MICROSPHERES: A BRIEF REVIEW

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ABSTRACT :
Microspheres are multiparticulate drug delivery systems 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. They are made from polymeric waxy or other protective materials such as natural, semi synthetic and synthetic polymers.
Microspheres are characteristically free flowing powders having particle size ranging from 1-1000 µm consisting of proteins or synthetic polymers. The range of techniques for the preparation of microspheres provides multiple options to control as drug administration aspects and to enhance the therapeutic efficacy of a given the drug. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Such systems often use macromolecules as carriers for the drugs. The present review highlights various types of microspheres, different methods of preparation, its applications and also various parameters to evaluate their efficiency. Microspheres are various types like Bioadhesive microspheres, Magnetic microspheres, Floating microspheres, Radioactive microspheres, Polymeric microspheres, Biodegradable polymeric microspheres, Synthetic polymeric microspheres and are prepared by methods like Spray Drying, Solvent Evaporation, Single emulsion technique, Double emulsion technique, Phase separation coacervation technique, Spray drying and spray congealing, Solvent extraction, Quassi emulsion solvent diffusion. Microspheres have wide range of applications because of controlled and sustained release.
Keywords: Microspheres, Types of microspheres, Method of preparation, Application.

INTRODUCTION:[1,2,3,4,5]

Oral route drug administration is by far the most preferable route for taking medications. However, their short circulating half life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. Rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamics profile is to release the drug in a controlled manner and site specific manner.

Microspheres are small spherical particles, with diameters 1 µm to 1000 µm. They are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall. and micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Microsphere play an important role to improve bioavailability of conventional drugs and minimizing side effects.

Ideal characteristics of microspheres: [5,6]

- ✓ The ability to incorporate reasonably high concentrations of the drug.
- ✓ Stability of the preparation after synthesis with a clinically acceptable shelf life.
- ✓ Controlled particle size and dispersability in aqueous vehicles for injection.
- ✓ Release of active reagent with a good control over a wide time scale.
- ✓ Biocompatibility with a controllable biodegradability.
- ✓ Susceptibility to chemical modification.

Advantages of microspheres: [6]

1. Particle size reduction for enhancing solubility of the poorly soluble drug.
2. provide constant and prolonged therapeutic effect.
3. provide constant drug concentration in blood there by increasing patent compliance,
4. Decrease dose and toxicity.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery

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of protein.
6. Reduce the dosing frequency and thereby improve the patient compliance
7. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
8. Microsphere morphology allows a controllable variability in degradation and drug release.
9. Convert liquid to solid form & to mask the bitter taste.
10. Protects the GIT from irritant effects of the drug.
11. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
12. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitation: [5]

Some of the disadvantages were found to be as follows

1. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.

TYPES OF MICROSPHERES:

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres
   i)Biodegradable polymeric microspheres
   ii)Synthetic polymeric microspheres

1. Bioadhesive microspheres: [7,8]

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

2. Magnetic microspheres: [9,10]

This kind of delivery system is very much important which localises 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 types of

a.Therapeutic magnetic microspheres used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

b.Diagnostic microspheres, 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.

3. Floating microspheres: [11,12,13]

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, and the system is found to be floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of dose dumping. It produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) is given in the form of floating microspheres.

4. Radioactive microspheres: [3,14]

Radio embolization therapy microspheres sized 10-30 nm are of larger than the diameter of the capillaries and gets tapped in first capillary bed when they come across. They are injected in the arteries that leads them to tumour of interest so all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. 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.

5. Polymeric microspheres: [14]

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

i) Biodegradable polymeric microspheres: [15]

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium , results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in

a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment.

ii) Synthetic polymeric microspheres: [4,16]

Synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible but the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

METHOD OF PREPARATION:

1. Spray Drying
2. Solvent Evaporation
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Spray drying and spray congealing
7. Solvent extraction
8. Quassi emulsion solvent diffusion:

1. Spray Drying: [14]

In Spray Drying technique, 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 with 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 1-100μm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of this process is feasibility of operation under aseptic conditions.

2. Solvent Evaporation: [14,17]

This process is carried out in a liquid manufacturing vehicle phase. The microcapsule 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. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.

3. Single emulsion technique: [2]

The micro particulate carriers 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. In the next step, the cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation3 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.

4. Double emulsion technique: [2]

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction.

5. Phase separation coacervation technique: [18,19]

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. In this method, the drug particles are dispersed 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. 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. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.

6. Spray drying and spray congealing: [18,19]

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading 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. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmiticacid using spray congealing. Very rapid solvent evaporation, howeverleads to the formation of porous microparticles.

7. Solvent extraction: [2,18,19]

Solvent evaporation method is used for manufacturing of microparticles, involves removal of the organic phase by extraction of the or non aqueous solvent. This method involves water miscible organic solvents as isopropanol. Organic phase can be removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to polymer organic solution. Rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and solubility profile of polymer.

8. Quassi emulsion solvent diffusion:[18,19]

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by a quasi emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase consists of drug, ethanol and polymer.The concentration of polymer is in order to enhance plasticity. At first, the internal phase is manufactured at 60°C and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40°C for a day.

Polymerization techniques: [2,14,21,22]

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

I. Normal polymerization

II. Interfacial polymerization.

Both are carried out in liquid phase.

I. Normal polymerization:

It is carried out by using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization methods. In bulk, a monomer or a combination of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the polymerization process. Suspension polymerization also referred as bead or pearl polymerization. It is carried out by heating the monomer or composition of monomers as droplets dispersion in a continuous aqueous phase. Droplets may also contain an initiator and other additives. Emulsion polymerization deviates from suspension polymerization as due to the presence initiator in the aqueous phase, which afterwards diffuses to the surface of micelles. Bulk polymerization has merits of formation of pure polymers.

II. Interfacial polymerization:

This involves the reaction of various monomers at the interface between the two immiscible liquids to form a film of polymer that essentially envelops the dispersed phase.

MATERIALS USED IN THE PREPARATION OF MICROSPHERE: [2,22]

Microspheres used usually are polymers. They are classified into two types:

1. Natural polymers
2. Synthetic Polymers

1. Natural polymers obtained from different sources like carbohydrates proteins and chemically modified Carbohydrates

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

Proteins: Albumin, Collagen and Gelatin

Chemically modified carbohydrates: Poly dextran,

Poly starch.

2. Synthetic polymers are divided into two types.

Biodegradable polymers

E.g. Lactides, Glycolides & their co-polymers,Poly anhydrides,Poly alkyl cyano acrylates

Non-biodegradable polymers

E.g. Poly methyl methacrylate (PMMA), Glycidyl methacrylate, Acrolein, Epoxy polymers

EVALUATION OF MICROSPHERES: [3,21,22,23,24]

1. Particle size and shape

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM).

2. Electron spectroscopy for chemical analysis:

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

3. Density determination:

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

4. Isoelectric point:

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

5. Angle of contact:

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

6. In vitro methods:

Release studies for different type of microspheres are carried out by using different suitable dissolution media, mostly by rotating paddle apparatus (USP / BP).

7. Drug entrapment efficiency:

Drug entrapment efficiency can be calculated using following equation,

% Entrapment = Actual content/Theoretical content x 100.

8. Swelling index :

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.

APPLICATION OF MICROSPHERES IN PHARMACEUTICAL INDUSTRY: [21,22,25]

1. Ophthalmic Drug Delivery
2. Oral drug delivery
3. Gene delivery
4. Nasal drug delivery
5. Intratumoral and local drug delivery
6. Buccal drug delivery
7. Gastrointestinal drug delivery
8. Transdermal drug delivery
9. Colonic drug delivery
10. Vaginal drug delivery
11. Targeting by using microparticulate carriers

1. Ophthalmic Drug Delivery:

Microspheres developed using polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Eg. Chitosan, Alginate, Gelatin.

2. Oral drug delivery:

The ability of microspheres containing polymer to form films permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make microspheres more suitable for oral drug delivery applications. Eg. Chitosan, Gelatin.

3. Gene delivery:

Microspheres could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Eg. Chitosan, Gelatin, viral vectors, cationic liposomes, polycation complexes.

4. Nasal drug delivery:

Polymer based drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Eg. Starch, Dextran, Albumin, Chitosan+Gelatin.

5. Intratumoral and local drug delivery:

In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films are fabricated. Mixture of drug has promising potential for use in controlled delivery in the oral cavity. Eg. Gelatin, PLGA, Chitosan and PCL.

6. Buccal drug delivery:

Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Chitosan, Sodium alginate.

7. Gastrointestinal drug delivery:

Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug . eg. Eudragit, Ethyl cellulose+Carbopol BSA, Gelatin.

8. Transdermal drug delivery:

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Eg. Chitosan, Alginate, PLGA.

9. Colonic drug delivery:

Polymer has been used for the specific delivery of insulin to the colon. Eg. Chitosan.

10. Vaginal drug delivery:

Polymer, modified by the introduction of thioglycolic

acid to the primary amino groups of the polymer is widely used for the treatment of mycotic infections of the genitourinary tract. Eg. Chitosan, Gelatin, PLGA.

11. Targeting by using microparticulate carriers:
Pellets are prepared with polymer by using the extrusion/spheronization technology. Eg. Chitosan, Microcrystalline cellulose.

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