Review Article

A Review on Sustained Release Microshere

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ABSTRACT

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 offers a Variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. The approach is using microspheres as carriers for drugs also known as microparticles. Such a dosage forms having a major advantage of patient compliance. Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. 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. Microspheres received much attention not only for prolonged release, but also for targeting of at side of effect. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, Safe targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

Keywords: Sustained Release Drug Delivery System, Types, Method of Preparation and Evaluation of Microsphere.

INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rates or target drug to a specific body site have had an enormous impact on the health care system. The last two decades there has been a remarkable improvement in the field of novel drug delivery systems. 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. Microspheres constitute an important part of these particulate DDS by virtue of their small size and efficient carrier characteristics.

Ion gelation technique is one of the several methods that is used for production of microspheres. Although this way may not be the main method, but it is the simplest one that several variables can affect the outcome, as well.[1, 2]

Sustained release microspheres may be produced by several methods utilizing emulsion system (oil-in-water, oil-in-oil, water-in-oil-in-water), as well as by spray drying. The common emulsion system used oil-in-water (o/w), with microspheres being produced by the emulsion solvent evaporation method. This relatively simple method enables the entrapment of a wide range of hydrophobic drugs.[3]

TYPES OF MICROSPHERE[4]

Bioadhesive 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 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.

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 are chitosan, dextran etc.

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, if the system is floating on gasteric contentand increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) given through this form.

Radioactive Microspheres - Radio embolization 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 all these conditions radcioactive 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 microsphers are α emitters, β emitters, γ emitters.

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

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. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner.

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

CHARACTERISTICS MICROSPHERE PROPERTY[5]

S. No.	Properties	Consideration
1	Size	Diameter Uniformity/distribution
2	Composition	Density Refractive index Hydrophobicity/hydrophilicity Nonspecific binding Autofluorescence
3	Surface chemistry	Reactive groups Level of functionalization Charge
4	Special properties	Visible dye/fluorophore Super-paramagnetic

IDEAL CHARACTERISTICS OF MICROSPHERES[6]

1. The ability to incorporate reasonably high concentrations of the 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.
6. 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

LIMITATION[6]

1. The costs of the materials and processing of the controlled release preparation, are substantially
2. higher than those of standard formulations.
3. The fate of polymer matrix and its effect on the environment.
4. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.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.

MATERIALS USED[7]

1. **Synthetic Polymers** - Polymers used in Microspheres Development Synthetic polymers are divided into two types.

A] Non-biodegradable polymers
- Poly methyl methacrylate (PMMA)
- Acrolein
- Glycidyl methacrylate
- Epoxy polymers

B] Biodegradable polymers
- Lactides, Glycolides & their co polymers
- Poly alkyl cyano Acrylates
- Poly anhydrides

2. Natural polymers - Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

A] Proteins:
- Albumin
- Gelatin
- Collagen

B] Carbohydrates:
- Agarose
- Carrageenan
- Chitosan
- Starch

C] Chemically modified carbohydrates:
- Poly dextran
- Poly starch.

MICROSPHERES CAN PREPARED BY USING DIFFERENT TECHNIQUES LIKE[8]

1. Complex Coacervation

Principle of this method is under suitable conditions when solutions of two hydrophilic colloids were mixed, result into a separation of liquid precipitate. In this method the coating material phase, prepared by dissolving immiscible polymer in a suitable vehicle and the core material is dispersed in a solution of the coating polymer under constant stirring. Microencapsulation was achieved by utilizing one of the methods of phase separation, that is, by changing the temperature of the polymer solution; by changing the pH of the medium, by adding a salt or an incompatible polymer or a non-solvent to the polymer solution; by inducing a polymer polymer interaction. Generally coating is hardened by thermal cross linking or desolvation techniques, to form a self-sustaining microsphere.

2. Hot Melt Microencapsulation

Microspheres of polyanhydride copolymer of poly bis (p-carboxy phenoxy) propane anhydride with Sebacic acid were firstly prepared by this method. In this method the polymer is firstly melted and then the solid drug particles are added to it with continuous mixing. The prepared mixture is then suspended in a non-miscible solvent like silicone oil with stirring and heated at the temperature above the melting point of the polymer with continuous stirring so as to get stabilized emulsion. The formed emulsion is cooled to solidify polymer particles followed by filtration and washing of the microspheres with petroleum ether.

3. Single Emulsion Technique

The microspheres of natural polymers are prepared by single emulsion technique. The polymers and drug are dissolved or dispersed in aqueous medium followed by dispersion in organic medium e.g. oil, results in formation of globules, and then the dispersed globule are cross linked by either of heat or by using the chemical cross-linkers. The chemical cross-linkers used are formaldehyde, glutaraldehyde, diacid chloride etc.

4. Double Emulsion Method

This method is firstly described by Ogawa Y et al. in year 1988, and is the most widely used method of microencapsulation. In this method an aqueous solution of drug and polymer is added to the organic phase with vigorous stirring to get primary water-in-oil emulsion. This emulsion was then poured to a large volume of water containing an emulsifier like polyvinyl alcohol or polyvinyl pyrolidone, under stirring, to get the multiple emulsions (w/o/w); and stirring was continued until most of the organic solvent evaporates, leaving solid microspheres. The microspheres are then washed and dried.

5. Solvent Removal
This is a non-aqueous method of microencapsulation and is most suitable for water labile polymers such as the polyanhydride. The method involves dissolving the polymer into volatile organic solvent and the drug is dispersed or dissolved in it, this solution is then suspended in the silicone oil containing span 85 and methylene chloride under stirring, then petroleum ether is added and stirred until solvent is extracted into the oil solution. The obtained microspheres were then subjected for vacuum drying.

6. Ionotropic Gelation
This method was developed by Lim F and Moss RD. Using this method Microspheres are formed by dissolving the gel-type polymers, such as alginate, in an aqueous solution followed by suspending the active ingredient in the mixture and extruding the solution through needle to produce micro droplets which fall into a hardening solution containing calcium chloride under stirring at low speed. Divalent calcium ions present in the hardening solution crosslink the polymer, forming gelled microspheres.

7. Phase Inversion Method
The method involves addition of drug into dilute polymeric solution, in methylene chloride; and resultant mixture is poured into an unstirred bath of strong non-solvent, petroleum ether, in a ratio of 1: 100. Microspheres produced are then clarified, washed with petroleum ether and air dried.

8. Spray Drying
This method involves dissolving/dispersing of the drug into the polymer solution which is then spray dried. By this method the size of microspheres can be controlled by manipulating the rate of spraying, feeding rate of polymer drug solution, nozzle size, and the drying temperature.

EVALUATION PARAMETER[9]
Percentage yield - The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula.

$$\text{Percentage yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer used}} \times 100$$

Drug content - The various batches of the microspheres were subjected for drug content analysis.
Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of phosphate buffer pH 7.4 then filter. Th e UV absorbance of the filtrate was measured using a UV spectrometer at 220nm.

Drug loading and Entrapment efficiency - Drug loading and encapsulation effi ciency was determined for all batches using the following formulas Values are expressed as percentage.

$$\text{DEE}(\%) = \frac{\text{Amount of drug actually present in the sample}}{\text{Theoretical drug content in the sample}} \times 100$$

Particle size analysis - Size distribution plays a very important role in determining the release characteristics of the microsphere. Particle size distribution analysis was done by optical microscopy method, using calibrated eye piece micrometer, nearly 200 particles were measured and the results were determined.

Scanning electron microscopy (SEM) - The optimized microspheres were taken for the shape and surface characteristic studies. The microspheres were scanned using scanning Electron microscopy, the microspheres were mounted directly on to the Scanning Electron Microscopy samples stub using double sided sticking tape, coated with gold in quick auto coater, with a thickness of 200 nm under reduced pressure of 0.001 torr. Th e shape and surface characteristic of the microspheres were observed in Electron micro analyzer and photographs were taken using Jeol Jsm 5610LV Scanning electron microscope at diff erent magnifi cation.

Swelling Index - Swelling index illustrate the ability of the mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption, which is a primary requirement for initiation of Mucoadhesion. The percent swelling value can be determined using following equation.

Percent swelling = DT - D0 / D0 × 100

Where - D0 = weight of dried microspheres, DT = weight of swelled microspheres

6. *In - Vitro* Release Study - Standard IP/BP/USP dissolution apparatus is used to study *in-vitro* release profile in the dissolution media that is similar to the fluid present at the absorption site as per monograph, using rotating basket or paddle type dissolution apparatus

7. *Ex-Vivo* Mucoadhesion Study - The mucoadhesive property of the microspheres is evaluated on goat's intestinal mucosa by using phosphate buffer, as per monograph. Weighed microspheres are spread onto wet rinsed tissue specimen and immediately thereafter the slides are hung onto the arm of a USP tablet disintegrating test machine with suitable support at 370C. The weight of microspheres leached out at different intervals is measured. The % Mucoadhesion is calculated by the following equation.

$$\% \text{ Mucoadhesion} = \frac{Wa - W1}{Wa} \text{ X } 100$$

Where – Wa = is the weight of microspheres applied, W1 is the weight of microspheres leached out.

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