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A REVIEW ON MICROSPHERE

K. S. Lavhate*, Prof. K. J. Kore and Prof. R. V. Shete

Department of Pharmaceutics, Rajgad Dnyanpeeth's College of Pharmacy Bhor, Pune, Maharashtra, India.

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***Corresponding Author**
K. S. Lavhate
Department of Pharmaceutics, Rajgad Dnyanpeeth's College of Pharmacy Bhor, Pune, Maharashtra, India.

ABSTRACT

Microsphere are characteristically free flowing powder consisting of proteins or synthetic polymer having particle size ranging from 1µm-1000 µm. This is a carrier technology achieved by incorporating therapeutic agent into biodegradable polymer or proteins. Microsphere are multiparticulate drug delivery system have a wide range of applications because of controlled and sustained release, it's reduced toxicity/ side effect and enhance efficacy of drug toward a targeted site. Oral modified- release multiple-unit dosage form have always been more effective than conventional dosage form. The targeted drug delivery system attempting concentration of drug in tissue of interest or reducing the relative concentration of drug in the remaining other tissue. So that in future microsphere will find the central place in novel drug delivery system, particularly in diseased cell sorting, diagnostic, safe, gene and genetic material. The present review gives focus on type of microsphere, material used, method of preparation or evaluation of microsphere.

KEYWORDS: Microsphere, controlled release, novel drug delivery, type of microsphere, method of preparations, application.

INTRODUCTION

Microsphere are a small spherical particle solid in nature size ranging from 1µm-1000µm. microsphere are free flowing consisting of proteins or synthetic polymers which are biodegradable in nature.

Microsphere are multiparticulate drug delivery system which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the

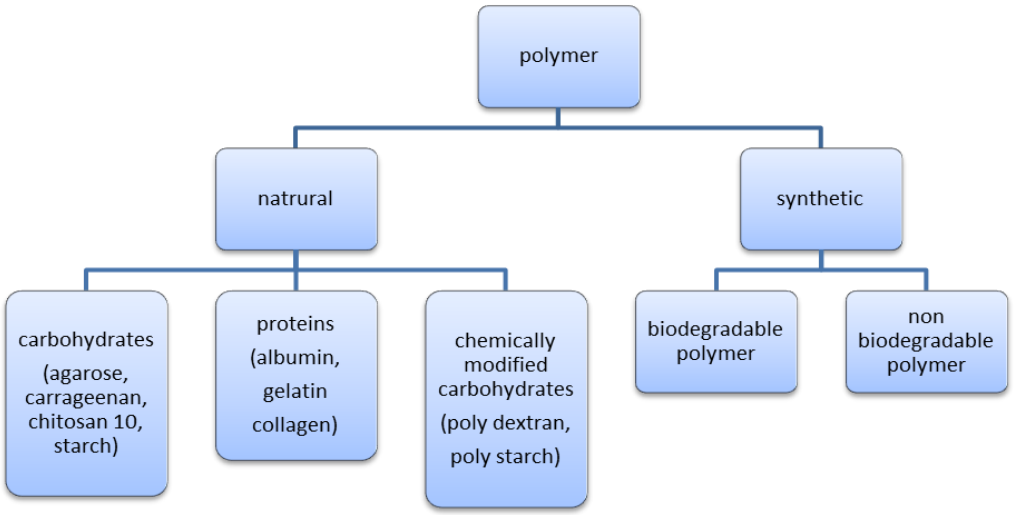
drug to specific site at a predetermined rate. To obtained maximum therapeutic efficacy, it's most important to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing less toxicity and minimal side effects. For the sustained release or controlled drug delivery system microsphere using as a carrier for a drug its releases drug at a targeted site and shows action. Each particle is a basically a mixture of a drug or polymer. Drug is dispersed in a polymer from with drug release occurs by 1st order process & Drug release in controlled by dissolution/degradation of matrix its influence by size and shape, microsphere offer a ball-bearing effect. Microsphere is small in size so that microsphere provide a larger surface area and possess an easier estimation of diffusion and mass transfer behavior.[1]

Microsphere are defined as a "monolithic sphere or therapeutic agent distributed throughout the matrix either as molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymer in which drug particle are dispersed at the molecular or macroscopic level. Microsphere can be made up of various natural and synthetic materials. Glass microsphere, polymer microspheres and ceramic microsphere are commercially available. Polymer microsphere having a two main type polyethylene and polystyrene microspheres. Polystyrene microsphere are typically used in cell sorting and immune precipitation so this are used in biomedical application. Polystyrene also used in a medical research and biological laboratory experiments because of proteins and ligands adsorb onto polystyrene readily and permanently so the polystyrene becomes stable for this use. Polyethylene used as temporary and permanent filler. High sphericity of polyethylene makes them highly desirable for fluid flow analysis and flow visualization, health sciences, microscopy techniques, process troubleshooting and numerous research applications.[2] microsphere for the oral use have been employed to sustain the drug release and to reduce irritation in gastrointestinal tract. Multiparticulate drug delivery system spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduce local irritation when compare with single-unit dosage form. Due to the small particle size the particles are widely distributed throughout the gastrointestinal tract which reduce side effect due to localized build-up of irritating drugs against the gastrointestinal mucosaor improve absorption of the drug.

Material used[3]

Microsphere containing usually as polymer. They are two type of polymer.

1. Natural polymer
2. Synthetic polymer



- Natural polymers obtained from different sources like carbohydrates, proteins, chemically modified carbohydrates.
- Synthetic polymer-

Synthetic polymer classified into two type

1. Biodegradable – biodegradable carriers which degrade into body to non-toxic degradation products do not pose the problem of carrier toxicity and are more suited for parenteral application.

eg. Lactides, glycolides & their co polymers poly alkyl cyano acrylates, poly anhydrides.

2. Non-biodegradable- non biodegradable drug carrier, when administered parenteraly, it may causes toxicity because drug remaining in the body after the drug is completely released.

eg. Poly methyl methacrylate (PMMA) Acrolein Glycidyl methacrylate Epoxy polymers.

CLASSIFICATION

There are different types of Microspheres.

1. Glass microspheres

- Hollow glass microspheres
- Solid glass microspheres

2. Polymer microspheres

- Polyethylene microspheres

- Polystyrene microspheres
- Fluorescent microspheres

3. Starch microspheres

- Cross-linked starch microspheres

4. Ceramic microspheres
5. Albumin microspheres
6. Gelatin microspheres
7. Dextran microspheres
8. Polylactide and polyglycolide microspheres
9. Poly anhydride microspheres
10. Poly phosphate microspheres
11. Chitosan microspheres
12. Lipid cross linked chitosan microspheres
13. Carrageenan microspheres
14. Alginate microspheres
15. Poly (alkyl cynoacrylate) microspheres
16. Poly acrolein microspheres

Advantages,[5.6]

1. Microsphere provide prolong and constant therapeutic effect.
2. Microsphere is Reliable 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 untoward effects.
3. Microsphere Provide constant drug concentration in blood there by increasing patient compliance.
4. The size, surface hydrophilicity and surface charge of microspheres have been found to be important in determining the fate of particles in *vivo*.
5. Microsphere Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
6. Convert liquid to solid form & to mask the bitter taste and studies on the macrophage uptake of microsphere have demonstrated their potential in targeting drug to pathogens residing intracellularly.

7. Controlled release delivery biodegradable microspheres are used to control drug release rates there by decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitation[5,6]

1. The fate of polymer matrix and its effect on the environment.
2. Process conditions like change in temperature, pH, solvent addition, and evaporation/ agitation may affect the stability of core particles to be encapsulated.
3. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may causes potential toxicity.
4. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
5. The release rate of the controlled release dosage form may vary from a variety of factors like food and the of rate of transit though gut.
6. Difference in the release rate from one dose to another.
7. Dosage form of this kind should not be crushed or chewed.

TYPE OF MICROSPHERES

1. Bio adhesive microsphere
2. Magnetic microsphere
3. Radioactive microsphere
4. Floating microsphere
5. Mucoadhesive microsphere
6. Polymeric microsphere.

Bioadhesive microsphere[7,8]

Adhesion means the sticking of the drug to the mucosal membrane such as buccal, ocular, rectal, nasal etc. by using sticking property of the water soluble polymers. The term "bioadhesion" defined that the materials bind to biological substrates such as mucosal members. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration and produce better therapeutic action. This prolonged residence can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Microspheres constitute an important part of these particulate drug delivery system by virtue of their small size and efficient carrier capacity.

Magnetic microsphere[9]

magnetic microsphere are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion but are (ferromagnetic) to be captured in micro vessels. This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by 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. The different type are Therapeutic and magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour.

i. Therapeutic Magnetic Microspheres: It is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system.
ii. Diagnostic Microspheres: It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

Radioactive microsphere[10]

Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. The therapy of tumors using radiolabeled antibodies, i.e. radioimmunotherapy, or radiolabeled peptides, has been nicely described by Wilder and Papatheofanis.

General properties of radioactive microspheres

The sub group of microspheres that is radioactive behaves and is generally used in a similar fashion to non-radioactive microspheres. But in addition to the matrix substance, which defines the microsphere and gives it its targeting properties in a desired tissue or organ, the radioactive microsphere also contains one or more radionuclide(s) that are intimately bound to it.

It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

Alpha-emitters: Alpha particles are positively charged ions consisting of two protons and two neutrons, emitted during the radioactive decay of many nuclei with high atomic numbers. During decay, energy is released mainly as the kinetic energy of the α-particles. Since the path length of an α-particle with an energy of 5 to 8 MeV is on the order of 40 to 80 Φm, the effective treatment radius is limited to several cell diameters from the atom that emits the particle, and nonspecific irradiation of distant tissues is eliminated.

Beta-emitters: In 1896, Henri Becquerel discovered β-decay, which is the commonly used name for β- - or negatrondecay. During β-decay, a neutron in the unstable nucleus is transformed into a proton, an electron and a neutrino, which is an uncharged particle with undetectable small mass. Additionally free energy is produced and released in the form of kinetic energy and given to the electron and the neutrino.

Gamma-emitters: A large group of radioisotopes emits γ-rays during decay. Gamma rays represent excess energy that is given off as the unstable nucleus breaks up and decays in its efforts to reach a stable form. The energy is emitted in the form of electromagnetic radiation (photons), with a radioisotope-characteristic photon energy typically expressed in kiloelectron volts (keV).

Floating microsphere[11]

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. Most of the floating systems reported in literature are single-unit systems, which are generally unreliable and non-reproducible in prolonging the GRT, in virtue of their unpredictable all-or-nothing emptying process. On the other hand, multiple-unit dosage forms appear to be better suited, since they claim to reduce inter-subject variability in absorption and have a lower dose-dumping probability (Singh, Kwon, 2000). The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave way to the development of gastroretentive floating microspheres.

Gastric emptying is a complex process, one that is highly variable and that makes in vivo performance of drug delivery systems uncertain. A controlled drug delivery system with prolonged residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. The main limitations are attributed to the inter- and intra-subject variability of gastrointestinal (GI) transit time and to the non-

uniformity of drug absorption throughout the alimentary canal. Floating or hydrodynamically controlled drug delivery systems are useful in such applications. Various gastroretentive dosage forms are available, including tablets, capsules, pills, laminated films, floating microspheres, granules and powders. Floating microspheres have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation. Such systems have more advantages over the single-unit dosage forms.

Mucoadhesive microsphere[7,12]

The term "mucoadhesion" define the adhesion of the polymers with the surface of the mucosal layer. Mucoadhesive microspheres provide better drug absorption as they get adhere to the mucosal surface and release drug for prolonged time. Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, *e.g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much moreintimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc.

The drugs are loaded in the microspheres principally using two methods i.e. during the preparation of the microsphere or after the preparation of the microsphere by incubating them with the drug solution.

Drug release kinetics - Release of drug is an important consideration in case of microspheres. Many theoretically possible mechanisms for the release of drug from the microsphere may be as follows:

- Liberation of the drug due to polymer erosion or degradation.
- Self diffusion of drug through the pore of the microspheres.
- Release of the drug from the surface of the polymer.
- Pulsed delivery initiated by the application of an oscillating or sonic field.

Polymeric microsphere[13]

The use of polymeric microsphere systems (including polypeptides) as vehicles for delivering drugs by a variety of routes is considered with particular reference to parenteral

administration. The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

Biodegradable polymer: Biodegradable microspheres can be prepared from certain synthetic as well as natural polymers. An important requirement of such polymers is that the degradation products should be non-toxic because such products eventually enter circulation or result in tissue deposition. Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also Bioadhesive in nature.

Natural polymer such as proteins and polysaccharides undergo enzymatic degradation in the body. Most synthetic biodegradable polymers contain hydrolysable linkages like amide, esters, ureas and urethanes. Polypeptides undergo enzymatic degradation while synthetic polyesters such as poly(lactic acid) and poly(glycolic acid) degrade by simple hydrolysis.

Synthetic polymeric microspheres

Synthetic polymeric microspheres find application in a wide range of medical applications. Among other applications, microspheres are being used as bulking agents, embolic- or drug-delivery particles. The number of medical applications for synthetic biomaterials continues to expand. One particularly interesting development concerns the use of injectable polymeric biomaterials. The forms in which the biomaterials are injected can vary from particulate matter, e.g., microspheres or irregularly shaped particles, to gels and cements that are injected in liquid form and which harden inside the body. but there is some disadvantage because of the migration of the drug from the site of administration that causes the embolism and further organ damage.

CRITERIA METHOD OF PREPARATION[14,15]

Different method used for various microspheres preparation depend on particle size, route of administration , duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, co-precipitation. Certain criteria is given below for the preparation of the microsphere

1. The ability to incorporate reasonably high concentration of drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability and

6. Susceptibility to chemical modification.

METHOD OF PREPARATION

1. Polymerization techniques
2. Spray drying and spray congealing
3. Single emulsion techniques
4. Double emulsion techniques
5. Emulsion solvent evaporation techniques
6. Phase separation coacervation techniques
7. Quassi emulsion solvent diffusion
8. wax coating and hot melt
9. Ionic gelation method
10. Hydroxyl appetite (HAP) microsphere in sphere morphology

1. Polymerization technique[15]

There are two type of preparation of microsphere by Polymerization technique

a. Normal polymerization
b. Interfacial polymerization

Normal polymerization

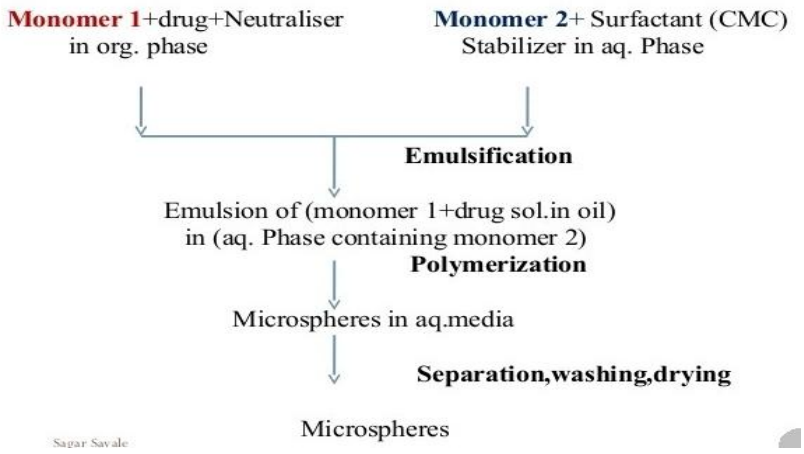
It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk polymerization, a monomer or a mixture of number of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Suspension polymerization also referred as bead or pearl polymerization. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. 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 and other additives. Bulk polymerization has an advantage of formation of pure polymers. Drug loading may be done during the process of polymerization.

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. In this

technique two reacting monomers are employed; one is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet.

Eg.



Spray drying and spray congealing[1,16,17,18,19]

The advantage of the spray drying and spray congealing are feasibility of the operation. These methods are based on the drying of the mist of the polymer and drug in the air. Concept of spray drying technique depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray congealing. Both processes are similar, except for energy flow. 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 the formation of the microspheres in a size range 1-100 µm. Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. Spray drying is the most widely used industrial process involving particle formation and drying. Therefore, spray drying is an ideal process where the end product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and particle shape.

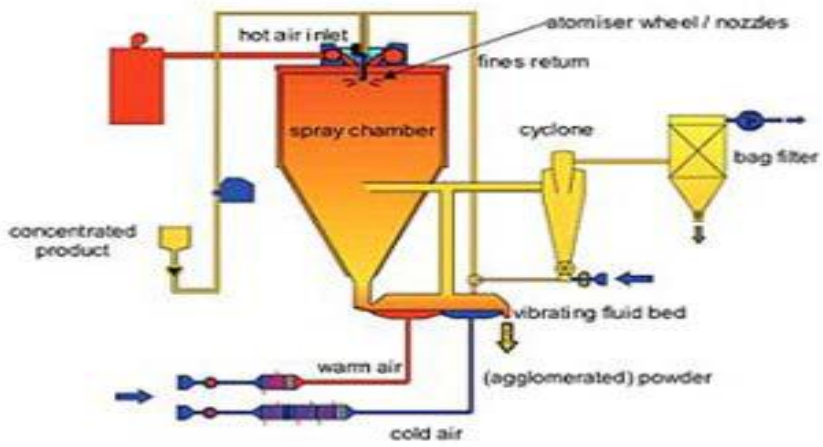


Figure 1: Spray drying method for preparation of microspheres.

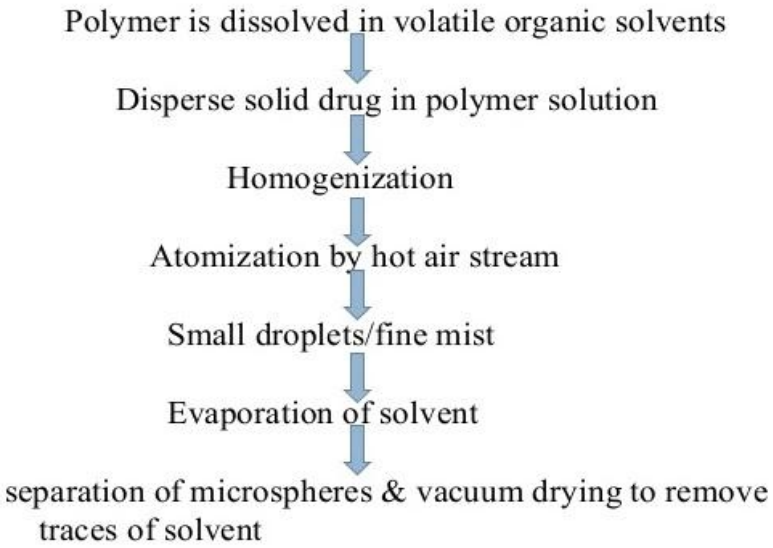
Principle: Three steps involved in spray drying

a.) Atomization: of a liquid feed change into fine droplets.

b.) Mixing: it involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.

c.) Dry: Dried powder is separated from the gas stream and collected.

This technique is very useful to encapsulate various penicillins.

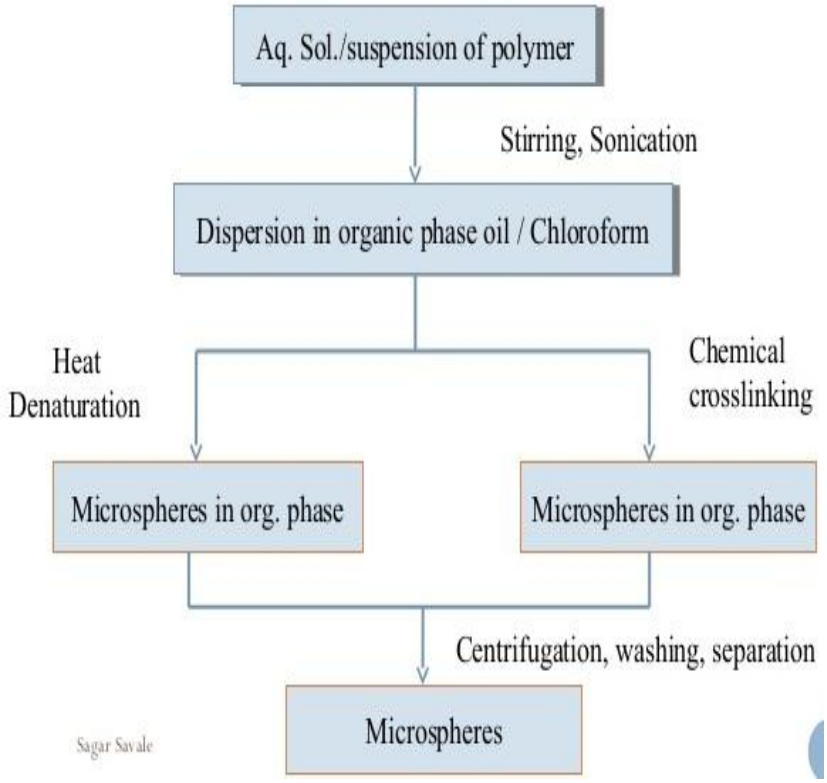


3. Single emulsion technique.[20,21]

The micro particulate carriers of natural polymers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. That is the first step in Next step cross linking is carried out by two methods.

(1) Cross linking by heat.

(2) Chemical cross linking agents.



(1) Cross linking by heat: by adding the dispersion into heated oil, but it is unsuitable for the thermolabile drugs.

(2) Chemical cross linking agents: - by using agents i.e. formaldehyde, di acid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) by adding to Liquid paraffin containing a surfactant resulting formation of w/o emulsion. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25% solution as a cross linking agent. The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, loading, drug release, and bio performance of the final multiparticulate product.

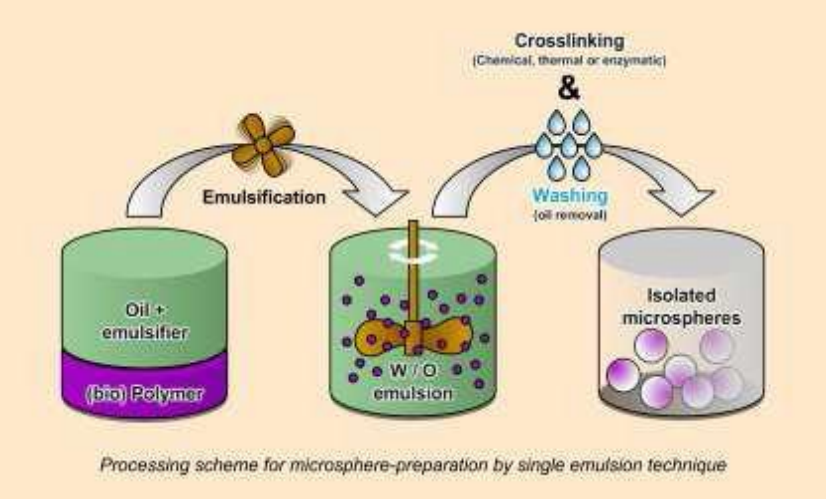
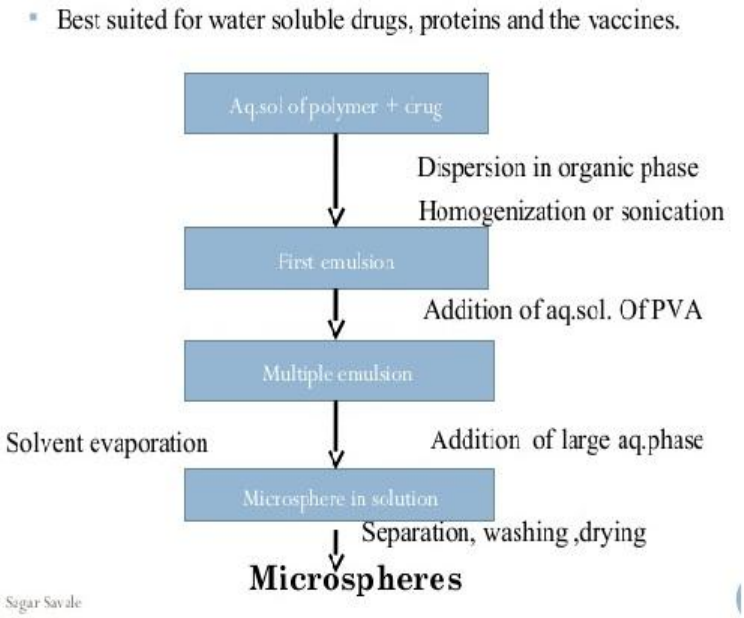


Fig. 2: Microspheres by Single Emulsion Technique.[3]

4. Double emulsion technique[3,20,22]

It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put at constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under vacuum. It is best suited to water soluble drugs, peptides, proteins and the vaccines.



Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase homogenization/vigorous i.e. formation of

first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) i.e. multiple emulsion formed now by addition to large aqueous phase denaturation/hardening after this separation, washings' and drying and collection of microspheres. genistein chitosan microsphere were prepared by the o/w/o multiple emulsion method by Wu and Li (2002).

Under optimized condition discrete microspheres were formed during this phase.

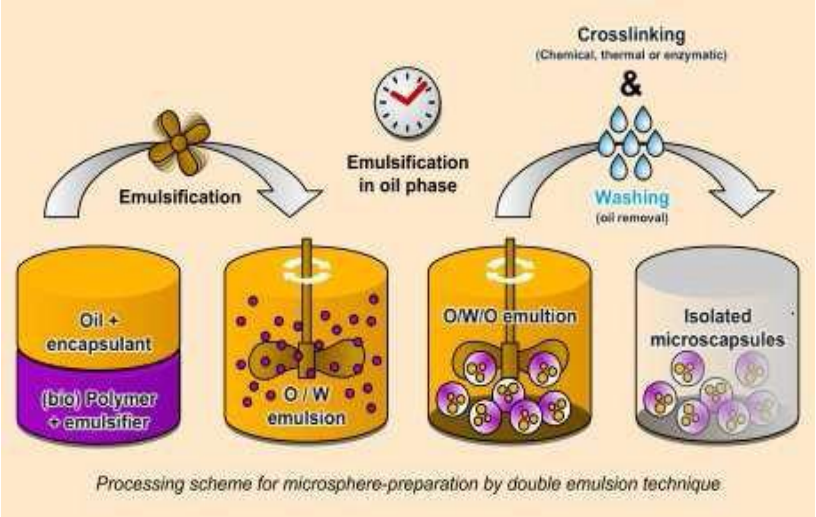
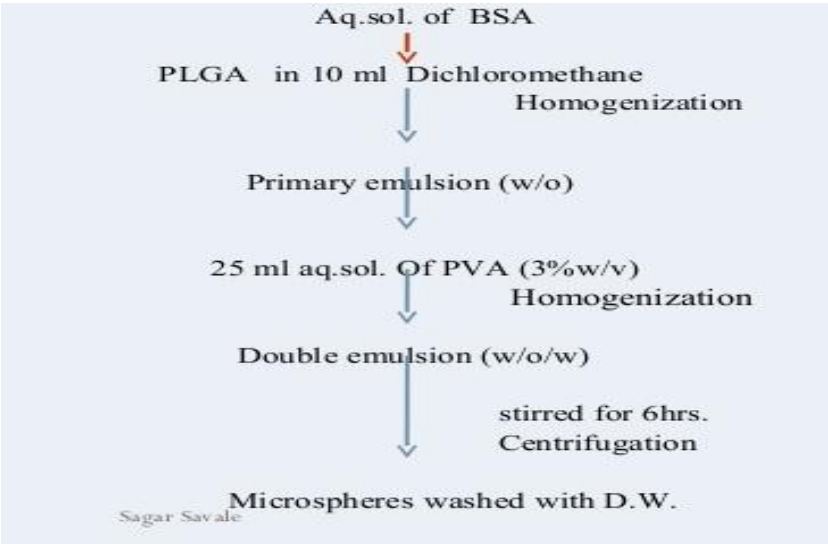


Fig. 3: Microspheres by Double Emulsion Technique.

For example preparation of BSA loaded PLGA polymer



5. Solvent evaporation techniques

In this technique the volatile solvent is used in a coating material. The microsphere coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. After the agitation the core material mixture is dispersed in the liquid

manufacturing vehicle phase. Then the appropriate size microcapsules are obtained. Then the mixture get heated if necessary to evaporate the solvent for the polymer of the core material is dispersed in the polymer solution, then the polymer shrinks around the core. This is a matrix- type microsphere formation.

The core material is may be either water soluble or water insoluble. This process involves the formation of an emulsion between polymer solution and immiscible continuous phase. The continuous phase whether aqueous (o/w) or non-aqueous.

6. Phase separation Cocervation method[1,15]

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. It is the simple separation of a micromolecular solution into two immiscible liquid phase. In this process, the polymer is solubilized to for a solution. This process is designed for preparing the reservoir type system e.g. encapsulate water soluble drugs i.e. peptides, proteins etc. In this method, formation of dispersion of drug particles in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Matrix types preparations can also be prepared by this process for hydrophilic drug e.g. steroids, Addition of non-solvent results in the solidification of polymer. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as 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 agglomeration of the formed particles. But this method is not suitable for organic solvents and glutaraldehyde which are toxic in nature. Berthold et al. (1996a) prepared prednisolone sodium phosphate loaded chitosan microspheres using sodium sulphate as a precipitant.

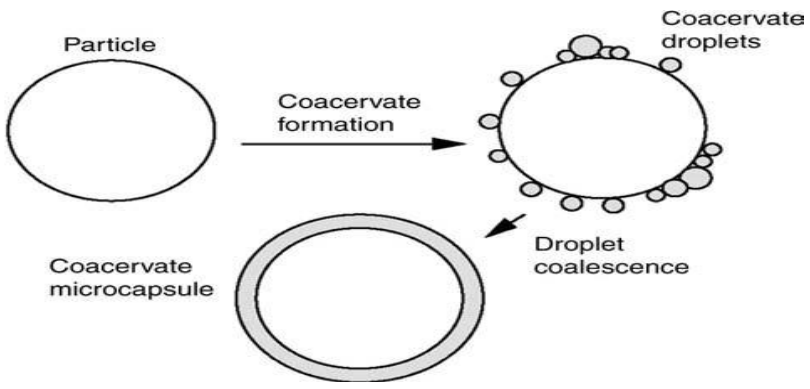


Figure 4: Schematic diagram of the formation of a coacervate around a core material.

7. Quassi emulsion solvent diffusion[25]

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported. Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The inner phase is consisting of drug, ethanol and polymer is added at an amount of 20% of the polymer in order to enhance plasticity. At first, the internal phase is manufactured at 60ºC and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred at 500 rpm for 1 to 2 hours. Then the mixture can be filtered to separate the solid microsponges. The product is washed and dried and then collect.

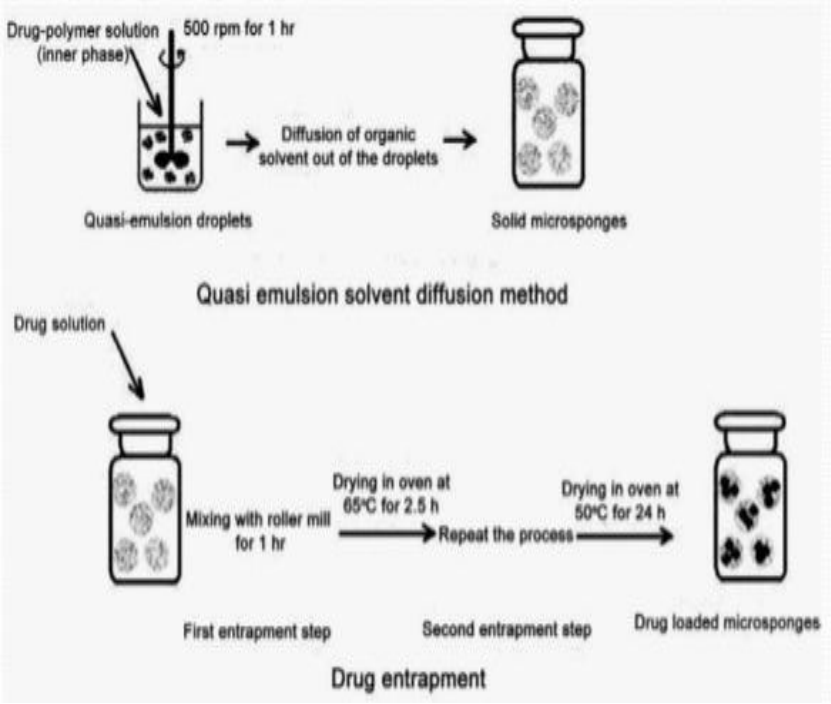


Figure 5: **Quassi emulsion solvent diffusion method.**

8. Wax coating and hot melt[26,27]

In this method the wax is used to cote the core particle Mostly Carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics. In this technique polymer is disperse in suitable dispersion medium and slowly cooled to form the microspheres. The polymers which having low melting point fabricated into microspheres by this technique easily. For coating and coring of particle wax is use mostly. In which encapsulate the drug by dispersion in the molted wax. The wax suspension is dispersed by high speed mixing into cold solution for example liquid paraffin.

Agitate the mixture for one hour. Then decanted the external phase and suspended microspheres collect from solvent. And allow drying it in air. It is inexpensive method as comparison to others and drug release is more rapid.

9. Ionic gelation method[28]

Alginate/chitosan particulate system for diclofenac sodium or nateglinide release was prepared using this technique. 25% (w/v) of diclofenac sodium was added to 1.2% (w/v) or different % (w/v) of nateglinide was added to 2% (w/v) aqueous solution of sodium alginate respectively. In order to get the complete solution stirring is continued and after that it was added drop wise to a polyelectrolyte solution containing Ca2+ /Al3+ and chitosan solution in acetic acid.

Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filteration for separation. The complete release was obtained at pH 6.4-7.4 but the drug did not release in acidic pH.

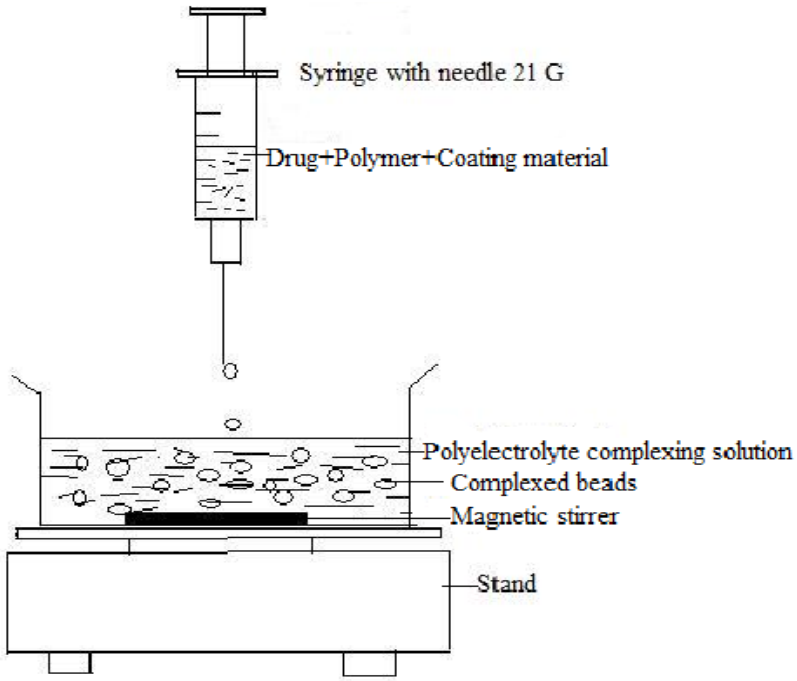


Figure 6: **Ionic gelation method.**

10. Hydroxyl appetite (HAP) microsphere in sphere morphology[29]

This method is used to prepare microspheres with peculiar spheres in sphere morphology. The microspheres prepared by o/w emulsion followed by solvent evaporation. At first o/w emulsion was prepared by dispersing the organic phase in aqueous phase of surfactant. The

organic phase is Diclofenac sodium containing 5% w/w of EVA and appropriate amount of HAP. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co-solvencing and helped them to stay individual droplets .While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.

EVALUATION OF MICROSPHERE

Characterization

The characterization helps to design a suitable carrier for the proteins, drug or antigen delivery. The microsphere having a different microstructures that determine release and the stability of the carrier.[30]

Particle size and shape

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determinethe shape and outer structure of microparticles LM provides a control over coating parameters in case of double walled microspheres. SEM provides higher resolution in contrast to the LM.[31]

Electron spectroscopy for chemical analysis

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. That gives spectra that used to determine surficial degradation.

Density determination

Multi volume pycnometer are used to determine the density of microsphere. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined.

Isoelectric point

For the determination of isoelectric point we can measure the electrophoretic mobility by using the micro electrophoresis apparatus. The electrophoretic mobility can be related to

surface contained charge, ionisable behavior or ion absorption nature of the microspheres. The mean velocity at different pH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined.

Angle of contact

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres. The angle of contact is measured at the solid/air/water interface.

***In- vitro* method**

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of *in vitro* and *in vivo* techniques have been reported. *In vitro* drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development.[22]

Beaker method

In this method beaker and stirrer play important role in determination. The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.[32,33]

Interface diffusion system

It consists of four compartments. The compartment A represents the oral cavity, and initially contained an appropriate concentration of drug in a buffer. The compartment B representing the buccal membrane, contained 1-octanol, and compartment C representing body fluids, contained 0.2 M HCl. The protein binding also contained 1-octanol is representing compartment D. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned to compartment A with a syringe.

This method is developed by Dearden & Tomlinson.[34]

Modified keshary chiten cell

The apparatus comprises A Keshary Chien cell containing distilled water (50ml) at 370 C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min. This apparatuse was designed in the laboratory.

Dissolution apparatus

In a pharmaceutical industry, drug dissolution testing is routinely used to provide critical in vitro drug release information for both quality control purposes, i.e to assess batch to batch consistency of solid oral dosage form such as tablet, and drug development, i.e to predict in vivo drug release profiles. Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using both rotating elements, paddle**41, 42, 43** and basket**44, 45**. Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

***In vivo* method**

To studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrants at the surface. Some of the earliest and studies of mucosal simple permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However *in vivo* studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.[35]

In vitro-In vivo correlations

In vitro- in vivo correlation depend on blood concentration, urinary excretion and metabolism of drug, Correlations between in vitro dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "*in vitro-in vivo* correlations". Such correlations allow one to develop product specifications with bioavailability.[22]

Drug entrapment efficiency[4]

The Drug entrapment efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement.

The Drug entrapment efficiency is calculated using following equation:

% Entrapment = Actual content/Theoretical content x 100

Surface amino acid residue

The radioactive c14-acetic acid conjugate is used to determine surface associated amino acid residue. The carboxylic acid residue is measured through the liquid scintillation counter and hence the amino acid residue can be determined indirectly. The amino group and the c14 – acetic acid carboxylic acid residue is condense by using EDAC.

The method used for determining the free amino or the free carboxylic acid residues are based on indirect estimation, by measuring the radioactivity of the c14 having acetic acid or the glycine conjugate. The accuracy of the method however, depends on the time allowed for conjugation of the radioactive moiety and the reactivity of free functional group.

Swelling index

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. The swelling index of the microsphere was calculated by using the formula, Swelling index= (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) 100.

Dissolution Rate Vs Absorption Rate

The absorption time is easy to determine than the rate of absorption. Rate of absorption is difficult to determine. Since the absorption rate and absorption time of a drug are inversely correlated, the absorption time may be used in correlating the dissolution data to the absorption data. In the analysis of in vitro and in vivo drug correlation, rapid drug absorption may be distinguished from the slower drug absorption by observation of the absorption time for the dosage form. The quicker the absorption of the drug the less is the absorption time required for the absorption of the certain amount of the drug. The time required for the absorption of the same amount of drug from the dosage form is correlated.

Percent of Drug Dissolved Vs Serum Drug Concentration

The drugs whose absorption from GIT is dissolution rate limited, a linear correlation may be established between the percent of drug dissolved at specified times and the serum drug concentrations at corresponding times.

Percent of Drug Dissolved Vs Percent of the Dose Excreted in urine

The percent of a drug dissolved and the percent of drug absorbed are linearly correlated. There exists a correlation between the amount of drug in body and the amount of drug excreted in the urine. Therefore, a linear relation may be established between the percent of the drug dissolved and the percent of the dose excreted in the urine.[36]

 Percent of Drug Dissolved *In Vitro* Vs Peak Plasma Concentration

One of the ways of checking the in vitro and in vivo correlation is to measure the percent of the drug released from different dosage forms and also to estimate the peak plasma concentrations achieved by them and then to check the correlation between them. It is expected that a poorly formulated dosage form releases amount of drug than a well formulated dosage form, and, hence the amount of drug available for absorption is less for poorly formulated dosage form than from a well formulated dosage form.

 Percent of Drug Dissolved Vs Percent of Drug Absorbed

If the dissolution rate is the limiting step in the absorption of the drug, and is absorbed completely after dissolution, a linear correlation may be obtained by comparing the percent of the drug absorbed to the percent of the drug dissolved. If the rate limiting step in the bioavailability of the drug is the rate of absorption of the drug, a change in the dissolution rate may not be reflected in a change in the rate and the extent of drug absorption from the dosage form.

APPLICATIONS

- Pharmaceutical Application in drug delivery system that are follow

1. Ophthalmic drug delivery system
2. Intratumoral and local drug delivery
3. Oral drug delivery
4. Nasal drug delivery

Table 1: Microspheres for nasal drug delivery[1]

Drug	Route of administration	Polymer use	Result
Gentamicin	Nasal	Degradable starch microspheres and lysophosphatidylcholine	Increased nasal absorption
Insulin	Nasal	Degradable starch microspheres and lysophosphatidylcholine	Efficient delivery of insulin into the systemic circulation via nasal route
Human growth hormone (Hgh)	Nasal	Degradable starch microspheres and lysophosphatidylcholine	Rapid and increased absorption
Desmopressin	Nasal	Starch	Addition of LPC causes a five folds increase in Cmax and two folds increase in bioavailability
Haemagglutinin (HA)Obtained from influenza A virus	Nasal	Hyaluronic acid esters	With mucosal adjuvant serum lgG antibody response as compared to i.m. immunization

5. Buccal drug delivery
6. Gene delivery
7. Gastrointestinal drug delivery

Table 2: Microsphere for Gastrointestinal drug delivery[1]

Drug	Route of administration	Polymer	Result
Amoxicillin	GI	Ethyl cellulose-Carbopol-934P	Greater anti H. pylori activity
Delapril HCL	GI	Polyglycerol esters of fatty acids (PGEFs)	MRT of drug is increased
Glipizide	GI	Chitosan	Prolonged blood glucose reduction
Glipizide	GI	Chitosan-alginate	Prolonged blood glucose reduction
Vancomycin6	Colonic	PGEF(polyglycerol esters of fatty acids coated) with Eudragit S 100	Well absorbed even without absorption enhancers.
Furosemide	GI	Polyglycerol esters of fatty acids (PGEFs)	Increased bioavailability Higher AUC effective absorption from the absorption window.

8. Peroral drug delivery
9. Vaginal drug delivery
10. Transdermal drug delivery
11. Colonic drug delivery
12. Multiparticulate delivery system

- **Microsphere in vaccine delivery**[27]

The prerequisite of a vaccine is protection against the microorganism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, Safety and convenience in application and cost. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

1. Improved antigenicity by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen.

- **Monoclonal antibodies mediated microspheres targeting**

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The Mabs can be attached to microspheres by any of the following methods[1]

1. Nonspecific adsorption
2. Specific adsorption
3. Direct coupling
4. Coupling via reagents

- **Chemoembolisation**

Chemoembolisation is an endovascular therapy, which involves the selective arterial embolisation of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent. The theoretical advantage is that such embolisations will not only provide vascular occlusion but will bring about sustained therapeutic levels of

chemotherapeutics in the areas of the tumour. Chemoembolisation is an extension of traditional percutaneous embolisation techniques.[4]

- **Imaging**

The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labelled microspheres.[37] The particle size range of microspheres is an important factor in determining the imaging of particular sites. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labelled human serum albumin microspheres.[38]

- **Medical application.[4]**

1. Release of proteins, hormones and peptides over extended period of time.
2. Gene therapy with DNA plasmids and also delivery of insulin.
3. Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin, toxoid, diphtheria, birth control.
4. Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra-arterial/ intravenous application.
5. Tumour targeting with doxorubicin and also Treatments of leishmaniasis.
6. Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
7. Used in isolation of antibodies, cell separation and toxin extraction by affinity chromatography.
8. Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.

- **Radioactive microsphere's application[39]**

Can be used for radio embolisation of liver and spleen tumours. Used for radio synvectomy of arthiritis joint, local radiotherapy, interactivity treatment. Imaging of liver, spleen, bone marrow, lung and even imaging of thrombus in deep vein thrombosis can be done.

- **Surface Modified Microspheres[15]**

Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns. The adsorption of the poloxamer on the surface of the polystyrene, polyester or poly methyl methacrylate microspheres renders them more hydrophilic and hence decrease their MPS

uptake. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance. The most studied surface modifiers are:

1. Antibodies and their fragments
2. Proteins
3. Mono-, oligo- and polysaccharides
4. Chelating compounds (EDTA, DTPA or Desferroxamine)
5. Synthetic soluble polymers Such modifications are provided surface of microspheres in order to achieve the targeting to the discrete organs and to avoid rapid clearance from the body.

RECENT ADVANCEMENT IN MICROSPHERE[2]

1. Important utilizations of chitosan polymer Cholesterol-lowering effects
2. Cosmetics industry
3. Orthopedic patients
4. Dental Medicine
5. Increase stability of drug
6. Chitosan as Permeation Enhancer
7. Chitosan as Mucoadhesive Excipient
8. Effect of chitosan: citric acid ratio on drug
9. Release
10. Wound healing properties
11. Direct compressible excipients and as binder
12. Enhanced bone formation by transforming
13. growth factor (TGF-pl)

FUTURE CHALLENGES

In a medicinal field microsphere have wide spectrum of application in molecular biology, eg: microsphere based genotyping platform is used to detect six single nucleotide polymorphism, yittrium-90 microspheres. It is used to prevent tumour after liver transplantation and it's advanced way in delivery of vaccines and proteins. microsphere have a bright future in upcoming days.

CONCLUSION

In this present review the general information about microsphere, material use, method of preparation, evaluation, recent development and the future challenges are studied. The present review shows the microsphere are the better choice of drug delivery system than the conventional drug delivery system because it is a targeted drug delivery system that shows action on the targeted site rather than other tissue site. Due to reason the toxicity can minimize and improve the therapeutic action. In future by combining various other strategies, microsphere will find the central and significant place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, specific and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body. Microsphere by the double emulsion techniques is the suitable method for preparation of microsphere. It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put at constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under vacuum. It is best suited to water soluble drugs, peptides, proteins and the vaccines.

Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase homogenization/vigorous i.e. formation of first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) i.e. multiple emulsion formed now by addition to large aqueous phase denaturation/hardening after this separation, washings' and drying and collection of microspheres. genistein chitosan microsphere were prepared by the o/w/o multiple emulsion method. Under optimized condition discrete microspheres were formed during this phase.

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