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Review Article

Mucoadhesive Drug Delivery Systems: Principles, Polymers, Pharmaceutical Applications, and Recent Advances

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ABSTRACT

Mucoadhesive drug delivery systems have emerged as an effective strategy to enhance drug residence time at mucosal surfaces and improve therapeutic efficacy. These systems function through interactions between mucoadhesive polymers and the mucus layer covering epithelial tissues, leading to prolonged retention, improved absorption, and enhanced bioavailability. Mucoadhesion is governed by mechanisms such as wetting, adsorption, and interpenetration of polymer chains, which are explained by theories including electronic, adsorption, diffusion, and fracture theories. Polymer characteristics such as molecular weight, chain flexibility, degree of cross-linking, and functional groups play a critical role in determining adhesive strength. Mucoadhesive systems offer advantages such as avoidance of first-pass metabolism, reduced dosing frequency, improved patient compliance, and site-specific drug delivery. Various mucosal routes, including buccal, nasal, ocular, vaginal, rectal, and gastrointestinal routes, have been explored for both local and systemic therapy. Natural and synthetic polymers are widely employed, with chitosan and its derivatives receiving particular attention due to their biocompatibility and strong mucoadhesive properties. Recent advancements focus on thiolated polymers, bio-inspired materials, and nano-based systems to enhance adhesion and controlled drug release. Although significant progress has been made, challenges related to formulation stability, standardization, and clinical translation remain. Overall, mucoadhesive drug delivery systems represent a promising approach for improving therapeutic outcomes.

.INTRODUCTION

Drug delivery systems have undergone significant evolution over the past few decades with the objective of improving therapeutic efficacy, minimizing side effects, and enhancing patient compliance. Conventional dosage forms often face limitations such as short residence time at the site of absorption, frequent dosing requirements, and variable bioavailability due to enzymatic

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degradation and first-pass metabolism. These challenges have driven the development of novel drug delivery systems (NDDS) that can provide controlled, targeted, and sustained drug release. Among these, mucoadhesive drug delivery systems have emerged as a promising approach for enhancing drug localization and absorption across mucosal surfaces [8,9].

Mucoadhesion refers to the ability of a material, typically a polymer, to adhere to a mucosal surface for an extended period of time. Mucosal membranes line various regions of the human body, including the oral cavity, nasal cavity, gastrointestinal tract, ocular surface, vaginal tract, and rectum. These surfaces are covered by a mucus layer composed mainly of water, mucin glycoproteins, electrolytes, enzymes, and lipids. The presence of this mucus layer provides an attractive target for drug delivery, as adhesion to mucus can prolong the residence time of a dosage form at the site of absorption, thereby improving drug bioavailability and therapeutic effectiveness [1,4–6].

Mucoadhesive drug delivery systems are designed to interact with the mucus layer or epithelial surface through physical and chemical interactions such as hydrogen bonding, electrostatic attraction, van der Waals forces, and mechanical interlocking. The process of mucoadhesion is generally described as a two-step phenomenon: an initial contact stage, where the dosage form comes into close contact with the mucosal surface, followed by a consolidation stage involving interpenetration and entanglement of polymer chains with mucin chains. Several theories have been proposed to explain the mechanism of mucoadhesion, including electronic theory, adsorption theory, wetting theory, diffusion theory, and fracture theory. These theories collectively explain the complex nature of polymer–mucus interactions.

The performance of mucoadhesive systems is strongly influenced by the physicochemical properties of the polymers used. Important polymer characteristics include molecular weight, chain length, flexibility, degree of cross-linking, hydration capacity, and the presence of functional groups capable of forming strong intermolecular interactions with mucin. Both natural and synthetic polymers have been extensively investigated for mucoadhesive applications. Natural polymers such as chitosan, alginate, pectin, gelatin, and xanthan gum are widely preferred due to their biocompatibility and biodegradability. Synthetic polymers such as polyacrylic acid derivatives, carbomers, cellulose derivatives, and polyvinyl alcohol offer reproducibility, controlled properties, and strong mucoadhesive strength.

Mucoadhesive drug delivery systems offer several advantages over conventional dosage forms. These include bypassing hepatic first-pass metabolism, protection of drugs from enzymatic degradation, reduction in dosing frequency, improved patient compliance, and the possibility of site-specific drug delivery. As a result, mucoadhesive systems have been explored for a wide range of therapeutic agents, including peptides, proteins, vaccines, hormones, and drugs with poor oral bioavailability. Various dosage forms such as tablets, films, patches, gels, microspheres, nanoparticles, and sponges have been developed using mucoadhesive principles.

Different routes of administration have been investigated for mucoadhesive drug delivery. Buccal and sublingual routes provide rapid onset of action and avoidance of first-pass metabolism, while nasal delivery offers a large surface area and potential for systemic and brain targeting. Ocular

mucoadhesive systems help overcome rapid tear turnover, and vaginal and rectal routes provide localized and systemic delivery for specific therapeutic needs. Gastroretentive mucoadhesive systems are designed to prolong gastric residence time and improve the absorption of drugs with narrow absorption windows.

Recent advancements in mucoadhesive drug delivery focus on the development of novel polymers and advanced technologies. Thiolated polymers (thiomers) exhibit enhanced mucoadhesive strength through covalent bond formation with mucin glycoproteins. Bio-inspired and biomimetic materials aim to replicate natural adhesion mechanisms, while nanotechnology-based mucoadhesive systems offer improved penetration, controlled release, and targeted delivery. Despite these advances, challenges such as formulation stability, variability of mucus properties, lack of standardized evaluation methods, and limited clinical translation remain significant [13–15].

This review aims to provide a comprehensive overview of mucoadhesive drug delivery systems, focusing on fundamental principles, theories of mucoadhesion, types of polymers, dosage forms, evaluation methods, recent advancements, and current challenges. Understanding these aspects is essential for the rational design and successful development of effective mucoadhesive drug delivery systems for improved therapeutic outcomes.

Limitations of Conventional Dosage Forms

Conventional dosage forms, including tablets, capsules, syrups, and injections, are extensively employed in clinical practice due to their simplicity, cost-effectiveness, and ease of manufacturing. Despite these advantages, such dosage forms are associated with several limitations that can compromise therapeutic efficacy and patient compliance.

A primary limitation is the short residence time at the site of absorption. Following administration, dosage forms are rapidly cleared by physiological processes such as saliva secretion, gastrointestinal motility, tear turnover, and mucociliary clearance. This rapid elimination often results in reduced drug absorption and low bioavailability, particularly for drugs with narrow absorption windows.

Another critical drawback is extensive first-pass metabolism, especially for orally administered drugs. Drugs absorbed from the gastrointestinal tract are transported to the liver via the portal circulation, where metabolic degradation can significantly reduce the fraction of drug reaching systemic circulation, necessitating higher or more frequent dosing.

Conventional dosage forms also lead to fluctuations in plasma drug concentrations, characterized by peaks and troughs that may cause sub-therapeutic effects or dose-related adverse reactions. Frequent dosing required to maintain therapeutic levels can further reduce patient adherence [16,17].

Additionally, many drugs are susceptible to enzymatic degradation and chemical instability, including peptides, proteins, and acid-labile compounds. Conventional systems generally lack site-specific targeting, resulting in non-selective drug distribution and increased risk of systemic side effects. Other challenges include variable bioavailability due to physiological or pathological factors, food–drug interactions, and poor absorption of drugs with low solubility or permeability [18].

Need for Controlled and Site-Specific Drug Delivery

The limitations of conventional dosage forms, including short residence time, fluctuating plasma concentrations, first-pass metabolism, and non-specific drug distribution, have highlighted the necessity for controlled and site-specific drug delivery systems. Controlled drug delivery aims to maintain therapeutic drug concentrations within a desired range over an extended period, thereby reducing dosing frequency, minimizing side effects, and improving patient compliance. By avoiding peaks and troughs in plasma drug levels, controlled release systems enhance therapeutic efficacy and reduce the risk of toxicity [19–21].

Site-specific drug delivery further enhances therapeutic outcomes by targeting the drug to a specific tissue, organ, or mucosal surface, thereby maximizing local drug concentration while minimizing systemic exposure. This approach is particularly important for drugs with narrow therapeutic windows, drugs susceptible to enzymatic degradation, or those that require localized action. Site-specific delivery can also bypass first-pass metabolism and improve bioavailability for orally administered drugs.

Mucoadhesive drug delivery systems represent a promising strategy to achieve both controlled and site-specific drug release. By adhering to mucosal surfaces, these systems prolong residence time at the target site, enhance drug absorption, and allow for sustained and localized therapeutic action [22,23]. The combination of mucoadhesion with controlled-release technologies addresses many of the challenges associated with conventional dosage forms, offering improved efficacy, safety, and patient adherence.

Importance of Mucosal Routes in Drug Delivery

Mucosal routes of drug administration have gained considerable attention due to their unique anatomical and physiological advantages, which make them ideal for both local and systemic drug delivery. Mucosal surfaces are lined by epithelial cells covered with a mucus layer composed of water, mucin glycoproteins, electrolytes, and enzymes, providing a site for drug absorption and localized therapeutic action. Major mucosal routes include oral (buccal/sublingual), nasal, ocular, vaginal, and rectal administration.

The oral mucosa offers rapid drug absorption, avoidance of first-pass metabolism, and ease of administration, making it suitable for systemic delivery of drugs with poor gastrointestinal stability. Nasal delivery provides a highly vascularized surface, rapid onset of action, and potential for central nervous system targeting via the olfactory region. Ocular delivery can overcome limitations such as tear turnover and corneal barriers, enhancing drug retention and local therapeutic effect. Vaginal and rectal routes enable both local and systemic delivery while bypassing hepatic first-pass metabolism.

Mucosal routes also allow for site-specific drug targeting, which enhances therapeutic efficacy and reduces systemic side effects. Furthermore, these routes are particularly advantageous for delivering macromolecules such as peptides, proteins, and vaccines that are poorly absorbed via conventional oral dosage forms. The high permeability, rich vascularization, and surface area of mucosal tissues make them attractive for developing innovative drug delivery systems that improve bioavailability, patient compliance, and overall therapeutic outcomes.

Overall, exploiting mucosal routes is crucial in modern drug delivery strategies, especially when combined with mucoadhesive technologies to

prolong residence time and achieve controlled, site-specific drug release.

Definition of Mucoadhesion

Mucoadhesion can be defined as the interfacial interaction between a polymer and the mucosal surface, resulting in the prolonged retention of a dosage form at the site of administration. This phenomenon occurs due to the adhesion of a material typically a polymeric system to the mucus layer covering epithelial tissues. The term "mucoadhesion" encompasses both physical interactions (such as van der Waals forces, hydrogen bonding, and electrostatic attractions) and mechanical interlocking between polymer chains and mucin glycoproteins.

In simpler terms, mucoadhesion is the ability of a drug delivery system to stick to the mucous membrane, thereby increasing residence time and enhancing drug absorption and bioavailability. It forms the basis for various mucoadhesive drug delivery systems designed to deliver drugs via mucosal routes, including buccal, nasal, ocular, vaginal, and rectal administration.

Mucoadhesion is a critical concept in pharmaceutical sciences, as it enables controlled drug release, localized therapy, and improved patient compliance by reducing dosing frequency and minimizing systemic side effects. Understanding the principles of mucoadhesion is essential for the rational design and development of novel mucoadhesive formulations that exploit mucosal surfaces for effective drug delivery [24–26].

Objective of the Review

The objective of this review is to provide a comprehensive overview of mucoadhesive drug delivery systems, focusing on their underlying principles, types of mucoadhesive polymers, evaluation methods, and diverse pharmaceutical applications. The review aims to highlight the advantages of mucoadhesive systems in enhancing drug bioavailability and therapeutic efficacy, summarize recent advancements in the field, and discuss current challenges and future perspectives to guide researchers and formulation scientists in the development of effective mucoadhesive drug delivery strategies.

Mucus and Mucosal Membrane

Mucus Composition and Properties

Mucus is a viscoelastic gel that serves as a protective barrier covering mucosal epithelial surfaces throughout the body. The primary non-aqueous component of mucus is mucin, a complex polymer with heterogeneous structures capable of multiple molecular interactions, including hydrophilic and hydrophobic interactions, hydrogen bonding, and electrostatic interactions [10,11].

Mucus exhibits several critical physicochemical properties that directly impact drug delivery, such as pore size, viscoelasticity, pH, and ionic strength. These properties create a selective barrier that restricts the penetration of particles and molecules to the epithelial surface while simultaneously offering opportunities for mucoadhesive drug delivery systems. The mucus layer functions as both a protective mechanism and a potential anchoring site for dosage forms, trapping pathogens and foreign particles to prevent their entry into underlying epithelium, which can be strategically utilized to improve residence time and enhance drug delivery effectiveness.

Mucosal Membrane Structure and Function

Mucosal membranes are highly specialized tissues lining various body cavities and passages, including the oral cavity, gastrointestinal tract, respiratory system, and urogenital tract. These membranes consist of the mucus layer covering the epithelial surface, supported by underlying mucin molecules [27–29].

The anatomy and physiology of mucosa vary significantly across different body regions, each presenting unique characteristics relevant to drug delivery. For example, the buccal mucosa is relatively permeable and richly vascularized, making it suitable for both local and systemic delivery [30,31]. The oral mucosa provides a large surface area, high permeability, and abundant blood supply, which enhances its attractiveness for drug administration.

Regional Variations and Clinical Significance

Distinct mucosal sites exhibit unique properties that influence the effectiveness of mucoadhesive drug delivery. The gastrointestinal mucosa presents challenges such as variable pH, enzymatic activity, and rapid transit times. Vaginal mucosa allows opportunities for both local and systemic delivery, with considerations for mucus composition and turnover rates.

Understanding mucus composition and mucosal membrane characteristics is essential for designing effective mucoadhesive systems. Factors such as mucus viscosity, mucin turnover, and regional differences directly affect adhesion and drug release. Additionally, the hydration of polymers is critical, as mucoadhesive properties are exhibited only on moist surfaces. These fundamental properties form the basis for developing mucoadhesive drug delivery systems that overcome traditional limitations and enhance therapeutic outcomes.

Theories of Mucoadhesion

The phenomenon of mucoadhesion is explained through several complementary theories that describe the complex interactions between mucoadhesive polymers and mucosal surfaces. Understanding these theories is essential for the rational design of effective mucoadhesive drug delivery systems [12–14].

Primary Theories of Mucoadhesion

1. **Electronic Theory**

This theory proposes that mucoadhesion occurs due to electron transfer between the mucoadhesive polymer and mucus glycoproteins, resulting in the formation of an electrical double layer at the interface. Attractive forces develop due to differences in electronic structure between the two surfaces.

2. **Adsorption Theory**

According to this theory, mucoadhesion arises from secondary forces such as van der Waals interactions and hydrogen bonding between the polymer and the mucus. Surface energy and the ability of polymers to form multiple contact points are critical for adhesion [37,38].

3. **Wetting Theory**

The wetting theory emphasizes the ability of polymers to spread and establish intimate contact with the mucosal surface. Adequate wetting is essential for subsequent adhesive interactions to occur effectively [32,33].

4. **Diffusion Theory**

This theory describes mucoadhesion as the interpenetration of polymer chains into the mucus network. The depth of penetration depends on the

diffusion coefficient of the polymer chains and the duration of contact [34–36].

5. Fracture Theory

Fracture theory relates to the force required to separate two surfaces after adhesion has occurred. It helps in understanding the mechanical strength and durability of the adhesive bond.

6. Mechanical Interlocking Theory

This theory suggests that adhesion occurs through physical entanglement and mechanical interlocking of polymer chains with the mucus structure. The irregular surface topography of both the polymer and mucus contributes to this mechanical adhesion.

Stages of Mucoadhesion

a. **Contact Stage** – The initial stage involves intimate contact between the polymer and mucosal surface, governed primarily by wetting mechanisms.
b. **Consolidation Stage** – Adhesive bonds are strengthened through polymer chain interpenetration, formation of secondary bonds, and mechanical interlocking.
c. **Three-Stage Process Model** – A comprehensive model integrates wetting or swelling of the polymer, interpenetration of chains, and formation of chemical bonds between entangled chains.

Integrated Understanding

Mucoadhesion is best explained as a combination of these theories rather than a single mechanism. The relative contribution of each theory depends on factors such as the polymer type, environmental conditions, and the specific mucosal site. Polymer properties including molecular weight, chain flexibility, degree of cross-linking, and functional groups significantly influence the success and degree of mucoadhesion. Understanding these fundamental principles provides the scientific basis for designing mucoadhesive drug delivery systems with optimized performance.

Factors Affecting Mucoadhesion

The effectiveness of mucoadhesive drug delivery systems depends on several interconnected factors, which can be broadly categorized into polymer-related, environmental, physiological, and formulation-specific parameters [15–17].

Polymer Related Factors

- **Molecular Weight and Chain Length:** Higher molecular weight and longer polymer chains generally enhance mucoadhesive strength due to increased chain entanglement and interpenetration with the mucus network [39,40].
- **Degree of Cross-linking:** Optimal cross-linking provides sufficient structural integrity while maintaining chain flexibility for effective interpenetration. Excessive cross-linking may reduce chain mobility and decrease adhesion.
- **Functional Groups and Chemical Structure:** Polymers with functional groups capable of hydrogen bonding, ionic interactions, or appropriate charge distribution exhibit superior mucoadhesive performance.
- **Chain Flexibility:** Flexible polymer chains conform more readily to mucosal surface irregularities and establish multiple contact points.
- **Hydration and Swelling Properties:** Proper hydration facilitates polymer chain relaxation

and interpenetration. Excessive swelling, however, may lead to rapid dissolution and reduced adhesion.

Environmental and Physiological Factors

- **pH Conditions:** pH influences polymer ionization, mucus properties, and the strength of electrostatic interactions [41,42].
- **Ionic Strength and Electrolyte Concentration:** Ionic conditions can either enhance or inhibit adhesion depending on polymer type and concentration.
- **Contact Time:** Longer contact allows greater chain interpenetration and stronger adhesive bonds.
- **Mucus Turnover Rate:** Rapid mucus secretion and clearance can limit residence time and mucoadhesive effectiveness.
- **Mucus Viscosity and Composition:** Variations in mucin content, water content, and viscoelastic properties affect polymer-mucus interactions.

Formulation-Specific Factors

- **Polymer Concentration:** Optimal polymer concentration ensures sufficient adhesion without compromising other formulation properties.
- **Moisture Content:** Adequate moisture is necessary for mucoadhesive activation.
- **Particle Size and Surface Area:** Smaller particles offer higher surface-to-volume ratios, enhancing adhesive contact.

Biological and Anatomical Factors

- **Nature of Mucosal Tissue:** Mucus thickness, composition, surface roughness, and underlying tissue structure vary across anatomical sites, influencing adhesion.
- **Physiological Conditions:** Local blood flow, enzymatic activity, and mechanical stress can affect stability and residence time.
- **Surface Charge and Wettability:** Electrostatic interactions and polymer spreading are influenced by the surface properties of both polymer and mucosa.

A thorough understanding and careful optimization of these factors are essential for developing mucoadhesive drug delivery systems with predictable and reproducible performance across diverse therapeutic applications.

Mucoadhesive Polymers

Mucoadhesive polymers form the foundation of mucoadhesive drug delivery systems, providing the essential adhesive properties that enable prolonged contact with mucosal surfaces. These polymers can be broadly classified into natural and synthetic categories, with various modifications enhancing their mucoadhesive capabilities [18–21].

Classification of Mucoadhesive Polymers

First-Generation vs Second-Generation Polymers

Mucoadhesive polymers are classified as non-specific first-generation polymers and novel second-generation polymers based on their mechanism of adhesion. First-generation polymers rely primarily on non-specific interactions, while second-generation polymers are designed for specific binding to particular receptors or structures within the mucus layer.

Natural Mucoadhesive Polymers

Chitosan Derivatives

Chitosan, a cationic polysaccharide, exhibits inherent mucoadhesive properties and is widely used in mucoadhesive dosage forms. Its limitations include limited adhesion strength and poor solubility at neutral and basic pH. To overcome these, various derivatives have been developed [43,44].

- **Trimethyl chitosan:** Enhanced water solubility across pH ranges
- **Carboxymethyl chitosan:** Improved mucoadhesive properties
- **Thiolated chitosan:** Increased mucoadhesive strength via disulfide bonds
- **Chitosan-EDTA conjugates:** Enhanced permeation
- **Glycol chitosan:** Improved solubility
- **Chitosan-catechol:** Bio-inspired adhesive properties [45–47]

Other Natural Polymers

Natural biopolymers offer advantages such as biocompatibility, non-toxicity, stability, and cost-effectiveness. Important examples include:

- **Cellulose derivatives:** Modified for mucoadhesion
- **Natural gums:** Guar gum, xanthan gum, karaya gum, arabic gum
- **Starch and derivatives:** Biodegradable mucoadhesive properties
- **Pectin:** pH-dependent mucoadhesion
- **Alginate:** Marine-derived polymer with excellent biocompatibility

Synthetic Mucoadhesive Polymers

Polyacrylic Acid Derivatives

Polyacrylic acid and its derivatives, such as Carbopol, are widely used due to their high density of carboxyl groups, facilitating hydrogen bonding and electrostatic interactions with mucus [48,49].

Poloxamers

Poloxamers, including poly(ethylene oxide-propylene oxide-ethylene oxide) copolymers, are used for their thermogelling behavior and biocompatibility, making them suitable for in situ gel formation.

Modified and Functionalized Polymers

- **Thiolated Polymers (Thiomers):** Incorporation of thiol groups enhances adhesion through disulfide bond formation, improves matrix cohesion, and allows controlled drug release.

- **Bio-Inspired Polymers:** Polymers designed to mimic natural adhesion mechanisms achieve superior performance under physiological conditions.

Ideal Characteristics of Mucoadhesive Polymers

An ideal mucoadhesive polymer should possess:

- Biocompatibility and safety
- Optimal molecular weight for chain interpenetration
- Functional groups capable of hydrogen bonding and electrostatic interactions
- Controlled swelling and chemical stability
- Minimal interference with drug release
- Ability to enhance drug permeation across mucosal barriers

Polymer Selection Considerations

- Selection depends on factors such as:
- Surface charge and hydrophilic groups

- Molecular weight, chain flexibility, and conformation
- Wettability and initial contact with mucosa

Recent Advances and Future Directions

Current research focuses on developing novel polymers with enhanced biodegradability, biocompatibility, and targeted delivery capabilities. Integration with advanced technologies, including nanoparticles and microparticles, is a promising direction. Innovations in polymer chemistry continue to advance mucoadhesive drug delivery systems, improving efficacy, patient compliance, and expanding therapeutic applications.

Dosage Forms of Mucoadhesive Systems

Mucoadhesive drug delivery systems have been developed in various dosage forms to accommodate different administration routes and therapeutic requirements. These formulations are designed to maximize contact time with mucosal surfaces while providing controlled drug release [22–25].

Solid Dosage Forms

Mucoadhesive Tablets

Mucoadhesive tablets are extensively used solid dosage forms, which can be designed as:

- **Buccal tablets:** Placed in the buccal cavity for local or systemic delivery, bypassing first-pass metabolism [50,51].
- **Matrix tablets:** Drug uniformly distributed within a mucoadhesive polymer matrix.
- **Reservoir tablets:** Drug core surrounded by a mucoadhesive coating.

These tablets provide prolonged retention, controlled drug release, and enhanced bioavailability.

Films and Patches

Mucoadhesive films and patches are flexible dosage forms that conform to mucosal surfaces, offering [52,53].

- Uniform drug distribution
- Controlled thickness for predictable release
- Enhanced patient comfort and compliance
- Immediate or sustained release applications

Semi-Solid Dosage Forms

Mucoadhesive Gels and Hydrogels

Gel-based systems are advantageous due to their physicochemical properties and include:

- **Conventional hydrogels:** Sustained release and strong mucoadhesion
- **In situ gels:** Transition to gel phase under physiological conditions (pH, temperature, ions)
- **Nanogels:** Enhanced penetration and controlled release
- **Emulgels:** Combination of emulsion and gel properties

Ointments and Creams

These are mainly used for topical or localized delivery, providing extended contact time and protection for sensitive drugs.

Particulate Systems

Mucoadhesive Microspheres

Microspheres offer high surface area, controlled release, site-specific targeting, and improved

bioavailability. They can be prepared via emulsion cross-linking, ionotropic gelation, spray drying, and other methods.

Nanoparticles and Nanosystems

Advanced systems, including nanoparticles and liposomes, enhance penetration, provide targeted delivery, protect sensitive drugs, and improve therapeutic efficacy [54–56].

Liquid and Semi-Liquid Forms

Mucoadhesive Solutions and Suspensions

These allow easy administration and rapid onset, suitable for oral, nasal, and other mucosal routes.

Emulsions and Microemulsions

Mucoadhesive emulsions enhance permeation of lipophilic drugs and stabilize sensitive compounds.

Specialized Dosage Forms

- **Suppositories:** Designed for rectal or vaginal delivery, enabling localized action and systemic absorption while avoiding first-pass metabolism.
- **Powders:** Rapidly hydrate and adhere upon mucosal contact; useful for dry powder inhalers and nasal delivery.

Route-Specific Applications

- **Oral and Buccal Delivery:** Tablets, films, gels, and patches for buccal, sublingual, and gingival administration.
- **Nasal Delivery:** Gels, sprays, and particulate systems to enhance residence time.
- **Ocular Delivery:** Drops, gels, and inserts for prolonged ocular contact.
- **Vaginal and Rectal Delivery:** Mucoadhesive tablets, gels, suppositories, and films tailored for local or systemic effects.

Design Considerations

Selection of dosage forms depends on:

- Target site of delivery
- Drug properties and stability
- Desired release profile (immediate, sustained, or controlled)
- Patient compliance and ease of administration
- Manufacturing feasibility and cost

Modern mucoadhesive dosage forms continue to evolve with advances in polymer science and nanotechnology, providing sophisticated strategies to enhance drug delivery efficiency and improve patient experience.

Evaluation of Mucoadhesive Drug Delivery Systems

Evaluation of mucoadhesive drug delivery systems is essential for characterizing their properties and predicting in vivo performance. Various methodologies have been developed to assess mucoadhesive strength, residence time, and drug release, though standardization remains a challenge [26–28].

Categories of Evaluation Methods

In Vitro Evaluation Methods

In vitro methods provide controlled conditions for initial screening and comparative studies, offering reproducibility, cost-effectiveness, and ease of implementation.

- **Tensile Strength Testing:** Measures the maximum force required to detach the mucoadhesive system from a substrate.

- **Detachment Force Measurement:** Evaluates the force needed to separate the formulation from a model surface.
- **Shear Stress Testing:** Measures the force required to slide the mucoadhesive system across a surface, simulating physiological conditions.

Ex Vivo Evaluation Methods

Ex vivo studies use freshly excised animal or human tissues, providing physiologically relevant conditions [59].

- **Animal Tissue Studies:** Common tissues include rat intestinal mucosa, porcine buccal mucosa, and bovine nasal mucosa.
- **Gut Sac Method:** Provides insights into mucoadhesion and drug permeation simultaneously.
- **Mucin Interaction Studies:** Assess molecular interactions between polymers and isolated mucin.

In Vivo Evaluation Methods

In vivo studies provide clinically relevant assessments but are more complex and costly.

- **Residence Time Studies:** Track duration at the application site using gamma scintigraphy, fluorescence imaging, or pharmacokinetic profiles.
- **Bioavailability Studies:** Compare absorption and therapeutic efficacy between mucoadhesive and conventional formulations.

Specialized Evaluation Techniques

- **Atomic Force Microscopy (AFM):** Visualizes interactions at the molecular level.
- **Texture Analysis:** Measures mucoadhesive forces under controlled conditions.
- **Rheological Studies:** Evaluate viscoelastic properties, particularly for gel-based formulations.

Specific Evaluation Parameters

- **Mucoadhesive Strength:** Force required to detach the formulation from mucosal surfaces [57,58].
- **Work of Adhesion:** Energy needed to separate the system from the substrate.
- **Contact Time Evaluation:** Effect of contact duration on adhesive strength.
- **Swelling Studies:** Assess polymer hydration and its influence on adhesion.

Drug Release Studies

- **In Vitro Release Testing:** Dissolution studies to assess release kinetics, mucoadhesion impact, and environmental influences.
- **Permeation Studies:** Evaluate drug permeation across mucosal barriers using diffusion cells.

Challenges in Evaluation

- **Lack of Standardization:** Variability in methods limits comparability between studies.
- **Selection of Appropriate Models:** Depends on site, dosage form, duration, and objectives.
- **Correlation Between Methods:** Linking in vitro, ex vivo, and in vivo results requires careful validation.

Modern Evaluation Approaches

- **Multi-Parameter Assessment:** Combines complementary methods for comprehensive characterization.
- **Biomimetic Models:** Advanced in vitro systems simulate physiological conditions, including mucus turnover and dynamic flow.
- **Advanced Imaging Techniques:** Confocal and electron microscopy visualize interactions at microscopic levels.

Integration of these evaluation approaches enables comprehensive assessment of mucoadhesive systems, guiding the rational development of optimized drug delivery formulations.

Pharmaceutical Applications of Mucoadhesive Drug Delivery Systems

Mucoadhesive drug delivery systems (MDDS) have extensive applications across multiple therapeutic areas and administration routes, offering solutions for both local and systemic delivery challenges [29–32].

Oral and Buccal Applications

Systemic Drug Delivery: Buccal mucoadhesive systems serve as an effective alternative for drugs undergoing extensive first-pass metabolism. The rich vascularization and high permeability of buccal mucosa enable direct entry into systemic circulation [12,26,45].

Biological Drug Delivery: Oral mucosal delivery is particularly advantageous for biologics such as proteins and peptides, which are prone to enzymatic degradation in the gastrointestinal tract. Mucoadhesive systems protect these molecules while enhancing bioavailability.

Gastrointestinal Applications

Gastroretentive Systems: MDDS prolong gastric residence time, benefiting drugs with narrow absorption windows, local gastric treatment, or drugs requiring extended absorption periods.

Targeted GI Delivery: These systems enable precise delivery to specific regions of the gastrointestinal tract, including the stomach, small intestine, and colon, facilitating local disease treatment and controlled systemic delivery.

Nasal Drug Delivery

Systemic Absorption: Nasal mucoadhesive systems provide rapid drug absorption while bypassing first-pass metabolism, suitable for drugs requiring rapid onset [14,29,33].

CNS Drug Delivery: The nasal route offers potential access to the central nervous system, making mucoadhesive systems valuable for neurological therapies.

Ocular Applications

Mucoadhesive ocular formulations enhance drug retention on the eye surface, reduce dosing frequency, improve drug penetration, and enhance compliance for chronic eye conditions.

Vaginal Applications

Local Therapeutic Effects: Vaginal mucoadhesive systems are used for antifungal therapy, hormone replacement, contraception, and treatment of local conditions.

Systemic Hormone Delivery: These systems provide effective systemic delivery of hormones while avoiding hepatic first-pass metabolism.

Rectal Applications

Rectal mucoadhesive systems allow both local and systemic drug delivery, particularly for patients unable to take oral medications, drugs requiring bypass of the upper GI tract, and local treatment of inflammatory conditions.

Specific Drug Classes

Protein and Peptide Drugs: MDDS protect these drugs from enzymatic degradation, enhance mucosal permeation, enable controlled release, and improve bioavailability.

Antimicrobial Therapy: Provides sustained local concentrations at infection sites while minimizing systemic exposure and side effects.

Poorly Soluble Drugs: Prolonged mucosal contact enhances solubilization and bioavailability.

Commercial and Emerging Applications

Several mucoadhesive products have reached the market, demonstrating clinical viability. Patent literature shows significant innovation in formulation approaches, manufacturing, and therapeutic applications. Emerging uses include delivery of biologics, pandemic-related therapeutics, and personalized medicine, enabling tailored dosing and release profiles.

Advantages Across Applications

- **Enhanced Bioavailability:** Improves drug absorption compared to conventional formulations.
- **Improved Patient Compliance:** Reduced dosing frequency and non-invasive administration.
- **Targeted Delivery:** Localized treatment with minimal systemic exposure.

Future Prospects

Advances in polymer science, nanotechnology, and mucosal physiology continue to expand the applications of mucoadhesive systems. Integration with advanced drug delivery technologies promises enhanced therapeutic outcomes and broader clinical adoption.

Recent Advances in Mucoadhesive Drug Delivery Systems

The field of mucoadhesive drug delivery has seen significant technological advancement, with innovations spanning polymer development, nanotechnology, evaluation methodologies, and clinical translation [33–36].

Advanced Polymer Technologies

Second-Generation Mucoadhesive Polymers: Modern polymers demonstrate enhanced specificity and stronger adhesive interactions with mucosal surfaces compared to conventional materials

Thiolated Polymers (Thiomers): Advances include more efficient thiolation methods, novel thiolated derivatives with improved stability, and combination approaches using multiple thiol-containing polymers. These polymers enhance adhesion through disulfide bond formation and improve controlled drug release[34,47,55].

Functionally Modified Polymers: Chemical functionalization, surface modification, and hybrid polymer systems have been developed to improve mucoadhesive performance and enable targeted interactions.

Bio-Inspired Mucoadhesive Materials: Nature-inspired design principles, such as mussel-inspired catechol adhesion, gecko-inspired reversible adhesion, and plant-based mucilage analogues,

have been applied to mimic natural adhesion mechanisms for enhanced physiological performance.

Nanotechnology Integration

Nanoparticle-Based Systems: Mucoadhesive nanoparticles, hybrid nanoparticles, and smart nanocarriers offer enhanced mucosal penetration, targeted delivery, and responsive behavior under physiological conditions [48,54,56].

Advanced Nanoformulations: Solid lipid nanoparticles, liposomes, and polyelectrolyte nanoparticles improve drug protection, biocompatibility, and adhesion through electrostatic interactions.

Novel Dosage Form Developments

Advanced Oromucosal Systems: Innovations include smart patches responsive to physiological changes, multilayer systems for controlled release, and 3D-printed dosage forms for customizable geometries.

In Situ Gel Technologies: Temperature-, pH-, and ion-responsive gel systems enable in situ gelation, improving bioavailability and patient compliance.

Advanced Evaluation and Characterization

Modern evaluation employs high-resolution imaging, real-time monitoring, and biomechanical testing. Standardized protocols are increasingly being developed to improve reproducibility and comparability across studies.

Clinical Translation and Regulatory Advances

Regulatory frameworks now include standardized safety, efficacy, and quality control guidelines. Clinical translation has been demonstrated across multiple therapeutic areas, including pandemic-related applications such as nasal or oral delivery systems for emergency therapeutics.

Emerging Therapeutic Areas

Mucoadhesive systems have been extended to biologics, peptides, nucleic acids, and personalized medicine applications, enabling tailored dosing, improved stability, and enhanced bioavailability.

FUTURE DIRECTIONS AND CHALLENGES

Scalability, continuous manufacturing, quality by design, and cost-effective production are being addressed. Integration with digital health technologies, biodegradable polymers, green synthesis methods, and AI-driven optimization are shaping the future of mucoadhesive drug delivery systems. These advances promise to overcome existing limitations while broadening clinical and pharmaceutical applications.

CONCLUSION

Mucoadhesive drug delivery systems represent a significant advancement in pharmaceutical technology, offering prolonged mucosal contact, enhanced bioavailability, and improved patient compliance across multiple administration routes, including oral, buccal, nasal, ocular, vaginal, and rectal delivery. By bypassing first-pass metabolism, these systems enable both local and systemic therapeutic effects, making them particularly advantageous for biologics, peptides, and other sensitive molecules.

Advances in polymer science, including natural, synthetic, and second-generation thiolated polymers, alongside bio-inspired designs, have significantly improved mucoadhesive performance. Integration with nanotechnology has

further enhanced targeted delivery, controlled release, and mucosal penetration. The diversity of dosage forms—from tablets and gels to nanoparticles and responsive formulations—allows customization to therapeutic needs and patient populations.

Despite these achievements, challenges remain, including standardization of evaluation methods, scalability, and formulation optimization to predict in vivo performance. Future directions focus on personalized medicine, gene therapy, pandemic response, sustainable polymer systems, and the application of artificial intelligence for formulation design and optimization.

Overall, mucoadhesive drug delivery systems have transitioned from conceptual innovation to clinically viable technology. Continued research and technological integration promise to expand their therapeutic potential, making them a key component of advanced, patient-centric drug delivery strategies.

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