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Review Article: Microspheres as a novel drug delivery system

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ABSTRACT

Microspheres are multiparticulate drug delivery systems designed to achieve prolonged or controlled drug delivery in order to improve bioavailability, stability, and to target the drug to a specific site at a predetermined rate. They are made of polymeric waxy or other protective materials like natural, semi-synthetic, or synthetic polymers.Microspheres are a novel drug delivery system that can be used as a therapeutic alternative to traditional or immediate release single-unit dosage forms. Microspheres are free-flowing spherical powders with particle sizes less than 1000 micrometers, consisting of biodegradable ,synthetic polymers and proteins. The microsphere increases bioavailability and the side effects are reduced also stability is improved, dose frequency is reduced, and the drug is delivered to a specific site at a predetermined rate.The current review focuses on different types of microspheres, different methods of preparation, applications, and various parameters to evaluate their efficiency.

Keywords: Controlled drug delivery, Microsphere, Polymers, Novel drug delivery, Preparation methods Types.

INTRODUCTION

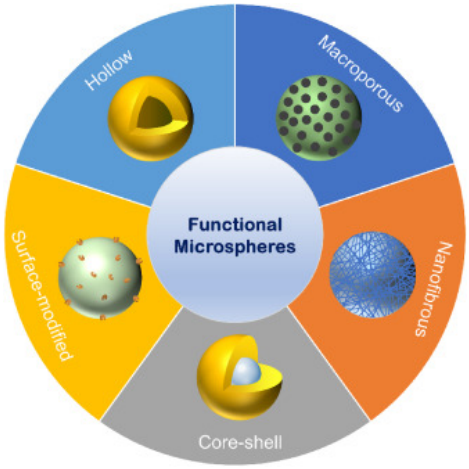

Figure No. 1: TypeofMicrospheres

The limitations of traditional dosage forms and traditional oral drug delivery systems are propelling the pharmaceutical community into a new era of drug delivery systems known as Novel Drug Delivery Systems (NDDS). The concept of targeted drug delivery, as a subset of NDDS, is currently being extensively researched. The concept of targeting, on the other hand, is not new in the drug delivery domain. Sir Paul Ehrlich proposed the concept of the'magic bullet' in 1906, laying the groundwork for a new paradigm in the field of drug delivery. Since then, the concept has been constantly evolving, with newer and more innovative approaches adding to the existing knowledge[1].

The selective accumulation of cargo in organs, tissues, cells, or intracellular structures by systemic or local drug delivery is referred to as targeting. The preferential accumulation of drugs at the targeted site prevents the rest of the body's healthy tissues and increases the drug's therapeutic index, improving the entire therapeutic outcome. Targeting a drug delivery system requires the use of carriers such as nanoparticles, liposomes, micellar systems, microspheres, and so on. The increasing number of studies in recent years demonstrating the potential use of microspheres as drug delivery carriers for targeted delivery increased the interest of researchers worldwide. Microspheres are free-flowing particles with diameters ranging from 1 μm to 1000 μm that can deliver therapeutics with a satisfactory sustained release/controlled release profile[2].

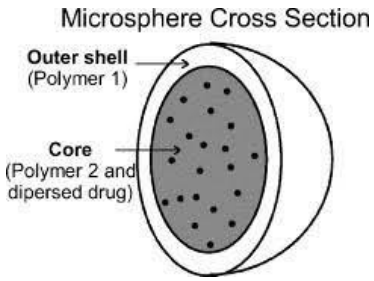

Figure No.2:Microspheres

Advantages of microspheres [3,4,5]:

- Reduced microsphere size contributes to increased surface area of the drug delivery system, which increases the potency of the poorly soluble material.
- Reduces the dosing frequency which increases patient compliance.
- Microspheres provide controlled and prolonged therapeutic effect.
- Because of their spherical shape and small size, they could be injected into the body.
- Dose dumping is decreased.
- It masks odor and taste.
- Increases bioavalibility of the drug.

Limitations of microspheres[6,7] :

- The costs of the controlled release preparation's materials and processingare significantly higher than those of standard formulations.
- Non uniform release of drug may cause toxic effects.
- Process variables such as temperature, pH, solvent addition, and evaporation/agitation may all have an impact on the stability of the product core.

TYPES OF MICROSPHERES

There are various types of microspheres are as follows:

- Bioadhesive microspheres
- Magnetic microspheres
- Floating microspheres
- Radioactive microspheres
- Polymeric microspheres

1. Bioadhesive microspheres[8] :

Adhesion is the sticking of a drug to a membrane using the sticking property of water soluble polymers. Bio adhesion refers to the adhesion of a drug delivery device to a mucosal membrane such as the buccal, ocular, rectal, or nasal membrane. These microspheres have a longer residence time at the application site, resulting in close contact with the absorption site and improved therapeutic action.Natural polymers such as starch are used with the idea that they are naturally biodegradable, biocompatible and bioadhesive also.

2. Magnetic microspheres[9,10] :

This type of delivery system is critical for localizing the drug to the disease site. A greater amount of freely circulating drug can be replaced by a smaller amount of magnetically targeted drug in this case. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials such as chitosan, dextran, and others.

The various types are :

- Therapeutic magnetic microspheres: These are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

- Diagnostic microspheres: They can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

3. Floating microspheres[11] :

Because the bulk density of floating forms is lower than that of gastric fluid, they remain buoyant in the stomach without affecting the rate of gastric emptying. As the body floats on gastric content and decreases gastric residence and plasma, the drug is gradually released at the target rate.The drug is released slowly at the desired rate,The prolonged therapeutic effect reduces the frequency of dosing.

4. Redioactive microspheres[12]:

Therapy for radio emobilisation Microspheres 10-30 nm in size are larger than capillaries and, when encountered, get tapped in the first capillary bed. They are injected into the arteries leading to the tumour of interest. In all of these circumstances, radioactive microspheres deliver high radiation doses to the targeted areas while causing no harm to the normal surrounding tissues. It differs from drug delivery systems in that radioactivity is not released from microspheres but instead acts from within a ^{radioisotope} typical distance, and the various types of radioactive microspheres areα emitters, β emitters, γ emitters.

5. Polymeric microspheres[13] :

There various types of polymeric microspheres are classified as:

a) Biodegradable Polymeric microspheres:

Natural polymers like starch are used because they are biodegradable, biocompatible, and bio adhesive in nature. Because of their high degree of swelling in aqueous medium, biodegradable polymers have a longer residence time when in contact with mucous membranes, resulting in gel formation. The rate and extent of drug release are controlled in a sustained manner by polymer concentration and release pattern. The main disadvantage is that drug loading efficiency of biodegradable microspheres in clinical use is complex, making drug release difficult to control. They do, however, have a wide range of applications in microsphere-based treatment.

b) Synthetic polymeric microspheres:

Synthetic polymeric microspheres are widely used in clinical applications; they are also used as bulking agents, fillers, embolic particles, drug delivery vehicles, and so on, and have been shown to be safe and biocompatible. However, the main disadvantage of these microspheres is that they tend to migrate away from the injection site, posing a risk of embolism and further organ damage.

PREPARATION METHODS OF MICROSPHERES

1. Solvent Evaporation
2. Single emulsion technique
3. Double emulsion technique
4. Coacervation Method
5. Spray drying and spray congealing
6. Solvent extraction
7. Quasi Emulsion Solvent Diffusion

1. Solvent Evaporation[14,15]:

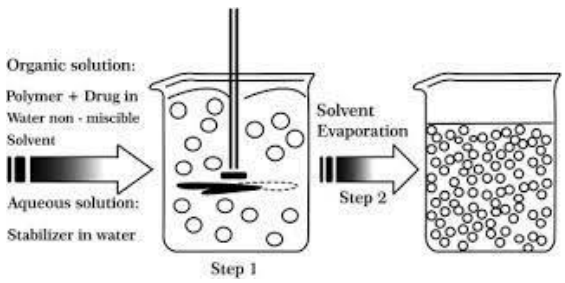

Figure No. 3 :Solvent evaporation technique.

The polymer is dispersed in an organic solvent, and the drug is either dissolved or dispersed in the polymer solution. The product solution is then emulsified into an aqueous phase containing the required additives (surfactants / polymer) in water emulsion to form oil. The natural After emulsion formation, the solvent is evaporated either by increasing the temperature under pressure or by increasing the pressure or by constantly stirring. When the solvent is removed, the polymer precipitates at the droplet / water interphase, resulting in cavity formation.

2. Single emulsion technique[16] :

Single emulsion technique is used to produce micro particulate carriers of natural polymers, such as proteins and carbohydrates. Natural polymers are dissolved or dispersed in aqueous medium before being dispersed in a non-aqueous medium such as oil. The dispersed globules are then crosslinked in the following step. Cross linking can be accomplished using either heat or chemical cross linkers. Chemical cross linking agents such as glutaraldehydes, formaldehyde, acid chloride, and others are used. Heat denaturation is not suitable for the more labile substances. Chemical cross linking has the disadvantage of exposing the active ingredient to chemicals excessively if added during preparation and then subjected to centrifugation, washing, and separation. Size, size distribution, surface morphology, loading, drug release, and bio performance of the final multi particulate product are all greatly influenced by stabilizing the emulsion phase.

3. Double emulsion technique[16] :

The dual microspheric emulsion preparation process includes the production of several emulsions or dual emulsions of type w / o / w and is ideal for water-soluble medications, peptides,proteins, and vaccines. This method works well with both natural and synthetic polymers. The solution of the aqueous protein is distributed in a continuous lipophilic organic flow. The active ingredients can contain this protein solution. In general, the continuous phase is made up of polymer solution. This eventually encapsulates the protein in the dispersed aqueous phase. The initial The emulsion is then homogenized or sonicated before the polyvinyl alcohol (PVA) is added. Aqueous solution is introduced. As a result, a double emulsion is formed.The solvent is then removed from the emulsion, either by evaporation with solvent or extraction with solvent.

Using the process of evaporating / extracting double emulsion solvent, a variety of hydrophilic drugs, vaccines, proteins / peptides, and traditional molecules are successfully introduced into the microspheres.

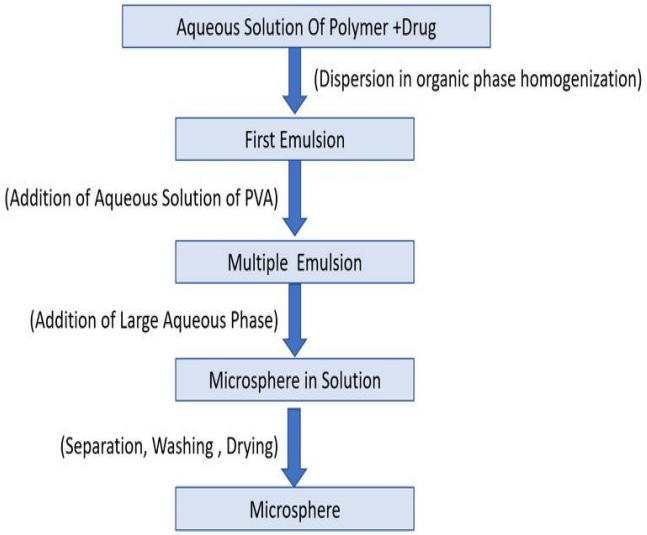

Figure No. 4 : Double emulsion technique.

4. Phase separation coacervation Method[17] :

It is a simple process that separates a micro molecular solution into two immiscible liquid phases. The co-conservation principle involves decreasing polymer solubility in organic phases, which affects the formation of polymer-rich phases known as coacervates. This method involves the formation of the dispersion of drug particles in a polymer solution and the addition of an incompatible polymer system for separating the first polymer and encasing the drug particle.

5. Spray drying and spray congealing[18,19] :

These methods rely on the drying of polymer and drug mists in the air. The two processes are known as spray drying and spray congealing, depending on whether the solvent is removed or the solution is cooled. The polymer is first dissolved in a suitable volatile organic solvent, such as dichloromethane, acetone, or a mixture of these. The solid drug is then dispersed in the polymer solution using high-speed homogenization. This dispersion is then atomized in a hot air stream. Atomization produces small droplets or fine mists from which the solvent evaporates instantly, resulting in the formation of microspheres with sizes ranging from 1 to 100 m.The cyclone separator separates micro particles from hot air, while vacuum drying removes any traces of solvent. One of the major advantages is its ability to operate under aseptic conditions.

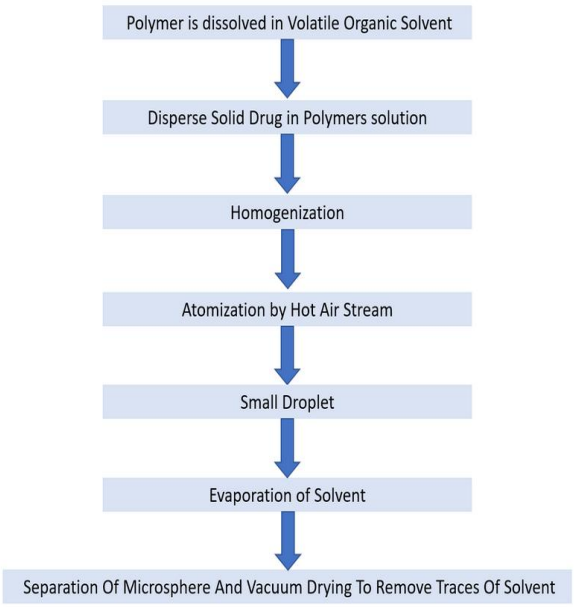

Figure No. 5 :Spray drying technique.

6. Solvent extraction[20] :

For the production of microspheres, the solvent extraction method is used, which involves the removal of the organic phase via extraction of the non-aqueous solvent. Water miscible organic solvents such as isopropanol are used in this method. Water extraction can be used to remove the organic phase. This procedure shortens the hardening time of the microspheres. One method involves directly incorporating the drug or protein into a polymer organic solution. The rate of solvent removal by extraction method is affected by water temperature, emulsion volume to water ratio, and polymer solubility profile.

7. Quasi Emulsion Solvent Diffusion[21]:

The quasi-emulsion solvent diffusion method is used to create controlled release microspheres of drugs using acrylic polymers. Microsponges can be used. Manufactured through the use of an external phase which is made up of distilled water and polyvinyl alcohol. The drug, ethanol, and polymers make up the internal phase. First, the internal phase is heated to 60^{o}C and added to the external phase.The external phase at room temperature. The combination is for 2 hour continuously stirred. Themicrosponges were separated by filtering from the mixture.

EVALUATION PARAMETERS[22,23]

1. Physicochemical Evaluation Characterization :

Characterization of the microparticulate carrier is an important phenomenon that aids in the development of a suitable carrier for protein, drug, or antigen delivery. The microstructures of these microspheres vary. These microstructures regulate the carrier's release and stability.

2. Particle size and shape

The most common methods for visualising microsphere are light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine microsphere shape and outer structure.

3. Entrapment efficiency:

Microspheres containing drug (5mg) are crushed and then dissolved in distilled water for 3 hours using an ultrasonic stirrer, filtered, and analysed using uv-vis spectroscopy. The ratio of actual drug content to theoretical drug content equals entrapment efficiency.

4. Fourier Transform-Infrared Spectroscopy (FT-IR):

FT-IR is used to determine the degradation of the carrier system's polymeric matrix. Alternate total reflectance (ATR) is used to investigate the surface of the microspheres.

The IR beam reflected many times through the sample as it passed through the ATR cell, providing IR spectra primarily of surface material. Depending on the manufacturing procedures and conditions, the ATRFTIR provides information about the surface composition of the microspheres.

5. Stability studies :

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

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

It was carried out for 60 days and content of the drug and effect of temperature inmicrosphere is analysed.

6. X-ray diffraction:

By this technique, change in thecrystalinity of drug can be determined. Micro particles and its individual components are analysed by the help of XRD Instrument. Scanning range angle between 80^{o}C - 70^{o}C.

7. Thermal analysis:

Thermal analysis of the microcapsule and its components can be performed using Differential scanning calorimetry (DSC), thermo gravimetric analysis (TGA), and differential thermometric analysis (DTA). The sample is accurately weighed and heated on an alumina pan at a constant rate of 10^{0}C/min under a nitrogen flow rate of 40 ml/min.

APPLICATION OF MICROSPHERES

1) Microspheres in vaccine delivery[24]:

A vaccine must be safe to use against microbes and their toxic components. An ideal vaccine should meet the requirements of effectiveness, protection, ease of use, and cost. The issue of safety and avoiding negative consequences is complicated. The mode of application has a strong influence on the aspect of safety and the extent of antibody response production. Biodegradable vaccine delivery systems for parenteral vaccines may address the shortcomings of conventional vaccines. The involvement in parenteral (subcutaneous, intramuscular, and intradermal) carriers exists, despite those who provide significant benefits, which include

a. Modulation of antigen release
b. Improved antigenicity
c. Stabilization of antigens

2) Gene delivery using microspheres [25,26] :

Technologies for genotype drug delivery include viral vectors, non-ionic liposomes, polycation complexes, and microcapsules. Even though viral vectors are extremely efficient and have a wide range of cell goals, they are important for genotype delivery. Even so, when used in vivo, they activate the immune system, causing pathogenic effects. Non-viral delivery systems for gene therapy have been developed to address the issues with viral vectors.The benefits of a non-viral delivery system include ease of preparation, cell/tissue targeting, a reduced immune system, unrestricted plasmid size, and large-scale replicable manufacture. Polymers are used in gene delivery applications as a DNA transporters.

3) Transdermal drug delivery[27] :

Polymers have excellent film-forming properties. The system's release profile is influenced by membrane thickness as well as film crosslinking. In-situ preparation of chitosan-alginate polyelectrolyte structures in beads and microspheres for potential applications in packaging, controlled release systems, and surgical instruments. Polymer gel beads are a highly biocompatible vehicle for the chemotherapy of inflammatory cytokines for medications such as prednisolone, and they also have a prolonged release action, which improves treatment efficacy. The amount of drug released was discovered to be dependent on the cell wall characteristics used. A chitosan membrane and chitosan hydrogel mixture containing lidocaine hydrochloride, a local anaesthetic, is an excellent overall process for controlled drug release and release kinetics.

4) Monoclonal Antibodies[28,29]:

Physiologically, immunomicrospheres are monoclonal antibodies that target microspheres. Monoclonal antibodies are highly precise compounds that can be used to direct microspheres containing bioactive molecules to specific sites. One of the following methods can be used to attach monoclonal antibodies to microspheres:

a. Non-specific adsorption
b. Specific adsorption
c. Direct coupling
d. Coupling via reagent

5) Other applications[29] :

Microspheres are used in membrane technology for mass spectrometry, cell biology, cell biology, and the Fluorescent-Linked Immuno-Sorbent Assay. Yttrium can be used to treat hepatocellular carcinoma as a standard treatment.

Microencapsulation has numerous applications in other industries. Microencapsulated products include carbonless copying paper, photosensitive paper, and microencapsulated fragrances such as "scent-strips" (also known as "snap-n-burst") and microencapsulated aromas ("scratch-n-sniff").

Microspheres are also widely used in diagnostic tests, such as temperature-sensitive microspheres for the temperature-dependent visual detection of cancer. Microspheres microbial cells are used in the biotech industry to produce recombinant and proteins.

CONCLUSION

Microspheres are important component of novel drug delivery system. It is more effective drug delivery system that can solve problems associated with traditional dosage forms.In the long run, a microsphere dosage form could be a novel technique for more effective treatment of a variety of diseases, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted, specific, and effective indelivery,they are found to be effective carriers for the novel drug delivery system.

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