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Microsphere: a Novel Drug Delivery System

Pharmacy

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ABSTRACT

Microspheres are particulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to deliver the drug at a predetermined rate. They are made from polymers, waxy or natural, semi synthetic materials such as proteins and Carbomers. Microspheres are characteristically free flowing fine to cores powders having particle size ranging from 1-1000 µm. The method for the preparation of microspheres provides multiple aspects to control as drug delivery and to enhance the therapeutic efficacy in multiples of a given drug. These delivery systems offers maximum advantages over conventional dosage forms, which accounts for improved efficacy, reduced toxicity, improved patient compliance and convenience, reduced dosage frequency. The literature study highlights applications of microspheres, types of microspheres, methods of preparation and their parameters to evaluate microsphere efficiency. Microspheres are like Floating microspheres, Bioadhesive microspheres, Polymeric microspheres, Biodegradable polymeric microspheres, Magnetic microspheres, Radioactive microspheres, Synthetic polymeric microspheres and are prepared by methods like Spray Drying, Solvent Evaporation, Single emulsion technique, Double emulsion technique, Phase separation co-acervation technique, Spray drying and spray congealing, Quassi emulsion solvent, diffusion Solvent extraction. Due to convenience of preparation, formulations stability, controlled and sustained release behaviors of microspheres have wide range of applications.

Microspheres are small particulate spherical particles, with diameters 1 µm to 1000 µm. They are sometimes referred to as micro-particles and can be manufactured from various natural and synthetic and semi-synthetic materials including Polystyrene, polyethene, chitosan, cellulose derivatives, alginates[1].

Oral route drug administration is most preferable route for taking medications. However, their short circulating half-life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. Rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamics profile is to release the drug in a controlled manner and site specific manner [1,5,9].

Materials used[1,3]: Microspheres used usually are polymers. They are classified into two types

1. **Synthetic polymers**
2. **Semi-synthetic polymers**
3. **Natural polymers**

1 Synthetic polymer

Nonbiodegradable polymers[5]: Polymethyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

Biodegradable polymers[6]: Lactides, their glycolides and their copolymers, Polyalkyl Cyano Acrylate, Polyanhydrides

2 semi synthetic[2]: metal anginate derivatives, cellulose derivatives, acrylic acid derivatives. Modified Carbohydrates: Poly (acryl) dextran, Poly (acryl) starch.

3 Natural polymers[4]

These are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin, And Collagen, Carbohydrates: Agarose, Carrageenan, Chitosan, Starch.

Ideal characteristics of microspheres: [5,6]

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: [6,7,9,11]

1. Increase solubility of the poorly soluble drug due to particle size reduction.
2. Drug release is constant hence prolonged therapeutic effect.
3. Provide constant drug concentration in blood there by less or no toxicity,
4. Decrease dose and increase efficacy.
5. Protect the drug from enzymatic and photolytic cleavage hence stable for long time.
6. Provides prolonged therapeutic effect.
7. Improve the patient compliance by reducing the dosing frequency.
8. The spherical shape and smaller size makes them to be injected into the body.
9. Polymers used in microspheres prevents drug metabolism at their cost hence less drug with increase bioavailability under controlled incidence or intensity of adverse effects.
10. Microsphere morphology allows a controllable variability in degradation and drug release.7
11. Conversion of oil and other liquids to solids for ease of handling
12. Taste and odor masking
13. To delay the volatilization
14. Safe handling of toxic sybstances[1]

Disadvantages of microspheres: [6,8]

1. The altered release from the formulations.
2. The release rate of the controlled release dosage form may vary from a variety of factors like GI content and the rate of transit though gut.
3. Differences in the release rate from one dose to another due to manufacturing faults.
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.7
6. Dose dumping: loss of physical integrity by various factors like manufacturing faults, crushing and co administering with other drugs.
7. Release reproducibility is difficult.

Types of Microspheres

1. **Bioadhesive Microspheres[10]:** These microspheres exhibit a prolonged residence time at the site of application due to bio-adhesiveness and causes intimate contact with the absorption site and maintains continuous drug release.

2. **Magnetic Microspheres[11]:** Magnetic microspheres are magnetically controlled releasable supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<5**µm)but are sufficiently** susceptible Microspheres: as carriers used for novel drug delivery system to be captured in micro vessels and dragged into the adjacent tissues by magnetic field of below 1.0 tesla.

3. **Floating Microspheres[12]:** Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period without affecting gastric emptying rate. The drug is released slowly at the predetermined rate.

4. **Radioactive Microspheres[18]:** Radioactive microspheres deliver high radiation dose to the targeted areas for example tumor cells with minimal damage to the normal surrounding tissues. They are injected to the arteries that lead to tumors of interest.

5. **Biodegradable Polymeric Microspheres[13]:** Biodegradable polymeric microspheres prolongs the residence time when contact with mucous membrane due to its high degree of swelling property within aqueous medium that results in gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner.

METHOD OF PREPARATION:

1. Spray Drying
2. Solvent Extraction
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Spray drying and spray congealing
7. Solvent extraction

1. Spray drying[14]: The polymer dissolved in a suitable volatile organic solvent such as acetone, dichloromethane etc. The drug in the solid form is then dispersed or dissolved in the polymeric solution under high speed homogenization. This dispersion is then atomized in a stream of hot and dry air in opposite flow that leads to the formation of small droplets from which the solvent evaporates instantaneously leading the formation of microspheres before settle down into the bottom of spray dryer.

2. Solvent extraction[14,15]: this method involves in the preparation of the microsphere, by extraction of the organic solvent phase. The process involves direct addition of the drug or protein to polymeric organic solution followed by solvent removal by extraction method that depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

3. Single emulsion technique[16]: The natural polymers are dissolved/dispersed in aqueous medium followed by dispersion in the non-aqueous medium e.g. oil with simultaneous continuous stirring. 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.

4. Double emulsion technique[17]: Double emulsion technique is best suited to water soluble drugs, peptides, proteins and vaccines. The aqueous protein solution containing active drug is dispersed in a lipophilic organic continuous phase with simultaneous continuous sonication. The continuous phase is generally consisted of the polymer solution that eventually encapsulates the protein contained in dispersed aqueous phase results in primary emulsion. This is then subjected to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA that results in formation of a double emulsion. Emulsion is then subjected to solvent removal by solvent evaporation at reduced pressure. The solid microspheres are subsequently obtained by filtration and washing with acetone.

5. Polymerization: The polymerization techniques conventionally used for the preparation of the microspheres, it is carried out by mixing a mixture of monomers and drug along with the catalyst usually heat is used to initiate polymerization.

6. Phase separation-coacervation: This method is used to encapsulate water soluble drugs e.g. peptides, proteins. The method includes the dissolution of polymer in a suitable solvent followed by drug dispersion. Phase separation is then accomplished by changing the solution conditions by the salt addition, odd-solvent addition, addition of the incompatible polymer or change in PH.

7. Emulsion Solvent Evaporation: this technique includes the drug is dissolved in polymer solution of chloroform and the resulting solution is added to aqueous phase containing 0.3 % sodium of PVP as emulsifying agent. The above mixture was agitated continuously then the drug and polymer was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralized water and desiccated at room temperature for 24 hrs

EVALUATION PARAMETERS

1. **Physicochemical Evaluation Characterization[12]:** The characterization of the micro-particulate carrier is an important phenomenon, which helps to design a suitable carrier for the drug, proteins or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.

2. **Particle size and shape:** The most widely used procedures to visualize microparticles are conventional light microscopy (LM), scanning electron microscopy (SEM) and Laser light scattering may be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned.

3. **Electron spectroscopy for chemical analysis:** The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the degradation of the biodegradable microspheres

4. **Attenuated total reflectance Fourier Transfom- Infrared Spectroscopy:** FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material.
5. **Density determination[21]:** The density of the microspheres can be measured by using a pycnometer. Accurately weighed sample

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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.

6. **Isoelectric point15:** The 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, or ion absorption nature of the microspheres.

7. **Angle of contact[19]:** The angle of contact is measured to determine the wetting property of a microsphere carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres.

8. **Drug entrapment efficiency:** Drug entrapment efficiency can be calculated using following equation.
   % Entrapment = Actual content/Theoretical content x 100.

9. ***In vitro methods*[18]:** In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc.
   Dissolution apparatus[20]: Standard USP, BP or I.P. dissolution apparatus have been used to study in vitro release profiles using both rotating basket. Dissolution medium used for the study 900 ml and speed of rotation from 50-100 rpm.

10. **Swelling Index[11]:** Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using balance. The hydrogel microspheres then dried in an oven at 60° for 5 h until there was no change in the dried mass of sample. 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

Conclusion:

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Hollow microsphere promises to be potential approach for gastric retention that's why microspheres are of great interest that having wide applications in drug delivery systems. Most important are ocular, buccal, Bioadhesive, nasal, rectal etc., Magnetic microspheres and Radioactive microspheres are becoming promising tool for tumors treatments, Sustained and controlled drug delivery (Polymeric microspheres, Floating microspheres). By combining various strategies simultaneously, microspheres will find central place in novel drug delivery systems mainly particularly in cell sorting, diagnostics and Genetic engineering. From the study it is proved that Microspheres act as effective carriers for the novel drug delivery system.

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