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REVIEW ON MICROSPHERES

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ABSTRACT

Microspheres are tiny, round particles with diameters typically between 1 to 1000 micrometers, extensively studied and utilised for their unique characteristics in various fields, including pharmaceuticals and biotechnology. This review explores the key Characteristics, Microsphere types, Preparation methods, Recent advancements, and diverse Applications of microspheres. Microspheres come in various types, including bioadhesive microspheres, Magnetic microspheres, floating microspheres, and Polymer microspheres. The preparation of microspheres involves several techniques, including spray drying, Solvent Evaporation, Microencapsulation by Hot Melt Method**,** single emulsion method, Double emulsion method**,** Spray congealing and drying**.** Recent Advancements in microspheres like Important applications for the polymer chitosan, effects of reducing cholesterol, Orthopaedic Patients, Chitosan as Permeation Enhancer, Transforming growth factor (TGF-β) promotes the formation of bones. In terms of applications, microspheres have been predominantly employed in regulated medication administration, where they enhance the bioavailability and reduce side effects. Using Microspheres to Deliver Vaccines, Tissue Engineering, Biomedical Imaging, and Chemoembolization. Challenges such as Scalability, stability, biocompatibility, and large-scale production are also discussed.

KEYWORDS: Microspheres, Microencapsulation, Controlled drug delivery, Novel drug delivery, Applications.

INTRODUCTION

The microspheres are tiny, round particles that usually possess a diameter of one to a thousand micrometers. They are made of synthetic polymers or proteins and are distinguished by their biodegradability and free-flowing nature. Because of their special qualities and adaptability, microspheres have drawn a lot of interest in a variety of domains, such as medication delivery, tissue engineering, and medicinal applications.[1]

It becomes essential to transport the drug to the target tissue in the ideal quantity within the ideal time frame in order to achieve optimum therapeutic efficiency, resulting in minimal side effects and minimal toxicity.[2] A medicinal drug can be delivered to the target site in a prolonged controlled-release form using a variety of techniques. Using microspheres as drug delivery vehicles is one such strategy. Among the most fascinating pharmaceutical domains, scientific research represents the production of new delivery methods regarding the regulated distribution of pharmaceuticals. A well-thought-out use of a regulated drug delivery system can increase a medication's effectiveness and address some of the problems with conventional treatment. Attaching bioactive molecules to liposomes, bioerodible polymers, implants, monoclonal antibodies, and other particles allows for pinpointing and site-specific administration with perfect accuracy. Drugs, vaccines, antibiotics, and all hormones can be released under controlled circumstances by employing microspheres.

As an example, through utilizing the characteristics of microspheres, along with their basic benefits, they could provide a larger surface area and make it simpler to estimate the behaviour of mass transfer and diffusion. In addition to being a configuration where drug particles are distributed at the molecular or macroscopic level within a continuous phase of one or more miscible polymers, microspheres can be defined as "therapeutic agents or monolithic spheres dispersed throughout the matrix either as a molecular dispersion of particles". Microspheres are small, spherical particles with typical sizes ranging from 1 μm to 1000 μm, which is in the micrometer range. Microparticles are another name for microspheres. Modified natural products, including proteins, lipids, gums, starches, and waxes, as well as biodegradable synthetic polymers. The solvents selected for dissolving the polymeric substances are based on drug and polymer solubility as well as stability, economic factors and process safety. Examples of manufactured polymers include polyglycolic acid and polylactic acid, whereas albumin and gelatin are examples of natural polymers.[3] Oral

microspheres have been used to maintain medication release and lessen or completely eradicate gastrointestinal tract discomfort.[4]

CHARACTERISTICS

1. The microsphere's size may be crucial to the proper functioning of the assay or secondary to other characteristics. The format of the test or assay frequently determines the particle size when employing conventional techniques for diagnosis. For instance, in tests of lateral flow, extremely tiny spheres (around 0.1–0.4 μm) are used to guarantee adequate wicking, but in flow cytometric tests based on beads, bigger, cell-sized spheres (~4–10μm) are used.
2. PS (polystyrene), silica, and PMMA (or poly (methyl methacrylate)) are typical compositions of microspheres. The physical and optical characteristics of these materials vary, which could be either beneficial or detrimental based on the use. Polymer crystals have a strong ability to bind proteins since they are frequently hydrophobic. To make handling easier, they often need to employ a surfactant (such as SDS or Tween® 20, 0.01–0.1%) in the buffer for storage. In the process of synthesis, functional monomers are able to co-polymerize with methyl methacrylate or styrene to produce reactive groups on the surface of the beads. Functional groups can be applied to processes involving covalent bonds in addition to aiding in suspension stabilization. Microspheres of silica are hydrophilic and naturally inversely charged. As a consequence, surfactants and other stabilizers are rarely needed for aqueous silica suspensions. Plain silica microspheres can be changed using a range of silanes to create functional groups or change surface characteristics, and silica spheres functionalized with amines and carboxyl groups can be used in standard covalent coating procedures.
3. The microsphere can be covered in molecules that capture peptides, oligonucleotides, or antibodies for use in separation or diagnostic procedures. In order to minimize nonspecific interactions and obtain the desired specific activity, microsphere coatings are usually adjusted. The necessary stability, the budget and schedule for development, and the specific biomolecule that needs to be coated ought to all be taken into account. These elements will be beneficial in choosing the best covering approach for both immediate and enduring goals.
4. For many applications in the biological sciences, further features like magnetic separations, fluorescence or a visible colour, or iron oxide inclusions, are necessary. Numerous standard goods are available, and Internal colouring of Polymer spheres (and

magnetic spheres made of polymers) is commonly accomplished by organic solvent swelling. To address specific needs, concentrations of dyes can be changed to create beads that have varying levels of intensity. For instance, our Flash Red Intensity Standards or Dragon Green help with imaging applications and associated instrument quality control, while the Quantum Plex® is ideal for flow cytometric multiplexing tests. Numerous fluorescent beads with internal or surface labels are also offered as customized flow cytometry standards.[5]

Materials Employed

Numerous materials, both materials that are biodegradable and non-biodegradable, have been researched for the production of microspheres. These materials consist of modified organic compounds, polymers of synthetic and natural origin. Carrier materials include ethylene vinyl acetate copolymer, lactide, glycolide and its copolymers, methyl methacrylate, acrolein, polyanhydrides, and other synthetic polymers. Natural polymer examples used for this include collagen, carrageenan, albumin, gelatin, and starch.

Polymer Classification[6]

A) Artificial Polymers: classified into two categories:

1. Polymers that are not biodegradable, like epoxy, glycidyl methacrylate, and acrolein, among others.[7,8]
2. Biodegradable: Lactides, glycolides, polyalkyl cyanoacrylates, polyanhydride, and their copolymers.

B) Natural resources: They come from an assortment of references, consisting of[9,10]

- Proteins (albumin, gelatin, and collagen)
- Carbohydrates (carrageenan, agarose, and starch)
- Carbohydrates with chemical modifications, like poly (acryl starch) and poly (acryl dextran)

MICROSPHERE TYPES

Microspheres that are bio-adhesive[11]

Adhesion is the process by which a medication adheres to a membrane by utilizing the water-soluble polymers' ability to stick. Bioadhesion is the word used to describe the inclusion of a drug delivery mechanism to a mucosal membrane, including the nasal, buccal, ocular, and

rectal regions. The microspheres here make close contact with the absorption site, possess a lengthier residence period on the application website and have superior medicinal effects.

Magnetic microspheres

This kind of delivery system is essential since it localizes the drug to the site of the illness. In this case, a lower quantity of magnetically targeted medication may be used in place of a larger quantity of freely circulating medication. Chitosan, dextran, and other materials employed within magnetic microspheres provide magnetic carriers with magnetic reactions to the field of magnetic attraction.[12]

The different types are

1. Chemotherapy drugs are administered to the liver tumours with magnetic microspheres for therapeutic purposes. This method can also target medications such as peptides and proteins.[11]
2. Diagnostic microspheres: By creating nanoparticles of superparamagnetic iron oxides can be utilized for imaging liver metastases and differentiating bowel loops from other parts of the abdomen.[13]

Microspheres that float

Because gastric fluid has a higher bulk density than floating types, they stay buoyant in the abdomen without floating on gastric contents, increasing gastric residence and plasma concentration fluctuation. It also reduces the chance of striking and dose dumping. Additionally, it influences how quickly the stomach empties. If the system delivers a long-term healing effect, it decreases the occurrence of doses and releases the drug gradually at the desired rate. This is the method used to deliver ketoprofen.[14]

Microspheres of radioactivity

The 10–30 nm radioembolization treatment microspheres are caught in the first capillary bed and are bigger than the capillaries they encounter. They're administered by injection through the arteries that supply the targeted tumour. Therefore, among all these circumstances, Microspheres of radioactivity provide large radiation dosages to specific areas without damaging the environment's normal tissues.[15] In contrast to drug delivery systems, radioactivity isn't emitted via microspheres, but rather acts from inside a normal separation of radioisotopes. Microspheres filled with radioactivity can be classified as α, β, or γ emitters.[16]

Microspheres made of polymers

The following are several kinds of polymeric microspheres: Microspheres of biodegradable polymers. Starch and other natural polymers are utilized to create microspheres of biodegradable polymers, having the belief that they are biocompatible, biodegradable, and naturally bioadhesive. These polymers extend the time spent residing there when they come into interaction with the mucosa due to their elevated level of oedema in a water-based medium, leading to the development of a gel. The polymer's concentration controls the rate and extent of drug release of and the release pattern is sustained. The primary disadvantage of biodegradable microspheres is that controlling the medication release is difficult in clinical settings due to the complexity of drug loading efficiency. They provide numerous uses in treatment based on microspheres.[17]

Synthetic polymer-based microspheres

In addition to their extensive use in clinical settings, synthetic polymeric microspheres have demonstrated their safety and biocompatibility in their use as drug delivery vehicles, fillers, bulking agents, and embolic particles. Their tendency to spread out from the injection site, however, is the main disadvantage of these microspheres and raises the possibility of embolism and further organ injury.[18]

PREREQUISITES FOR THE PREPARATION OF MICROSPHERES

The possibility exists that includes liquids, solids, or gases into a couple of polymer coverings by applying the microencapsulation technique.[19] The length of drug release, particle size, and administration route all influence the various manufacturing processes utilized to create different microspheres. These variables are also connected to the evaporation duration, the cross-linking procedure, the cross-linking drug, and the rpm, such as co-precipitation.[20] Microsphere preparation should follow specific guidelines:[21]

- Extended duration of regulated release of an active reagent.
- It should be able to incorporate moderately high medication concentrations.
- It should be able to be modified chemically.
- The preparation's stability after synthesis and its clinically acceptable shelf life.
- Combining biocompatibility and controlled biodegradability.
- The aqueous injection controlled the dispersibility and particle size of vehicles.

THE PREPARATION METHODS

Drying by Spraying

The process of spray drying begins with dissolving the polymer in a suitable organic volatile solvent, like dichloromethane or acetone, etc. Following accelerated homogenization, the solid medication is subsequently distributed throughout the solution of polymers. After that, a stream of heated air atomizes this dispersion. The atomization process produces a thin mist or small droplets, which the solvent originate from the solvent and instantly vaporise to generate microspheres with a size range of 1–100 μm. Using a cyclone separator, the microparticles are separated from the heated vapor and vacuum drying removes any leftover solvent. Among its primary advantages is the process's capacity to operate under aseptic conditions. It's also a quick process, which causes porous microparticles to develop.[22]

Solvent Evaporation

Procedures are carried out using a liquid production device. Disseminating the microcapsule coating involves a volatile solvent that is incompatible with the liquid production vehicle phase. The polymer solution for coating dissolves or disperses the core substance to be enclosed in microcapsules. To create the right size microcapsule, the central material mixture is dispersed and stirred during the liquid production vehicle stage. If the solvent needs to be evaporated, heating the mixture causes the polymer to contract around the core, as the core material disperses in the polymer solution. Matrix-type microcapsules are created when the core material dissolves in the covering polymer solution. The solvent evaporation method is displayed. The core components can be either water soluble or water insoluble. Solvent evaporation is the process of forming an emulsion between a polymer solution and an immiscible continuous phase, which can be either aqueous (o/w) or non-aqueous. Hyaluronic acid microcapsules and gelatin generated by complicated coacervation were compared with mucoadhesive microspheres of hyaluronic acid, chitosan glutamate, and a mixture of the two made by solvent evaporation.

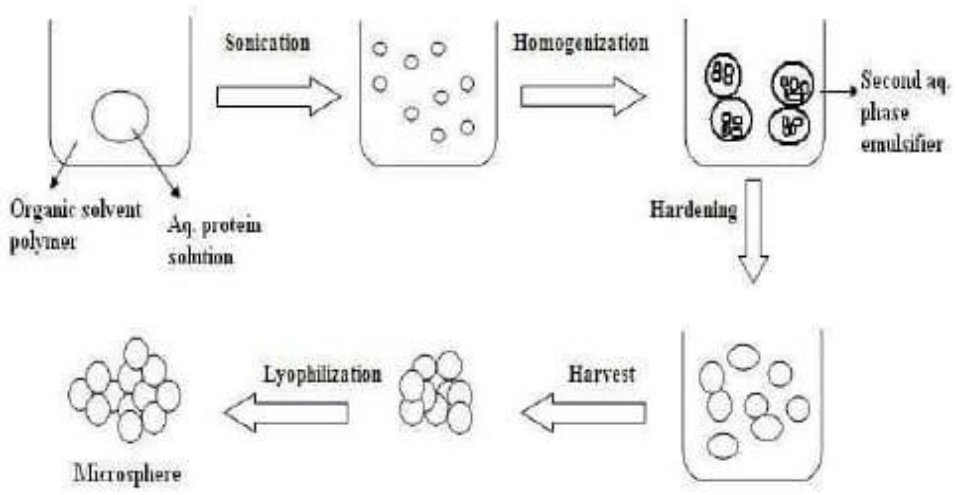

Fig.1: Microsphere preparation by the solvent evaporation method.

Wet Inversion Method: Using a nozzle, a chitosan solution in acetic acid was dropped into an aqueous solution of sodium tripolyphosphate, a counterion. The resulting microspheres were cross-linked using 5% ethylene glycol diglycidyl ether after being left to stand for an hour. After washing, the microspheres were freeze-dried. Altering the coagulation medium's pH may change the CS microspheres' pore shape.

Coacervation of Complexity: Another method for creating CS microparticles is complicated coacervation. CS can generate microspheres by complicated coacervation with sodium polyacrylic acid, sodium alginate, and sodium CMC. Ionic interaction between KCl & CaCl2 solutions and oppositely charged polymer solutions forms these microparticles. Before washing and drying, the resulting capsules were solidified in the counterion solution.[22]

Microencapsulation by Hot Melt Method

The drug's solid particles that have been sieved to less than 50 µm are combined with the polymer after it has first been heated. When the solvent is non-miscible (like silicone oil), the mixture is suspended, constantly swirled, and brought to 5°C above the melting point of the polymer. Following stabilization, an emulsion is chilled until the polymer particles harden. By using petroleum ether for decantation, the resultant microspheres are cleaned. The creation of a microencapsulation technology appropriate for water-labile polymers, such as poly anhydrides, is the main goal of this approach. By adjusting the stirring rate, microspheres ranging in diameter from 1 to 1000 µm can be produced with ease, and the size distribution can be easily controlled. This method's only drawback is that the medicine is exposed to a moderate temperature.[22]

The single emulsion method

Microparticle carriers of natural polymers, like proteins and carbohydrates, are made using the single emulsion approach. Following their dissolution or dispersion in an aqueous medium, the natural polymers are subsequently disseminated in a non-aqueous medium, like oil. Cross-linking of the scattered globules is then done. The cross-linking can be done with heat or chemical cross-linkers. Glutaraldehyde, formaldehyde, acid chloride, as well as other chemicals, are utilized as agents that cross-link. Heat should not be used to denature thermolabile substances. Chemical cross-linking has the disadvantage of subjecting the active component to excessive chemical exposure if it's added while preparation and subsequently centrifuged, washed, and separated.[23] The properties of the surfactants that stabilize the phases of emulsions have a significant influence on the finished multi-particulate product's size, size distribution, surface morphology, loading, drug release, and bio-performance.[24]

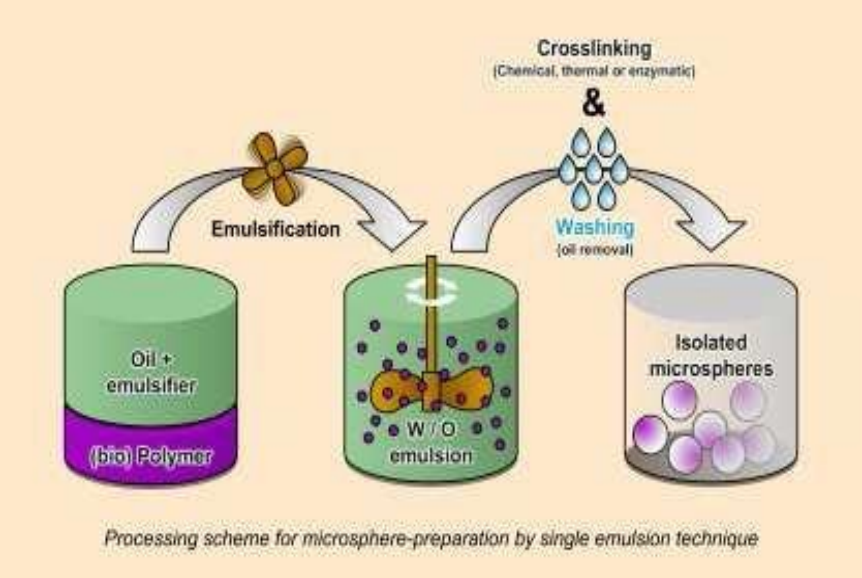

Fig. 2: Single emulsion method for microsphere preparation.

Double emulsion method

The double emulsion method of creating microspheres is best suited for proteins, peptides, vaccines, and drugs that dissolve in water. It requires the creation of several kinds of emulsions or a w/o/w double emulsion. This method works with both natural and manmade polymers. Protein solution in water is dispersed by the lipophilic organic continuous phase. There may be active substances in this protein solution. The polymer solution that eventually wraps the protein in the dispersed aqueous phase typically makes up the continuous phase. The protein solution may contain the active substances. The solution of polymers that

ultimately wraps the protein in the dispersed phase of water typically constitutes the continuous phase. Before being added to the polyvinyl alcohol (PVA) aqueous solution, the primary emulsion is first homogenized or sonicated. As a result, a twofold emulsion forms. After that, the emulsion is exposed to solvent extraction or solvent evaporation. Through the use of the double emulsion solvent extraction/evaporation process, several hydrophilic medications, including proteins/peptides, vaccinations, luteinizing hormone-releasing hormone (LH-RH) agonists, and traditional compounds, are effectively integrated into microspheres.[23]

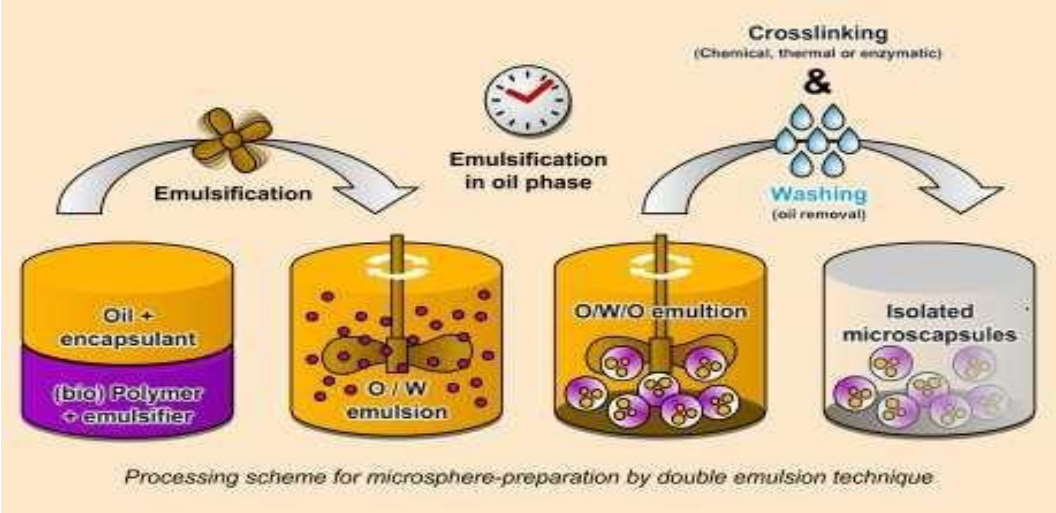

Fig. 3: Double emulsion method for microsphere preparation.

Spray congealing and drying

The drying of the medication and polymer mist in the air is the foundation of these techniques. The two procedures are called spray drying and spray congealing, respectively, depending on whether the solvent is removed or the solution is cooled. First, the polymer is dissolved in an appropriate volatile organic solvent, like acetone, dichloromethane, etc. Following high-speed homogenization, the solid medication is subsequently distributed throughout the polymer solution. After that, a stream of heated air atomizes this dispersion. Atomization results in the formation of tiny droplets or a fine mist, from which the solvent immediately evaporates to form microspheres with sizes ranging from 1 to 100 µm. After the microparticles are separated from the hot air using a cyclone separator, any leftover solvent is removed using vacuum drying. One of the primary characteristics of the method is its capacity to operate in aseptic environments. Many penicillins are encapsulated using the spray drying method. With spray congealing, thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a blend of stearic acid mono- and diglycerides and palmitic acid.

Nevertheless, extremely quick solvent evaporation results in the creation of porous microparticles.[23]

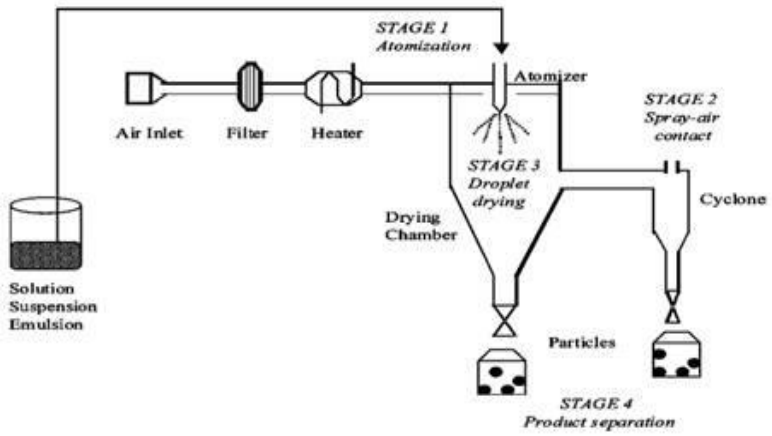

Fig. 4: Spray congealing method for microsphere preparation.

Benefits and drawbacks of microspheres

Microsphere Benefits[27]

- Poorly soluble Drugs may become more soluble if their size is reduced because it improves surface area.
- Maintain a steady blood level of the medication, which can improve patient compliance; lower dosage and toxicity.
- The ideal method for medication distribution is to coat the drug with polymers, which prevent enzymatic cleavage.
- Better patient compliance results from fewer doses.
- Better medication use will lessen the frequency the severity of negative consequences and boost bioavailability.
- Protects the GIT from the irritating effects of the medication.
- Transform liquid into solid and cover up the bitter flavour.
- If altered, dependable methods to transport the medication to the intended location with precision and sustain the appropriate concentration in the target area without causing negative consequences.
- Decrease the core's sensitivity concerning the external environment.
- The benefit of biodegradable microspheres over big polymer implants is that they can be implanted and removed surgically.

- Delivery of controlled release. By regulating drug release rates, biodegradable microspheres reduce harmful side effects and do away with the need for frequent injections.[26]

Restrictions[27]

The following were identified as some of the drawbacks:[25]

1. Compared to typical formulations, the ingredients and handling costs for the preparation of the controlled release are much higher.
2. The destiny of the polymer matrix and its environmental impact.
3. The destiny of polymer additives, such as fillers, stabilizers, plasticizers, and antioxidants.
4. Less reproducibility
5. Process variables like evaporation/agitation, solvent additions, temperature variations, and pH changes can affect the stability of the core particles to be encapsulated.

Recent Advancements in Microspheres

Important applications for the polymer chitosan: Effects of reducing cholesterol

Fiber examples having elevated, moderate, and poor binding of bile acids capabilities were chitosan and cellulose, respectively. For three weeks, mice in a control group were fed a diet heavy in fat and cholesterol, the blood cholesterol levels rose by approximately two times to 4·3 mM. This increase was avoided by adding either of these fibres at a rate of 7·5% of the diet. Additionally, treatment with these fibres decreased the quantity of cholesterol that is stored in the liver as a result of the HFHC diet. Although the hypocholesterolemic action of the three types of fibres was comparable, cholestyramine caused the highest reduction in liver tissue cholesterol. The following processes underlie cholestyramine's ability to decrease cholesterol:

1. Reduced consumption of foods high in cholesterol
2. Decreased efficiency of cholesterol absorption and
3. Elevated excretion of cholesterol and bile acid in the faeces.

The latter effects are a result of cholesterol's high bile acid binding capacity. However, adding chitosan or cellulose to the diet decreased the amount of cholesterol (food) consumed, but did not affect the absorption of intestinal cholesterol or the production of faecal sterol. The current study offers compelling evidence that the decrease in cholesterol is mostly due to satiety and satiation effects.[29]

Increase the Stability of the Drug

By complexing the medicine with chitosan and creating a slurry, the polymer chitosan is utilized to boost the drug's stability. This dough is then kneaded for 45 minutes till it becomes a mass. After passing through sieve number 16, this dough mix forms particles that are entirely steady in a range of circumstances.[29]

Orthopaedic Patients

Using chitosan as a bioactive covering to increase the osseointegration of orthopaedic and craniofacial implant devices is appealing due to its bactericidal, osteoconductive, and enhanced wound healing qualities. This has been demonstrated to be helpful in expediting wound healing and bone regeneration, as well as encouraging tissue growth in tissue repair.[29]

Chitosan as an Enhancer of Permeation

According to reports, chitosan's cationic nature allows it to form strong connections in a cell membrane. This trait has led to a number of investigations to look at the Chitosan's potential as a hydrophilic enhancement of permeability for medications, including Peptides that could ordinarily be poorly absorbed orally. The phenomenon depends on pH and concentration since the relationships between the membrane of the cell and the polymer's favourable charges are what produce the absorption amplification. Moreover, enhanced permeability would result from an increase in the density of charge in the polymer.[29]

Chitosan as an Excipient for Mucoadhesion

A common method to extend a medication's half-life in the gastrointestinal tract and boost its oral bioavailability is bioadhesivity. Chitosan has a higher bioadhesivity than more natural polymers, including starch, cellulose, and xanthan gum, according to a comparison with other widely used polymeric excipients.[29]

Transforming growth factor (TGF-β) promotes the formation of bones

As bone substitutes, chitosan composite microgranules were developed to attain superior bone-forming activity. To produce the chitosan microgranules, a mixed solution was poured into a NaOH/ethanol mixture. A TGF-pl solution was used to soak the microgranules of chitosan to load them with TGF-pl.[29]

Excipients that are directly compressible and can act as a binder

When 50% chitosan is added to tablets, it has the good property of being an excipient for direct compression, which causes quick disintegration. The amount of moisture absorption is determined by the degree of deacetylation. Higher than 5% chitosan outperformed microcrystalline cellulose and maize starch as a disintegrant. The molecular weight, particle size, degree of deacetylation, and chitosan crystallinity all affected the efficiency. When compared to other excipients, chitosan is a better tablet binder based on the rank order correlation for binder efficiency. Methyl cellulose > sodium carboxymethyl cellulose > hydroxy propyl methylcellulose > chitosan.[29]

Applications

Microspheres are used extensively in several different fields:

1. Using Microspheres to Deliver Vaccines: A vaccination must protect from the microorganism or its harmful byproducts. The perfect vaccination should meet the following criteria: affordability, ease of use, safety, and effectiveness. Safety and minimizing negative reactions are complicated topics.[30] The mode of application has a direct impact on both the intensity of the production of an antibody response and safety. The drawback of traditional immunizations may be addressed by biodegradable delivery methods for parenterally administered vaccines.[31] The following advantages make parenteral (subcutaneous, intramuscular, and intradermal) carriers interesting:

1. Increased antigenicity by adjuvant action
2. Adjusting the release of antigens
3. Antigen stabilization

2. Drug Delivery: By delivering medications in a precise and regulated way, microspheres increase bioavailability and lessen adverse effects.[33,34] They can be made to distribute medications over long periods of time or at specific locations, which makes them appropriate for treating chronic conditions.[33,34]

3. Tissue Engineering: To help with tissue regeneration and repair, porous microspheres are employed as scaffolds for cell adhesion and proliferation.

4. Biomedical Imaging: To improve picture quality and diagnostic precision, contrast agent-loaded microspheres are employed in imaging procedures like magnetic resonance imaging (MRI) and ultrasound.

5. Radionuclide Therapy: Targeted radiotherapy uses radioactive microspheres to deliver high radiation doses to cancerous tumours while causing the least amount of harm to healthy tissues.

4. Chemoembolization: This endovascular technique of treatment entails local delivery of a chemotherapeutic agent either concurrently or later, along with the selective arterial embolization of a tumour. Theoretically, the benefit of such embolization is that it will result in prolonged therapeutic levels of chemotherapeutics in the tumour regions in addition to providing vascular blockage. Traditional percutaneous embolization methods are expanded upon by chemotherapy**.**

Challenges and Future Perspectives

Notwithstanding their many benefits, there are several obstacles to the creation and use of microspheres:

1. Scalability: It's still very difficult to transfer laboratory-scale production techniques to industrial-scale manufacturing while preserving consistency and quality.[34]

2. Stability: The commercial success of microspheres depends on their capacity to remain stable both in vivo and during storage.[33]

3. Regulatory Approval: Clinical use of microspheres requires regulatory approval for biocompatibility, safety, and efficacy. To fully realize their promise in biomedical applications, future research should concentrate on creating sophisticated fabrication processes, enhancing the stability and functionality of microspheres, and resolving regulatory issues.

CONCLUSION

Microspheres are adaptable and promising delivery systems for a range of biological uses. They are perfect for drug administration, tissue engineering, and imaging because of their special qualities, which include high surface area, controlled release capabilities, and biocompatibility. It is anticipated that continued research and development will address current issues and broaden the range of uses for microspheres in the biomedical industry.

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