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Review on Microparticulate Drug Delivery System

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Abstract: The controlled release of drugs in slow and sustained manner is one of the major challenges in drug delivery system. Targeting of drug to the particular site is an important aspect of drug delivery system. Microparticles were initially developed as carrier for vaccines & anticancer drugs. They have now been used to increase the efficiency of drug delivery system & improve release profile & for drug targeting. Microparticles have been proven to be useful in this manner for the delivery of various active pharmaceutical ingredients. The current aim of this review is to study various aspects of the microparticulate drug delivery system including method of formulation, evaluation & characterization.

Key words: microparticles, emulsion, centrifugation, evaluation, characterization.

INTRODUCTION:

Microparticulate drug delivery system is one of the processes to provide the sustained & controlled delivery of drug to long periods of time. They are small particles of solids or small droplets of liquids surrounded by walls of natural & synthetic polymer films of varying thickness & degree of permeability acting as a release rate controlling substance & have a diameter upto the range of 0.1µm-200µm [1].

Initially use of albumin microspheres in drug delivery system was suggested by Kramer in 1974. In 1997, Java Krishna & Catha proposed the use of microspheres as sustained release vehicles. There are also reports about using heamoglobin as natural biodegradable carriers for drugs for microparticulate administration [2]. Microparticles have been proved to be an ideal way of preparing sustained & controlled release dosage forms. They are also a beneficial way of delivering APIs which are pharmacologically active but are difficult to deliver due to limited solubility in water. In such drugs the attainment of high Cmax, Tmax, and Area under the curve is problematic. Thus a need exists for immediate release products containing these agents [3]. Microsphere-based formulations can be formulated to provide a constant drug concentration in the blood or to target drugs to specific cells or organs [4,5].

ADVANTAGES OF MICROPARTICLES :

Recently, controlled release has become a very useful tool in pharmaceutical area, offering a wide range of actual and perceived advantages to the chronic diseases such as rheumatoid arthritis, osteoarthritis, and musculoskeletal disorders including degenerative joint conditions still demand long-term therapy. With the advent of microparticles following advantages were noted in the dosage forms-

(1) Effective delivery of agents which re insoluble or sparingly soluble in water.
(2) They give the products which exhibit immediate release properties & can give 80% or more of

active agent in about 10 minutes or less. Ex. Nimesulide

(3) The technique provides the way for improving taste of an active agent.
(4) They increased the relative bioavailability of drugs.
(5) The formulation of microparticles also provides the method of targeting the drug delivery to specific sites.
(6) The microparticles hold great potential in reducing the dosage frequency & toxicity of various drugs.
(7) Microparticles in the form of microcapsules can also be used as carrier for drugs & vaccines as diagnostic agents & in surgical procedures.
(8) They can also be used to produce amorphous drugs with desirable physical properties.
(9) They also caused the reduction of the local side effects ex. GI irritation etc of drugs on oral ingestion.
(10) They provide the sustained release formulation with lower dose of drug to maintain plasma concentration & improved patient compliance.
(11) The PH triggered microparticles are used in immunization, transfection & gene therapy.
(12) Parentral microparticles have the advantage of administering high concentration of water soluble drugs without severe osmotic effects at the site of administration.
(13) They also have an advantage of being stored in dry particle or suspension form with little or no loss of activity over an extended storage period.
(14) They are useful in administration of effervescent dosage form of medicaments to individual unable to chew. Ex. Debilitated patients having difficulty in swallowing solids & the elderly.
(15) In contrast, smaller microparticles need to be prepared for application to other sites such as the eye, lung, and joints [14].

POLYMER & OTHER SUBSTANCES USED IN MICROPARTICLE PREPARATION:

Wall Materials- The coating material can be selected from a wide variety of natural and synthetic polymers depending on the core material to be encapsulated and the desired characteristics. The amount of coating material used ranges from 3% to 30% of the total weight, which corresponds to a dry film thickness of less than 1–200 μm, depending on the surface to be coated.

1. **Natural or synthetic hydrophilic colloids** are large molecules that are soluble or dispersible in aqueous solutions.

- Some examples of natural and synthetic hydrophilic colloids [21,25,44] are agar acrylic polymers, polyacrylic acid, poly acryl methacrylate, gelatin, poly(lactic acid), pectin(poly glycolic acid), waxes(poly hydroxyl butyrate-co-valerate), cellulose derivatives, cellulose acetate phthalate, Nitrate, Ethyl cellulose, Hydroxy ethyl cellulose, Hydroxypropylcellulose, Hydroxy propyl methyl cellulose, Hydroxypropylmethylcellulose phthalate, Methyl cellulose, Sodium carboxymethylcellulose, Poly(ortho esters) ,Polyurethanes, Poly(ethylene glycol), Poly(ethylene vinyl acetate), Polydimethylsiloxane, Poly(vinyl acetate phthalate), Polyvinyl alcohol, Polyvinyl pyrrollidone, shellac.
- Here the capsule wall presents a good barrier to oily and hydrophobic materials, but it is usually a poor barrier to hydrophilic substances. Hydrophobic colloids are realized in encapsulating water-soluble drugs.
- Soluble starch & its derivatives including Amylodextrin, Amylopectin & Carboxy methyl starch is used as wall forming material in solid microsphere preparation.

2. **Biocompatible polymer** used includes poly (lactic) acid (PLA), poly (glycolic acid) (PLGA). PLGA is a water-insoluble polymer; strength, hydrophobicity, and pliability are the significant physical advantages [6]. As a polymeric vehicle, biocompability, biodegradability, predictability of degradation, ease of fabrication, and regulatory approval are features that make PLGA desirable for medical applications [7-10]. Natural polymers Albumin Chitin Starch, Collagen Chitosan Dextrin, Gelatin, Hyaluronic acid, Dextran, Fibrinogen, Alginic acid ,Casein, Fibrin, Poly(ortho esters). Polyalkylcyanoacrylate, Polyanhydrides. A list of polymers is given in **table 1.**

- The bioavailability enhancers used are lysophatide, lysophosphatidyl choline.
- Permeability modifier & membrane fluidity modifier used include enamines like phenyl alanine enamine. Malonates like diethylene ox methylene malonate, salicylates, bile salts, fusidates etc.

TECHNIQUES OF MICROPARTICLE PREPERATION: When preparing controlled release microspheres, the choice of the optimal method has utmost importance for the efficient entrapment of the active substance. Various pharmaceutically acceptable techniques for the preparation of microparticles have been given. Some of the methods include:

1. Emulsion–solvent evaporation (o/w, w/o, w/o/w).
2. Phase separation (nonsolvent addition and solvent partitioning).
3. Interfacial polymerization.
4. Spray drying.
5. Emulsion extraction process.
6. Jet milling technique.
7. Fluidization & solvent precipitation method.

(1)Emulsion-solvent evaporation- The solvent evaporation method involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The schematic representation is given in F**ig. 1.**

Table 1 – list of polymers used for microparticle formation

Coating material	Solvent for coating material	Phasing out solvent (non-solvent)
Acrylonitrite styrene	Methyl ethyl ketone	Polybutadiene
Benzyl cellulose	Trichloroethylene	Propanol
Cellulose nitrate	Methyl ethyl ketone	Polybutadiene
Epoxy resin	Toluene	Polybutadiene
Ethyl cellulose	Methyl ethyl ketone	Polydimethyl siloxane
Natural rubber	Benzene	Methanol
Polyethylene	Xylene	Ethanol
Polymethyl methacrylate	Benzene	Polybutadiene siloxane
Polystyrene	Xylene	Petroleum ether
Polyvinyl acetate	Chloroform	Isopropanol
Polyvinyl formaldehyde	Nitropropane	Polybutadiene
Styrene maleic acid	Ethanol	Isopropyl ether
Vinyl diene chloride acrylonitrile	Methylethyl ketone	Polybutadiene

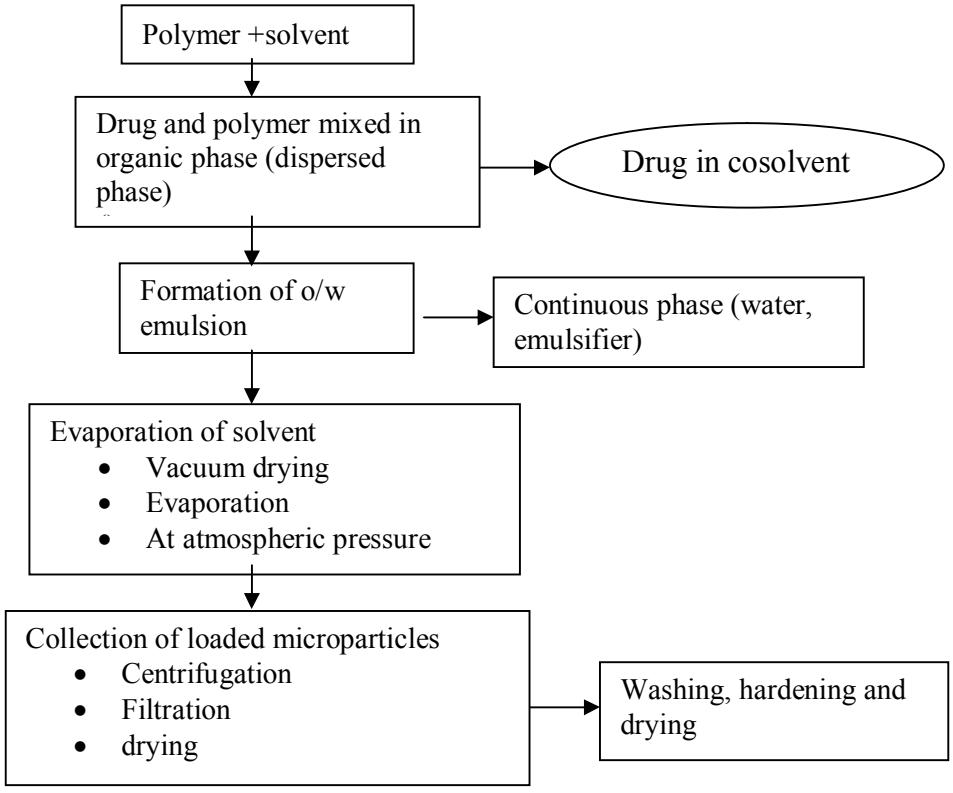

Figure-1 Schematic representation of the preparation of microspheres by o/w emulsification/ solvent evaporation technique

The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is realized under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric microparticles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation, or lyophilization [5].

Single-Emulsion Solvent Evaporation

1—O/W Emulsion Solvent Evaporation Technique - For emulsion solvent evaporation, there are basically two systems from which to choose: oil-in-water (o/w) or water-in-oil (w/o). Oil-in- water emulsion was [11, 12] to encapsulate progesterone. Afterward lipid-soluble drugs such as steroids [13], local anesthetics [14, 15], bleomycin sulfate [16], doxorubicin [17], chlorpromazine [18], naltrexone, promethazine [19], were encapsulated successfully.

In general, solvent evaporation method is particularly suitable for the microencapsulation of lipophilic drugs that can be either dispersed or dissolved in the dispersed phase of a volatile solvent. Sansdrap and Moes [20] suggested that in order to obtain batches of microspheres with reproducible sizes, manufacturing factors such as emulsifier concentration, stirring rate, and organic phase volume should be under control.

2—Oil-in-Oil Emulsification–Solvent Evaporation Technique - Oil-in-oil (sometimes referred as water-in-oil) emulsification process was developed for the encapsulation of highly water soluble drugs. In this technique, polymer and drug, contained in a polar solvent such as acetonitrile, are emulsified into an immiscible lipophilic phase, with light mineral oil commonly being used, in the presence of an oil-soluble surfactant such as Span. However, an important drawback of using an oil external phase is cleaning up the final product. The oil has to be removed using organic solvents such as *n*-hexane [21]. Diphenylhydramine hydrochloride [22], mitomycin C [23], adriamycin [24], cephradine and cefadroxil [25], phenobarbitone [26], and timolol maleate [27] are some examples of drugs that have been encapsulated by this procedure.

B— Multiple-Emulsion Technique (w/o/w) - Multiple-emulsion or double-emulsion technique is appropriate for the efficient incorporation of water-soluble peptides, proteins, and other macromolecules [28, 29-34]. This method allows the encapsulation of water-soluble drugs with an external aqueous phase when compared to nonaqueous methods as the o/o solvent evaporation or organic phase separation. In brief, the polymers are dissolved in an organic solvent and emulsified into an aqueous drug solution to form a w/o emulsion [35]. This primary emulsion is reemulsified into an aqueous solution containing an emulsifier to produce multiple w/o/w dispersion. The organic phase acts as a barrier between the two aqueous compartments, preventing the diffusion of the active material toward the external aqueous phase. Microspheres manufactured by the (w/o/w method exhibit various morphologies such as porous or nonporous external polymer shell layers [36, 37] enclosing hollow, macro porous, or micro porous internal structures, depending on different parameters.

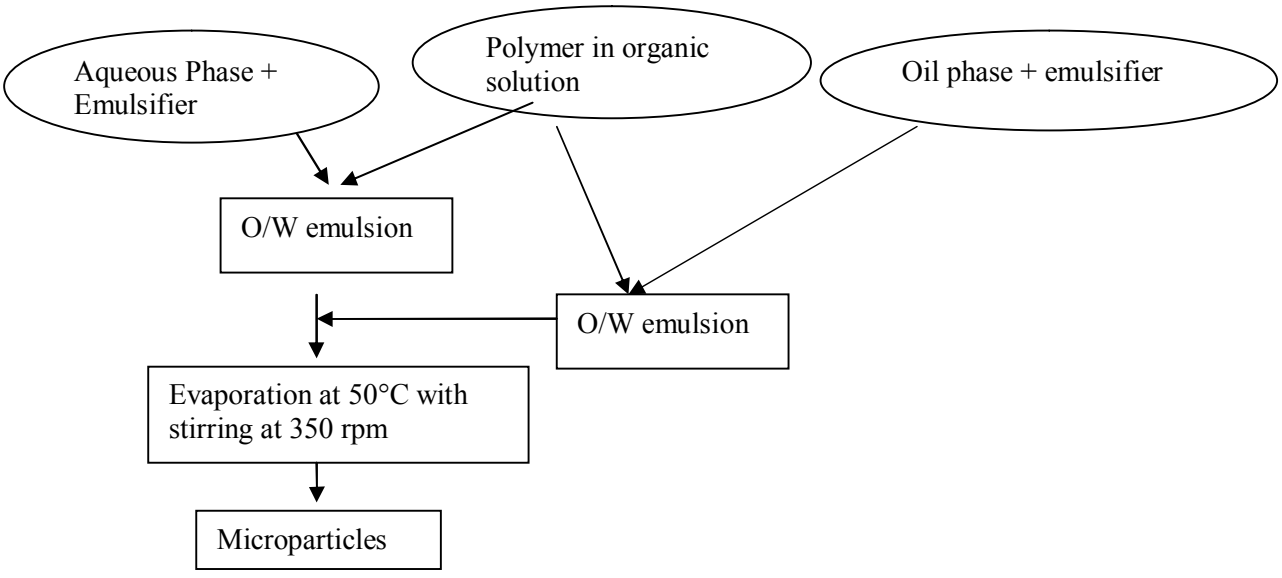

Figure 2 Schematic representation of micro particle production by liquid drying processes O/w emulsion method, o/o system method

Coacervation/Phase Separation: The term *coacervation* was suggested for the first time by two Dutch scientists [38]. The word *coacervation* comes from the latin *acervus*, meaning aggregation, and the prefix *co,* signifying the preceding union of the colloidal particles. In this process, both the drug and the polymer should be insoluble in water, while a water-immiscible solvent is required for the polymer. A schematic representation of o/w emulsification–solvent evaporation technique is shown in **Fig. 2**. Problems relating to the efficient incorporation of water-soluble active substances into biodegradable polymer matrices using simple o/w emulsification with solvent evaporation are originating to a great extent from the separation and/or removal of water-soluble material into the aqueous continuous phase [39-41].

Using this method microparticle can be prepared using following steps with continuous with continued agitation:

1. The 1st step consists of formation of three immiscible chemical phases. In this the core material is dispersed in solution of coating polymer, the solvent for polymer being liquid manufacturing vehicle phase.
2. The 2nd step consists of deposition of coating polymer on core material & absorption at interphase between core material & liquid vehicle phase.
3. The final step comprise of rigidising of coating by thermal, cross linking or desolvation techniques to form microparticles.

Coacervation/phase separation can be obtained by temperature change, nonsolvent or salt addition, incompatible polymer addition, and polymer–polymer interaction. Drugs belonging to different pharmacological groups have been encapsulated. Antibiotics,

Anti-inflammatory agents, analgesics, and antihypertensive are some of these groups.

Description of Coacervation/Phase Separation Methods This method is divided into two main groups: aqueous and organic. Aqueous phase separation has been subdivided by Bungenberg de Jong and Kruyt as complex and simple coacervation.

1—Simple Coacervation - Simple coacervation can be accomplished by the addition of chemical compounds with a high affinity for water, such as salts and alcohols. In principle, simple coacervation can be brought about in any aqueous polymer solution when temperature, pH, solvent, and salt are properly chosen [42, 43-55].

This process depends primarily on the degree of hydration produced. The added substances cause two phases to be formed, one rich in colloid droplets and the other poor. Its principal requirement is the creation of an insufficiency of water in a part of the total system. Figure illustrates the preparation of microcapsules by simple Coacervation [56]. The microencapsulation process can be explained by the following steps [57]:

1. Dispersion of the core material in an aqueous solution of the polymer
2. Creation of insufficiency of water for the hydrophilic colloid and the deposition of the coacervate around the core
3. Gelation of the coacervate and hardening of the microcapsules

2— Complex Coacervation - This technique of complex coacervation was first described by Phares and Sperandio [58, 59]. It involves neutralization of the charges on the colloids and depends primarily on pH. This is accomplished by mixing two colloids of opposite charges together [60, 61-63]. The encapsulation process in complex coacervation consists of four steps:

1. Preparation of a hydrophilic colloid solution
2. Addition of a second hydrophilic colloid solution of opposite charge to induce coacervation
3. Deposition around the core
4. Gelation of the coacervate and hardening of the microcapsules.

Organic Phase Separation Methods- Organic phase separation is the inverse of the aqueous phase separation process in that the wall-containing phase is hydrophobic in nature and the core material is water miscible. The principle is to enclose water-soluble material with a polymeric wall material in an organic solvent by adding a nonsolvent or a second polymeric material to induce phase separation [64]. A schematic representation is given in **Fig. 3.**

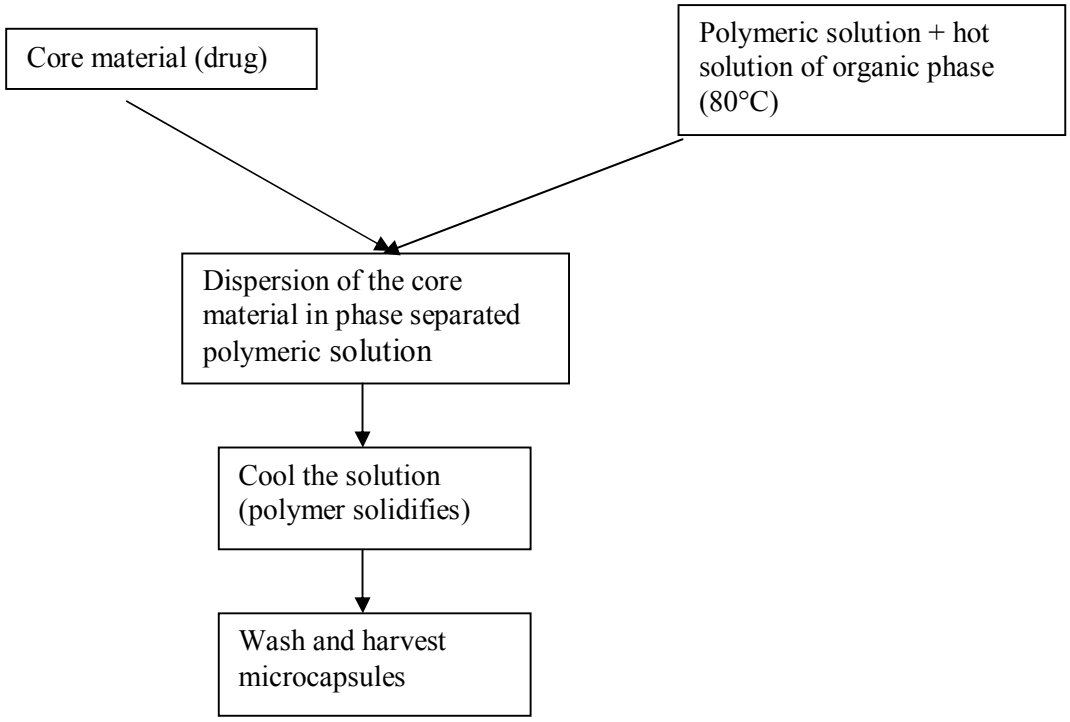

Figure 3: Flow diagram of microencapsulation by organic phase separation.

Interfacial Polymerization Method - Interfacial polymerization technique is one in which two monomers, one oil-soluble and the other water-soluble, are employed and a polymer is formed on the droplet surface. The method involve the reaction of monomeric units located at the interface existing between a core material substance & a continuous phase in which the core material is dispersed.

Spray drying - Spray drying is used to protect sensitive substances from oxidation based on the atomization of a solution by compressed air and drying across a current of warm air [65]. Microparticle formulation by spray drying is conducted by dispersing a core material in a coating solution, in which the coating substance is dissolved & in which the core material is insoluble, & then by atomizing the mixture into an air stream. The heated air causes removal of solvent from the coating solution thus causing formation of the microcapsule.

Gelatin Dispersion -This is a specific embodiment of a more general approach in which the polymer filaments or monomer subunits used in forming the microparticles are mixed with a suspension of proteins, such as agar, gelatin, or albumin . One method employs alginate plus Ca^{+2} in producing the particles. The mixture is then dispersed under conditions effective to produce desired sized particles containing the mixture components. In the case of gelatin containing particles, the mixture may be cooled during the dispersion process to produce gelled particles having a desired size. The particles are then treated under polymerization and/or cross linking conditions, preferably under conditions that do not also lead to cross linking of gelatin molecules to the polymer structure. After microparticle formation, the gelatin molecules may be removed from the structure, with such in a decondensed form, e.g., by heating the material or enzymatic digestion.

Superficial antisolvent precipitation technique - This technique is useful if the drug is insoluble in gas & gas is soluble in liquid. The drug is dissolved in polymeric solution of suitable solvent. Then the application of an antisolvent decreases the solubility of material the dissolved in solution leading to microparticle beads formation.

PH-triggered microparticle- Microparticles that are designed to release their payload when exposed to acidic conditions are provided as a vehicle for drug delivery. Any therapeutic, diagnostic or prophylactic agent may be encapsulated in a lipid-protein-sugar or polymer matrix with a PH- triggering agent to form

microparticles. Preferably the diameter of the pH triggered microparticles ranges from 50 nm to 10 micrometers. The matrix of the particles may be prepared using any known lipid (e.g., DPPC), protein (e.g., albumin), or sugar (e.g., lactose). The matrix of the particles may also be prepared using any synthetic polymers such as polyesters.

The process of formulation include providing an agent & contacting with a PH triggering agent & component selected from lipid, proteins, sugars & spray drying the resultant mixture to create microparticles.

Typically, the pH triggering agent is a chemical compound including polymers with a pKa less than 7. PH triggering agent used is poly (butyl methacrylate-co-(2-dimethyl amino ethyl) methacrylate-co-methyl methacrylate) (1:2:1) i.e. Eudragit 110.

The PH triggered microparticles release the encapsulated agent when exposed to an acidic environment such as in phagosome or endosome of a cell that has taken up particles thereby allowing for efficient delivery of agent intracellularly.

Condensed phase microparticles: They are an alternative method for storing & administration of drugs at high concentration in condensed phase with sizes ranging between 0.05-50 microns. They consists of-

- matrix of cross linked polyionic polymer filaments capable of swelling from a condensed phase to an expanded, decondensed phase or state, when the matrix is exposed to monovalent counter ions.
- small molecules entrapped in microparticle matrix, with such in its condensed phase.
- Polyvalent counter ions effective to retard the release of small molecules from the micro particles, when exposed to monovalent counter ions.

The composition is useful in delivery of vehicle for reagents is unstable on storage, or where it is desirable to introduce reagent at a selected step in reaction

The method of preparation include infusing the compound into polymer suspended in a decondensed phase typically containing 10-200millimole concentration of monovalent counter ions leading to hydration & increase in size. After compound infusion into open particle matrices, multivalent counter ion mainly Calcium ion is added to fully condense the microparticle.

This technique is used for small, water soluble drug molecules. They are having advantages that high concentration of water soluble rugs can be administered without severe osmotic effect at site of administration thus they are essentially nonosmotic until they decompose & release drug.

EVALUATION OF MICROPARTICLES- The various evaluation techniques for microparticle preparation are as follows:

1. Particle shape & size determination. It can be done by microscopy, sieve analysis, laser light scattering, coulter counter method, photon correlation spectroscopy.

- Crystallinity can be evaluated by differential scanning calorimetery analysis.
- Shape & surface morphology can be studied by freeze fracture microscopy & freezes etch electron microscopy.
- Laser diffractometer & light microscope is also used to measure the size range of the microparticles.
- Size analysis of all the batches of prepared microparticles can be carried out using a set of standard sieves ranging from 10-100 meshes. The microparticles are passed through the set of sieves and the amount retained on each sieve is weighed. The arithmetic average diameter is determined by dividing the total weight size by 100.

2. Bulk & tap density of microparticles is also evaluated. Porosity, specific area can also be evaluated by Mercury or Helium intrusion potensiometry. Flow properties of microparticles can be evaluated by determining the angle of repose by fixed funnel & free standing cone method & the compressibility index by tapped density method.

3. The Thermal Properties are detected by Differential Scanning Calorimetry, Thermo gravimetric analysis.

In Differential scanning calorimetry or **DSC** the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned.

Thermogravimetric analysis or **thermal gravimetric analysis** (**TGA**) is a type of testing that is performed on samples to determine changes in weight in relation to change in temperature. Analysis is carried out by raising the temperature gradually and plotting weight (percentage) against temperature. The temperature in many testing methods routinely reaches 1000°C or greater, but the oven is so greatly insulated that an operator would not be aware of any change in

temperature even if standing directly in front of the device. After the data are obtained, curve smoothing and other operations may be done such as to find the exact points of inflection.

4. Electrostatic interaction is detected by rheological & FTIR assays (Fourier Transform Infra red spectroscopy) using potassium bromide pellets.

5. Peptide entrapment & entrapment efficacy can be evaluated by HPLC.

6.The Drug release studies was evaluated by USP method II or dissolution test method using phosphate buffer PH 6.8 with the temperature of release medium at 37 ±0.5 & then assaying spectophotometrically.

Release kinetics to model the dissolution profile from the microparticles system two different mathematical differential equation can be used i.e., (1) first order equation; (2) Higuchi's square root of time equation.

(1) First order model can be expressed as

$M_t / M_\infty = 1- e^{-} k_1^t$

(2) Higuchi's square root of time model is given by

$M_t / M_\infty = k_H t^{1/2}$

Where M_t is the amount of drug released at time t, M_∞ is the maximal amount of drug released at infinite time, k_1 and k_H are the rate constants for first order and Higuchi model, respectively.

Stability studies were evaluated to find out stable product under storage. Micro particles can be stored in Blass bottles at elevated temperature i.e. 4±1ºC freezing temperature, 25±1ºC room temperature, & 50±1ºC hot temperature for a period of 30 days & observed for change in drug content & morphology.

Applications of microparticles

1. Application areas of microcapsules include pharmaceutical and biotechnology products, cosmetics, diagnostic aids, biological filtration devices, veterinary and zoo technical products, foods and food additives, flavors, fragrances, detergents, paints, agricultural chemicals, adhesives, industrial chemicals, household products, packaging, textiles, photographic and graphic arts materials.
2. These microcapsules are important in providing sustained and controlled release, improving drug stability, reducing vaporization of volatile oils, protecting moisture/light/oxidation–sensitive drugs, masking unpleasant taste and odor, converting liquids to powders, and separating incompatible substances within a single system.
3. Amoxicillin, ampicillin, bacampicillin, cephalexin, cephradine, chloramphenicol, clarithromycin, eryithromycin, potassium pheneticillin, ofloxacin, and ciprofloxacin are some examples of the encapsulated antibiotics [66, 67, 68, 69, 70].
4. Anti-inflammatory drugs are another group in which microencapsulation is employed. Diclofenac sodium, flufenamic acid, glaphenine, hydrocortisone, ibuprofen, indomethacin, naproxen, oxyphenbutasone, and prednisone are examples of encapsulated drugs in this group [71, 72, 73, 74, 75].
5. Sulfadiazine, sulfamethizole, sulfamethoxazole, sulfamerazine, and sulfisoxazole are some representatives of sulfa drugs that are encapsulated [76, 77, 78-80, 81-85, 86].
6. Furosemide, chlorothiazide, and sulfonamide were encapsulated in order to prepare sustained release formulations that would offer the advantage of avoiding short periods of peak diuresis observed with the conventional formulations [87, 88].
7. Isosorbide-5-mononitrate (IS-5-MN), dihydralazine sulfate, piretanide and propranolol HCl, captopril, nicardipin, and dipyridamole are examples of microencapsulated antihypertensives. *IS-5-MN* microcapsules were optimized and formulatedto sustain the action and to overcome the tolerance developed in conventional preparations [89, 90].
8. Vitamins A, B1, B2, B6, B12, C, D, were encapsulated [91, 92, 93, 94, 95] to provide formation of smooth- and thick-walled microcapsules largely prevented the aggregation of microcapsules and showed low dissolution rate.
9. Converting Liquids to Free-Flowing Powders Citrus essential oil, cod liver oil, benzaldehyde, carbon tetrachloride, and oil droplets were coated and recovered as fine powders [96, 97, 98]. The authors have stated that the bulk droplet size of the encapsulated material appeared to be a factor in the strong capsule wall, which protects against vaporization and oxidation.
10. Air filled micro particles are used in echocardiography & other ultrasonic imaging techniques. They are also used as opacifier or reflectivity enhancers in cosmetics.

11. Solid microspheres are of particulars used in nasal delivery of drugs including polypeptides, insulin, somatostain, metolopromide etc.
12. PH triggered micro particles have been used to deliver drugs by various means ex-by IV inject, intra dermal inj, rectally, orally, intra vaginally, inhalationally, mursoual delivery etc.
13. They are also used for administering. An antigenic epitote of a pathogen or a tumor.
14. The micro particles are useful in transficting cells & gene therapy.
15. Condensed phase micro particles are used as stable strong kit for enzymes, antibodies, dye.

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