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Formulation and Evaluation of Microspheres - A Review

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ABSTRACT

Multiarticulate drug delivery systems called microspheres are created to achieve delayed or controlled drug administration in order to increase bioavailability, stability and to target the drug to a specific place at a predetermined rate. They are made of natural, semisynthetic and synthetic polymers as well as other protective ingredients like polymeric wax. Microspheres are typically free-flowing powders made of proteins or synthetic polymers, with particle sizes ranging from 1-1000micro meters. The present review emphasizes numerous microsphere types, preparation methods like single emulsion techniques, double emulsion techniques, polymerization, phase separation /coacervation technique, spray drying, emulsion crosslinking method, solvent evaporation method, ionic gelation method, evaluation parameters like particle size analysis, density determination, isoelectric point, flow properties, angle of contact, determination of percentage yield, swelling index, drug content, entrapment efficiency, scanning electron microscope, zeta potential, Fourier transform infrared spectroscopy, differential scanning calorimetry, *invitro* drug release, and applications.

INTRODUCTION

The innovative medication delivery method aims to send the active ingredient to the site of action as soon as feasible and distribute pharmaceuticals at a rate that is suitable for the body's needs during therapy the most effective method drug delivery gets the active ingredient to the treatment site at a rate determined by the body's needs during the course of the course therapy. Drug carrier technology offers a clever way to distribute medications by fusing the drug to carrier particle like microspheres, nanoparticles, or lipids. [1]

Microspheres

Microspheres are tiny, spherical particles that typically have dimensions between 1 and 1000 micro meters. Microparticles are another name for microspheres. [2] Microspheres can be created from a variety of organic and inorganic materials, such as ceramics are commercially available polymers. They can also be created from a variety of natural and synthetic polymeric materials. Commercially available microspheres include glass, polymer, and ceramic varieties. Microspheres that are solid are hollow can be employed for a variety of purposes because of vastly varying densities the two most popular varieties of polymer microspheres are made of polyethylene and polystyrene. Microspheres made of polystyrene are frequently employed in biomedical applications. Microspheres made of polyethylene are frequently employed as permanent or temporary fillers. [3]

Advantages

- Microspheres have a consistent and long-lasting therapeutic impact.
- Reduces the frequency of dosing and there by improves patient compliance.
- Along with their spherical form and smaller size they may be inserted into the body.
- Improved drug utilization will improve bioavailability while lowering the risk of side effects.
- The morphology of microspheres allows for controlled variability in drug release and degradation.
- Oils and other liquids are converted to solids to make them easier to handle. [4]

Disadvantages

- A number of variables, including food and the rate of transit through the gut, can affect the release rate of the controlled release dosage form.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed. [5]

Applications

- Release of proteins, peptides and hormones over the extended period of time.
- Passive targeting of leaky tumor vessels, active targeting of tumor cells, antigens, by parenteral route.
- Magnetic microspheres can be used in stem cell extraction.
- Used for various diagnostic tests for infectious diseases like bacterial, viral and fungal.
- Used for the specific delivery of insulin to the colon.
- Used in transdermal drug delivery, buccal drug delivery, nasal drug delivery, gastrointestinal drug delivery etc.

Types of microspheres

1. Bio adhesive microspheres.
2. Magnetic microspheres.
3. Floating microspheres.
4. Radioactive microspheres.
5. Polymeric microspheres.

1. Bio adhesive microspheres

Adhesion is the process of a medication adhering to a membrane using the adhesive properties of water-soluble polymers. Bio adhesion can be defined as the attachment of a

medication delivery device to a mucosal membrane, such as the buccal, ocular, rectal, nasal, etc. These types of microspheres have a longer residence duration at the application site, which results in close contact with the site as absorption and improve therapeutic activity. [6]

2. Magnetic microspheres

The ability to deliver the medicine to the precise spot where it is required makes this form of delivery device crucial. In this circumstance, a smaller amount of magnetically targeted medicine will take the place of a large amount of the drug that is freely circulating. Magnetic responses to a magnetic field response to a magnetic field can be observed in chitosan, dextran, and other integrated materials utilized in magnetic microspheres. [7]

3. Floating microspheres

Gastro retentive medication delivery systems are based on floating microspheres because of their non-effervescent design. Hollow microspheres, micro-Ballons, or floating microspheres are terms used interchangeably with floating microspheres. Floating microspheres can be described as small, hollow objects without a core. The scale of these free-flowing cells ranges from 1 to 1000 micrometers. [8]

4. Radioactive microspheres

In radioembolization therapy larger than capillary microspheres, 10-30 nm-sized microspheres are tapped in the first capillary bed as they pass through and then inserted into the arteries that give rise to an interesting tumor. In each of these scenarios, radioactive microspheres provide a high dosage of radiation to the desired locations while sparing the healthy tissues around them. [9] It is different from a medicine delivery system in that radioactivity is not emitted from the microspheres; instead, it acts from a distance that is usual for a radioisotope, and the various radioactive microspheres types are $\propto -\text{emitters}$, $\beta - \text{emitters}, \gamma - \text{emitters}.$ [10]

5. Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres. [11]

- **Biodegradable polymeric microspheres**

Biodegradable microspheres are made of polymers. The idea behind using natural polymers like starch is that they are biodegradable. Both biocompatible and bioadhesive. Due to their high degree of swelling in aqueous media, biodegradable polymers extend the residence duration when in contact with mucous membranes, resulting in gel formation. The concentration of the polymer and the sustained release pattern regulate the rate and degree of medication release. The main disadvantage of using biodegradable microspheres for medication loading in clinical settings is that it can be challenging to regulate drug release.

- **Synthetic polymeric microspheres**

Synthetic microspheres made of polymer synthetic polymeric microspheres are utilized extensively in clinical moreover, it has been demonstrated to be safe and biocompatible when employed as a bulking agent, filler, embolic particles, drug delivery vehicles, etc. As relative activity is not released from microspheres but rather acts from within a radio isotope typical distance, the main drawback of these types of microspheres is that they have a tendency to migrate away from the injection site and pose a risk of embolism and further organ damage.

Method of preparation

Methods used for the preparation of microspheres are:

1. Single emulsion technique
2. Double emulsion technique
3. Polymerization

- Normal Polymerization
- Interfacial Polymerization

4. Phase separation / coacervation technique
5. Spray drying
6. Emulsion crosslinking method
7. Solvent evaporation method
8. Ionic gelation method. [12]

1. Single emulsion technique

This approach is used to create the microparticulate carries of natural polymers such as those of proteins and carbohydrates. After being dissolved or dispersed in an aqueous media such as water, the natural polymers are then disseminated in a non-aqueous media, such as oil. The crosslinking of scattered globules is done in the second step of preparation. There are two ways to cross-link materials using heat or chemical crosslinking agents like glutaraldehyde, formaldehyde, diacid chloride, etc. [13] [14] [15]

2. Double emulsion technique

The process of making two emulsions, or W/O/W, involves adding the primary W/O emulsion to a solution of aqueous polyvinyl alcohol. For 30 minutes, W/O/W emulsion must be continuously stirred, pour water into the emulsion gradually over the course of 30 minutes. Microcapsules collection through filtration and drying under vacuum. It works best for vaccinations, peptides, proteins, and water-soluble medications. Both natural and artificial polymers can be applied in this technique. The continuous organic lipophilic phase distributes the aqueous protein solution. This protein solution contains active ingredients. Disperse in oil/organic phase or the creation of the initial emulsion, followed by the addition of the PVA aqueous solution, or the many emulsions now created by the addition of the wide aqueous phase denaturation/hardening following this separation, the O/W/O multiple emulsion process is prepared for washing, drying, and collecting the microspheres. [16] [17]

3. Polymerization

Polymerization techniques are conventionally used for the preparation of the microspheres. They are mainly classified as:

- **Normal polymerization**

It is accomplished using a variety of procedures, including bulk, suspension, precipitation, emulsion and micellar polymerization. To begin polymerization a monomer or combination of monomers along with the initiator or catalyst, are typically heated in bulk. The resulting polymer can be molded into microspheres. During the polymerization process drugs may be loaded. Bead or pearl polymerization is another name for suspension polymerization. Here it is accomplished by heating the monomer or mixture of monomers while they are dispersed as droplets in an ongoing aqueous phase. An initiator and additional chemicals could be present

in the droplets. Because an initiator is present in the aqueous phase and later diffuses to the surface of micelles, emulsion polymerization differs from suspension polymerization. The advantage of bulk polymerization is the creation of pure polymers. [18]

- **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. In order to create a polymer film that basically envelops the dispersed phase, different monomers react at the interface between the two immiscible liquid phases. This method uses two reacting monomers, one of which is disseminated throughout the continuous phase while the other is dissolved in it. [19]

4. Phase separation / co acervation

The phase separation method is primarily made to prepare reservoir-type systems. When the approach is utilized to encapsulate water soluble pharmaceuticals, such as peptides, proteins, and some preparations with matrix type. In this method, the medicine is first dispersed by generating an aqueous solution if it is hydrophobic or by dissolving it in the polymer solution itself if it is hydrophobic. Phase separation is then achieved by altering the condition of the solution through the addition of salt, an additional solvent, an incompatible polymer, or a change in pH. [13] [14] [20]

5. Spray drying

A method of drying. This was done to make polymer microspheres that were drug charged. In order to achieve this, the raw material must be mixed with a liquefied coating liquid before being sprayed into the air where it will quickly solidify on the surface and evaporate the solvent. In particular laboratory settings, an organic solvent and polymer solution are prepared, sprayed in varied weight ratios, and treated to produce microspheres containing pharmaceuticals. Although quick, the crystallinity may be lost because to the quick drying. [21]

6. Emulsion crosslinking technique

In this technique, the aldehyde group of cross-linking agents is combined with the reactive functional group of polymers to form a cross-link. This technique involved emulsifying the polymer aqueous solution in the oily phase to create a water-in-oil (w/o) emulsion. With an

appropriate surfactant, such as span 80 or dioctyl sodium sulphosuccinate, aqueous droplets were stabilized. A suitable cross-linker, such as glutaraldehyde, was used to cross-link the stable emulsion and harden the droplets. To get rid of any remaining oil residue, microspheres are filtered and repeatedly washed with petroleum ether or hexane. After washing them in water to remove the cross-linkers, they were allowed to dry for 24 hours at room temperature. [22]

7. Solvent evaporation

This technique has also been widely utilized to create PLA and PLGA microspheres that contain a wide range of medications. There are a number of factors that have been found to have a substantial impact on micro-spheric properties, including drug solubility, internal morphology, solvent type, diffusion rate, temperature, polymer composition, viscosity, and drug loading. Because the effectiveness of the solvent evaporation system relies on the effective entanglement of the active ingredient into the particles, this process is especially effective with medications that are either insoluble or only partially soluble in the liquid medium that makes up the constant phase. [23]

8. Ionic gelation method

the alginate/chitosan particulate system was prepared for the release of diclofenac sodium using the ionic gelation process. This procedure involves adding the medication to a solution of aqueous sodium alginate. The stirring is added dropwise to create a full solution. The created microspheres were kept in the original solution for 24 hours to allow for internal jellification and then were filtered to separate them. The drug will not release at an acidic pH, but the full release is achieved between Ph 6.4 and 7.2. [24]

Evaluation of microspheres

1. Particle size

The most often utilized methods for, micro particular visualization are standard light microscopy. The dried microspheres were determined by microscopic method employing calibrated optical micrometer (LM). [25] [26]

2. Density determination

A multi volume pycnometer can be used to determine the density of the microspheres. A cup containing a precisely weighed sample is inserted inside the multi volume pycnometer. In the chamber, helium is supplied at a steady pressure and given room to expand. The pressure inside the chamber decreases as a result of this expansion. It is noted that there are two consecutive readings of pressure reduction at various initial pressures. The density of the microsphere carrier is calculated from two pressure readings. [27]

3. Isoelectric point

The micro electrophoresis is a device that measures the electrophoretic mobility of microspheres and uses that information to calculate the isoelectric point. By timing the particle movement across 1mm distance, the mean velocity at various pH values from 3 to 10 may be determined. This information can be used to estimate the particle's electrical mobility. [28]

4. Flow properties

By calculating Carr's compressibility index, Hausner's ratio, and resting angle of repose, the flow properties can be examined. It was determined bulk density and tapped density using a volumetric cylinder. [29]

5. Angle of contact

The contact angle used to determine the wetting properties of the microparticle carrier. Angle of contact is measured in order to ascertain a microparticulate carrier's wetting capacity. It establishes the type of the hydrophilicity or hydrophobicity of microspheres. At the interface of the solid, air, and water, the angle of contact is measured. A droplet is placed in a circular cell that is put above the objective of an inverted microscope to determine the angle of contact. Within a minute of the microspheres being deposited, the contact angle is measured at 200°C. [30]

6. Determination of percentage yield

The measured amount of the product, the polymers utilized in the microsphere's formulation, and the total number of microspheres generated can all be added up to determine the percentage yield. [31]

7. Swelling index

The swelling index of the microsphere was determined by using the formula.

Swelling index = Mass of swollen microspheres – Mass of dry microspheres/ Mass of dried microspheres. [24]

8. Drug content

filter,1ml was adjusted into a volumetric flask and the volume adjusted with 0.1N NaoH. Spectrophotometric drug measurements were performed after the appropriate dilution. [32]

9. Entrapment efficiency

5 mg of the drug were contained in microspheres, which were crushed and then dissolved in distilled water using an ultrasonic stirrer for three hours. The solution was then filtered and examined using UV-vis spectroscopy. The ratio of the actual drug content to the theoretical drug content is the entrapment efficiency. [33]

$$\% \text{ entrapment} = \text{actual content} / \text{theoretical content} \times 100$$

10. Scanning electron microscopy

The sample were examined using a scanning electron microscope (SEM), which is well suited for image analysis and x-ray diffraction analysis (EDXA), which determines the elemental structure and identifies specific elements. In this technique, a centered electron beam was used to scan the sample in parallel lines. Microspheres were first coated with a conductive metal, such as platinum or zirconium, using a sputter coater before being set up on a sample holder for SEM analysis. An electron beam with precision guidance was then used to scan the material. The secondary electrons that leaked from the sample surface were used to determine its surface characteristics. [34]

11. Fourier transform infrared spectroscopy

FT-IR is used to assess the polymeric matrix of the carrier system's deterioration. The outside the microspheres is examined using alternated total reflectance measurements (ATR). Depending on the conditions and methods of manufacture, the ATRFT-IR can reveal information about the microspheres surface composition. [28]

12. Thermal analysis

Thermal analysis methods regularly examine these shifts by using planned changes in specimen atmospheres and pressures were applied, as well as a specified temperature for heating and chilling. The minute changes in heat and enthalpy, weight loss or gain, young's modulus, thermal expansion or shrinkage, and gas evolution are among the most frequently noted characteristics. [21]

13. *In-vitro* drug release studies

Invitro release profiles using standard USP or BP dissolution apparatus have been studied. Both the paddle and the basket rotate. The study's dissolution media ranges from 100 to 500 ml, while the rotational speed ranged from 50 to 100 rpm. [35]

CONCLUSION

Microspheres are a better drug delivery method than other types, according to the current review. This microsphere new drug delivery technology, which appears to be more effective in the treatment of cancer. This microsphere formulation has greater potency and has a more efficient in in vivo delivery method when it comes to conditions affecting the lungs, heart and nervous system. This formulation primarily ensures the safety of the active pharmaceutical component and other formulation excipients.

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