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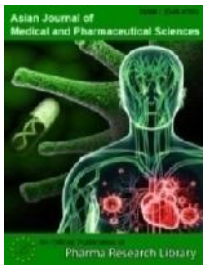

R E V I E W A R T I C L E

Review on Design and Evaluation of Microspheres

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A B S T R A C T

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. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Solid biodegradable microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. It is the 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. 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.

Keywords: Microspheres, polymers, bioavailability, Controlled release, Stability, conventional dosage form.

A R T I C L E I N F O

A U T H O R D E T A I L S

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C O N T E N T S

1. Introduction

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To achieve maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the

optimal amount in the right period of time there by causing little toxicity and minimal side effects. The ideal drug delivery system delivers drug at rate decided by the need of the body throughout the period of treatment and it provides the active entity solely to the site of action. So, carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc which modulates the release and absorption characteristics of the drug [1].

Types of drug delivery system are;

- Liposomes
- Neosomes
- Nanoparticles
- Microspheres

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature. Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" or can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular level or macroscopic level. It has particle size of 1-1000 nm. Due to smaller particle size it spreads to a large area in gastrointestinal tract which improves drug absorption and reduces side effects due to localized buildup of irritating drugs against the gastrointestinal mucosa[2,3].

Advantages:

- Controlled release delivery there by reducing side effects and eliminating the inconvenience of repeated injections.
- Protein/peptide stability – microspheres helps to protect proteins because they are not allowed to react with anything until the polymer is degraded, thus minimizing the contact with solutions that could cause the proteins to react. Ex: albumin prototype and lyzozymes.
- Drug targeting – it is the greatest advantage. Most drugs are targeted in the body to give desired results either in specific tissues or organs. Ex: It could be employed in targeting cancer cells in chemotherapy, as drugs and chemical agents attack cancer cells but have a toxic effect on healthy ones which could easily cause them to die.
- Gene delivery – Encapsulation of therapeutic agents such as DNA in microspheres protects the agent from enzymatic degradation, enhances tissue specificity due to localized delivery, eliminates the need for multiple administrations and allows for sustained and controlled delivery. Microspheres are used with Gamma emitters such as Tc99 and 1131 for diagnostic purposes.

Disadvantages:

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

2. Types of Microspheres

Bio-adhesive microspheres:

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 bioadhesion. 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[4].

Magnetic microspheres:

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.

Floating microspheres:

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 increases gastric residence and fluctuation in plasma concentration. It also reduces chances of sticking and dose dumping[5].

Radioactive microspheres:

In Radio emobilisation therapy microspheres sized of 10-30 nm are 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. In all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues.

Polymeric microspheres:

The different types of polymeric microspheres can be classified as follows:

a) Biodegradable polymeric microspheres:

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[6].

b) Synthetic polymeric microspheres:

The interest of 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 kinds of microspheres, are

tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

3. Method of Preparation

Various methods are used to preparation of Microspheres. They are described below;

- 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

Spray Drying: 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[7].

Solvent Evaporation:

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[8,9].

Single emulsion technique:

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[10].

Double emulsion technique:

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[11].

Phase separation coacervation technique:

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 havebeen 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.

Spray drying and spray congealing:

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, however leads to the formation of porous microparticles[12].

Solvent extraction:

Solvent evaporation method is used for manufacturing of microparticles, involves removal of the organic phase by extraction of the 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.

Quassi emulsion solvent diffusion:

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 60ºC 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 40ºC for a day[13].

Materials used in preparation of Microspheres

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres; these materials include polymers of natural origin or synthetic origin and also semisynthetic substances. Microspheres can be prepared by using both hydrophilic and hydrophobic polymers[14,15].

Hydrophilic polymers:

These are includes gelatin, agar, egg albumin, starch, chitosan, cellulose derivatives; HPMC, DEAE cellulose.

Hydrophobic polymers: These are include ethyl cellulose, polylactic acid, PMMA, acrylic acid esters etc.

Biodegradable polymers:

These materials also slowly disappear from the site of administration; however it occurs in response to a chemical reaction such as hydrolysis.

Example:

Polylactic acid (PLA), poly glycolic acid (PGA), Polycaprolactone (PCL) and several generic classes such as the poly anhydrides and poly orthoesters.

Non-Biodegradable Hydrophobic Polymers: These materials are inert in the environment of use, are eliminated or extracted intact from the site of administration.

Example:

Polyethylene vinyl acetate (EVA), Polydimethyl siloxane (PDS), Polyether urethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene (PE) and Polyvinyl chloride (PVC), Acrycoat, Eudragit S etc.

Hydrogels:

These polymers swell but do not dissolve when brought in contact with water. As with the hydrophobic polymers, hydrogels are inert, removed intact from the site of administration, and function by forming a rate limiting barrier to the transport and release of drugs.

Example:

Polyhydroxy ethyl methyl acrylate (PHEMA), cross-linked poly vinyl alcohol (PVA), cross linked poly vinyl pyrrolidone (PVP), poly acryl amide etc.

Soluble polymers:

These are moderate molecular weight (less than 75,000 Daltons) uncross linked polymers that dissolve in water. The rate of dissolution decreases with increasing molecular weight. These materials can be used alone or in combination with hydrophobic polymers to provide devices that slowly erode over time.

Example:

polyethylene glycol (PEG), uncross linked poly vinyl alcohol or poly vinyl pyrrolidone, hydroxyl propyl methyl cellulose (Methocel) and copolymers of methacrylic acid and acrylic acid methyl ester (Eudragit L) etc.

Evaluation of Microspheres [16]

Particle size and shape:

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

Electron spectroscopy for chemical analysis:

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

Density determination:

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

Isoelectric point:

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

Angle of contact:

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

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).

Drug entrapment efficiency:

Drug entrapment efficiency can be calculated using following equation,

% Entrapment = Actual content/Theoretical content x 100.

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.

Applications of Microspheres

Microspheres in vaccine delivery:

The prerequisite of a vaccine is protection against the microorganism or its toxic product. An ideal vaccine must fulfil the requirement of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines.

Targeting using micro particulate carriers:

The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. Placement of the particles in discrete anatomical compartment leads to their retention either because of the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.

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. The Mabs can be attached to microspheres by any of the following methods

- Nonspecific adsorption
- Specific adsorption
- Direct coupling
- Coupling via reagents

Chemoembolization:

Chemoembolization is an endovascular therapy, which involves the selective arterial embolisation of a tumor together with simultaneous or subsequent local delivery to 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 tumor.

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. The particle size range of microspheres is an important factor in determining the imaging of particular sites. **Topical porous microspheres:**

Micro sponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 µm. These micro sponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carrier system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders.

Surface modified microspheres:

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 methacrylate microspheres renders them more hydrophilic and hence decreases their MPS uptake.

4. Conclusion

The present review concluded that microspheres are better choice of controlled drug delivery system than many other types of drug delivery system. Microspheres are promises to be a potential approach for gastric retention enhances the bioavailability and controlled delivery of various therapeutic agents. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development.

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