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MICROSPHERES: AN OVERVIEW ON, METHODS OF PREPARATION, CHARACTERIZATION AND PHARMACEUTICAL APPLICATIONS

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ABSTRACT

The pharmaceutical industry has demonstrated a strong interest in microparticulate drug delivery technologies. They enable the decrease of adverse effects and an improvement in the therapeutic efficiency of drugs. Microspheres are one of these carrier devices that have been studied extensively as they allow for both delivery of the drugs to a particular therapeutic target and control over it. The unstable drugs which include enzymes, proteins, and peptides are temporarily shielded by the microspheres for the effective delivery. Numerous drugs, including nucleic acids and small compounds, can be encapsulated in microspheres. The drug can be delivered to the target site with precision, even if modified, and the desired concentration can be maintained by this reliable method. Microspheres have drawn a lot of interest for their capacity to target cancer cells in addition to their sustained release. Combining with other approaches, it finds its main use in novel drug delivery, specifically in the areas of miserable cell sorting, diagnostics, and also in gene and genetic materials.

KEYWORDS: Microspheres, Controlled drug delivery, Biodegradable polymer, Therapeutic Efficacy, Targeted drug delivery.

INTRODUCTION

The continual advancement of drug delivery methods, particularly those that enable a prolonged and controlled action of drugs to its intended region of impact, has revolutionised the idea of drug delivery.[1] These innovative drug delivery systems have the ability to target the distribution of the drug to a particular location, maintain the duration of therapeutic activity, and/or regulate the frequency of drug delivery.[2,3] Therapeutic components can be delivered to the target location through several ways via extended controlled release techniques. Attaching bioactive molecules to liposomes, bioerodible polymers, implants, monoclonal antibodies, and other nanoparticles can accomplish precise targeting and site-specific delivery. Using microspheres as drug carriers is one such method. The controlled release of drugs, vaccines, antibiotics, and hormones can be achieved by using microspheres. As a drug carrier's microspheres is one of the most modern approaches for sustaining and controlling the activity of a drug at specific points (such as tissue). These are spherically shaped, free-flowing powders made of synthetic polymers or proteins that can either be biodegradable or non-biodegradable in nature, with the optimal particle size falling between 1 and 1000 μm.[4,5] Microcapsules and micrometrics are the two forms of microspheres. Figure 1 represents the two different forms of microspheres. The former is characterised by the entrapped substance being surrounded by a distinct capsule wall, while the latter is dispersed or dissolved through the particle matrix, offering the possibility of controlled drug release.[5] They are composed of waxy, polymeric, or other protective compounds, such as modified natural products and synthetic polymers that degrade bio-degradable. The stability, solubility, and drug release of microspheres are influenced by the type of polymer that is utilised to produce them. Expandable microspheres, polystyrene, and polyethylene are the three most often used types of polymeric microspheres.[6] Some of the issues with traditional therapy can be resolved and the therapeutic efficacy of particular drugs can be increased with a well-designed controlled drug delivery system. The drug must be delivered to the target tissue in the ideal amount and at the ideal time to achieve optimum therapeutic efficacy with the least degree of toxicity and adverse effects.[7,8]

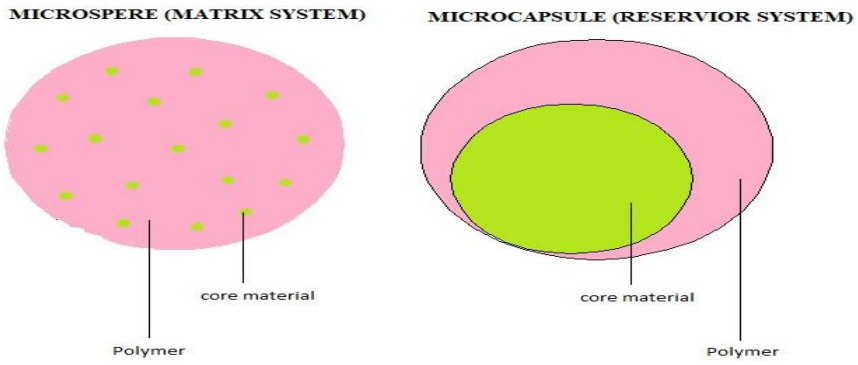

Fig. 1: Different forms of microspheres.

Advantages of microspheres

- Microspheres have a consistent and long-lasting therapeutic impact.
- Patient compliance is improved by reducing the frequency of dosing.
- Their spherical form and smaller size make it possible to insert them into the body.
- Enhanced drug utilization can enhance bioavailability while reducing the chance of side effects.
- Microspheres have a morphology that enables controlled variability in drug release and degradation.
- The conversion of liquids into solids is done to make them more manageable.[9]

Types of polymers

For the creation of microspheres, a variety of materials both biodegradable and non-biodegradable have been studied. The polymers that make up these compounds fall into two groups:

1. Synthetic polymers
2. Natural polymers

1. Synthetic polymers: They are employed as carrier materials and are divided into two types:

a. Non-biodegradable polymers: for ex- Poly methyl methacrylate, Acrolein, Glycidyl methacrylate, Epoxy polymers.

b. Biodegradable polymers: for ex- Lactides and Glycolides and their copolymers, Poly alkyl cyanoacrylates, Poly anhydrides and Poly-caprolactone (PCL).[10]

2. Natural polymers: They are obtained from different sources like proteins, carbohydrates, and chemically modified carbohydrates.

a. Proteins- Albumin, Gelatin, Collagen.

b. Carbohydrates- Agarose, Gelatin, Starch, Chitosan, Carrageenan.
c. Chemically modified carbohydrates- Poly(acryl) dextran, Poly(acryl) starch, DEAE cellulose.[11]

Ideal microparticulate carriers

The following qualities should be present in the material used to make microparticulates:

- Extended action time.
- Offer drug protection.
- Sterilizability.
- Solubility or dispersibility in water.
- Not harmful.
- A degree of steadiness.
- Biodegradable.
- A rise in the effectiveness of treatment.
- Management of content dissemination.[12]

Types of microspheres[13]

a. Bio adhesive microspheres

Adhesion is the process by which a drug sticks to a membrane by exploiting of its water-soluble polymers' sticky properties. Bio adhesion is the phrase used to describe the adherence of a drug delivery device to a mucosal membrane, such as the nasal, rectal, ophthalmic, or buccal. These particular microspheres have a longer residence period at the application site, which results in close contact with the absorption site and improves the therapeutic effect.[13]

The figure 2 gives the description of Bio adhesive microsphere.

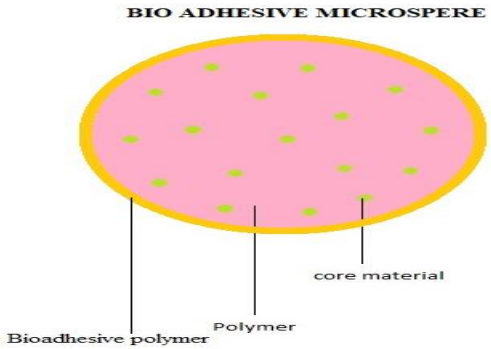

Fig. 2: Bio adhesive microsphere.

b. Magnetic microspheres This form of drug delivery system, which targets the exact location of the disease, is crucial. A smaller quantity of magnetic targeting can take the place of the greater quantity of the drug that is freely circulating. Chitosan, dextran, and other materials that are integrated into magnetic microspheres cause magnetic carriers to respond magnetically to a magnetic field. Therapeutic magnetic microspheres and diagnostic microspheres are the two forms.[14] Figure 3 represents the magnetic microsphere.

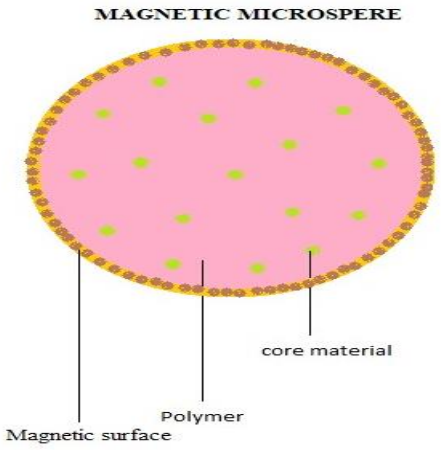

Fig. 3: Magnetic microsphere.

1. **Therapeutic magnetic microspheres:** Chemotherapeutic agents are delivered to liver tumours using this method. This technique can also target drugs such as proteins and peptides.
2. **Diagnostic magnetic microspheres:** By generating nanoscale particles of supra magnetic iron oxides, it may be applied to the imaging of liver metastases as well as the differentiation of intestinal loops from other abdominal structures.

c. Floating microspheres

The buoyancy of floating sorts in the stomach is not impacted by the velocity of gastric emptying since their bulk density is lower than that of gastric fluid. If the system is floating on stomach content, the drug is released gradually at the intended pace, increasing gastric residency and variation in plasma concentration. It also lowers the likelihood of dosage dumping and striking. Another method is that it has a longer-lasting therapeutic impact, requiring fewer doses.[15,16] Figure 3 represents the Floating microsphere.

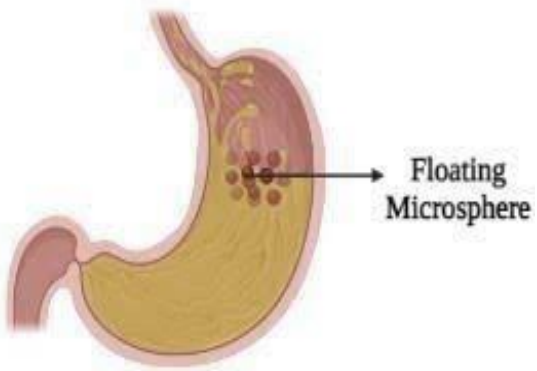

Fig. 3: Floating microsphere.

D. Radioactive microspheres

Microspheres, which are bigger than capillaries in radio immobilization treatment, are tapped into the first capillary bed they come across. They range in size from 10 to 30 nm. They are injected into the arteries that supply the target tumour. Under all of these circumstances, radioactive microspheres provide strong radiation doses to the intended regions without endangering the healthy tissues nearby. It is distinct from drug delivery systems in that radioactivity acts from inside a radioisotope's normal distance rather than being discharged from microspheres, and there are several types of radioactive microspheres.[17] Figure 4 represents the radioactive microsphere.

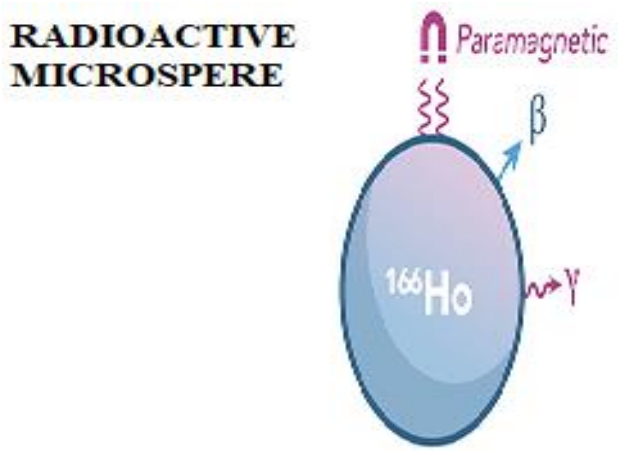

Fig. 4: Radioactive microsphere.

Mechanism of microspheres drug delivery

Most microparticle-based drug delivery systems inhibit the development of an internal solid dispersion morphological structure resembling a matrix. It's possible that the drug is insoluble in the polymeric matrix and that erosion releases it. Prior to dissolving the resultant near the device's surface, water diffuses into the matrix. In the first drug burst, a predefined amount of

medicine is released through a channel formed to the surface to relieve the osmotic pressure that results.[9] Figure 5 shows the mechanism of microsphere drug delivery.

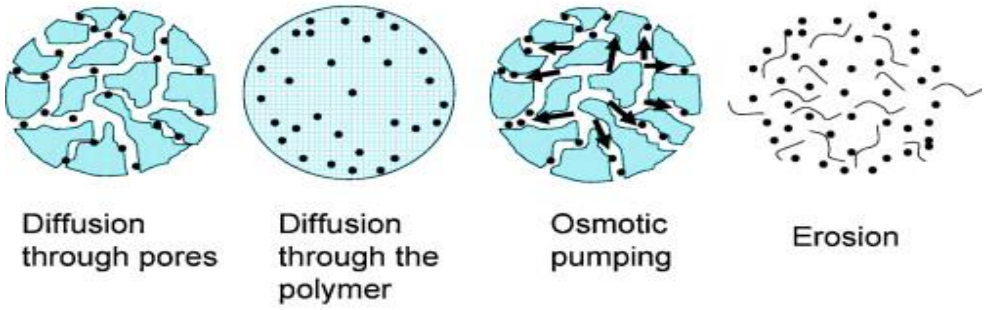

Fig. 5: Mechanism of microsphere drug delivery.

Method of preparation of microspheres

When compared to large implanted devices, the dosage dumping potential is reduced by the production of sustained release, controlled release, and targeted drugs. The following are many ways that microspheres are used. Methods used for the preparation of microspheres are:

1. Single emulsion techniques

The single emulsion method is used to create the microparticulate carriers of natural polymers, such as proteins and carbohydrates. Natural polymers are first dissolved or dispersed in an aqueous media, such as oil, and then they are disseminated in a non-aqueous medium. Cross-linking can be accomplished in the second preparation phase by applying heat or by utilising chemical cross-linkers. Various chemical cross-linking agents are employed, such as formaldehyde, terephthaloyl chloride, glutaraldehyde, and diacid chloride. Heat-induced crosslinking is influenced by the dispersion added to heated oil beforehand. However, heat denaturation is not appropriate for thermolabile pharmaceuticals, and chemical cross-linking, if introduced during manufacturing, has the drawback of exposing the active component to large amounts of chemicals.[18] Figure 6 shows the schematic representation of Single emulsion techniques.

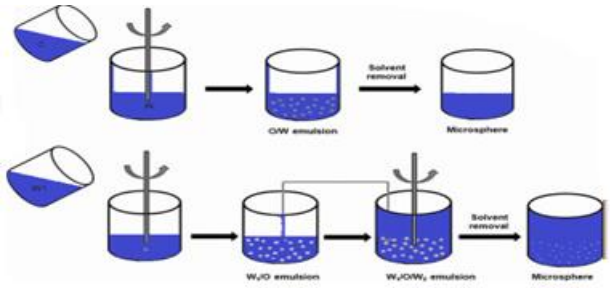

Fig. 6: Single emulsion techniques.

2. Double emulsion techniques

In summary, the double emulsion technique of manufacturing microspheres is best suited for water-soluble drugs, peptides, proteins, and vaccines. It requires the development of several emulsions or double emulsion of type w/o/w. This technique works with both synthetic and natural polymers. There is a lipophilic organic continuous phase in which the aqueous solution is distributed. The active ingredients could be present in this protein solution. The polymer solution that finally encapsulates the protein found in the scattered aqueous phase often makes up the continuous phase. After that, the main emulsion is homogenised or sonicated before being added to the poly vinyl alcohol (PVA) aqueous solution. A double emulsion is created as a result of this. Next, the emulsion undergoes a solvent extraction or solvent evaporation procedure to remove the solvent.[19,20] Figure 7 shows the schematic representation of the double emulsion technique of manufacturing microspheres

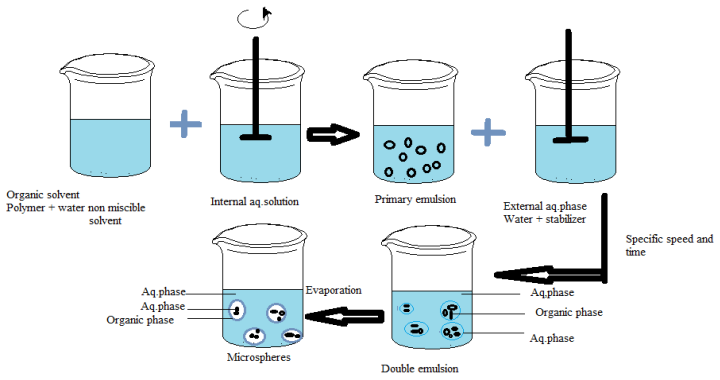

Fig. 7: Double emulsion techniques.

3. Polymerization techniques

a) Interfacial polymerisation methods

Three popular ways of interfacial polymerization include suspension, emulsion, and dispersion polymerizations. These methods usually involve a combination of a monomer and an initiator, which are polymerized in such a way that the developing polymer is forced or constrained to form particles.[21] Figure 8 shows the schematic representation of the interfacial polymerization technique of manufacturing microspheres.

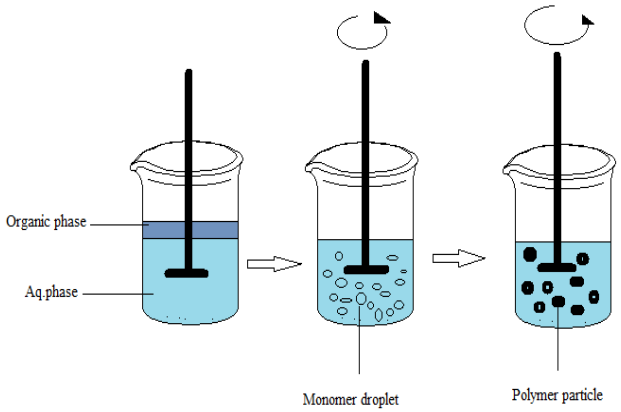

Fig. 8: Interfacial polymerization.

b) Suspension polymerisation

A suitable solvent is used to create a solution of the initiator and monomer, which is then added to an immiscible suspension medium where the monomer and initiator are insoluble, to accomplish suspension polymerization. In the presence of dispersion stabilisers like surfactants or low molecular weight polymers, agitation (such as stirring) produces droplets of solvent. These solvent droplets are subsequently the site of polymerization, and the polymer which is also insoluble in the suspension medium acquires the shape and dimensions of the solvent droplets hosting the process.[22] Figure 9 shows the schematic representation of the suspension polymerization technique of manufacturing microspheres.

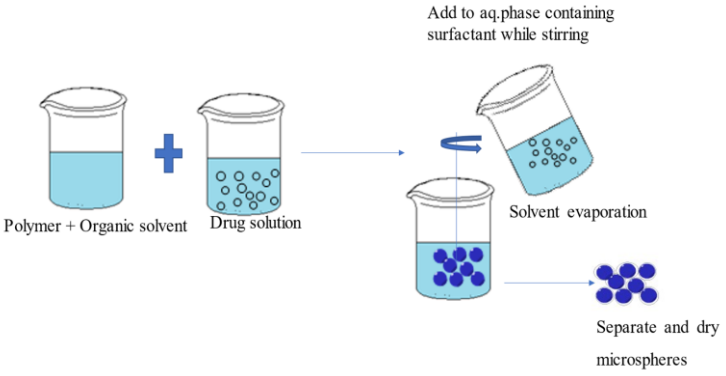

Fig. 9: Suspension polymerization.

4. Phase separation coacervation technique

The phase separation technique is specifically meant to prepare the reservoir type of the system, that is, to encapsulate drugs that are soluble in water, such as proteins or peptides. Nevertheless, certain preparations are matrix-type, especially when the drug is hydrophobic, like steroids. The method works on the basis of reducing the polymer's solubility in the

organic phase to influence the development of a polymer-rich phase known as coacervates. This method involves dissolving the polymer in an appropriate solvent first, and then dispersing the drug either in an aqueous solution (if hydrophilic) or in the polymer solution itself (if hydrophobic). Subsequently, phase separation is achieved by adjusting the solution conditions using techniques including adding salt, adding a non-solvent, adding an incompatible polymer, or adjusting the pH. The procedure is executed with constant stirring to regulate the size of the microparticles.[23] Figure 10 shows the schematic representation of the Phase separation coacervation technique of manufacturing microspheres.

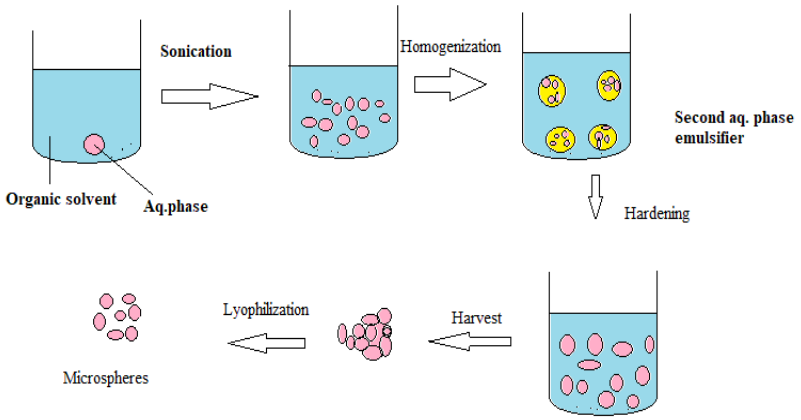

Fig. 10: Phase separation coacervation technique.

5. Spray drying

The principles of spray drying and spray congealing rely on the drying of the drug and polymer mist in the atmosphere. The two procedures are referred to as spray drying and spray congealing, respectively, depending on whether the solvent is removed or the solution cools. After dissolving the polymer in an appropriate volatile organic solvent (such as acetone, dichloromethane, etc.), the drug is distributed throughout the polymer solution using rapid homogenization. A hot air stream is then used to atomize this dispersion. Small droplets or fine mist are formed as a result of atomization, and when the solvent instantly evaporates, microspheres with sizes between one and one hundred micrometres are created. The cyclone separator removes microparticles from the hot air, and hoover drying eliminates any remaining solvent.[24] Figure 11 shows the schematic representation of the spray drying and spray congealing technique of manufacturing microspheres.

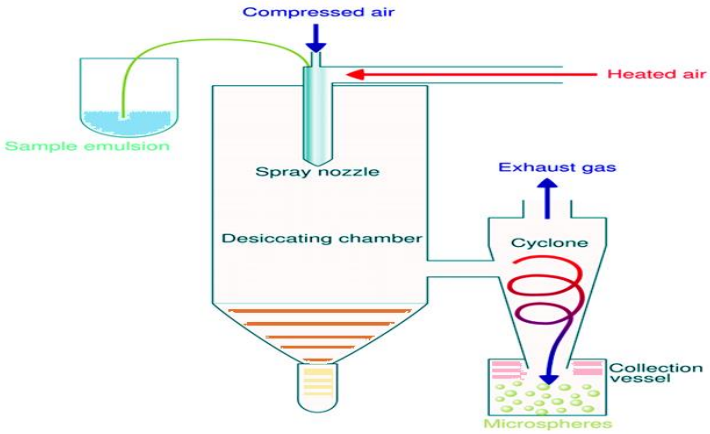

Fig. 11: Spray Drying and Spray congealing.

6. Emulsion crosslinking method

Using cross-linking agents such as glutaraldehyde, formaldehyde, acid chloride, etc. A solution of chitosan in aqueous acetic acid was made as a cross-linking agent. To create a water in oil (w/o) emulsion, this dispersed phase was introduced to a continuous phase that included light and heavy liquid paraffin in a 1:1 ratio and 0.5% (wt./vol) Span 85. The stirring was kept up to 2000 rpm. At 15, 30, 45, and 60 minutes, a drop-by-drop solution of a determined amount (2.5 mL each) of aqueous glutaraldehyde (25% v/v) was added. After 2.5 hours of stirring, the microspheres were separated by vacuum-assisted filtering and cleaned twice: once with petroleum ether (60°C to 80°C) and once with distilled water to get rid of the adhering liquid paraffin. Finally, the microspheres were dried in vacuum desiccators.[25] Figure 12 shows the schematic representation of the Emulsion crosslinking method technique of manufacturing microspheres.

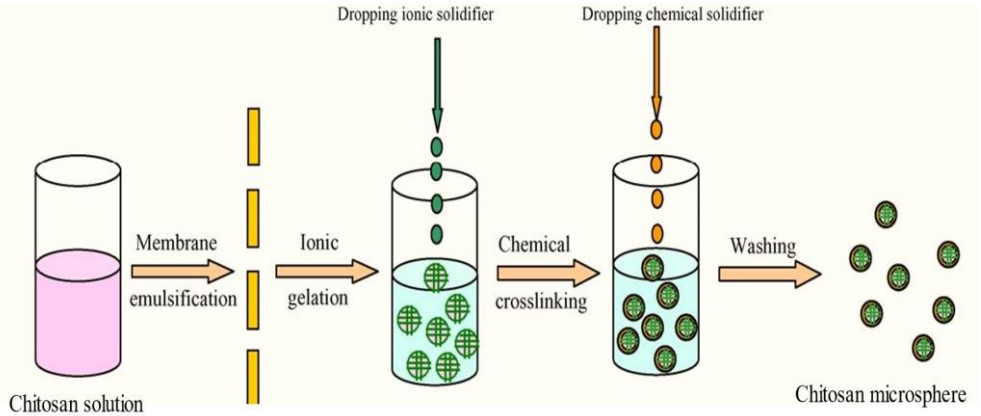

Fig. 12: Emulsion crosslinking method.

7. Ionic gelation method

In the presence of counter ions, ionotropic gelation is dependent on the propensity of polyelectrolytes to cross link to form hydrogel beads, also known as gelispheres. Gelispheres, which are hydrophilic circular cross-linked polymeric agents, have the ability to significantly thicken and gel in model biological fluids and release drugs under the control of polymer relaxation. A polymeric solution containing drugs is added to an aqueous solution containing polyvalent cations to produce hydrogel beads. The drug-loaded hydrophilic molecules allow the cations to move through them, forming a three-dimensional lattice in which the moiety is crosslinked ionically. These gelispheres can also hold biomolecules to preserve their three-dimensional shape in milder environment.[26] Figure 13 shows the schematic representation of the Ionic gelation method technique of manufacturing microspheres.

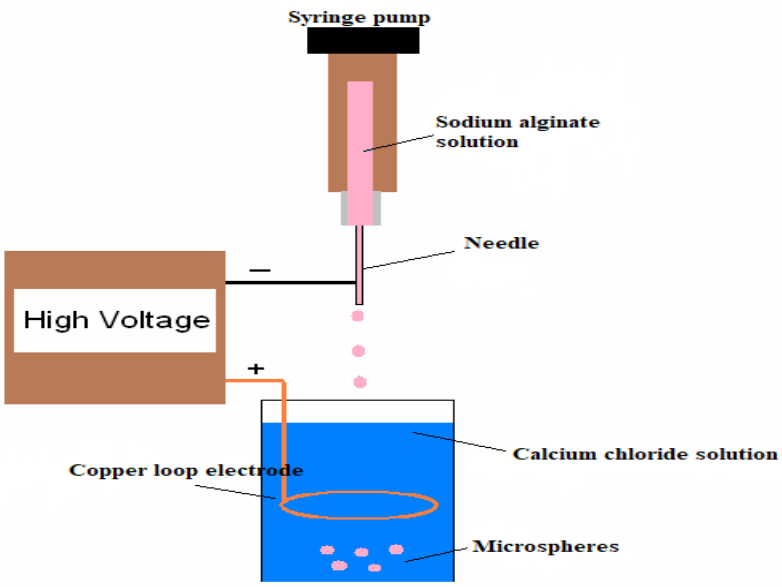

Figure 13: Ionic gelation method.

Microsphere evaluations

1. Particle size analysis

The dried microsphere was measured using a calibrated optical micrometre in a microscopic manner. Standard light microscopy (LM) is the approach most often employed for micro particular visualisation.[27]

2. Scanning electron microscopy (SEM) study

The samples were examined using a scanning electron microscope (SEM), which was well-suited for image analysis using a back-scattered electron sensor. Additionally, x-ray diffraction analysis (EDXA) was performed to determine the elemental structure of the

samples, identifying specific elements. Using a focused electron beam, the sample was scanned in parallel lines in this approach. After that, microspheres were mounted on a sample holder for SEM characterization. Previously, a sputter coater was employed to apply a conductive metal, such zirconium or platinum, on the microspheres. Next, a finely focused electron beam was used to scan the material. The sample's surface characteristics were determined by analysing the secondary electrons that were released from the surface.[28,29]

3. Flow properties

The carr's compressibility index, Hausner ratio, and resting angle of repose may be used to assess the flow characteristics. A volumetric cylinder was employed to evaluate the bulk and tapped densities.[30]

4. Thermal analysis

By applying defined Specimen atmospheres and pressures together with planned temperature fluctuations for heating and cooling, thermal analysis tools assess these changes on a regular basis. Subtle changes in heat and enthalpy, weight gain or loss, Young's modulus, thermal expansion or shrinkage, and gas evolution are among the most often observed characteristics.[31]

5. Determination of percentage yield

The measured quantity of the product, the polymers employed in the microspheres' formulation, and the total number of microspheres produced may all be utilised to calculate the percentage yield.[32]

$$\% \text{ Yield } = \frac{mass\ of\ microsphere\ obtained}{total\ weight\ of\ drug\ \&\ polymer} \times 100$$

6. Drug content

To enable the particles to settle and subsequently wash, the mixture should be set aside. One millilitre (litre) of the filtrate was transferred into a volumetric flask, and 0.1N NaOH was used to adjust the volume. After the proper dilution, the drug was measured using spectrophotometry.[33]

7. Determination of drug loading

The proportion of the weight of the nanoparticles that are connected to the encapsulated product is indicated by the loading ability, which is the quantity of drug loaded per unit of

nanoparticle weight. The whole amount of drug captured divided by the entire weight of nanoparticles yields the loading capacity (LC percent). The amount of drug supplied per quantity is represented by the yield, which is a percentage in drug delivery.[34]

Applications of microspheres

A number of pharmaceutical microencapsulated products are currently on the market.

1. Microspheres in vaccine delivery

A vaccine's prerequisite is immunity to the damaging component of the microorganisms. The perfect vaccination should meet these similar requirements for safety, efficacy, and cost-effectiveness. It's difficult to defend against harmful consequences and avoid them. The technique of application is closely related to both the safety factor and the degree of antibody response production. One potential solution to address the shortcomings of intravenous vaccinations is the use of biodegradable delivery technology. Parenteral (subcutaneous, intramuscular, and intradermal) carriers are used despite the fact that they don't always provide noticeable advantages.[35]

2. Microspheres in gene delivery

Viral vectors, non-ionic liposomes, polycation complexes, and microcapsule technologies are all used in the delivery of genotype drugs. Even though viral vectors are very effective and have a wide range of cell objectives, they are still advantageous for genotype delivery. Nevertheless, when applied in vivo, they elicit harmful consequences and immunological reactions. Gene therapy has been considering nonviral delivery techniques as a solution to the limitations of viral vectors. Benefits of nonviral delivery systems include easy preparation, targeted distribution to specific cells or tissues, less immune response, unlimited plasmid size, and large-scale, reproducible manufacturing. Polymer will be employed in gene delivery applications as a DNA transporter.[36,37]

3. Oral drug delivery

Research using rabbits has assessed the potential of polymer matrix, which typically comprises diazepam as an oral drug delivery method. Results suggested that a film with a drug-polymer ratio of 1:0.5 would have been a useful dosage form that is similar to manufactured tablet formulations. Because of its ability to create films, polymers may be used in combination with drug tablets to make film dosage forms. The polymer becomes unique for oral drug delivery applications due to its sensitivity to pH and the responses of its two major amine groups.[38,39]

4. Transdermal drug delivery

Polymer has good properties for creating films. The thickness of the membrane and the crosslinking of a film affect the release profile from the devices. Additionally, chitosan-alginate polyelectrolyte structure has been synthesised in situ in beads and microspheres for possible use in surgical tools, controlled release systems, and packaging. Impressively, polymer gel beads are a highly biocompatible delivery system for inflammatory cytokines used in chemotherapy for drugs such as prednisolone. They also exhibit prolonged release properties that improve the efficacy of treatment. It was discovered that the properties of the cell wall being employed also affected the amount of drug release. A fantastic complete approach for controlled drug release and release kinetics is a blend of chitosan membrane and chitosan hydrogel that is known to contain the local anaesthetic lidocaine hydrochloride.[40]

5. Targeting by Using Micro Particulate Carriers

Targeting is a well-established doctrine that refers to attempting to get significant attention in the modern day. The capacity of a drug to engage with a binding site and produce a response is dependent on its availability. Generally, pellets made using extrusion or spheronization technologies, such as chitosan and microcrystalline cellulose (MCC), are proved to be effective.[41]

6. Monoclonal antibodies

Targeting microspheres and monoclonal antibodies are examples of biologically immunologic microspheres. One such method of attempting to target is the use of selective targeting to achieve certain organ system locations. Highly specific substances called monoclonal antibodies also attach to a specific area of the body's structure, allowing for absorption through.[42,43]

- Non particular adsorption and particular adsorption
- Direct coupling
- Coupling via reagent

7. Intratumoral and Local drug delivery

Polymer films were also produced in order to produce solid lipid nanoparticles at the cancer cells at a therapeutically relevant intensity. The use of combination with medicine in regulated administration across the oral cavity shows promise. Such include PCL, PLGA, chitosan, and gelatine.[44,45]

8. Other applications

Microspheres are used for membrane technology developed for mass spectrometry,[46] cell biology,[47] Fluorescent connected Immuno-Sorbent Assay.[48] With encouraging outcomes, yttrium may be utilised for hepatocellular carcinoma regular therapy as well as pre-transplant care. Microencapsulation has many applications in several industry areas. The most well-known microencapsulated goods include carbonless copying paper, photosensitive paper, and microencapsulated scents like "scent-strips" (also called "snap-n-burst" and "scratch-n-sniff"). Gelatin and acacia coacervation complex are typically used in the preparation of these additional goods. Children's books, nutrition, and scent production have all employed the scratch-n-sniff technique. Additionally, microcapsules are widely used in diagnostic testing. For instance, temperature-sensitive microcapsules are used in temperature-dependent visual cancer detection. Microcapsules containing microbial cells are utilised in the biotech sector to produce proteins and recombinant DNA .[35]

9. Medical application

Microspheres are utilised in vaccine administration for illnesses including hepatitis, influenza, pertussis, diphtheria, and many more. They also have a wide range of additional medicinal uses, such as the long-term release of proteins, hormones, and peptides. The best delivery systems for insulin and DNA plasmids are microspheres. By intravenous or intraarterial administration, microspheres will be employed to actively target tumour cells and antigens as well as leaky tumour vasculature.[49]

10. Radioactive microspheres applications

It is applicable to radioembolization of liver and spleen tumours, local radiotherapy, radiosynovectomy of arthritic joints, and interactive care. Imaging of the liver, spleen, lung, bone marrow, and even the thrombus in a deep vein thrombosis is conceivable.[50]

CONCLUSION

The drug delivery method described in this review article microspheres is superior to other drug delivery methods. In the days to come, this innovative microsphere drug delivery system will prove to be more potent and effective in in-vivo delivery of drugs for treating diseases such as those pertaining to the heart, lungs, or nervous system. It will also prove to be more effective in cancer therapy and other medical treatments. This formulation primarily ensures the safety of the pharmaceutical component that is active as well as the additional excipients that are utilised in the formulation.

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