then drug loading was determined by using formula (Kumavat Suresh et al.,2013).

$$\text{Drug loading} = \frac{\text{Mass of drug in microspheres X 100}}{\text{Mass of Microspheres}}$$

5. **Solubility measurement:** Solubility measurements of microparticles were performed in simulated gastric fluid. The samples were magnetically stirred for 72h, the suspensions were filtered several times through 0.45µm membrane filter and filtrates were analyzed spectrophotometrically at λmax.

6. ***In-vitro* release study:** Dissolution test was done to determine the *in-vitro* drug release from a drug delivery system (dosages form). To perform the dissolution test USP type 2 [Paddle type, SHIMADZU UV-1800] apparatus was used that contains 900 ml of phosphate buffer (pH 7.4),0.1N HCl (pH 1.2) dissolution medium with stirring speed 100rpm and at temperature 37±5°C, the sink condition is maintain. The stirring must be constant and drug release start. The 5ml aliquots were withdrawn periodically and this replace with the same amount of fresh dissolution medium. The sample were analyzed spectrophotometrically (UV-1800 SHIMADZU) at the λmax of drug. The dissolution studies were carried out three times and the mean values were plotted as percentage cumulative release versus time (Atrey S. Joshi et al.,2013)

CONCLUSION: Microspheres are the promising drug delivery system for the sustained or controlled release doses forms. Microspheres used to target various sites like colon, pulmonary, vaginal, ocular, nasal and also found effective in management of Alzheimer's, parkinsonism and cancer like life threatening diseases. Microspheres shows high drug load with maximum therapeutic effect. Microspheres can prepare by using various method at the reasonable cost.

Discussion: The present review is based on the advancement of microspheres in the field of pharmaceutics that includes various parameters and techniques which have glorious research in future here we compare various technique with each other and studded its application in treating life threatening diseases by the mechanism of target delivery .

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