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Design and Identification of Microspheres: A Review

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Abstract: ***Microparticle delivery system is accepted as are reliable. Mean to delivery the drug to the target site with specificity,. The drug should be delivered to specific target site at a rate and concentration that provides optimum therapeutic efficacy and reducing the side effect to minimum. Microspheres are empty spherical particles, the particle size is less than 200 mm. Microspheres are free flowing powder consisting of natural and synthetic polymers. They have the potential controlled release drug. Polymers are the most important things of pharmaceutical drug delivery. There are many kind of polymers which varying the properties available those days for use in different pharmaceutical applications. Polymers use in the preparation of microspheres is the synthetic and natural polymers. Synthetic polymers are acrolein, poly anhydrides, methyl meth acrylate, lactides, and glycosides. Natural polymers are albumin, gelatin, collagen, agarose, chitosan, carragenene. Microspheres are the free flowing powders consist of protein and synthetic polymers having a particle size ranging from 1 – 1000 micrometer. Microspheres are prepared by several techniques but the choice of method depends upon the drug. The polymers used and duration of action required. The evaluation parameters of microspheres are micromeritic properties particle size and shape, swelling index, tapped density, drug loading efficiency. In coming days by combining numerous other sceniorio, we will find the microspheres in novel drug delivery. Specifically in disease cell sorting diagnostics, gene and genetic materials, safe targeted and effective in vivo delivery and supplements a tiny interpretation of diseased organ and tissue in the body. Keywords: Microencapsulation, novel drug delivery, synthetic and natural polymers, duration of action.***

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1. Introduction

Micro particles delivery systems are accepted as a reliable means to deliver the drug to the target site with specificity. Drug delivery has become increasingly important mainly due to awareness of the difficulties associated with conventional drug delivery system.

There are various approaches in delivering a therapeutic substance to the target site in a sustained/controlled release fashion. One of the approaches is the use of polymers in development of microparticulate drug delivery system by microencapsulation technique, in which a solid, liquid or gaseous active ingredient (core material) is enclosed or enveloped using a polymeric material resulting in uniform spherical microscopic particles/microspheres from 1 to 1000 µm in diameter. Benefits to patients would be enhanced if dosages could be sustained for controlled release. The drug should be delivered to specific target site at a rate and concentration that provides optimum therapeutic efficacy and reducing the side effects to minimum. Microspheres are empty spherical particles the particle size is less than 200mm. Microspheres are free flowing powders consisting of natural or synthetic polymers. They have the potential for control release drug. Microspheres are homogenous monolithic particles which improve the treatment by providing localization of the drug at the site of action and by prolonging the drug release. Microspheres carrier systems, made from natural polymers are attracting considerable attentions for several years for sustained drug delivery. Today, those dosage forms which can control the release rates and which are target specific have a great impact in development of novel drug delivery systems. Recently the novel dosage forms which can control the release rate and target the active drug molecule to a particular site have attained a great formulation interest. Precisely designed controlled drug delivery system can overcome many problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimum amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are defined as “monolithic spheres or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles” or can be defined as structure made up of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level.

2. Advantages

1) Microspheres provide constant and prolonged therapeutic effect.
2) Reduces the dosing frequency and thereby improve the patient compliance.
3) They could be injected into the body due to the spherical shape and smaller size.
4) Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5) Microsphere morphology allows a controllable variability in degradation and drug

3. Limitation

Some of the disadvantages were found to be as follows
1) The modified release from the formulations

2) The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
3) Differences in the release rate from one dose to another.
4) Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
5) Dosage forms of this kind should not be crushed or chewed

4. Materials Used

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres. These materials include the polymers of natural and synthetic origin and also modified natural substances. Synthetic polymers employed as carrier materials are methyl methacrylate, acrolein, lactide, glycolide and their copolymers, ethylene vinyl acetate copolymer, polyanhydrides, etc. The natural polymers used for the purpose are albumin, gelatin, starch, collagen and carrageenan. Microspheres used usually are polymers. They classified into two types:

1) Synthetic Polymers:
a) Non- biodegradable polymers. Eg. Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate Epoxy polymers
b) Biodegradable polymers. Eg. Lactides, Glycolides & their copolymers 3 Poly alkyl cyano acrylates Poly anhydrides

2) Natural Polymers can be obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.
a) Proteins: Albumin, Gelatin and Collagen
b) Carbohydrates: Agarose, carrageenan, Chitosan, starch
c) Chemically modified carbohydrates: Poly dextran, poly starch

Types of Microspheres

1) 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 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.

2) 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 gastric content and 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

3) Magnetic microspheres
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 types are therapeutic magnetic microspheres and diagnostic microspheres.

4) Polymeric microspheres
The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres 12.

A. Biodegradable polymeric Microspheres
Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bioadhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to it's 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.

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

5) Radioactive microspheres
Radioimmobilization therapy microspheres sized 10-30 nm is 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 radioactive microspheres deliver high radiation dose to the targeted are without damaging the normal surrounding tissues. It differs from drug delivery sys- tem, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microsphers are a emitters, ß emitters, α-emitters.

5. Methods of Preparation

1) Single Emulsion Technique
The microparticulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved/dispersed in aqueous medium followed by dispersion in the non-aqueous medium e.g. oil. In the second step of preparation, cross-linking of dispersed globule is carried out. The cross linking is achieved by two methods i.e. either by heat or by means of chemical cross linking agents including glutaraldehyde, formaldehyde, diacid chloride etc.

2) Hot Melt Microencapsulation

Microspheres of polyanhydride copolymer of poly bis(p-carboxy phenoxy) propane anhydride with sebacic acid were firstly prepared by this method19. In this metod 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) 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 nonsolvent 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 microspheres.

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 20. 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 polyvinylpyrrolidone, 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) Spray Drying

In Spray Drying 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 evaporate 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 process is feasibility of operation under aseptic conditions this process is rapid and this leads to the formation of porous micro particles.

6) Solvent Evaporation

The processes are carried out in a liquid manufacturing vehicle. 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. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelating prepared by complex coacervation were made.

7) Polymerization techniques

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

a) Normal polymerization
b) Interfacial polymerization. Both are carried out in liquid phase. Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture 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 process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. 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. 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. Bulk polymerization has an advantage of formation of pore polymers.

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.

Drug Loading in Microsphere

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. The active components may be loaded by means of the physical entrapment, chemical linkage and surface absorption. It was found that maximum of drug loading in microspheres may be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables like presence of additives, method of preparation, heat of polymerization, agitation intensity etc. The loading of drug after the preparation of microspheres may be achieved by

incubating them with high concentration of the drug in a suitable solvent. Here drug may be loaded in the microspheres via penetration or diffusion of the drug through the pores present in the microsphere as well as by absorption of drug on the surface of microspheres. The solvent is then removed, leaving drug-loaded microsphere. Evaluation of Microspheres

Particle size analyser

Microsphere (50 mg) are suspended in distilled water (5mL) containing 2%w/v of tween 80, to prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size is expressed as volume mean diameter in micrometer. Entrapment efficiency

Microspheres containing of drug (5mg) are crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, filtered then assayed by uv-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.

% Entrapment = Actual content/Theoretical content x 100

Scanning electron microscopy (SEM)

Surface morphology is determined by the method SEM. In this microcapsule are mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure and analyzed. Swelling index

This technique is used for characterization of sodium alginate microspheres. Different solution (100mL) are taken such as [distilled water, buffer solution of Ph (1.2, 4.5, 7.4)] and alginate microspheres (100mg) are placed in a wire basket and kept on the above solution and swelling is allowed at 37oC. Thus, changes in weight variation between initial weight of microspheres and weight due to swelling is measured by taking weight periodically and soaking with filter paper

Optical Microscopy

This method is used to determine particle size by using optical microscope (Meizer OPTIK) The measurement i done under 450x (10x eye piece and 45x objective) and100 particles are calculated. Zeta potential

The polyelectrolyte shell is prepared by incorporating chitosan of different molecular weight into the W2 phase and the resulting particles are determined by zeta potential measurement. Thermal analysis

Thermal analysis of microcapsule and its component can be done by using

- Differential scanning calorimetry (DSC)
- Thermo gravimetric analysis (TGA)
- Differential thermometric analysis (DTA)

Accurately the sample is weighed and heated on alumina pan at constant rate of 10oc/min under nitrogen flow of 40 ml/min. Stability studies

Stability Studies are done by placing the microspheres in screw capped glass container and storing them at following conditions

1. Ambient humid condition
2. Room temperature (27+/-2^{o}C)
3. Oven temperature (40+/-2^{o}C)
4. Refrigerator (5 0+/-8 ^{o}C).

It was carried out of for 60 days and the drug content of the microsphere is analysed.

Isoelectric point

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. 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. The electrophoretic mobility can be related to surface contained charge, ionisable behaviour or ion absorption nature of the microspheres. Angle of repose

Angle of repose (q) of the microspheres was measured using funnel method. The microsphere was poured through a funnel that can be raised vertically until a maximum cone of height was obtained. The radius of heap was measured and angle of repose was calculated.

$\tan \theta = h/r$

Where, θ = Angle of repose, h = Height of granules above the flat surface, r = radius of the circle formed by the granule heap Density determination

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

It is the ratio of mass of the blend to bulk volume. It was measured by pouring powder in measuring cylinder and measuring the volume occupied by powder. Bulk density=mass of microspheres/bulk volume

Tapped density

It is the ratio of mass of the blend to tapped volume. It was measured by digital tap densitometer by measuring the volume occupied by powder after 100 standard tapping. Tapped density=mass of microspheres/volume of microspheres after tapping

Carr's (compressibility) index

Compressibility index (C.I.) or Carr's index value of micro particles was computed according to the following equation

% compressibility = Tapped density – Bulk density X 100
Tapped density

The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flowability. Application of microspheres

I. Gastro retentive floating microspheres is very effective in the reduction of major adverse effect of gastric irritation; such as floating microspheres of NSAIDs drugs i.e. indomethacin are beneficial for rheumatic patients. II. These system can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral controlled release formulation, hence, can be overcome with these systems. III. These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance. IV. Intratumoral and local drug delivery strategies have gained momentum recently as apromising modality in cancer therapy. Inorder to deliver paclitax el at the tumor site in therapeutically relevant concentration, polymer films were fabricated. Paclitaxel could be loaded at 31% (w/w) in films, which were translucent and flexible. polymer films containing paclitaxels were obtained by casting method with high loading efficiencies and the chemical integrity of molecule was unaltered during preparation according to study V. 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. Due to their elastic properties, polymer hydro gels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments. Ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow. In addition, its penetration enhancement has more targeted effect and allows lower doses of the drugs. In contrast, polymer based colloidal system were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticulate containing cyclosporine). The micro particulate drug carrier (microspheres) seems a promising means of topical administration of acyclovir to the eye. The duration of efficacy of the of loxacin was increased by using high MW (1930 kd) chitosan. Gene delivery Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. They cause immune responses and oncogenic effects. To overcome the limitations of viralvectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production. Polymer has been used as a carrier of DNA for gene delivery applications. Also, polymer could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Mac Laughlin et al showed that plasmid DNA containing cytomegalo virus promoter sequence and a luciferase reporter gene could be delivered in vivo by chitosan and depolymerized chitosan oligomers to expressa luciferase gene in the intestinal tract Kanav et al. VI. Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer, embeds clotrimazole, animidazole derivative, is widely used for the treatment of mycotic infections of the genitourinary tract. By introducing thiol groups, the mucoadhesive properties of the polymer are strongly improved and this is found to increase the residence time of the vaginal mucosa tissue polymer). VII. Chitosan have been recognized to accelerate wound healing to attain an aesthetically valid skin surface, and to prevent excess scar formation. In dental medicine, chitosan is also applied as a dressing for oral mucous wound and a tampon following radical treatment of maxillary sinusitis. It is being investigated as an absorbing membrane for periodontal surgery. Chitosan has a variety of biological activities and advertised as a healthy food that is effective for improvement and/or care of various disorders, arthritis, cancer, diabetes.

6. Conclusion

Microspheres by ionotropic gelation technique promises to be potential approach for gastric retention. 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.

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