Review Article

Microspheres as suitable drug carrier in Sustained Release Drug Delivery: An overview

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Abstract

The word "sustained release" is recognized to have existed in the medical and pharmaceutical literature for many decades. Oral drug delivery is the most preferred route for the various drug molecules among all other routes of drug delivery, because ease of administration which lead to better patient compliance. The goal of any drug delivery system is to supply a therapeutic quantity of drug to the suitable site in the body and then maintain the desired drug concentration. A well designed controlled drug delivery system can overcome some of problems of conventional therapy and enhance therapeutic efficacy of the given drug. There are different approaches in delivering therapeutic material to the goal site in sustained release fashion. One such approach is of the microspheres as carriers for drug. There are various departments of medicine like cancer, pulmonary, cardiology, radiology, gynecology, oncology and diabetes etc, number of drugs are used and they delivered by various types of drug delivery system. Among the sustained release of drugs has gained enormous attention due to its wide range of application and maximum time up to drug release. Moreover the microspheres are of micron size so they can easily fit into various micron size capillary beds. The main purpose of this review is to compile various types of sustained release microspheres, method of preparation, its application and also various parameters to evaluate their efficiency.

Keywords: Microspheres, sustained release, characterization

Introduction

Oral route of drug delivery is the mainly prefer route of the diverse drug molecules among all other routes of drug delivery because of ease of administration, patient compliance, and flexible design of dosage form. The effectiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of the drugs that are administered by oral conventional method in the form of tablets and capsule (Alagusundaram et al., 2009). Conventional dosage requires multiple dosages so as to maintain a concentration above its minimum therapeutic level and below its minimum toxic level in order to;

a) Obtain the desired therapeutic effects.

b) Avoid undesired toxic effects.

c) Minimize side effects.

Sustained release drug delivery systems (SRDDS) are designed to achieve therapeutically effective concentrations of a drug in the systemic circulation for a prolonged period of time. The time release technology is also known as sustain action, extend release, sustained release (SR), controlled release, prolonged release and delayed release etc (Khachane et al., 2011; Pundir et al., 2013) A well designed controlled drug delivery system can solve overcome some of the problems of conventional therapy and increase the therapeutic effectiveness of a given drug. To achieve maximum therapeutic efficacy, it becomes essential to deliver the active agent to the target tissue in the optimal amount in the right period of time there by cause little toxicity with nominal side effects. There are various approaches in delivering a therapeutic substance to the target site in a controlled release approach. One such is using microspheres as carriers for drugs. Microspheres are usually free flowing powders contain of proteins or synthetic polymers are biodegradable in nature and ideally having a particle size less than 1-1000 μm (Alagusundaram et al., 2009; Thanoo et al., 1992).

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Advantages

1. Microspheres provide constant and prolonged therapeutic effect.

2. They decrease the dosing frequency and thus improve the patient compliance.

3. They could be injected into the body due to the spherical

Table 1. Specific characteristics of microspheres (Kunchu et al., 2010)

S. No.	Property	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

shape and smaller micron size.

4. Better drug utilization there by it will improve the bioavailability

5. Reduces the frequency or intensity of adverse effects.

6. Microsphere a controllable variability in degradation and drug release. (Kalyan et al., 2010)

7. Reliable means of site specific drug targeting by maintaining the desired concentration at the site of interest without any untoward effect.

8. Biodegradable microspheres provide sustained release of drug throughout the particle matrix.

9. Target drug to various diseased sites such as targeting of anticancer drugs to the tumour cells.

10. The size, surface charge and surface hydrophobicity of microspheres have been found to be an important factor in determining the fate of particles in vivo. (Bonita et al., 1998)

Limitations

Some of the disadvantages were found to be as follows

1. The modified release from the formulations.

2. The discharge rate of the controlled release dosage form may differ from a range 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 higher dose of drug and thus may lead to potential toxicity.

5. Dosage forms of this kind should not be crushed or chewed.

Applications

1. Microspheres applicable in different drug delivery systems:

2. Ophthalmic Drug Delivery

3. Oral drug delivery

4. Nasal drug delivery

5. Gene delivery

6. Intra-tumor and local drug delivery

7. Buccal drug delivery (Kalyan et al., 2010)

8. Gastrointestinal drug delivery

9. Transdermal drug delivery

10. Peroral drug delivery

11. Colonic drug delivery

12. Vaginal drug delivery

13. Multi-particulate delivery system

Materials used

Microspheres used usually are polymers.

They are classified into two types

1. Synthetic polymers

2. Natural polymers

1. Synthetic polymers

a) Nonbiodegradable polymers: Polymethyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

b) Biodegradable polymers: Lactides, their glycolides and their copolymers, Polyalkyl Cyano Acrylate, Polyanhydrides

2. Natural polymers: These are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin, and Collagen,

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch,

Chemically tailored Carbohydrates: Poly (acryl) dextran, Poly (acryl) starch **(**Bonita et al., 2010; Patel et al., 2011**)**

Types of Microspheres

Bioadhesive Microspheres (Prasanth et al., 2011; Vasir et al., 2003; Chandrawanshi et al., 2009)

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 (Chawla et al., 2009): Magnetic microspheres are supra-molecular particles that are tiny adequate to circulate throughout capillaries without construct embolic occlusion (<4μm)but are sufficiently subject(ferromagnetic)to be captured in microvessels and dragged into the adjuscent tissues by magnetic field of 0.5-0.8 tesla.

Floating Microspheres (Patel et al., 2011; Chawla C et al., 2003; Hafeli et al., 1992): Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for extended period without disturbing gastric

emptying rate. The drug is released slowly at the desired rate.

Radioactive Microspheres (Hafeli et al., 1992): Radioactive microspheres distribute high radiation dose to the targeted areas without damaging the normal adjacent tissues. They are injected to the arteries that lead to tumor of interest. The dissimilar kinds of radioactive microspheres are α emitters, β emitters and γ emitters.

Polymeric Microspheres (Gholap et al., 2010): Biodegradable polymeric microspheres are those which contain biodegradable polymers which prolong the residence time after contact with mucous membrane due to its high degree of swelling possessions with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and their release pattern in a sustained manner. Artificial polymeric microspheres are those which are made up of synthetic polymers and are used as used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. (Ramteke et al., 2012).

Application of microspheres in drug delivery

There are several applications of microspheres some of which are stated as follows:

1. Targeting of Active Agents

Inactive: Here the term inactive means that the microsphere surface is not modified in any means. These unmodified microspheres gather in specific tissue reticuloendothelial system

Active: The term active indicates to alter microsphere surface with ligand (antibodies, enzymes, protein, and polysaccharides)

Physical: Temperature or pH sensitive microspheres

2. Directly to diseased site

- Increasing Efficacy and Decreasing Toxicity
- Changes the absorbance and biodistribution
- Delivers drug in desired form
- In case of multidrug resistance helps to prevent drug interactions
- Protection of Active Agent
- Decreases harmful side effects
- Protects drug that undergoes metabolism in gastrointestinal environment
- Providing Desired Release Profile
- Affects the time in which the drug is released
- Prolong time -increases duration of action and decreases frequency of administration
- Dependent on drug and polymer properties

Methods of microsphere preparation

These techniques of microsphere preparation and its choice are determined by various formulation and technology related factors as mentioned below:

The physical, chemical and biological activity of the incorporated drugs should be maintained during the microencapsulation method. The microspheres should have high encapsulation efficiency and yield enough for mass production. The microspheres should possess the reasonable size range for the oral and parenteral administration. It should not be longer than 180 μm for parenteral administration. Particles greater than 7 μm get entrapped in the capillary. Particles coated with a polymer (poloxamer) and of size 60-150 nm are taker up to a considerable extent by the bone marrow. Similarly, particles of size larger than 250 nm can be used for spleen targeting. The release profile of the drug should be reproducible without significant initial burst. The technique employed for microspheres production should produce free-flowing microparticles effective for uniform suspension of the microparticle. The process should not adversely affect the stability of the drug. No toxic reaction or product should be produced with the final product.

Spray Drying (An anhydrous technique): Spray drying is another method for preparation of microspheres. It involves the use of volatile organic solvents such as dichloromethane, acetone, etc in which polymer is first dissolved as. Then the solid drug is slowly dispersed in this polymer solution along with continuous stirring at high speed homogenization. After a homogenous mixture is obtained, this dispersion is atomized in a stream of hot air and the process is known as atomization. Small droplets or the fine mist of drug polymer solutions form after evaporation of volatile solvent instantaneously that leads to the formation of the microspheres in a size range 1-1000 μm. These micro particles are then separated by means of the cyclone separator from the hot air and the traces of the left over solvent is removed by vacuum drying. Spray drying method has the major advantage of being rapid, feasible under aseptic conditions and leads to the formation of porous micro particles. The spray drying obtained microspheres can be improved in quality by the addition of plasticizers such as citric acid, which promote polymer coalescence on the drug particles and hence help in the formation of spherical and smooth surfaced microspheres. Further, the rate of spraying, the feed rate of polymer drug solution, nozzle size, and the drying temperature affects the size of microspheres. This method of microencapsulation is however simple, reproducible, easy to scale up and independent of the solubility characteristics of the drug and polymer.

Solvent Evaporation: Solvent evaporation method is again similar to spray drying involving the use of volatile organic solvent. This process is the most extensively used for microencapsulation and carried out in a liquid manufacturing vehicle. Here the process consists of two phases: first is the buffered or plain aqueous solution phase of the drug with or without a viscosity building or stabilizing agent and second is the organic phase consisting of polymer solution in volatile solvents likes dichloromethane (or ethyl acetate or chloroform). This polymer solution dispersed in a volatile solvent is immiscible with the liquid manufacturing vehicle phase. The core material that needs to be microencapsulated is first dispersed in the liquid manufacturing vehicle phase with vigorous stirring to form the primary water in oil emulsion. The emulsion mixture is then either added to a large volume of water containing an emulsifier like PVA (polyvinyl alcohol) or PVP (poly vinyl pyrrolidone) to form the multiple emulsions (w/o/w). The double emulsion mixture is heated if necessary to evaporate the volatile solvent under continuous stirring. The polymer shrinks around the core material that may be either water soluble or water insoluble materials. After a particular time when whole of the solvent evaporates the core materials get encapsulated by the polymer solution leaving solid microspheres. These microspheres can then be washed, centrifuged and lyophilized to obtain the free flowing and dried microspheres of appropriate size.

Hot Melt Microencapsulation: In this the polymer is first melted and then mixed with drug molecules that already have been sieved to a particular size. Then this mixture is suspended in a non-miscible solvent like silicone oil with continuous stirring, and heating at 5°C above the melting point of the polymer. After the emulsion gets stabilized, it is cooled to solidify polymer particles. The resulting microspheres obtained range in diameter from 1-1000 m, are then washed by decantation with petroleum ether as represented. This method is appropriate for microencapsulation of water labile polymers, e.g. polyanhydrides. The only advantage of this technique is moderate temperature to which the drug is exposed.

Single emulsion technique: In this method a dispersion or solution of natural polymers is prepared in aqueous medium. This mixture is then dispersed in the non-aqueous medium such as oil followed by cross linking of dispersed globules either by means of heat or chemical cross linking agents. Based on the type of cross linking the method is classified as:

Thermal cross-linking method: In this method cross linking is done by adding dispersion to previously heated oil under continuous stirring to obtain microspheres of specific size range. However this method is suitable for thermo labile drugs as heat denaturation of drug occurs.

Cross linking agent method: This method involves the use of certain cross linkers such as glutaraldehyde, formaldehyde, di-acid chloride, etc. for microsphere preparation. This technique suffers from excessive exposure of active ingredients to chemicals if added at the preparation time. First, a specific concentration solution of polymer in aqueous medium is prepared which is then added under continuous stirring to the continuous phase consisting of oil and surfactant to form water in oil (w/o) emulsion. Then a drop-by-drop solution of a measured quantity of aqueous cross linkers is added at specific time intervals to allow uniform mixing. Stirring was continued for a particular time until microspheres of specific size range are obtained which are then separated using a washing organic solvent.

Double emulsion method (A hydrous technique): This method involves the formation of multiple emulsions or double emulsion of type water in oil in water (w/o/w) and is best suited for water soluble drugs. It involves both natural as well as synthetic polymers in formulation. First an aqueous drug polymer solution is dispersed in a lipophilic organic continuous phase under vigorous stirring to form a homogeneous mixture. The continuous phase consists of polymer solution that eventually encapsulates the drug present in dispersed aqueous phase. This primary emulsion is then subjected to sonication before addition to aqueous solution of polyvinyl alcohol (PVA) that results in the formation of double emulsion. The later double emulsion formed is subjected to solvent evaporation or solvent extraction process by maintaining emulsion at reduced pressure or stirring so that volatile organic phase evaporates out. The emulsion is added to the large amount of water (with or without surfactant) into organic phase diffuse out and the solid microspheres are separated out by filtration and washing.

Polymerization (Pundir et al., 2013; Chawla et al., 2003; Hafeli et al., 1992): The polymerisation techniques conventionally used for the preparation of the microspheres, are mainly classified as:

1. Normal polymerisation

2. Interfacial polymerisation

Normal polymerization (Kalyan et al., 2010) - Normal polymerisation proceeds and is carried out using different techniques as bulk, suspension precipitation, emulsion and micellar polymerisation processes. In bulk polymerisation, a monomer or a mixture of monomers alongside with the initiator or catalyst is generally heated to initiate polymerization. Polymer so obtained may be molded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also transformed as bead or pearl polymerization. Now it is

reputable out by heating the monomer or combination of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also include an initiator and other additives. Emulsion polymerization differs from suspension polymerization as payable to the presence initiator in the aqueous phase, which afterward on diffuses to the surface of micelles. Bulk polymerization has an improvement for the formation of pure polymers.

Interfacial polymerization: It involves the reaction of various monomers at the crossing point 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 of which is dissolved in the continuous phase while the other being dispersed in the continuous phase.

Phase separation/ Coacervation (Kalyan et al., 2010): Phase separation method is mostly considered for preparing the reservoir type of the system. This method is used to encapsulate water soluble drugs like peptides, proteins and some of preparations having matrix type particular, when the drug is hydrophobic in nature as steroids. In this procedure the polymer is first dissolved in a suitable solvent and then drug is dispersed by making its aqueous solution, if hydrophobic or dissolved in polymer solution itself, If hydrophobic. Phase separation is then proficient by changing the solution conditions by the salt addition, on-solvent addition, addition of the incompatible polymer or change in PH.

Solvent extraction (Alagusundaram et al., 2009): Solvent extraction method is used for the preparation of the micro particles, involves elimination of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents like as Isopropanol and organic phase is removed by extraction with water. This method may decrease the hardening time of microspheres. The process involves through addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

Emulsion solvent diffusion technique (Kunchu et al., 2010, Sharma et al., 2017): The colon floating microspheres were prepared with using emulsion solvent diffusion technique in order to get better the residence time. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and subsequently the mixture was added drop wise to sodium lauryl sulphate (SLS) solution. The solution was well stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. as a result the formed floating microspheres were washed and dried in a dessicator at room temperature.

Physicochemical characterization and evaluation

1. Particle size and shape: Characterized by Laser microscopy, scanning electron microscopy.

2. Electron spectroscopy for chemical analysis: Find out surface chemistry.

3. Attenuated total reflectance of Fourier Transfom-Infrared Spectroscopy: Determines degradation of polymeric matrix.

4. Capture efficiency: % Entrapment = Actual content/Theoretical content x 100

5. Thermal analysis: By Differential Scanning Calorimetry (DSC)

6. Swelling index: Characterization of microspheres is performing with swelling index technique. Different solution (100mL) are in use such as (distilled water, buffer solution of pH (1.2, 4.5, 7.4) are take and alginate microspheres (100mg) are to be place in a wire basket and set aside on the above solution and swelling is allow at 37°C and changes in weight variation among initial weight of microspheres and weight due to swelling was measure by taking weight periodically and soaked with filter paper (Sharma et al., 2016).

Swelling Index = Initial weight – Final weight/ Initial weight × 100

7. Floating behavior: 50 milligrams of the floating microspheres are place in 100 ml of the simulated gastric fluid (SGF, pH 2.0) contain 0.02% w/v Tween 20. The mixture is stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant microspheres is pipette out and separate by filtration. Particles in the sinking particulate layer are separated by filtration. Particles of both types are dried in desiccators until constant weight is achieved. Together the fractions of microspheres weighed and buoyancy is calculated by the weight ratio of floating particles to the addition of floating and sinking particles.

Buoyancy (%) = Wf/Wf+Ws

Where, Wf and Ws are the weights of the floating and settle microparticles.

8. Micromeritic properties like as tapped density, bulk density, compressibility index, angle of repose are also studied.

9. Release studies for diverse type of microspheres are carried out by using different suitable dissolution media, generally by rotating paddle apparatus (USP / BP).The speed of rotation varies from 50-100 rpm. The samples are in use at a specific time interval and replaced by same amount of dissolution medium. The active ingredient withdrawn in the sample is analysed as per monograph requirement and release profile is measured by using the plot amount released as a function of time. Dialysis and Franz diffusion cell method is also used.

10. Isoelectric point, Surface carboxylic acid residue, Surface

amino acid residue are also calculated (Sharma et al., 2017).

Factors Affecting Release Rates of drug through microspheres

The microsphere formulation method is a governing factor in the encapsulation and release of therapeutics (Sharma et al., 2016). In addition, a complicated array of factors with the type of polymer, the polymer molecular weight, the copolymer composition, the nature of any excipients mixed to the microsphere formulation (e.g., for stabilization of the therapeutics) (Sharma et al., 2017), and the microsphere size can have a physically powerful impact on the delivery rates of drug. On the basis of the rate of hydrolysis of their functional groups, polymers can be generally categorized into two types: surface eroding and bulk-eroding (Sharma et al., 2017).Bulk-eroding polymers, such as PLG, readily permit permeation of water into the polymer matrix and degrade during the microsphere matrix. In contrast, surface-eroding polymers, such as polyanhydrides, are consists of relatively hydrophobic monomers linked by labile bonds (Sharma et al., 2016). In this manner, they are able to oppose the penetration of water into the polymer bulk, while degrading quickly into oligomers and monomers at the polymer/water interface through hydrolysis.

Bulk-eroding polymer microspheres are frequently characterized by a "burst" of drug molecules as a large amount as 50% of the total drug load released through the first few hours of incubation, followed by a slow, diffusion-controlled release and sometimes a third phase in which the left behind drug is released quickly as a result of severe degradation of the polymer matrix. In microspheres collected of surface-eroding polymers, drug molecules are released mainly at the surface as the polymer breaks down around it. Erosion of such polymers usually proceeds at a constant velocity. If the drug of concern is homogeneously dispersed throughout a microsphere, the largest rate of release will occur at the beginning. As time proceeds, the surface area of the sphere and the release rate decrease asymptotically (Sharma et al., 2017).

Future prospects of microspheres formulations in controlled drug delivery

A variety of formulations are come under in novel drug delivery such as herbosomes, quantum dots, microsponge, effervervescent granules and nanoparticles (Shukla et al., 2012; Sen et al., 2015; Garg et al., 2016; Gupta et al., 2013; Garg et al., 2015). Microsphere like other formulation are using in delivery of herbal active constituents. Controlled drug delivery faces many challenges but, still it poses a tremendous way of future prospects. Therefore, a huge devotion deserves for its growth and exposure. Also, we can transform the design and development of controlled drug delivery by the application of different types of polymers. Challenges in controlled drug delivery such as compounds having large molecular weight that firstly degrade in the blood therefore, some proteins, carbohydrates, nucleic acids and peptides are found in the form of DNA. These biopharmaceuticals having limited capacity to pass the biological barriers and less oral bioavailability produced. To overcome this problem, we have to develop a number of drug delivery technologies. It can be achieved by contributing some more ways (Sharma et al., 2017).

1. Designing a novel drug- delivery system with drug molecules which having multi-potential activity.

2. Designing a drug delivery which acts locally.

3. More accurate route for making the drug responsive and greater sensitivity.

4. Delivering the insulin orally with body- friendly polymers with improved systemic absorption.

5. We can increase the commercial availability by reducing the cost.

Nowadays, controlled drug delivery technologies are able to incorporating a drug with newer delivery systems to provide maximum therapeutic efficacy and safety. A number of pharmaceutical companies are forwarded to develop new delivery technologies and marketing a number of products.

Conclusion

Microsphere is a small word but it is having wide applications in drug delivery systems. Mainly important in targeted drug delivery such as (Bioadhesive microspheres-nasal, ocular, buccal, rectal etc., Magnetic microspheres and radioactive microspheres – For tumours), Controlled and sustained drug delivery (Polymeric microspheres, Floating microspheres). By combinations through various strategies, microspheres will discover central place in novel drug delivery mainly particularly in cell sorting, diagnostics and Genetic engineering. From the study it is proved that Microspheres act as precious carriers for the novel drug delivery system.

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