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Research Article

A Comprehensive Overview of Microspheres as A Novel Drug Delivery System

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ABSTRACT

Many novel, more effective, and targeted treatments are being developed as a result of developments in biotechnology, genomics, and combinational chemistry. Due to common issues with many of these novel medications, including limited solubility, high potency, and/or poor stability, drug delivery methods can affect efficacy and potential for commercialization as much as the drug's actual characteristics. Consequently, there is a commensurate need for safer and more efficient drug delivery techniques and equipment. In fact, a medicine delivery system must to be made to offer a therapeutic agent in the appropriate quantity, at the appropriate moment, and at the appropriate site within the body in a way that reduces adverse effects, boosts compliance, and maximizes efficacy. Among the many different gadgets that have Microspheres are among the most widely utilized forms for regulated medication delivery and contain several advantages. Numerous medication kinds, such as tiny molecules and nucleic acids, can be encapsulated in microspheres. This article's goal is to highlight the fundamental ideas behind the creation and assessment of microspheres. as a method of focused and regulated drug distribution.

INTRODUCTION

Many issues with traditional therapy can be resolved by a precisely planned controlled medication delivery system, which can also improve the therapeutic effectiveness of a certain medication [1]. To achieve optimal treatment effectiveness, it becomes essential to transport the agent to the ideal quantity of the target tissue in the appropriate amount of time, resulting in minimal negative effects and low toxicity [2]. There are several methods for providing a medication to the intended location in a long-term, controlled release style [3]. One Microspheres are used in this method as a drug carrier. One definition of microspheres is "monolithic." spheres or medicinal substance dispersed within the matrix as a molecular particle dispersion," or what is known as

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composition of one or more miscible polymers that contain drug particles scattered at the macroscopic or molecular level level. Its particles are smaller than 200 µm [4].

DISCUSSION

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. Bioadhesion is the word used to describe the attachment of a drug delivery device to a mucosal membrane, such as the nasal, buccal, ocular, or rectal membrane. These microspheres have a longer residence duration at the application site, make close touch with the absorption site, and have superior therapeutic effects[5].

2. Magnetic Microspheres

This type of delivery mechanism, which localizes the medication to the disease site, is crucial. In this case, a lower quantity of magnetically targeted medication may be used in place of a larger quantiy of freely circulating medication. Chitosan, dextran, and other materials employed in magnetic microspheres provide magnetic carriers with magnetic responses to a magnetic field. Therapeutic magnetic microspheres and diagnostic microspheres are the two varieties [6].

A. Therapeutic magnetic microspheres

Chemotherapeutic agents are delivered to liver tumors using this method. This technology can also target drugs like proteins and peptides[7].

B. **Diagnostic microspheres**

By creating supramagnetic iron oxide nanoparticles, it can be used to image liver metastases and differentiate bowel loops from other abdominal structures [8].

3. Floating Microspheres

Because their bulk density is lower than that of the gastric fluid, floating kinds stay buoyant in the stomach without influencing the rate at which the stomach empties. If the system is floating on stomach content, increasing gastric residency and increasing variability in plasma concentration, the drug is released gradually at the desired rate. Additionally, it lessens the likelihood of dose dumping and striking. Another way it lowers dose frequencies is by producing a longer therapeutic impact [9].

4. Radioactive Microspheres

Treatment with radio immobilization When 10–30 nm microspheres are encountered, they are tapped in the first capillary bed because they are larger than capillaries. They are administered to the arteries leading to the target tumor [10]. Thus, in all of these circumstances, radioactive microspheres deliver a high dosage of radiation to the targeted locations without causing harm to the surrounding normal tissues. The many types of radioactive microsphers are an emitters, ß emitters, and α-emitters. It is distinct from medicine delivery systems in that radioactivity is not discharged from microspheres but acts from within a normal distance of radioisotopes [11].

5. 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 like starch is used as they are biodegradable, biocompatible, and naturally bioadhesive. Because biodegradable polymers have a high degree of swelling with aqueous media, they cause gel formation and extend the residence period when they come into contact with mucosal membranes. The polymer concentration and the release pattern regulate the drug release's pace and magnitude over time. The primary disadvantage is that the drug loading efficiency of biodegradable microspheres in clinical settings is complicated, making it challenging to regulate the drug release [13].

B. Synthetic Polymeric Microspheres

In addition to their extensive use in clinical applications, synthetic polymeric microspheres have demonstrated their safety and biocompatibility as bulking agents, fillers, embolic particles, and drug delivery vehicles. However, these microspheres' primary drawback is their propensity to move away from the injection site, which increases the chance of an embolism and additional organ damage [14].

MATERIALS

Microspheres are made up of polymers. They classified into three types:

1. Synthetic Polymers*:*

a. Non- biodegradable polymers: Eg. Poly methyl methacrylate (PMMA) Acrolein 2 Glycidyl methacrylate Epoxy polymers.

b. Biodegradable polymers: Eg. Lactides, Glycolides & their copolymers Poly alkyl cyano acrylates Poly anhydrides [15].

2. Semi-synthetic Polymers: Cellulose Derivatives, Cellulose Nitrates, Cellulose Acetates

3. Natural Polymers: They can be obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates. Proteins: Albumin, Gelatin and Collagen

Carbohydrates: Agarose, carrageenan, Chitosan, Starch, Chemically modified carbohydrates: Poly dextran, Poly starch [16].

Preparation Of Microspheres

Microsphere preparation needs to meet specific requirements.

These include:

(i) the capacity to include drug concentrations that are reasonable.

(ii) stability of the preparation following synthesis with a clinically acceptable shelf life.

(iii) controllable particle size and dispensability in aqueous injection vehicles.

(iv) controlled release of the active agent over a broad time scale.

(v) biocompatibility with controllable biodegradability.

(vi) susceptibility modification [17].

METHODS OF PREPARATION

Single Emulsion Technique

The single emulsion technique is used to create the microparticulate carriers of natural polymers, such as proteins and carbohydrates.After being dissolved or dispersed in an aqueous media, the natural polymers are then distributed in a non-aqueous medium, such as oil. Cross-linking of the scattered globule is done in the second preparation stage. There are two ways to accomplish cross-linking: using heat or chemical cross-linking agents such glutaraldehyde, formaldehyde, diacid chloride, etc [18].

Double Emulsion Technique

Using this technique, a multiple emulsion or double emulsion of type w/o/w is formed. Water-soluble medications, peptides, proteins, and vaccinations are its ideal candidates. Both synthetic and natural polymers can be employed using this technique. A lipophilic organic continuous phase disperses the aqueous protein solution.The active ingredients may be present in this protein solution [19].

The polymer solution that ultimately encapsulates the protein contained in the dispersed aqueous phase often makes up the continuous phase. After that, the primary emulsion is homogenized or sonicated before being added to the polyvinyl alcohol (PVA) aqueous solution.A double emulsion is created as a result. After that, the emulsion is exposed to a solvent extraction procedure or solvent evaporation. The emulsion is kept at a lower pressure or stirred to allow the organic phase to evaporate in order to carry out the solvent evaporation. After that, a significant amount of water is added to the emulsion, allowing the organic phase to diffuse out [20].

After that, the solid microspheres are obtained by filtering and cleaning them with acetone,

nhexane, or any other organic solvent to get rid of any remaining oil residue.

Polymerization

The traditional polymerization methods for creating the microspheres fall into the following categories:

1. **Normal polymerisation**
2. **Interfacial polymerisation**
3. **Normal polymerization**

Various methods, including bulk, suspension precipitation, emulsion, and micellar polymerization procedures, are used to carry out normal polymerization. A monomer or combination of monomers, an initiator, or a catalyst are typically heated to start the polymerization process in bulk polymerization [21].The resulting polymer can be shaped into microspheres. It is possible to load drugs during the polymerization process.

Another name for suspension polymerization is pearl or bead polymerization. Heating the monomer or mixture of monomers as droplets dispersed in a continuous aqueous phase is how it is done here. An initiator and additional ingredients might also be included in the droplets. The presence of an initiator in the aqueous phase, which subsequently diffuses to the micelle surface, is how emulsion polymerization varies from suspension polymerization. The creation of pure polymers is a benefit of bulk polymerization [22].

Interfacial Polymerization

In order to create a polymer film that effectively envelops the dispersed phase, different monomers react at the interface between the two immiscible liquid phases. Two reactive monomers are used in this method; one is disseminated in the continuous phase and the other is dissolved in the continuous phase [23].

Phase Separation/Coacervation

The primary purpose of the phase separation procedure is to prepare the system's reservoir type. This technique is used to encapsulate water-soluble medications, such as proteins and peptides, as well as some preparations with a specific matrix type, such as steroids, which are hydrophobic in nature. This method involves dissolving the polymer in an appropriate solvent first, and then dispersing the medication either in the polymer solution itself, if it is hydrophobic, or in its aqueous solution, if it is. Phase separation is then achieved by altering the conditions of the solution through the addition of salt, an on-solvent, an incompatible polymer, or a pH shift [24].

Spray Drying

First, the polymer is dissolved in an appropriate volatile organic solvent, such as acetone, dichloromethane, etc. After that, the solid medication is dissolved in the polymer solution while being homogenized at a high speed. A stream of hot air is then used to atomize this dispersion. Small droplets or a fine mist are created as a result of atomization, and the solvent instantly evaporates from these to form microspheres [25].

Solvent Extraction

The organic phase is eliminated by extracting the organic solvent in the solvent extraction process, which is employed to prepare the microparticles. Water-miscible organic solvents like isopropanol are used in the process. The organic phase is extracted using water. The microspheres' hardening period is shortened by this procedure. The medication or protein is directly added to an organic polymer solution during the procedure. The temperature of the water, the emulsion volume to water ratio, and the polymer's solubility profile all affect how quickly the solvent is removed using the extraction procedure [26].

Emulsion Solvent Evaporation

This method involves dissolving the drug in a polymer that has already been dissolved in

chloroform, then adding the resultant solution to an aqueous phase that contains 0.2% sodium PVP as an emulsifying agent. After 500 rpm of agitation, the medicine and polymer (Eudragit) created tiny droplets that hardened into rigid microspheres through solvent evaporation. These droplets were then collected by filtering, cleaned with demineralized water, and allowed to desiccate for 24 hours at room temperature [27].

Emulsion Solvent Diffusion Technique

To increase the residence period, the emulsion solvent diffusion technique was used to create the colon floating microspheres. After dissolving the drug polymer mixture in a 1:1 ethanol and dichloromethane mixture, the mixture was gradually added to a sodium lauryl sulphate (SLS) solution. At room temperature, the solution was agitated for one hour at 150 rpm using a propeller-style agitator. As a result, the generated floating microspheres were cleaned and allowed to dry at room temperature in a desiccator [28].

Characterization of Microspheres

Particle size and shape:

For double-walled microspheres, light microscopy (LM) offers control over coating settings. Before and after coating, the structures of the microspheres can be seen, and the difference can be quantified at the microscopic level.The surfaces of microspheres can be examined using scanning electron microscopy (SEM), which can also be used to examine double-walled systems once particles have been cross-sectioned [29].

Attenuated total reflectance FT-IR

This technique is used to assess how the carrier system's polymeric matrix is degrading. Alternate total reflectance, or ATR, is measured on the microspheres' surface. Depending on the circumstances and production processes, the ATRFT-IR gives information about the microspheres' surface composition[30].

Density Determination

A multivolume pychnometer can be used to measure the microspheres' density. A cup containing an accurately weighted sample is put inside the multivolume pychnometer. In the chamber, helium is added at a steady pressure and given time to expand. The pressure inside the chamber drops as a result of this expansion.Two successive pressure drop values at various starting pressures are recorded. The density of the microsphere carrier is calculated from two pressure readings [31].

Isoelectric point

The isoelectric point of microspheres can be ascertained by measuring their electrophoretic mobility using a device called micro electrophoresis. By timing the particle's movement across a 1 mm distance, the mean velocity for various pH values between 3 and 10 is determined. This information can be used to calculate the particle's electrical mobility [32].

Entrapment Efficiency

Drug-containing microspheres (5 mg) were crushed, dissolved in distilled water for three hours with the use of an ultrasonic stirrer, filtered, and then examined using UV-vis spectroscopy.

Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content [33].

% Entrapment = Actual content/Theoretical content x 100

Swelling index

The swelling index technique was employed to characterize microspheres. A wire basket containing 100 mg of microspheres was placed in a different solution (100 mL), such as distilled water or a buffer solution with pH values of 1.2, 4.5, or 7.4. The microspheres were then allowed to swell at 37°C, and the weight difference between their initial weight and the weight caused by swelling was measured by periodically taking their weight and soaking them in filter paper [34].

Angle of Contact

A microparticulate carrier's wetting property is ascertained by measuring the angle of contact. It establishes the hydrophilicity or hydrophobicity of the microspheres. At the solid-air-water interface, the angle of contact is measured.A droplet is positioned in a circular cell above the inverted microscope's objective to measure the angle of contact.Within one minute of the microspheres being deposited, the contact angle is measured at 200 ^{o}C [35].

Modified Keshary Chien Cell

In the lab, a unique piece of equipment was created. It was made up of a Keshary Chien cell with 50 milliliters of distilled water at 370 ^{o}C serving as the dissolution medium. The Trans Membrane Drug Delivery System, or TMDDS, was put in a glass tube with a 10# sieve at the bottom that responded to the medium at a rate of 30 strokes per minute [36].

Dissolution apparatus

Rotating elements, paddles, and baskets have all been employed in the research of in vitro release profiles utilizing standard USP or BP dissolution apparatus.The study's dissolution media ranged from 100 to 500 ml, and its rotational speed was between 50 and 100 rpm [37].

Animal models

Primarily, animal models are employed to screen a series of compounds, examine the workings and practicality of permeation enhancers, or assess a group of formulations. Usually, the process entails giving the animal anesthesia before administering the dosage form. To stop absorption channels other than the oral mucosa in rats, the esophagus is clamped. The blood is extracted and examined at various intervals [38].

Stability Studies

The microspheres were kept at the following conditions after being placed in a screw-capped glass container:

a. The level of humidity in the air At room temperature (27°C to -2°C)
b. Temperature of the oven (40+/-20^{o}C)
c. freezer (50^{o}C – 80^{o}C).

The drug content of the microsphere was examined after a 60-day period [39].

Advantages Of Microspheres

1. **Sustained Release**: Microspheres can encapsulate drugs and release them gradually over time, which is particularly useful for long-term therapies. This helps in maintaining a steady level of the drug in the bloodstream and minimizes the need for frequent dosing[40].
2. **Targeted Delivery**: Microspheres can be designed to release drugs at specific sites within the body, reducing side effects and enhancing the therapeutic efficacy of the drug.
3. **Protection of Drugs**: Encapsulation of drugs within microspheres protects them from degradation (e.g., by enzymes or pH changes), thus improving the stability and shelf-life of pharmaceuticals [41].
4. **Enhanced Bioavailability**: better therapeutic outcomes even with lower doses of the drug.They can also facilitate the solubilization of hydrophobic drugs, allowing for easier delivery into the bloodstream [42].
5. **Improved Stability**: By protecting sensitive drugs from environmental factors (such as moisture, light, and temperature), microspheres improve the stability of formulations. This is particularly beneficial for proteins, peptides, and vaccines [43].
6. **Reduced Toxicity**: Microspheres can reduce the toxicity of certain drugs by controlling their release rate, ensuring that the active drug is released slowly and only where it is needed. This minimizes side effects associated with high concentrations of drugs in non-target areas [44].

7. **Uniformity and Precision in Formulation**: Microspheres can be manufactured with uniform size and shape, which is critical in applications where consistent performance is required. For example, uniform-sized microspheres ensure consistent drug release rates, making them ideal for controlled-release drug formulations. This uniformity also makes them suitable for applications in cosmetics, where they are used to create smoother textures in products like creams and lotions[45].
8. **Reduced Immunogenicity**: Biodegradable microspheres, especially those made from materials like polylactic acid (PLA) or poly(lactic-co-glycolic acid) (PLGA), are less likely to induce immune responses in the body. This is advantageous in biomedical applications like drug delivery, as it minimizes the risk of adverse immune reactions [46].

Limitations Of Microspheres

1. **Production Complexity**: The methods for producing microspheres, such as solvent evaporation, spray drying, and emulsion methods, can be technically challenging and require precise control over many parameters, such as temperature, stirring speed, and solvent removal rates [47].
2. **Physical and Chemical Instability**: Some microspheres can be unstable during storage, potentially aggregating or changing their properties over time. This is especially true for biodegradable microspheres, which may begin to degrade prematurely [48].
3. **Uncontrolled Initial Release**: A common problem with microspheres used in drug delivery is the initial burst release, where a large amount of the encapsulated drug is released immediately after administration. This can result in a rapid rise in drug concentration, which may lead to side effects or toxicity.
4. **Risk of Aggregation**: During the process of surface modification, there is a risk that the microspheres may aggregate, which can alter their intended properties, such as size distribution and release profile, and reduce their effectiveness in targeting or controlled release[49].
5. **Poor Encapsulation of Hydrophilic Drugs**: Encapsulating hydrophilic drugs in microspheres can be difficult because they tend to leach out into the surrounding aqueous phase during the formulation process. This limits the range of drugs that can be effectively delivered using microspheres.
6. **Non-Biodegradable Materials**: Some microspheres, particularly those made from non-biodegradable polymers, can persist in the environment after use, leading to concerns about pollution and long-term ecological impacts [50].
7. **Interactions with Formulation Excipients**: Microspheres may interact with other ingredients in a formulation, such as stabilizers, preservatives, or surfactants, affecting their stability or drug release profile [51].
8. **Limited Targeting Accuracy**: Although microspheres can be designed for targeted delivery, achieving precise targeting in the body remains a challenge. Factors such as blood flow, cellular uptake, and biological barriers can affect the ability of microspheres to reach and release drugs at the intended site [52].

Applications Of Microspheres

1. **Oral Drug Delivery**: Microspheres are used in oral formulations to enhance the bioavailability of drugs, especially those that are poorly soluble in water. By encapsulating

the drug, they can improve absorption in the gastrointestinal tract. They can also protect drugs from degradation in the acidic environment of the stomach, allowing for the release in the intestines.

2. **Parenteral Delivery**: Injectable microspheres are used for delivering drugs subcutaneously or intramuscularly, providing a depot effect where the drug is slowly released over time. This is often used for long-term treatments, such as hormone therapy or antipsychotic medications [53].
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4. **Bone Repair and Regeneration**: Microspheres made of bioactive ceramics, such as calcium phosphate or hydroxyapatite, are used for bone grafting and repair. They support the growth of bone cells and are gradually resorbed as new bone tissue forms. They are often used in orthopedic surgery to fill bone defects and to support the healing of fractures [55].
5. **Immunotherapy and Vaccine Delivery**: Microspheres are used to deliver antigens in vaccine formulations, ensuring a controlled release and enhancing the immune response. They can also protect the antigens from degradation, allowing for a more effective vaccination. By presenting antigens in a sustained manner, microspheres can simulate a natural infection and stimulate both humoral and cellular immunity [56].
6. **Controlled Release of Active Ingredients:** In cosmetics, microspheres are used to deliver active ingredients like vitamins, retinoids, or moisturizing agents, allowing for a controlled release over time, thus prolonging their effects on the skin. This technology is used in creams, serums, and lotions to provide a long-lasting benefit without the need for frequent application.
7. **Encapsulation of Nutrients:** In the food industry, microspheres are used to encapsulate vitamins, minerals, and other bioactive compounds to protect them from degradation and improve their stability. This allows for the controlled release of these nutrients in the digestive tract. Encapsulation can also mask the taste or odor of certain nutrients, making them more palatable in dietary supplements and fortified foods [57].
8. **DNA and RNA Delivery:** In gene therapy research, microspheres are used to deliver DNA, RNA, or other genetic materials into cells. They protect nucleic acids from enzymatic degradation and facilitate their entry into target cells [58].

CONCLUSION

Microspheres are a versatile drug delivery system that offers controlled and targeted release of medications, improving drug efficacy and patient compliance. They can encapsulate a wide range of drugs, allowing for sustained release, reduced dosing frequency, and minimized side effects by delivering drugs directly to the desired site. This makes them especially useful in treating chronic conditions and in targeted therapies. While challenges like complex manufacturing exist, ongoing advancements are addressing these issues, making microspheres a valuable tool for modern medicine and therapeutic innovation.

Conflict Of Interest

The Authors declare that this article has no conflict of interest.

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