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MUCOADHESIVE DRUG DELIVERY SYSTEMS: MECHANISTIC FOUNDATIONS, ADVANCED POLYMERS, PHARMACEUTICAL APPLICATIONS, AND TRANSLATIONAL PERSPECTIVES

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ABSTRACT

The therapeutic efficacy of conventional drug delivery systems is frequently compromised by rapid mucociliary clearance, enzymatic degradation, and short residence times at biological absorption sites. Mucoadhesive drug delivery systems (MDDS) have emerged as a robust pharmaceutical strategy to overcome these physiological hurdles by utilizing the interfacial forces between polymeric carriers and mucosal membranes. This review critically examines the biophysical and molecular basis of mucoadhesion, with a particular focus on the transition from classical theories—such as wetting, diffusion, and adsorption—to advanced covalent bonding mechanisms facilitated by second-generation polymers. The evolution of mucoadhesive materials, ranging from natural polysaccharides (chitosan, alginate) to sophisticated thiolated, catechol-functionalized, and stimuli-responsive smart hydrogels. A route-specific synthesis is provided for route-wise applications, including buccal, nasal, ocular, gastrointestinal, and vaginal delivery, highlighting the impact of MDDS on bypassing first-pass metabolism and enhancing drug bioavailability. Particular emphasis is placed on recent technological

innovations (2020–2026), including 3D-printed mucoadhesive platforms and nanotechnology-driven strategies that balance mucoadhesion with mucus penetration. Finally, we address the current translational challenges, including the lack of standardized characterization methods and regulatory hurdles, and outline future perspectives for personalized mucosal therapy. Collectively, the evidence is synthesized to identify design principles, translational barriers, and research priorities for the next generation of localized and systemic transmucosal delivery systems.

KEYWORDS: Mucoadhesion; Thiolated polymers; Mucosal drug delivery; Mucin interaction; Bioavailability enhancement; Nanotechnology; Smart hydrogels; Stimuli-responsive systems; 3D printing; Pharmaceutical translation.

1. INTRODUCTION

1.1 Conventional Drug Delivery Limitations

Conventional drug delivery systems, particularly oral and topical routes, face significant physiological hurdles that limit their therapeutic efficiency. In the gastrointestinal tract, the acidic environment of the stomach and the presence of digestive enzymes can degrade sensitive drugs, such as proteins and peptides.[1],[53] Moreover, the rapid transit time through the absorption sites and the "wash-out" effect of biological fluids (saliva, tears, mucus) necessitate frequent dosing, which reduces patient compliance and leads to fluctuations in plasma drug concentrations.[5],[93] Mucoadhesive drug delivery systems (MDDS) address these limitations by providing a prolonged residence time at the site of absorption, thereby enhancing drug bioavailability and therapeutic efficacy.[2],[87]

1.2 Definition and Significance of Mucoadhesion

Mucoadhesion is defined as the state in which two materials, at least one of which is a biological mucosal surface, are held together for extended periods by interfacial forces. In the context of drug delivery, this interaction occurs between a polymeric carrier and the mucus layer or the epithelial surface.[1],[85] The significance of mucoadhesion lies in its ability to:

- Increase the residence time of the dosage form at the site of absorption.
- Enhance the local concentration of the drug.
- Improve bioavailability by bypassing first-pass metabolism (e.g., buccal and nasal routes).
- Protect sensitive drugs from degradation in the GI tract.
- Reduce dosing frequency and improve patient compliance.[2],[87]

1.3 Historical Development

Mucoadhesive drug delivery has evolved from simple viscous liquids used to treat oral lesions to sophisticated "smart" polymers that respond to physiological stimuli.[17],[88] Early research focused on identifying natural gums and mucilages that could prolong contact with mucosal membranes.[7],[9] However, the field has transitioned toward synthetic and semi-synthetic polymers with tailored molecular weights, charge densities, and functional groups to maximize adhesion and controlled drug release.[30],[38] The timeline of mucoadhesion research reflects a shift from simple adhesion to multifunctional platforms.[45],[53]

1.4 Objectives of the Review

This review aims to:

- Elucidate the biological and biophysical basis of mucoadhesion.
- Analyze the mechanical and molecular theories governing polymer-mucin interactions.
- Classify mucoadhesive polymers from first-generation to advanced stimuli-responsive systems.
- Examine pharmaceutical applications across various mucosal routes, including buccal, nasal, and ocular delivery.
- Critically evaluate recent technological innovations (2020-2026) and their translational status.

2. Literature Search Strategy / Review Methodology

A structured literature search was conducted to identify mechanistic, formulation, preclinical, clinical, and translational evidence relevant to mucoadhesive drug delivery. Literature published primarily between 2015 and 2026 was considered, while seminal earlier studies were retained where necessary to explain foundational concepts. PubMed, ScienceDirect, and SciSpace were used for literature identification. Because the present article is a narrative critical review rather than a registered systematic review, the search strategy was designed to provide broad thematic coverage rather than to support meta-analytic inference.

Keywords and Search Terms

Primary keywords included "mucoadhesion," "mucoadhesive drug delivery," "mucoadhesive polymers," "mucin interaction," "buccal delivery," "nasal drug delivery," "ocular mucoadhesion," "thiolated polymers," "thiomers," and "stimuli-responsive mucoadhesion".[92]

Inclusion and Exclusion Criteria

Studies were prioritized when they provided mechanistic insight into polymer–mucin interactions, characterized mucoadhesive materials, reported in vitro, ex vivo, in vivo, or clinical evaluation, or addressed emerging technologies such as thiomers, bio-inspired adhesives, nanocarriers, stimuli-responsive systems, and additive manufacturing. Review articles were used to establish context and identify major themes, whereas original research was preferentially used to support quantitative or formulation-specific claims. Records lacking sufficient bibliographic information or direct relevance to pharmaceutical mucoadhesion were considered lower-priority evidence. Approximately 330 records were initially identified and screened during preparation of the review.

3. BIOLOGICAL BASIS

3.1 Mucus Structure and Composition

The mucosal membrane is the primary target for MDDS. It consists of an epithelial layer covered by a viscoelastic mucus layer. Mucus is a complex aqueous secretion containing 95% water, glycoproteins (mucins), lipids, inorganic salts, and enzymes.[62],[81],[96] Mucins, the key functional components, are high-molecular-weight glycoproteins characterized by a protein core rich in serine, threonine, and proline, extensively glycosylated with carbohydrate side chains.[72],[86]

3.2 Viscoelasticity and Barrier Functions

The viscoelastic properties of mucus are derived from the entanglement and cross-linking of mucin fibers, forming a three-dimensional gel network.[46],[83],[104] This network acts as a selective physical barrier, trapping pathogens and foreign particles while allowing the diffusion of small molecules.[52],[63],[90] The pH of the environment significantly influences mucus rheology; for instance, gastric mucus undergoes a sol-gel transition at low pH, which affects the adhesion of polymeric carriers.[46],[61],[81]

3.3 Mucosal Membrane Barriers

Beyond the mucus layer, the underlying epithelium presents additional barriers, including tight junctions (paracellular route) and the lipophilic cell membrane (transcellular route).[11],[44] Effective mucoadhesive systems must not only adhere to the mucus but often facilitate drug penetration through these epithelial barriers.[12],[69]

4. Mechanisms and Theories of Mucoadhesion

Mucoadhesion is a multi-stage process involving an initial contact phase (wetting and swelling) followed by a consolidation phase (interpenetration and bonding).[6],[17],[18],[23]

4.1 Wetting Theory

Applicable primarily to liquid and semi-solid systems, this theory emphasizes the ability of the mucoadhesive to spread over the mucosal surface. It is quantified by the contact angle and work of adhesion.[1],[4],[13],[21]

4.2 Diffusion Theory

This theory proposes that the mucoadhesive polymer chains and mucin glycoproteins interpenetrate across the interface to form a semi-permanent adhesive bond.[1],[4],[13] The depth of penetration depends on the diffusion coefficient, molecular weight, and chain flexibility of the polymer.[18],[60],[66]

4.3 Electronic Theory

Based on the premise that the mucosal surface and the mucoadhesive material have different electronic structures, this theory suggests that an electrical double layer forms at the interface, resulting in attractive electrostatic forces.[1],[3],[4],[22]

4.4 Adsorption Theory

This is the most widely accepted theory, involving secondary chemical bonds such as hydrogen bonding, van der Waals forces, and hydrophobic interactions between the polymer and the mucin.[1],[3],[4],[15],[19]

4.5 Fracture Theory

Unlike other theories that focus on the formation of the bond, fracture theory analyzes the force required to separate two surfaces after adhesion has occurred. It relates the adhesive strength to the mechanical properties of the interface.[1],[4],[21],[22]

Table 1: Comparative Analysis of Mucoadhesion Theories.

Theory	Principle Mechanism	Key Factors	Ref
Wetting	Surface spreading	Contact angle, spreading coefficient	[1], [13]
Diffusion	Chain entanglement	MW, chain mobility	[1], [4], [60]
Electronic	Electrostatic attraction	Surface charge, Zeta potential	[3], [21], [22]
Adsorption	Secondary bonding	Functional groups (-OH, -COOH)	[4], [19]
Fracture	Mechanical separation	Tensile strength, work of adhesion	[4], [23]

5. Factors Affecting Mucoadhesion

The efficiency of mucoadhesion is governed by polymer-related, environmental, and physiological factors.[5],[18]

5.1 Polymer-Related Factors

- Molecular Weight: Generally, an optimal molecular weight is required; too low results in weak interpenetration, while too high may limit chain mobility.[18],[60]
- Concentration: Higher polymer concentrations typically increase adhesive strength up to an optimum point.[18],[88]
- Flexibility: Flexible chains allow better interpenetration.[18],[47]
- Swelling: Necessary to expose adhesive sites but excessive swelling can lead to cohesive failure.[6],[15],[23]

5.2 Environmental and Physiological Factors

- pH: Influences the ionization state of the polymer and the mucin, as well as the mucus rheology.[46],[51],[83]
- Mucus Turnover Rate: Rapid turnover (e.g., in the respiratory tract) reduces the residence time of mucoadhesive systems.[80]
- Hydration: Optimal hydration is essential for polymer swelling; however, over-hydration can lead to premature detachment.[9],[102]

Table 2: Factors affecting Mucoadhesion.

Factor	Effect on Mucoadhesion	Ref
MW	Bell-shaped curve influence	[18], [60]
Charge	Increases (if opposite to mucin)	[46], [76]
pH	Variable based on ionization	[46], [104]
Hydration	Facilitates then hinders	[9], [102]
Turnover	Decreases residence time	[80]

6. Classification and Properties of Mucoadhesive Polymers

6.1 First-Generation Polymers

These are conventional mucoadhesive polymers that primarily utilize non-specific interactions like hydrogen bonding and electrostatic attraction.[1]

- Natural Polymers: Chitosan, sodium alginate, pectin, and hyaluronic acid.[7],[9],[34],[43],[59]
- Synthetic Polymers: Polyacrylic acid (Carbopol), HPMC, and PVA.[14],[26],[28],[32], [77]

Table 3: Comparative Properties of First-Generation Polymers.

Polymer	Charge	Mucoadhesive Strength	Ref
Chitosan	Cationic	High	[7], [36]
Sodium Alginate	Anionic	Moderate	[50], [98]
Carbopol	Anionic	Very High	[14], [28]
HPMC	Non-ionic	Moderate	[14], [26]

6.2 Second-Generation Polymers

Advanced polymers have been developed to provide site-specific adhesion.[18],[30],[38]

- Thiolated Polymers (Thiomers): Form covalent disulfide bonds with mucin.[1],[48],[57],[68]
- Lectin-Mediated Systems: Targeted sugar binding.[18],[93]
- Catechol-Functionalized Polymers: Mussel-inspired strong adhesion.[12],[38]
- Stimuli-Responsive Polymers: Phase transitions in response to pH or temperature.[18],[74],[75]

Table 4: Advanced/Second-Generation Polymers: Advantages and Applications.

Polymer Type	Advantage	Application	Ref
Thiomers	Covalent bonding	Oral, Ocular	[57], [68]
Lectins	High specificity	Cancer therapy	[18]
Boronic Acid	Sialic acid binding	Ocular, Vaginal	[56], [70]
Catechols	Wet adhesion	Oral cavity	[12], [38]

7. Evolution and Generations

- First Generation: Traditional cellulose derivatives and polyacrylic acids (1980s-1990s).[8],[15]
- Second Generation: Thiomers, lectins, and nanoparticles (2000s-2010s).[57],[99]
- Third Generation: Smart systems, 3D printing, and stimuli-responsive materials (2020-Present).[18],[45],[53]

8. Mucoadhesive Dosage Forms and Formulation Strategies

• Tablets: Multi-layered for unidirectional release.[14],[29]

• Films and Patches: Flexible, highly preferred for buccal delivery [9], [39], [84], [100].

• Hydrogels: Ideal for ocular and vaginal delivery [74], [75], [101], [105].

• Nanoparticles: Mucoadhesive or muco-penetrating [12], [67], [94].

Table 5: Mucoadhesive Dosage Forms: Pros and Cons.

Dosage Form	Advantages	Disadvantages	Ref
Tablets	High drug loading	Bulky, irritation	[14], [29]
Films/Patches	Flexible, fast dissolution	Limited drug loading	[9], [39], [84]
Hydrogels	Sustained release	Mechanical weakness	[74], [101]
Nanoparticles	Targeted delivery	Complex synthesis	[12], [67]

9. Route-wise Pharmaceutical Applications

• Buccal: Bypasses first-pass metabolism[3], [39], [65].

• Nasal: Large surface area, nose-to-brain targeting[25], [54], [73], [80].

• Ocular: Counteracts tear drainage[27], [35], [36], [49], [58].

• GI: Gastroretentive systems[37], [41], [53], [89].

• Vaginal/Rectal: Local and systemic delivery[5], [31], [71], [105].

Table 6: Route-specific Physiological Barriers and Delivery Strategies.

Route	Main Barrier	Strategy	Ref
Buccal	Saliva wash-out	Unidirectional patches	[39], [65]
Nasal	Mucociliary clearance	Viscous gels/sprays	[25], [80]
Ocular	Tear turnover	In situ hydrogels	[35], [75]
GI	Acidic pH, motility	Floating systems	[37], [41]

10. Evaluation and Characterization

- In Vitro: Tensile strength (detachment force), shear stress, rheological synergism[1],[4],[51],[77],[86]
- Ex Vivo: Retention on animal tissue samples[77], [79].
- In Vivo: Gamma scintigraphy, MRI tracking[1], [20].

Table 7: Evaluation Methods for Mucoadhesion.

Method	Parameter	Principle	Ref
Tensile Tester	Detachment Force	Mechanical pulling	[1], [77]
Viscometer	Rheological Synergism	Viscosity increase	[51], [86]
Scintigraphy	Residence Time	Radiotracking	[1]
AFM	Binding Force	Molecular interaction	[78]

11. Comparative Evidence and Quantitative Analysis

Table 8: Quantitative Experimental Comparison of Mucoadhesive Systems.

Formulation	Polymer	Detachment Force (mN)	Ref
Buccal Film	Chitosan/Alginate	12.5 ± 1.2	[50]
Buccal Patch	Carbopol 934P	25.4 ± 2.1	[100]
Ocular Gel	Thiolated HA	18.9 ± 0.8	[58], [68]
Nasal Spray	Iota-Carrageenan	8.4 ± 0.6	[64]

12. Nanotechnology in Mucoadhesive Drug Delivery

Mucoadhesive nanoparticles (e.g., chitosan-based) are trapped in the outer mucus layer.[12],[67] In contrast, mucus-penetrating particles (MPPs) use PEG or zwitterionic coatings to diffuse through the mucus to the epithelium.[33], [69], [70], [106].

13. Recent Advances and Emerging Technologies (2020-2026)

• Thiomer Advancements: Pre-activated thiomers and thiolated cyclodextrins.[1],[48],[68],[103]

• 3D Printing: Personalized mucoadhesive patches with complex profiles.[18],[45],[53]

• Bio-inspired Designs: Catechol-modified (mussel-inspired) and sugar-based polymers.[12],[38],[55]

Table 9: Recent Technological Innovations (2020-2026).

Innovation	Advantage	Ref
Thiomers	Covalent, long-term adhesion	[1], [57]
3D Printing	Personalized geometry	[18], [45]
Catechol Grafting	Strong wet adhesion	[12], [38]
Smart Micelles	Triggered release	[74], [75]

14. Therapeutic and Clinical Applications

• Cancer: Local doxorubicin delivery in oral cavity carcinoma.[12],[97]

• Inflammatory Disease: Sustained localized effect in chronic mucosal diseases.[16]

• Pediatrics/Geriatrics: Films and wafers for easier administration.[22]

15. Marketed Products and Translational Status

Table 10: Marketed Mucoadhesive Pharmaceutical Products.

Product	Drug	Route	Ref
Buccastem®	Prochlorperazine	Buccal	[14]
Striant®	Testosterone	Buccal	[10]
Crinone®	Progesterone	Vaginal	[10]
Arestin®	Minocycline	Periodontal	[24]

16. Safety, Toxicity and Biocompatibility

• Natural Polymers: Generally safe and biodegradable.[7],[9],[58]

• Synthetic Excipients: Require rigorous toxicity testing for irritation and systemic absorption,[10],[14],[19],[20]

• Challenges: Potential for local irritation or interfering with mucus protection.[22],[42]

17. Regulatory and Manufacturing Considerations

• Manufacturing: Scale-up challenges, batch-to-batch variation, and stability.[9],[12],[40]

• Regulatory: Lack of standardized monographs for novel polymers and functionalized thiomers.[9],[19],[20]

Table 11: Translational Challenges and Potential Solutions.

Challenge	Potential Solution	Ref
Standardization	Developing monographs	[9]
Mucus Variability	Stimuli-responsive systems	[12], [18]
Manufacturing Cost	Simplified fabrication (3D printing)	[12], [45]

18. Critical Discussion

A persistent translational gap exists between increasingly sophisticated polymer designs and their clinical adoptability.[12] While thiomers show remarkable adhesion in vitro, the dynamic human mucosal environment remains a challenge.[2], [22] The emergence of mucus-penetrating systems further demonstrates that maximal adhesion is not universally desirable; the optimal strategy depends on the therapeutic target, mucus turnover, and required epithelial access.[69],[106]

19. Current Challenges and Research Gaps

- Molecular Level: Lack of definitive models for mucin-polymer interactions.[2],[59]
- In Vitro Models: Need for better human-mimetic systems.[52],[90]
- Safety Data: Limited information on long-term effects of repeated applications.[22]

20. Future Perspectives

Future trends include "smart" mucoadhesive patches with digital health monitoring, bio-inspired adhesives for wet environments, and dual-action (adhesion + penetration) systems.[18],[38],[45],[55],[91],[103]

21. CONCLUSION

Mucoadhesive drug delivery systems have progressed from conventional polymeric platforms to multifunctional systems capable of prolonged residence, controlled release, epithelial targeting, and stimulus-responsive behavior. However, clinical translation remains constrained by variability in mucus biology, limited standardization of mucoadhesion testing, scale-up challenges, and incomplete long-term safety evidence. Future progress will depend on clinically relevant models, harmonized characterization methods, quality-by-design

manufacturing, and direct comparison of mucoadhesive and mucus-penetrating strategies.

Figure Concepts and Legends

Figure 1: Mucin Glycoprotein Structure.[62],[72],[81]

Figure 2: Two-Stage Mucoadhesion Mechanism.[6],[15],[17]

Figure 3: Biophysical Theories of Adhesion.[1],[4],[13]

Figure 4: Evolution of MDDS Generations.[1],[18],[45]

Figure 5: Major Routes for MDDS.[5],[18],[95]

Figure 6: Thiol-Disulfide Exchange Mechanism.[1],[57],[68]

Figure 7: Mucoadhesive vs. Mucus-Penetrating NPs.[69],[82],[106]

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Appendix: Abbreviation List

- MDDS: Mucoadhesive Drug Delivery Systems
- GI: Gastrointestinal
- BSM: Bovine Submaxillary Mucin
- PEG: Polyethylene Glycol
- CMC: Carboxymethyl Cellulose
- HPMC: Hydroxypropyl Methylcellulose
- PVA: Polyvinyl Alcohol
- GIT: Gastrointestinal Tract
- PVP: Polyvinylpyrrolidone
- HEC: Hydroxyethyl Cellulose
- PAA: Poly(acrylic acid)