Recent Trends in Pharmaceutical Technology & Industries
Volume 6, Issue 1 - 2024, Pg. No. 22-28
Peer Reviewed Journal

Review Article

Mucoadhesive Microspheres: Advances and Applications

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How to cite this article:
Tripathi K , Deshmukh P , Goel N. Mucoadhesive Microspheres: Advances and Applications. Rec Trends Pharm Tech Ind 2024 6(1): 22-28.

Date of Submission: 2024-03-02
Date of Acceptance: 2024-04-10

A B S T R A C T

Mucoadhesive microspheres have emerged as a significant innovation in the field of drug delivery systems. By enhancing the bioavailability and controlled release of therapeutic agents, these microspheres offer a promising solution for targeting specific mucosal tissues. The development of efficient drug delivery systems has always been a crucial aspect of pharmaceutical research. Among various delivery systems, mucoadhesive microspheres have gained considerable attention due to their ability to adhere to mucosal surfaces, thereby prolonging the residence time of the drug at the site of absorption. This review aims to provide a comprehensive overview of the principles, formulation techniques, and applications of mucoadhesive microspheres.

Keywords: Mucoadhesive, Microspheres, Pharmaceutical Research

Introduction

Mucoadhesive microspheres represent an innovative advancement in drug delivery technology, designed to improve the efficacy and precision of therapeutic interventions. These microspheres are engineered to adhere to mucosal surfaces—such as those found in the gastrointestinal tract, nasal passages, buccal cavity, or vaginal cavity—enhancing drug delivery directly at the site of action. Their development stems from the need to address limitations associated with conventional drug delivery methods, including poor drug absorption, frequent dosing, and systemic side effects.[1]

Mucoadhesive microspheres are typically composed of biocompatible polymers that form tiny, spherical particles capable of carrying a wide range of therapeutic agents. The mucoadhesive properties of these microspheres are derived from their ability to interact with the mucosal surface, forming a strong adhesion that prolongs the residence time of the microspheres at the target site. This extended contact time facilitates improved drug absorption and more efficient localized treatment.[2]

Mechanisms of Mucoadhesion

Mucoadhesion is the process by which a drug delivery system, such as mucoadhesive microspheres, adheres to the mucosal surfaces of the body. This adhesion prolongs the residence time of the drug at the site of absorption, enhancing its bioavailability and therapeutic efficacy. Understanding the mechanisms of mucoadhesion is crucial for the design and development of effective mucoadhesive drug delivery systems. The primary mechanisms involved in mucoadhesion include:

Wetting and Swelling

Wetting and swelling are initial steps in the mucoadhesion process. When mucoadhesive polymers come into contact with the mucosal surface, they absorb water and swell. This swelling increases the surface area of the polymer and promotes intimate contact with the mucosa. The extent of swelling is influenced by the polymer's hydrophilicity and its molecular weight. Hydrophilic polymers, such as chitosan and polyvinyl alcohol (PVA), tend to swell more readily, enhancing their mucoadhesive properties.[3]

Intermolecular Interactions

Mucoadhesion primarily occurs through a combination of physical and chemical interactions between the mucoadhesive polymer and the mucus layer. These interactions include:

- **Hydrogen Bonding:** Hydrogen bonds form between the hydroxyl, carboxyl, and amino groups of the polymer and the mucin glycoproteins in the mucus. Polymers like carbopol and hydroxypropyl methylcellulose (HPMC) exhibit strong hydrogen-bonding capabilities.
- **Van der Waals Forces:** These are weak, non-covalent interactions that contribute to the adhesion process. Although individually weak, van der Waals forces can collectively have a significant effect on mucoadhesion.
- **Hydrophobic Interactions:** Non-polar interactions between hydrophobic regions of the polymer and mucosal surfaces can also enhance mucoadhesion. These interactions are particularly important for hydrophobic polymers like ethyl cellulose.[4]

Electrostatic Interactions

Electrostatic interactions between the polymer and the mucosal surface can play a significant role in mucoadhesion. Polymers with charged groups can interact with the oppositely charged groups in the mucus layer. For instance, cationic polymers like chitosan can form electrostatic bonds with the negatively charged sialic acid and sulfate groups in mucin. These interactions can enhance the adhesion strength and stability of the mucoadhesive system.[5]

Diffusion and Interpenetration

Diffusion and interpenetration involve the mutual diffusion of the polymer chains and the mucin glycoproteins across the interface. This interpenetration of chains creates a semi-permanent bond, reinforcing the mucoadhesive interaction. Factors affecting this process include:

- **Polymer Molecular Weight:** Higher molecular weight polymers have a greater tendency to interpenetrate with the mucin network, enhancing mucoadhesion.
- **Cross-linking Density:** Polymers with lower cross-linking densities allow for more extensive chain interpenetration, which can strengthen mucoadhesion.
- **Contact Time:** Longer contact times between the polymer and mucosa allow for greater diffusion and interpenetration, leading to stronger adhesion.[6]

Bioadhesive Strength and Mechanical Properties

The mechanical properties of the mucoadhesive system, such as tensile strength and flexibility, also influence mucoadhesion. The bioadhesive strength is a measure of the force required to detach the polymer from the mucosal surface. Polymers with high tensile strength and appropriate flexibility can maintain intimate contact with the mucosa, even under physiological conditions of stress and strain.

Role of Mucus Turnover and Renewal

The continuous turnover and renewal of the mucus layer can affect the duration of mucoadhesion. While a high mucus turnover rate might lead to the rapid clearance of the mucoadhesive system, polymers that can penetrate and interact with the deeper layers of the mucus can sustain adhesion for longer periods. Formulating mucoadhesive systems that can adapt to the dynamic nature of mucus is essential for prolonged drug delivery.[7]

Environmental Factors

Several environmental factors within the mucosal tissues can influence mucoadhesion, including:

- **pH:** The pH of the mucosal environment can affect the ionization state of the polymer and mucin, influencing electrostatic interactions and hydrogen bonding.
- **Ionic Strength:** Higher ionic strengths can screen electrostatic interactions, reducing mucoadhesion.

Table 1. Mechanism, Description, Examples and Key Features of Mocoadhesion.[9]

Mechanism	Description	Examples	Key Features
Van der Waals Forces	Weak, non-specific interactions between the mucosal surface and the adhesive material.	General mucoadhesive polymers	Provides initial contact and contributes to adhesion but is not the primary mechanism.
Hydrogen Bonding	Formation of hydrogen bonds between mucosal glycoproteins and functional groups on the adhesive.	Carboxymethylcellulose (CMC)	Stronger than Van der Waals forces; crucial for creating stable adhesion.
Ionic Interactions	Electrostatic attraction between charged groups on the mucoadhesive material and mucosal surface.	Chitosan, Polymethacrylic acid	Useful for materials with ionic groups; provides specificity and strength to adhesion.

Covalent Bonding	Formation of covalent bonds between chemical groups on the mucoadhesive material and mucosal proteins.	None (mainly experimental)	Provides very strong and permanent adhesion, but may require specific conditions.
Mechanical Interlocking	Physical entanglement of the mucoadhesive material with the mucosal surface.	Certain types of hydrogels	Involves the penetration of the mucoadhesive material into the mucosal surface, enhancing retention.
Hydrophobic Interactions	Interaction between hydrophobic regions on the mucoadhesive material and the mucosal surface.	Polylactic acid (PLA)	Contributes to adhesion in hydrophobic environments, enhancing overall mucoadhesive properties.
Bioadhesion	Specific binding interactions between biological molecules on the mucosal surface and the adhesive.	Peptide-based adhesives	Highly specific; leverages biological recognition for targeted adhesion.

- **Presence of Other Biomolecules:** Proteins, enzymes, and other biomolecules present in the mucus can interact with the polymer, affecting its mucoadhesive properties.[8]

Formulation Techniques

Various techniques have been developed for the preparation of mucoadhesive microspheres, including:

- **Emulsion Solvent Evaporation:** Emulsion solvent evaporation is a robust and widely employed method for the fabrication of microspheres, particularly in the pharmaceutical industry. This technique is lauded for its versatility, simplicity, and effectiveness in encapsulating both hydrophilic and hydrophobic drugs. The primary objective of using this method is to create uniform, controlled-release microspheres that can enhance the bioavailability and therapeutic efficacy of drugs. The method involves dissolving a polymer and a drug in an organic solvent to form the dispersed phase, which is then emulsified in an aqueous phase containing a surfactant. Subsequent evaporation of the organic solvent results in the formation of solid microspheres.[10] The principle of emulsion solvent evaporation hinges on the creation of a stable emulsion, where the dispersed phase (containing the polymer and drug) is emulsified into a continuous aqueous phase with the aid of a surfactant. This emulsion forms small droplets that are stabilized by the surfactant molecules. Upon evaporating the organic solvent, usually under reduced pressure and controlled temperature, the polymer precipitates, encapsulating the drug within the formed microspheres. The evaporation can be conducted using equipment such as a rotary evaporator or through continuous stirring under ambient conditions, depending on the volatility of the solvent used.[11]
- **Spray Drying:** Spray drying is a widely used technique for the production of mucoadhesive microspheres in the pharmaceutical industry. This method transforms a liquid feed into dry powder particles by rapidly drying with a hot gas. It is particularly valued for its ability to produce fine, consistent particles and its suitability for heat-sensitive materials. The process involves atomizing a liquid solution or suspension containing the drug and polymer into a drying chamber, where the solvent rapidly evaporates, leaving behind solid microspheres.[12]Spray drying is favored for its scalability, efficiency, and the ability to produce particles with desirable properties for drug delivery applications. The principle of spray drying revolves around the rapid evaporation of a solvent from a sprayed liquid feed, resulting in the formation of solid particles. The liquid feed, which contains the drug and mucoadhesive polymer dissolved or dispersed in a solvent, is pumped into an atomizer. The atomizer creates a fine mist of droplets by breaking the liquid into small particles. These droplets are introduced into a drying chamber where they come into contact with a stream of hot gas, typically air or nitrogen. The heat causes the solvent to evaporate almost instantaneously, leaving behind dry microspheres.[13]
- **Ionotropic Gelation:** Ionotropic gelation is a popular technique for the preparation of mucoadhesive microspheres, especially for encapsulating hydrophilic drugs. This method exploits the gelation properties of certain biopolymers in the presence of multivalent ions. It is favored for its mild conditions, biocompatibility, and the ability to create microspheres with high drug loading efficiency. Commonly used biopolymers include alginate, chitosan, and carrageenan, which gel upon contact with divalent or trivalent cations such as calcium (Ca^{2+}) or tripolyphosphate (TPP). The principle of ionotropic gelation relies on the ionic cross-linking of polyelectrolytes. When a polyelectrolyte solution is introduced into a solution containing multivalent

counter-ions, the ions interact with the polymer chains, leading to the formation of a gel matrix. This gelation process is instantaneous, making it suitable for the encapsulation of drugs that are sensitive to heat or organic solvents.[14]

- **Coacervation:** Coacervation is a versatile and effective technique used for the formation of mucoadhesive microspheres, leveraging the phase separation properties of polymeric systems. This method involves the formation of a coacervate, a colloidal suspension of polymer droplets, which can be further processed to create solid microspheres. Coacervation is particularly beneficial for encapsulating both hydrophilic and hydrophobic drugs, and it is valued for its ability to produce microspheres with high drug loading efficiency and controlled release properties. The principle of coacervation is based on the phase separation of polymer solutions when specific conditions are met, such as changes in pH, temperature, or ionic strength. When a polymer solution undergoes coacervation, it separates into two distinct phases: a coacervate phase (rich in polymer) and a supernatant phase. The coacervate phase can be collected, stabilized, and then processed into microspheres.[14,15]

Recent Advances

- **Nanoparticles Integration :** Integrating nanoparticles into mucoadhesive microspheres represents a groundbreaking advancement in drug delivery technology, offering enhanced efficacy and precision. Nanoparticles, due to their minuscule size and high surface area, provide several benefits when incorporated into mucoadhesive microspheres. The primary advantage lies in their ability to significantly increase the drug loading capacity of the microspheres.[16]Nanoparticles possess a large surface-to-volume ratio, allowing for a higher amount of drug to be encapsulated within the microspheres, which is particularly useful for drugs with poor solubility or low bioavailability. This enhanced encapsulation capacity not only improves the overall therapeutic effectiveness but also enables the controlled release of drugs over extended periods. Moreover, nanoparticles can enhance the mucoadhesive properties of the microspheres through surface modifications and functionalization. By attaching specific ligands or polymers to the nanoparticles, the microspheres can form stronger interactions with mucosal surfaces, increasing their residence time and ensuring prolonged drug contact. This increased adherence enhances drug absorption by allowing more effective penetration through the mucosal barrier.[17]Additionally, nanoparticles can be engineered to target specific receptors on mucosal cells, providing targeted drug delivery that maximizes therapeutic impact while minimizing systemic side effects.
- **Biodegradable Polymers:** Biodegradable polymers are integral to the advancement of drug delivery systems, offering a blend of safety, efficacy, and environmental benefits. These polymers are designed to break down into non-toxic, biocompatible byproducts through natural physiological processes, which significantly enhances their suitability for medical applications. In the context of drug delivery, biodegradable polymers facilitate controlled and sustained release of therapeutic agents by gradually degrading over time. This process allows for a prolonged therapeutic effect, reducing the need for frequent dosing and improving patient adherence. Polymers such as poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) are widely used due to their predictable degradation profiles and compatibility with a range of drugs.[18] By adjusting the polymer's chemical structure, molecular weight, or formulation, researchers can tailor the degradation rate and drug release kinetics to meet specific therapeutic needs. Additionally, biodegradable polymers enhance drug stability by encapsulating sensitive compounds, thereby protecting them from environmental factors like moisture and oxygen that could otherwise lead to degradation. This protection helps maintain the drug's efficacy throughout its shelf life. Moreover, the use of biodegradable polymers aligns with environmental sustainability goals, as these materials reduce the accumulation of synthetic waste and minimize long-term ecological impact. Despite their advantages, challenges such as ensuring consistent degradation rates and optimizing polymer properties for different drugs remain.[19]
- **Thermo-responsive Systems:** Thermo-responsive systems are a cutting-edge innovation in drug delivery technology, characterized by their ability to alter their physical state or properties in response to temperature changes. These systems utilize temperature-sensitive materials, often polymers or hydrogels, that undergo reversible phase transitions at specific temperatures, thereby controlling drug release with remarkable precision. The fundamental principle behind thermo-responsive systems lies in the temperature-dependent behavior of certain polymers, such as poly(N-isopropylacrylamide) (PNIPAAm), which exhibit a phase transition from soluble to gel-like states when the temperature crosses a critical threshold.[20] This temperature-induced phase change allows these systems to form a gel in situ, creating a localized drug depot that can release therapeutic agents over an extended period. For instance, injectable thermo-responsive hydrogels can be administered in a liquid

form and solidify upon reaching body temperature, offering localized and controlled drug delivery. This mechanism is particularly advantageous in applications such as cancer therapy, where localized drug delivery to tumor sites can significantly enhance therapeutic efficacy while minimizing systemic side effects. Similarly, in tissue engineering, thermo-responsive materials can be used to create scaffolds that gel upon injection, providing a supportive matrix for tissue regeneration and controlled release of growth factors. Additionally, thermo-responsive systems are valuable in regenerative medicine and pain management, where they enable sustained release of therapeutic agents at physiological temperatures. Despite their advantages, designing thermo-responsive systems requires careful consideration of the phase transition temperature, biocompatibility, and manufacturing scalability to ensure consistent performance and safety.[21]

- **Multi-drug Delivery:** Multi-drug delivery systems are an advanced strategy designed to enhance therapeutic outcomes by simultaneously administering multiple drugs through a single delivery platform. These systems leverage the benefits of combining various therapeutic agents to address complex or multifaceted medical conditions more effectively than single-drug therapies. The primary advantage of multi-drug delivery systems is their ability to offer synergistic effects by delivering drugs that complement each other's mechanisms of action, thereby improving overall treatment efficacy.[22] For example, in cancer treatment, multi-drug delivery systems can combine chemotherapeutic agents with targeted therapies or immunotherapeutics, allowing for a more comprehensive attack on cancer cells and potentially overcoming drug resistance. These systems are meticulously engineered to provide controlled and sustained release of the drugs, ensuring that each drug is delivered at the appropriate dosage and timing to maximize therapeutic benefits while minimizing side effects. Various design approaches are employed, such as encapsulating different drugs in separate compartments within a single carrier or using a matrix that enables sequential or simultaneous release.[23]

Advantages of Mucoadhesive Microspheres

Mucoadhesive microspheres offer several significant advantages in drug delivery, leveraging their ability to adhere to mucosal surfaces for improved therapeutic outcomes. Here are some key benefits:

- **Enhanced Drug Absorption:** Mucoadhesive microspheres are designed to adhere to mucosal surfaces, such as those in the gastrointestinal, nasal, buccal, or vaginal areas. This adherence increases the residence time of the drug delivery system at the site of absorption, leading to improved drug uptake. By prolonging contact with the mucosal surface, these microspheres enhance the bioavailability of the drug, particularly for compounds that are poorly absorbed or rapidly degraded in the digestive tract.
- **Controlled and Sustained Release:** The formulation of mucoadhesive microspheres allows for controlled and sustained drug release. By encapsulating the drug within a polymeric matrix, these systems can release the drug gradually over time, reducing the need for frequent dosing. This controlled release not only improves therapeutic efficacy but also helps in maintaining optimal drug levels in the system, which is crucial for managing chronic conditions.[24]
- **Localized Delivery:** Mucoadhesive microspheres enable localized drug delivery, targeting specific mucosal tissues or organs. This localized approach is particularly beneficial for treatments requiring high drug concentrations at a specific site, such as topical treatments for infections or localized inflammation. By delivering the drug directly to the affected area, these microspheres can enhance therapeutic effects and minimize systemic side effects.
- **Improved Patient Compliance:** The sustained release and localized delivery provided by mucoadhesive microspheres can reduce the frequency of drug administration, leading to improved patient adherence to the treatment regimen. Patients benefit from fewer doses and reduced inconvenience, which can significantly enhance overall treatment effectiveness and quality of life.[25]
- **Protection of Sensitive Drugs:** Mucoadhesive microspheres can protect sensitive drugs from environmental factors such as moisture, oxygen, and acidic conditions. This protection is crucial for drugs that are unstable or easily degraded, ensuring that they remain effective until they reach their target site.
- **Versatility in Drug Formulation:** Mucoadhesive microspheres can be designed to accommodate a wide range of drugs, including small molecules, peptides, proteins, and nucleic acids. This versatility makes them suitable for various therapeutic applications, including hormone replacement, vaccine delivery, and treatment of chronic diseases.
- **Reduced Systemic Side Effects:** By targeting the drug directly to the mucosal surface, mucoadhesive microspheres can minimize systemic exposure and reduce the risk of side effects associated with oral or systemic drug administration. This targeted approach helps in achieving higher therapeutic concentrations at the desired site while avoiding unnecessary exposure to other body tissues.
- **Enhanced Drug Stability:** The encapsulation of drugs

in mucoadhesive microspheres can enhance their stability by protecting them from degradation due to environmental factors or metabolic processes. This stability is particularly important for drugs that are prone to degradation or have a short shelf life.[26]

Conclusion

Mucoadhesive microspheres represent a versatile and promising drug delivery system with the potential to revolutionize the way drugs are administered and absorbed. Advances in formulation techniques and a deeper understanding of mucoadhesion mechanisms will continue to enhance their effectiveness and broaden their applications in various therapeutic areas. Continued research and development are essential to overcome existing challenges and fully realize the potential of mucoadhesive microspheres in clinical practice.

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