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REVOLUTIONIZING DRUG DELIVERY: MICROSPHERE TECHNOLOGY FOR FUTURE GENERATIONS

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ABSTRACT
Microspheres are the small spherical shaped particles ranging size from 1 µm to 1000 µm in diameter. They are employed in pharmaceutical industries by developing the prolonged release formulations. Microspheres have emerged as a versatile and promising platform for drug delivery, with applications spanning across various domains, including cancer therapy, vaccine development, and ophthalmic drug delivery. The unique properties of microspheres, such as their biodegradability, biocompatibility, and controlled release kinetics, make them an attractive choice for delivering a wide range of therapeutic agents, including small molecules, proteins, and peptides. In cancer therapy, microspheres have been employed for the targeted delivery of chemotherapeutic agents, resulting in improved efficacy and reduced systemic toxicity. In vaccine development, microspheres have been utilized to enhance the stability, immunogenicity, and controlled release of vaccines, thereby improving their overall effectiveness. In ophthalmic drug delivery, microspheres have been used to deliver drugs directly to the eye, providing sustained release and improved bioavailability, thereby reducing the frequency of administration. Furthermore, microspheres have also been explored for the delivery of protein and peptides, with the potential to enhance their stability, bioavailability, and controlled release. This review provides a comprehensive analysis of microspheres and their advantages and applications.

KEYWORDS: Microspheres, Novel drug delivery, Biodegradability, Biocompatibility, Targeted drug delivery, Sustained release, Controlled release.

INTRODUCTION
Microspheres are the particles with size ranges from 1 µm to 1000 µm in diameter[1] (Sahil, *et al*., 2011). The history of microspheres shows that it had wide range of applications in diverse fields. Ongoing research finds the way to the advancements in the medicine, industry and technological fields with the microspheres technology. The size of the molecule of interest will decide the capabilities of the molecule like how strong a building is decided by how strong the materials used for building the house. Like the bricks of the house atoms are the bricks of the molecules by changing the number of electrons and protons it can change the whole property of the materials. Likewise, as the changes made at the basic level it shows the impact at the material level. Now a days the research in the medicinal field is focussed on the micro and nano level particles which shows a huge impact on the drug delivery, site specific drug delivery and for the prolonged release. The properties of the molecules at the basic level were exploited in the field of pharmaceutics to deliver the drug for their specific targets and also in the prolonged release categories.

In the field of pharmaceutics, Novel drug delivery systems polymers play a pivotal role. Polymers Like PLGA are the most important ingredients which play a major role and it occupies a great status in the field of novel drug delivery approaches[2] (Kapoor, *et al*., 2015). Utilizing the unique qualities of several polymers, the drug was able to reach its intended location within the human body and increase the pace of release by releasing it gradually over a predetermined amount of time. This achievement of sustained and controlled release formulations made the patient to reduce the frequency of medication which in turn will decrease the toxicity, side effects and major adverse effects of the medication. The patient suffering from some chronic diseases like cancer, diabetes etc are prescribed to take the medication frequently, even though intake of such medication daily may lead to its accumulation due to the conventional dosage forms here comes the role of prolonged acting medication or drug delivery technologies like microspheres, nanoparticles, hydrogels, carbon nanotubes, microparticles etc.

Various drug delivery methods such as hydrogels, liposomes, microspheres, nanoparticles, and nio somal formulations are available to administer drugs in a managed and prolonged fashion[3] (Helwa, *et al*.,2013). They are also site specific which is useful in the cancer drug delivery. Due to increased frequency of intake of the standard dose forms, this delivery system helps to provide the medication in a sustained way with continuous drug release rates, which makes the patient more comfortable and reduces toxicity and adverse effects of the medication accumulation. Most of the novel drug delivery approaches are injectable formulations which are either given through Intravenous route or Intra muscular route of administration based on their requirements. Some of the microspheres and nano formulations are employed in the ophthalmic drug delivery systems because of their nature sustained release of the drug substance.

Microspheres are categorized under the complex formulations[4] (Sahil, *et al*., 2011). since their process of preparation is complex and the process is should be under the controlled conditions. There are several different types of microspheres, including magnetic, bio-adhesive, polymeric, floating, and radioactive microspheres. Microspheres have potential applications in multiple domains, including gene delivery, ocular drug delivery, target drug delivery, oral drug administration, and cosmetics. Delivering the chemical to the target tissue at the proper dosage and in the right amount of time will result in minimum toxicity and adverse effects and maximum therapeutic efficacy. Although there are other methods for creating microspheres, the solvent evaporation method is now the most practical and widely used method.[5] (Bodmeier, *et al*., 1988) In the following review this technique is discussed in detail. In the present context the microspheres are studies as a part of the complex injectables which are employed under the prolonged release injectables.

The status of the microspheres in the injectable are deliberately represented in the Figure 1.

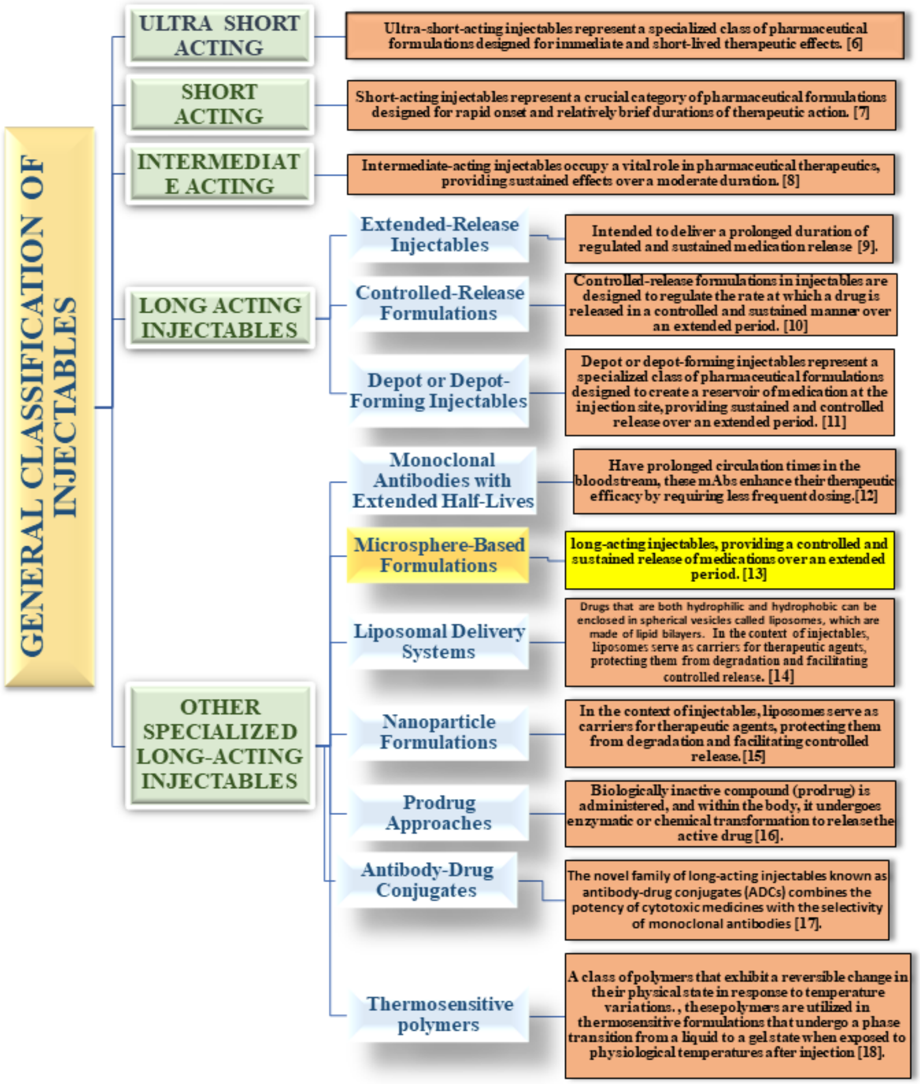


Figure 1: General classification of injectables.

Microspheres for parenteral administration

Multiparticulate drug delivery systems, or microspheres, are intended to administer medications at a set pace and location. Microspheres are free-flowing powders with particle sizes ranging from 1 to 1000µm that are composed of synthetic polymers or biodegradable proteins. The majority of microspheres that are ready for parenteral administration have a diameter of between 40 and 120µm.[19] Microspheres are majorly classified based on the position or placement of the drug the polymer microsphere. The microspheres are classified into two types which are mentioned in the **Figure 2.**

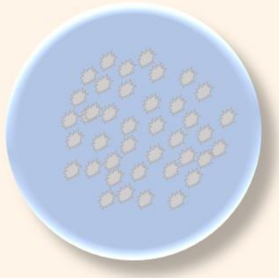
S.No	Micromatrices	Microcapsules
1	Micro matrices are those in which the entrapped substance is dispersed within the microsphere's matrix	microcapsules are those in which the entrapped substance is clearly enclosed by the distinct capsule wall
2		

Figure 2: Classification of microspheres.

The chronological evolution of microspheres reflects a progression from early exploration to diverse applications and sophisticated technologies. The goal of ongoing research is to overcome obstacles and open up new avenues for the pharmaceutical industry's use of microsphere-based drug delivery systems.

A potential method for controlled drug release is the use of solid biodegradable microspheres with a drug dissolved or distributed via a particle matrix. Microspheres' stability, solubility, and drug release are all influenced by the kind of polymer used to create them; common varieties include polyethylene, polystyrene, and expandable microspheres.[20] Both solid and hollow microspheres are available; the latter are added to materials to lower their density.[21] Topical formulations based on microspheres have gained popularity due to their extended duration of therapeutic efficacy.

Selection of a polymer in microsphere preparation

The primary component responsible for the whole regulated and sustained medication release feature of the microsphere is polymer. The prolonged drug release profile of the microspheres is significantly influenced by the properties of the polymers. The characteristics of the polymer required to select a polymer are mentioned in the F**igure 3.**

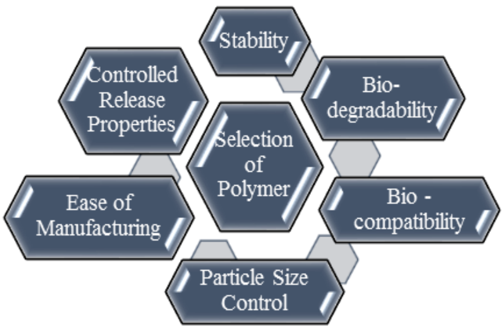


Figure 3: Selection of polymer.

Examples of polymers commonly used in medicine

1. **Polyethylene glycol (PEG):** PEG is a biocompatible and water-soluble polymer widely used in pharmaceuticals. It is frequently used to improve the bioavailability and solubility of poorly soluble medications. PEG is also employed in the creation of different medication administration methods.[22]
2. **Poly (lactic-co-glycolic acid) (PLGA):** PLGA is a biodegradable and biocompatible polymer frequently used in the formulation of controlled-release drug delivery systems. It is customizable to break down at particular speeds, enabling extended medication release.[23]
3. **Hydrogels:** These polymer networks are three-dimensional and have the ability to hold and absorb water. Because hydrogels may release pharmaceuticals in reaction to particular stimuli, such temperature, pH, or the presence of certain ions, they are employed in drug delivery systems.
4. **Chitosan:** Derived from chitin, chitosan is a natural polymer with antimicrobial properties. It is a

component of medication delivery systems that are administered orally, nasally, or transdermally.

5. **Polyethylene oxide (PEO):** PEO is a water-soluble polymer often used in controlled-release formulations. It can form gels and matrices that control the release of drugs over time.
6. **Polyvinyl alcohol (PVA):** PVA is a water-soluble synthetic polymer used in the development of drug delivery systems, particularly for ocular drug delivery.[24] Because these polymers enhance medication stability, bioavailability, and release kinetics, more patient-friendly and efficacious therapeutic formulations can be created. The exact needs of the medication, the intended release profile, and the mode of administration all influence the polymer selection.

Role of polymers in microspheres (long-acting injectables)

In the creation of long-acting injectables and microspheres, polymers are essential. They serve various functions, contributing to the formulation's stability, controlled release, and overall effectiveness.

1. **Encapsulation and Protection:** Polymers are used to encapsulate drugs within microspheres, protecting them from degradation, oxidation, or other destabilizing factors.
2. **Controlled Release:** Polymers enable controlled release of the encapsulated drug. The kind of polymer, its molecular weight, and the formulation design all affect the rate of release.
3. **Biodegradability:** Biodegradable polymers are often employed, allowing for the gradual degradation of microspheres over time, releasing the drug in a sustained manner.
4. **Size and Surface Characteristics:** Polymers influence the size, shape, and surface properties of microspheres, affecting their behaviour in the body and interactions with cells.
5. **Targeted Delivery:** Functionalized polymers can facilitate targeted drug delivery by modifying the surface properties of microspheres to enhance affinity for specific cells or tissues.
6. **Enhanced Stability:** Polymers contribute to the stability of microsphere formulations, preventing aggregation, coalescence, or other changes that may occur during storage.
7. **Ease of Processing:** Polymers provide a matrix for drug encapsulation and are chosen based on their compatibility with the chosen method of microsphere preparation (e.g., emulsion, solvent evaporation).[25]

The choice of polymers is an important part of formulation development for both long-acting injectables and microspheres, since it affects the overall efficacy and success of the drug delivery system. The specific requirements of the drug, the desired release kinetics, and considerations for patient comfort and compliance all contribute to the choice of polymers in these formulations.

Drug delivery research has shown a great deal of interest in biodegradable polymer microspheres, especially those composed of poly(lactide-co-glycolide) (PLGA), because of its biocompatibility, biodegradability, and easy processing. PLGA microspheres offer a versatile platform for controlling drug release kinetics by modulating microsphere size, molecular weight, and composition. PLGA is a desirable option for parenteral usage because, when biodegraded under physiological conditions, it produces lactic acid and glycolic acid, which are physiologically inert and may be eliminated from the body by regular metabolic routes. Because of its adaptable biodegradability, little toxicity, and strong biocompatibility, PLGA microspheres have great promise for a variety of drug delivery applications, such as the treatment of cancer, cardiovascular disorders, and the creation of vaccines.[26] Polymers used in the microspheres are listed in the below **Figure no4** according to their basic classification.

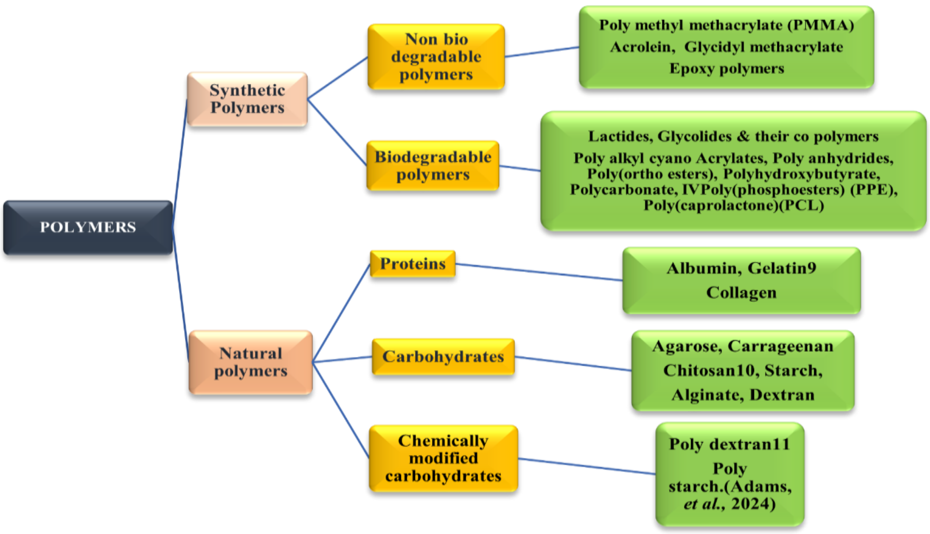


Figure 4: Polymers used in microspheres.

Criteria for the selection of microspheres

Expecting a drug in the formulation of a microsphere technology should need to satisfy some of the conditions which are listed below, by satisfying the below provided conditions the microsphere technology will be worth to its maximum.

1. The capacity to add medication in fairly high doses.
2. The preparation's stability following synthesis, with a shelf life that is therapeutically appropriate.
3. Regulated particle size and dispersibility in injectable aqueous media.
4. The active reagent is released over a long period of time with good control.
5. Biodegradability under control and biocompatibility.
6. Openness to changes in composition.[27]

CLASSIFICATION OF MICROSPHERES

Microspheres are classified according to the type of material of their preparation like magnetic, radioactive, polymeric, etc and also their role in their property in the living systems like floating etc. The list of classifications is given in the Figure 5 below.

Figure 5: Classification of microspheres.

PREPARATION TECHNIQUES OF MICROSPHERES

The below mentioned list are the microsphere preparation of microspheres techniques, they area selected based on the requirements of the industry and also the type of microspheres to be prepared, and economical techniques.

1. Single emulsion techniques
2. Double emulsion techniques
3. Polymerization
   a. Normal polymerization
   b. Interfacial polymerization
4. Phase separation coacervation technique
5. Spray drying
6. Emulsion crosslinking method
7. Solvent evaporation
8. Ionic gelation method
9. Solution enhancement dispersion method
10. Heat cross-linking
11. Emulsion-Solvent Diffusion Technique
12. Multiple Emulsion Method

These are some of the techniques available for the preparation of the microspheres at laboratory level and also in the industrial level. During the preparation of the microspheres some formulation variables are considered they are listed below

1. Particle size
2. Microspheres Bursts
3. Drug loading

4. Release profile
5. Surface Morphology
6. Polymer properties
7. Stabilizers
8. Osmolytes
9. Pore-forming agents
10. Polymer concentration
11. Solvent type
12. Continuous phase/dispersed phase ratio
13. pH
14. Microspheres Formation Environment[37]

The way that the microspheres are prepared and the kind and amount of materials—processing excipients or aids—that are utilized in the production process have a significant influence on how these formulation factors affect the microspheres' ultimate quality. The rate of drug release, drug encapsulation effectiveness, product syringe ability/injectability, in vivo destiny in terms of absorption by phagocytic cells, biodistribution of the particles following subcutaneous injection, efficacy, and adverse effect are all influenced by the size of microspheres.[38]

APPLICATIONS OF MICROSPHERES

1. Microspheres in vaccine delivery

Due to their capacity to increase immune responses, regulate release kinetics, and shield antigens from degradation, microspheres have been thoroughly investigated for their potential in vaccine drug delivery. Antigens can be encapsulated in microspheres to prevent deterioration and to guarantee their stability throughout transportation and storage. Antigens can be engineered into microspheres and released in a regulated way, resulting in longer-lasting immune responses and fewer dosage intervals. To promote enhanced immune responses, Microspheres have the potential to enhance the effectiveness of vaccines by inducing humoral and cellular immune responses. As adjuvants, microspheres can increase an antigen's immunogenicity and boost the effectiveness of vaccinations. Targeting particular cell types, such antigen-presenting cells, using tailored microspheres can improve immune responses. By co-delivering adjuvants and antigens, microspheres can increase vaccination effectiveness and minimize the number of shots needed.[39]

2. Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies conjugated to microspheres can target specific antigens or receptors on cells, enabling precise drug delivery to desired sites within the body. By targeting specific cells or tissues, monoclonal antibody-mediated microspheres can enhance the therapeutic efficacy of drugs, leading to improved treatment outcomes. Monoclonal antibodies help improve treatment safety by reducing the chance of adverse reactions and limiting off-target effects when utilized for targeted medication delivery. Personalized drug delivery systems are made possible by monoclonal antibody-mediated microspheres, which allow for the customization of therapies to specific patient features for optimal therapeutic outcomes. Microspheres conjugated with monoclonal antibodies can be used for combination therapy, delivering multiple drugs or therapeutic agents simultaneously to enhance treatment effectiveness. Monoclonal antibody-mediated microspheres can be utilized in immunotherapy approaches, delivering immune-modulating agents directly to immune cells or tumour sites for targeted treatment.[40]

3. Chemoembolization

Chemoembolization is a medical procedure that involves the injection of microspheres loaded with chemotherapeutic agents into the blood vessels supplying a tumour. By lowering systemic adverse effects and raising the medicine's concentration at the tumor site, this strategy enables targeted drug delivery. The microspheres used in chemoembolization can be made of various materials, including biodegradable polymers, and can be designed to have specific properties, such as controlled drug release kinetics and biocompatibility.[41]

4. Topical porous microspheres

Topical porous microspheres are useful for a variety of drug delivery applications, especially transdermal medication administration and dermatology. Drug distribution to the target location can be sustained and prolonged by designing topical porous microspheres with controlled drug release. This may decrease the frequency of application and increase the drug's effectiveness. Because of their porous shape, microspheres let medications penetrate the skin more easily, increasing their bioavailability and therapeutic impact. Topical porous microspheres can extend the shelf life and prevent medication deterioration by improving the stability of pharmaceuticals. Topical porous microspheres can reduce the systemic absorption of medications, hence reducing the risk of systemic toxicity and side effects.

Topical porous microspheres provide more individualized medication distribution and better therapeutic results by being customized to each patient's unique demands. Combination therapy and better treatment results are made possible by the simultaneous delivery of several medications or therapeutic agents using topical porous microspheres. Topical porous microspheres provide tailored medication administration and enhanced therapeutic results by being engineered to target particular skin layers or cell types. Topical porous microspheres are specifically used to treat eczema, psoriasis, acne, and other skin problems. In addition, they have been employed in the administration of various medicinal substances, gene therapy, and vaccinations. Topical porous microspheres provide a number of benefits over conventional medication administration techniques, such as increased patient compliance, less side effects, and increased effectiveness.[42]

5. Radioactive microspheres

Radioactive microspheres are used in medicine for a number of purposes, most notably the treatment of cancer. Microspheres containing radioactive isotopes are referred to as radioactive microspheres, or radioembolization. Hepatocellular carcinoma and liver metastases are two types of liver cancers that are treated with these microspheres. By injecting the microspheres into the blood arteries supplying the tumour, a high radiation dosage is delivered directly to the tumour with the least amount of damage to healthy tissue. In patients with liver tumours, this strategy can enhance tumour management, lower the chance of tumour progression, and increase overall survival. The use of radioactive microspheres in the treatment of neuroendocrine tumours and pancreatic cancer has also been investigated. Microspheres have been used in targeted and controlled release pharmaceutical delivery systems in addition to cancer therapy. These uses may enhance medication effectiveness, lessen adverse effects, and enhance patient outcomes.[43]

6. Ophthalmic drug delivery through microspheres

Microsphere-based ophthalmic medication delivery has several uses in ophthalmology and improves the management of several eye disorders. Drugs can be delivered using microspheres in a regulated and prolonged way, increasing drug bioavailability and lowering dosage frequency. This approach is particularly useful in the treatment of conditions such as glaucoma, age-related macular degeneration, diabetic retinopathy, uveitis, and dry eye syndrome. Ophthalmic medication delivery by microspheres can maximize therapeutic results, minimize adverse effects, and improve patient compliance by offering controlled release, increasing drug penetration into the eye, and improving drug stability.[44]

7. Nasal drug delivery though microspheres

Drugs can be directly delivered to the nasal cavity using microspheres to treat specific nasal disorders such sinusitis, allergic rhinitis, and nasal congestion. As an alternative to oral or injectable modes of systemic medication administration, nasal drug delivery using microspheres might be utilized. This method can be especially helpful for individuals who have trouble swallowing tablets or for medications with low oral bioavailability. Nasal vaccine administration with microspheres offers a convenient and non-invasive vaccination substitute for injectable immunizations. This strategy can boost vaccination effectiveness and increase patient compliance. By directly administering painkillers to the nasal cavity, microspheres can reduce the need for oral or injectable painkillers by delivering them with a quick beginning of action. Neural illnesses including epilepsy, cluster headaches, and migraines can be treated by nasal medication administration using microspheres. Improved medication bioavailability and a quick start of action are possible with this strategy. When compared to conventional drug administration techniques, nasal drug delivery using microspheres has a number of benefits, such as increased patient compliance, decreased dosage frequency, and better drug bioavailability. This strategy may help treat a variety of systemic illnesses and nasal ailments more effectively, improving patient outcomes and quality of life.[45]

8. Microspheres for delivery of protein and peptides

Microspheres are frequently utilized in the delivery of proteins and peptides because they have the capacity to stop degradation, control the rate of release, and boost the bioavailability of these substances.

Microspheres are used in the pharmaceutical industry to encapsulate peptides and proteins, guaranteeing their stability and tailored distribution to certain body regions. This method works especially well for the administration of biologics, such growth hormones and insulin, because the protein's bioactivity and structural integrity must be preserved for the treatment to be effective. Controlled release profiles may be obtained by encapsulating proteins and peptides in microspheres. This reduces dose frequency, improves patient compliance, and permits continuous delivery over an extended length of time. Moreover, other proteins and peptides may be added to the microspheres due to their versatility, offering a possible method for developing complex drug delivery systems for the treatment of a variety of diseases.[46]

CONCLUSION

Microspheres represent a versatile and innovative approach in drug delivery, offering a wide range of applications across various fields, including cancer therapy, vaccine development, ophthalmic drug delivery, and more. Microspheres are a versatile platform for drug delivery, offering numerous advantages such as controlled release kinetics, targeted delivery, and enhanced stability. They have been extensively explored for various applications, including cancer therapy, vaccine development, ophthalmic drug delivery, and nasal drug delivery. In cancer therapy, microspheres have been used for targeted chemoembolization, improving tumour control and reducing the risk of tumour progression. In vaccine development, microspheres have been utilized to enhance the stability, immunogenicity, and controlled release of vaccines, thereby improving their overall effectiveness. Microspheres have been utilized in ocular drug delivery to administer medications directly to the eye. This has led to a reduction in the frequency of administration due to the medicines' enhanced bioavailability and prolonged release. Microspheres have been used in nasal drug delivery to provide medications systemically and to treat specific nasal disorders by delivering the medication straight to the nasal cavity. Despite these advantages, microspheres also have limitations, such as potential toxicity due to the materials used, difficulty in achieving consistent particle size, and potential for drug leakage or burst release. Nevertheless, research and development efforts are being made to solve these issues and broaden the uses of microspheres, which continue to show promise as a drug delivery method.

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