International Journal of Nursing and Medical Science 2025:14(4), 10-19

IJNMS ISSN: 2454-6674

INTERNATIONAL JOURNAL OF NURSING AND MEDICAL SCIENCE

Nursing Education Health Science Research

PANACEA INTERNATIONAL JOURNAL

PRL PUBLISHER

Review Article **Volume 14 Issue 4** **July – August 2025**

BIOADHESIVE MICROSPHERES: A NOVEL STRATEGY FOR TARGETED AND SUSTAINED DRUG DELIVERY

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Abstract

Bioadhesive microspheres (MSs) have emerged as a promising and versatile drug delivery system due to their controlled release behavior, targeted delivery capability, and improved bioavailability. Their ability to adhere to mucosal tissues allows for prolonged residence time and localized drug action, which enhances therapeutic efficiency while minimizing systemic side effects. These microspheres are especially beneficial in transmucosal delivery routes, including nasal, buccal, ocular, and vaginal applications. The incorporation of bioadhesive properties into microspheres overcomes the limitation of brief mucosal retention and enhances patient compliance. Various polymers, both natural and synthetic, are employed in their fabrication, using advanced techniques such as solvent evaporation, spray drying, and phase inversion. They also offer applications in vaccine delivery, monoclonal antibody targeting, chemoembolization, and diagnostic imaging. Despite current limitations like manufacturing scalability and control over polymer degradation, bioadhesive MSs continue to evolve, integrating with nanotechnology and gene therapy to offer personalized therapeutic approaches. Thus, bioadhesive microspheres represent a significant advancement in pharmaceutical delivery, with the potential to revolutionize modern therapeutics.

Keywords: Bioadhesive microspheres, controlled drug release, transmucosal delivery, mucoadhesion, biodegradable polymers, drug targeting, microsphere formulation,

Introduction

Microspheres were included as a desirable drug delivery vehicle in recent years. The outstanding characteristic of MSs in clinical programs comes from their length and adequate carrier qualities, which make them ideal drug transporters in addition to regulated drug release. For this, MSs can transport medication to a specific location where it is needed, reducing undesired toxicity and medication removal (Ahmady and Samah, 2021; Gurung and Kakar, 2020). However, their brief mucosal residence period restricts the absorption of drugs administered transmucosally (Mahale and Saudagar, 2019).

The concept of "bio-adhesion" refers to the joining of artificial or natural large particles to the surface of organic tissue. The current mucoadhesive preparations typically handle transmucosal medication administration mediated by adhesion forces. The mucus layer or epithelial mobile layer generates adhesion forces. Mucoadhesive formulations come in a variety of forms, including tablet, film agent, powder, ointment, and gel. Numerous mucosal dermis cells, such as those on the vagina, ocular surface, nasal mucosa, and buccal mucosa, are their sites of absorption (Cleary et al., 2004; Chen et al., 2015).

Comparing bio-adhesive Microspheres to the competing existing Microspheres, they now provide clearer advantages. The adhesion influence among adhesive compounds and organic mucus or mucosal cells may occur when bio-adhesive Microspheres reach mucosal surfaces. Longer retention times, prolonged drug release times, and decline in the frequency of medicine management will eventually be implemented. As a result, bio-adhesive MSs can greatly improve patient compliance. In order to comprehend drug release, as well as the regional and overall effects of medication, bio-adhesive MSs may be directed attached to the majority of the mucosal tissue.

While most ocular mucoadhesive MSs are only used to treat oculopathy, In order to treat diseases systemically, certain MSs that adhere to the mucosa of the mouth or the nose may additionally wish to transfer tablets to the circulation 8. Similar to this, stimuli-responsive MSs are prospective methods for delivering medications on-site with good biodegradability and greater effect on bioavailability for treating both local and systemic disorders. Avoiding excessive first-pass metabolism and presystemic clearance

inside the GIT, enhancing bioavailability by efficient absorption, and precisely directing medicine to the absorption site through the use of lectins or other ligands, among other things., are just a few of the additional advantages that those bio-adhesive MSs also provided (Ahuja et al., 1997).

Applications of bioadhesive microspheres

1. The use of microspheres in the delivery of vaccines: The need for a vaccination is protection against the microorganism or its toxic byproduct. A ideal vaccination must meet the criteria for effectiveness, protection, software comfort, and cost. The problem of safeguarding and minimizing adverse reactions is challenging. The degree of antibody production and the factor of protection are closely related to the software approach. The incapability of conventional vaccinations may potentially be overcome by biodegradable transport devices for vaccines administered by parenteral route. Parenteral (subcutaneous, intramuscular, and intradermal) services are attractive because they offer a number of advantages, including:

a. Adjuvant effect increases antigenicity

b. modifying the release of an antigen

c. Antigen stabilization

2. Using microparticulate carriers for targeting: Targeting, or site-specific pharmaceutical delivery, is a well-mounted concept that is attracting a lot of interest. The drug's ability to enter and specifically interact with its target receptors determines how well it can treat illness. The ability to remove water from the pool in a repeatable, environmentally friendly, and exact manner is crucial to medication transportation mediated by use of a provider system. When debris is placed in a separate anatomical compartment, they are retained either because of the physiological properties of the environment or because of the biophysical interaction between the debris and the target tissue's cell composition.

3. Microspheres with mediated monoclonal antibodies targeting: Immune microspheres are a concentration of monoclonal antibodies. This focused on approach is used to get a selective focus on to the special spots. The chemicals that make up monoclonal antibodies are incredibly distinct. Monoclonal antibodies

(Mabs) with extreme specificity may be used to target microspheres that have bioactive chemicals loaded at particular places. The covalent interaction of Mabs with the microspheres allows for immediate connection. The antibodies may be connected to the free amino acids, hydroxyl groups, or aldehyde businesses near the bottom of the microspheres. Any of the aforementioned techniques may be used to attach the Mabs to the microspheres.

a. Non specific adsorption

b. Specific adsorption

c. Direct coupling

d. Coupling via reagents.

4. Chemoembolization: Chemoembolization is an endovascular therapy that combines the simultaneous or subsequent delivery of a chemotherapeutic drug with selective arterial embolization of a tumor. Theoretically, such embolisations will now not only provide vascular blockage but also result in prolonged healing levels of chemotherapeutics inside the tumor sites. A variation on traditional percutaneous embolization techniques is chemotherapy.

5. Imagery: The microspheres were extensively researched and used for the targeted goals. Radio-labeled microspheres can be used to scan a range of cells, cell lines, tissues, and organs. The range of microspheres' particle lengths has a crucial role in determining how to image unusual places. The material injected intravenously into a vein other than the portal vein becomes caught inside the pulmonary capillary bed. The use of tagged human serum albumin microspheres to image lung tumor burdens using scintigraphy takes advantage of this phenomena

Advantages of bioadhesive microspheres

1. Microspheres have a long-lasting, healing impact.

2. Lowers the frequency of administration and, as a result, increases patient compliance.

3. Because of their small size and rounded shape, they would be delivered within the body.

4. More effective medicine administration will boost bioavailability and lessen the frequency or severity of adverse effects.

5. The degradation and drug release all owe a controllable changeability to microsphere morphology.

6. The shape of microspheres permits a regulated degree of diversity in medication release and breakdown (Kunchu et al., 2010).

Mechanism of microspheres

The majority of drug delivery via microparticles inhibits the formation of a matrix-like internal solid dispersion morphology structure. The drug can be insoluble in the matrix of polymer, and it is released through erosion. First, water diffuses into the matrix, dissolving the resulting near the device's surface. The resulting osmotic pressure gets alleviated by forming a channel to the surface and releasing a predetermined amount of drug in the initial drug burst.

Drug release from the microspheres occurs by a general mechanism including

- Dissolution,
- Diffusion,
- Polymer degradation,
- Hydrolysis/erosion (Ganesan et al., 2014)

Polymers used in microsphere formulation

Microspheres usually use polymers. (Patel et al., 2011; Servat-Medina et al., 2015).

1. Natural polymers

2. Synthetic Polymers

1. Natural polymers

(i)Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

(ii)Proteins: Albumin, Collagen and Gelatin

(iii)Chemically modified carbohydrates: Poly dextran, Poly starch

2. Synthetic polymers

i)Biodegradable polymers: Lactides, Glycosides & their co-polymers, Poly anhydrides, Poly alkyl cyanoacrylates

ii)Non-biodegradable polymers: Polymethyl methacrylate (PMMA), Glycidyl methacrylate, Acrolein, Epoxy polymers

Bio-adhesive microsphere preparation

1. Solvent evaporation: The micro particulate carriers of the natural polymers i.e. proteins and carbohydrates are prepared by this technique. An aqueous medium is used to dissolve these natural polymers which is followed by dispersion in a non-aqueous medium such as oil. In the next step, the cross-linking of dispersed globules is carried out. The cross-linking can be gained by heat or by using chemical cross-linkers. The chemical cross-linking agents being used are glutaraldehyde, formaldehyde, and acid chloride. Heat denaturation is not considered suitable for thermolabile substances. Chemical cross-linking has the disadvantage of excessive exposure of active ingredients to the chemicals if added at the time of preparation and then subjected to centrifugation, washing, and separation, The nature of the surfactants being used to stabilize the emulsion phases can be greatly influenced by the size, size distribution, surface morphology and loading drug release, and bio performance of the final multi particulate product (Alagusundaram et al., 2009). This method of microsphere preparation involves the formulation of multiple emulsions or double emulsions of type w/o/wand it is best suited to water-soluble drugs, peptides, proteins and vaccines. This method can be carried out with both natural as well as synthetic polymers. The aqueous protein solution is dispersed in the lipophilic organic continuous phase or dispersion medium. This protein solution may containthe active constituents (Suvarna, 2015).

2. Microencapsulation using hot melt: (Mathiowitz and Langer, 1987) were the first to use this process to assemble polyanhydride copolymer of poly[bis(pcarboxy phenoxy) propane anhydride to sebacic acid microcapsules The polymer is first liquid and then blended with sieved strong medicine residue under this technique.. The aggregate is warmed to 5 °C over the polymer's melting point while suspended in a non-miscible solvent (such as silicone oil) and agitated continuously. The emulsion is further chilled until the polymer debris solidifies once it has reached a stable state. The resulting microspheres are then cleaned by petroleum ether decantation. Changes in

stirring rate allow for the easy management of the scale distribution and the acquisition of microspheres with diameters ranging from 1 to 1000 m. The modest temperature to which the medication is exposed is this method's most convenient flaw.

3. Removal of solvent: It is a non-absorptive microencapsulation technology that works well with water-labile polymers like polyanhydrides. In this technique, the medication is mixed with the selected polymer and an unstable natural solvent, such methylene chloride, to disperse or dissolve it. Then, span 85 and methylene chloride-containing silicone oil is used to suspend this aggregate. Petroleum ether is mixed and agitated till the solvent has been removed from the oils mixture after the polymer mixture has been poured into silicone oil. The resulting microspheres can then be vacuum dried.

4. Drying of Spray: In this technique, the medicine is liquified or distributed throughout the polymer mixture before being dried using a spray gun. Plasticizers like citrus fruits, which enhance polymer amalgamate at the medication debris and afterwards encourage the manufacture of round, clean-surfaced microspheres, can be used to advance the high-satisfaction of spray-dried microspheres. The rate of spraying, the feed rate of the polymer drug combination, the length of the nozzle, and the drying temperature may all be used to control the length of microspheres. This method of microencapsulation is straightforward, repeatable, and simple to expand since it depends less on the properties of solubility the drug and polymer.

5. Microencapsulation based on phase inversion: This technique requires adding medication to a diluted polymer mixture (often 1 to 5 percent, weight-to-volume in methylene chloride). The mixture is immersed in a bath of a strong non-solvent (petroleum ether) at a solvent to nonsolvent ratio of 1:100, resulting in the continuous generation of microspheres by section inversion. The microsphere can then be filtered, cleaned with petroleum ether, and dried with air for lengths between 0.5 and 5.0 meters. This quick and simple method of microencapsulation uses very small medication and polymer shortage.

Limitations

The following restrictions had been identified as some of them:

1. The modified release from the arrangements.

2. Other factors, including as meals and the velocity of transit through the stomach, may affect the liberation charge of the controlled release dosage form.

3. Variations in the rate of liberation between doses.

4. Managed liberation preparations frequently have a higher drug load, therefore any degradation of the dosage form's characteristics that affect how the drug is released might result in capacity toxicity.

5. This sort of dosage form no longer requires beating or chewing.

Challenges and future prospects

While bioadhesive microspheres offer significant advantages, challenges remain in:

- Scalable manufacturing with consistent size and drug release.
- Optimizing drug release profiles for specific therapeutic windows.
- Understanding and controlling the degradation rates of different polymers.

Future research aims to integrate bioadhesive microspheres with advancements in nanotechnology, gene therapy, and immunotherapy, paving the way for more efficient and personalized treatments.

Conclusion

It is evident that microspheres serve as a versatile and effective drug delivery system, offering various preparation methods and pharmaceutical applications. They facilitate the controlled delivery of medications in a precise manner, catering to diverse needs such as oral, targeted, sustained, topical, and even biotechnological applications like gene therapy. By continually advancing delivery technologies, microspheres promise significant therapeutic and commercial benefits, including improved safety profiles and reduced toxicity. Pharmaceutical companies are increasingly introducing innovative products to the market, demonstrating enhanced therapeutic responses compared to conventional delivery methods. The ongoing development of microsphere-based drug delivery technologies addresses challenges across pharmaceutical, biopharmaceutical, and pharmacokinetic domains, thereby fostering their widespread acceptance and utilization worldwide. Microspheres emerge as a superior choice in drug delivery systems, offering target specificity, enhanced patient compliance, and promising

solutions for sustained and targeted drug delivery across various biological systems. Their versatility extends beyond drug delivery to encompass applications in imaging tumors, diagnosing biomolecular interactions, and contributing to cancer treatment, making them pivotal components in future advancements in drug delivery and healthcare.

In general, because of the advantages, significantly less side effects, and controlled medication release, bio-adhesive MSs have outstanding capabilities. The retention period at the movement site is now the focus of the majority of research on bio-adhesive MSs, however there have been sporadic efforts to shed light on the adhesion processes of diverse bio-adhesive MSs and the reacting procedure of various stimuli-responsive MSs. In reality, there are three main categories into which the adhesion processes of bio-adhesive MSs may be divided: Adherence origined by the interconnection of bio-adhesive substances with mucosal membrane. Adhesion is entirely dependent on interactions between conjugate and receptors.

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