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Bio-enhancement in mucoadhesive drug delivery systems: A review

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Abstract

Mucoadhesive drug-delivery systems (MDDS) are designed to adhere to mucosal tissues, enhancing both local and systemic drug absorption. The addition of bioenhancers agents that improve membrane permeability, inhibit metabolic degradation, or modulate efflux transporters addresses issues of low mucosal permeability and first-pass metabolism affecting many therapeutic molecules, like peptides and poorly soluble drugs. This review examines the fundamentals of mucoadhesion, focusing on polymer–mucin interactions and mechanical retention forces, while categorizing bioenhancers into plant-derived molecules, surfactants, medium-chain fatty acids, bile salts, and synthetic promoters. It discusses their mechanisms, formulation strategies (such as buccal films and hydrogels), and co-loading principles that enhance absorption. Evaluation techniques, including *in vitro* and *in vivo* studies, are outlined to support systematic development. Case studies illustrate the effectiveness of bioenhanced systems, such as piperine for rifampicin delivery and medium-chain fatty acids. Key safety and regulatory considerations related to mucosal irritation and the acceptance of bioenhancers are also addressed. Lastly, emerging trends in mucoadhesive technologies suggest pathways for safer and more effective drug delivery.

Keywords: Mucoadhesion; Bioenhancer; Permeation Enhancer; Piperine; SNAC; Chitosan; Mucosal Delivery

1. Introduction

Mucoadhesive drug delivery systems (MDDS) have emerged as an important class of advanced drug-delivery technologies designed to prolong the residence time of therapeutic formulations at mucosal surfaces. These mucosa-lined sites, including the oral cavity, buccal mucosa, nasal passages, ocular surfaces, gastrointestinal tract, vaginal epithelium, and rectal mucosa, offer large surface areas and rich vascularization, making them attractive targets for non-invasive drug administration (Dey et al., 2024). Mucoadhesion enables formulations to maintain intimate contact with these tissues, thereby enhancing absorption, reducing dosing frequency, and improving bioavailability, especially for molecules that suffer from rapid clearance or degradation in the gastrointestinal environment.

Mucoadhesion is driven by physicochemical interactions between polymeric excipients and mucin, the main glycoprotein component of mucus. These processes include hydrogen bonding, electrostatic attraction, hydrophobic interactions, van der Waals forces, and interpenetration of polymer chains with the mucin network (Nafee et al., 2023). A wide range of natural and synthetic polymers exhibit mucoadhesive properties. Natural polymers such as chitosan, alginate, pectin, guar gum, and hyaluronic acid are biocompatible and possess functional groups capable of forming hydrogen bonds or ionic interactions with mucin (Patel et al., 2022). Synthetic polymers, including Carbopol (polyacrylic acid), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and polyethylene oxide (PEO), offer tunable mechanical strength and reproducible swelling and adhesion behaviors (Mortazavi and Smart, 2021). The combination of such polymers with advanced drug carriers e.g., hydrogels, films, nanoparticles, and in situ gelling systems has expanded the therapeutic possibilities of MDDS.

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Despite their promise, many molecules delivered via mucosal routes still face significant biological and physicochemical barriers. These include enzymatic degradation in the mucus layer, rapid mucociliary clearance, tight junctions limiting paracellular transport, and poor transcellular permeability of hydrophilic or macromolecular drugs such as peptides, proteins, and nucleic acids (Fakhraei et al., 2022). Peptides in particular are vulnerable to proteolytic enzymes, pH instability, and low epithelial permeability, making their oral bioavailability extremely low (Buckley et al., 2023). These limitations have stimulated considerable interest in the integration of bioenhancer molecules capable of improving drug permeation, stability, or absorption without possessing significant pharmacological action at therapeutic doses. Bioenhancers may act through several mechanisms, including inhibition of metabolic enzymes (e.g., CYP450 enzymes or proteases), downregulation or inhibition of efflux transporters such as P-glycoprotein (P-gp), transient modulation or opening of epithelial tight junctions, or enhancement of drug solubility and membrane fluidity (Khater et al., 2021). Natural bioenhancers include compounds such as piperine (from *Piper nigrum*), quercetin, glycyrrhizin, naringin, and curcumin many of which have demonstrated significant improvements in mucosal permeability and oral bioavailability in preclinical studies (Gurav et al., 2022). Synthetic permeation enhancers, including sodium caprate (C10 medium-chain fatty acid), bile salts such as sodium taurocholate, and salcaprozate sodium (SNAC), have shown strong ability to modulate mucosal permeability and enhance systemic absorption of both small molecules and peptides (Müller et al., 2023).

The integration of bioenhancers with mucoadhesive carriers offers a synergistic strategy. While mucoadhesive polymers prolong the residence time of the drug formulation at the mucosal surface and protect it from rapid clearance, bioenhancers facilitate epithelial transport, reduce pre-systemic metabolism, and increase effective drug flux across the mucosa. This combination significantly improves the therapeutic efficiency of challenging molecules. For example, recent studies demonstrate that mucoadhesive films containing piperine enhanced the permeation of acyclovir across buccal mucosa, supporting the role of natural alkaloids as adjuvants in mucosal delivery (Dangi et al., 2021). Similarly, chitosan-based microcapsules have been shown to improve the oral bioavailability of peptides by enhancing mucoadhesion and modulating tight junctions (Li et al., 2023). Several successful clinical applications highlight the potential of bioenhancer-assisted MDDS. The marketed anti-tuberculosis formulation Risorine®, which combines rifampicin and isoniazid with the natural bioenhancer piperine, exhibits significantly improved oral bioavailability compared to standard therapy (Sharma et al., 2020). Another breakthrough is the development of the first oral peptide drug, semaglutide (Rybelsus®), whose success was enabled by SNAC, a permeation enhancer that protects the peptide from degradation and facilitates its transcellular absorption through the gastric mucosa (Laugesen et al., 2022). These advancements underscore the translational promise of combining bioadhesive and permeation-enhancing strategies.

Furthermore, emerging technologies are focusing on multidisciplinary innovations such as bioinspired mucoadhesive polymers (e.g., lectin-functionalized systems), mucus-penetrating nanoparticles, stimuli-responsive hydrogels, and precision-engineered enhancers designed to produce reversible and safe modulation of mucosal barriers (Sahni et al., 2023). Advances in polymer chemistry, nanotechnology, and biopharmaceutics continue to expand the scope of MDDS for delivering complex biological drugs, vaccines, genetic material, and microbiome-based therapeutics. Collectively, bioenhancer-assisted mucoadhesive drug-delivery systems offer a powerful platform that addresses the limitations of traditional mucosal drug administration. Their ability to improve drug localization, enhance permeation, protect sensitive molecules, and reduce dosing frequency makes them promising tools for future pharmaceutical development.

2. Mucoadhesive drug delivery systems

Mucoadhesive drug delivery systems (MDDS) are advanced pharmaceutical platforms engineered to improve drug residence time and therapeutic efficacy at mucosal sites. Mucosal tissues, including the oral, buccal, nasal, ocular, gastrointestinal (GI), vaginal, and rectal surfaces, provide unique opportunities for both local and systemic drug delivery due to their large surface area, rich vascularization, and relatively high permeability. Despite these advantages, drug administration via mucosal routes often faces significant challenges: continuous mucus secretion and turnover, mucociliary or mucosal clearance, enzymatic degradation (particularly of peptides, proteins, or nucleic acids), and limited epithelial permeability due to tight junctions or unfavorable physicochemical properties of the drug molecule. These barriers reduce absorption, limit bioavailability, and may require high or frequent dosing, especially in conventional non-mucoadhesive formulations. MDDS overcomes these hurdles by using mucoadhesive polymers that adhere to the mucus layer covering mucosal epithelia. This adhesion prolongs residence time at the absorption site, protects the formulation from rapid clearance or degradation, and enhances the probability of drug absorption. Consequently, MDDS can improve bioavailability, enable controlled or sustained release, lower dosing frequency, and increase patient compliance by maintaining intimate contact between the drug and mucosal tissue.

2.1. Principles of Mucoadhesion

2.1.1. Hydrogen Bonding

Hydrogen bonding is one of the most fundamental and widely recognized mechanisms of mucoadhesion in mucoadhesive drug delivery systems (MDDS). It occurs when polymers containing functional groups capable of hydrogen donation or acceptance interact with complementary groups in the mucin glycoproteins present in the mucus layer. Common functional groups on polymers that participate in hydrogen bonding include hydroxyl (-OH), carboxyl (-COOH), amine (-NH_2), and thiol (-SH) groups (Boddupalli and Suryanarayana, 2010; Raza, Singh and Sharma, 2021). These groups form reversible, non-covalent interactions with the carbohydrate and peptide residues of mucin, providing adhesive strength without permanently altering the mucus structure (Hua, 2014).

Polymers that utilize hydrogen bonding effectively include both natural and synthetic mucoadhesive polymers such as chitosan, carbopol, hydroxypropyl methylcellulose (HPMC), alginate, and pectin. The efficiency of hydrogen bonding depends on factors such as polymer molecular weight, chain flexibility, degree of hydration, and the density of functional groups available for interaction. Hydration allows polymer chains to swell and extend, increasing the number of contact points with mucin and thereby enhancing mucoadhesive strength (Sonaje, Lin, Wey and Juang, 2011).

Hydrogen bonding often works in synergy with other mechanisms of adhesion, including electrostatic interactions, chain interpenetration, and physical entrapment, to produce stronger and longer-lasting mucoadhesion. This mechanism is particularly significant for formulations intended for oral, buccal, nasal, or gastrointestinal delivery, where mucus turnover and clearance could otherwise limit drug residence time (Illum, 2000).

2.1.2. Electrostatic / Ionic Interactions

Electrostatic (or ionic) interactions are a key mechanism contributing to mucoadhesion in drug delivery systems. Mucin, the primary glycoprotein in mucus, carries a net negative charge due to the presence of sialic acid and sulfate residues on its carbohydrate side chains. Positively charged (cationic) polymers, such as chitosan, poly-L-lysine, and certain cationic polyacrylates, can interact electrostatically with these negatively charged sites on mucin, enhancing the adhesion of the polymer to the mucosal surface (Bernkop-Schnürch and Dünnhaupt, 2012; Boddupalli and Suryanarayana, 2010). This type of interaction is highly pH-dependent. The degree of ionization of both the polymer and the mucin glycoprotein determines the strength of the electrostatic attraction. For instance, chitosan is protonated and positively charged under acidic to slightly neutral pH, which favors strong adhesion to negatively charged mucin. Conversely, at higher pH levels, deprotonation of polymer amino groups reduces cationic character and weakens electrostatic interactions, potentially decreasing mucoadhesive strength (Raza, Singh and Sharma, 2021; Illum, 2000). Electrostatic interactions often act synergistically with other mucoadhesive mechanisms such as hydrogen bonding, chain interpenetration, and physical entrapment. This synergy allows for longer residence time and improved drug retention at the mucosal site, which is particularly important for buccal, nasal, gastrointestinal, and vaginal drug delivery where mucus turnover and clearance are rapid (Sonaje, Lin, Wey and Juang, 2011).

2.1.3. Chain Interpenetration and Entanglement

Chain interpenetration and entanglement represent a physical mechanism of mucoadhesion in which polymer chains diffuse into the mucin network and form an interlaced structure, creating a mechanical “mesh” with mucin fibers. This process occurs primarily after the polymer has hydrated or swollen, which increases chain flexibility and mobility, allowing polymer segments to penetrate the mucus layer (Boddupalli and Suryanarayana, 2010; Raza, Singh and Sharma, 2021). The extent of interpenetration depends on polymer chain length, molecular weight, degree of crosslinking, and hydration properties. Longer and more flexible polymer chains typically achieve deeper interpenetration, resulting in stronger entanglement with mucin and more prolonged adhesion (Hua, 2014; Sonaje et al., 2011). This mechanism is especially important for mucoadhesive films, hydrogels, and in situ-forming gels, where the physical retention of the dosage form is critical for sustained drug delivery. By forming a network of interpenetrated polymer-mucin chains, the dosage form is effectively anchored to the mucosal surface. This not only increases residence time but also enhances drug bioavailability, particularly for molecules with low permeability or susceptibility to enzymatic degradation (Bernkop-Schnürch and Dünnhaupt, 2012). Chain interpenetration often works synergistically with hydrogen bonding and electrostatic interactions, amplifying overall mucoadhesive strength and ensuring more reliable drug delivery (Boddupalli and Suryanarayana, 2010; Raza et al., 2021).

2.1.4. Physical Entrapment / Mechanical Adhesion

Physical entrapment, also called mechanical adhesion, is a mucoadhesive mechanism in which polymeric materials or gels are physically interlocked within the mucus layer covering mucosal surfaces. In this mechanism, the polymer does

not rely on chemical interactions like hydrogen bonding or electrostatic forces; instead, it becomes mechanically trapped within the viscous and mesh-like structure of mucus. This entrapment slows clearance by mucus turnover or mucociliary action and allows for sustained residence of the dosage form at the absorption site, improving drug bioavailability and therapeutic effect (Boddupalli and Suryanarayana, 2010; Raza, Singh and Sharma, 2021). Hydrogels and in situ-forming gels are common formulations that exploit physical entrapment. Upon contact with mucosal surfaces, these materials can swell, conform to the shape of the mucosa, and embed themselves within the mucus network, creating a depot effect for the encapsulated drug. The efficiency of physical entrapment depends on factors such as polymer viscosity, molecular weight, degree of crosslinking, and swelling behavior (Hua, 2014; Sonaje, Lin, Wey and Juang, 2011). Physical entrapment often works synergistically with other mucoadhesive mechanisms, including hydrogen bonding, electrostatic interactions, and chain interpenetration, to produce stronger and longer-lasting adhesion. This mechanism is particularly useful for oral, buccal, nasal, vaginal, and gastrointestinal drug delivery, where rapid mucus turnover can otherwise limit drug residence time and absorption (Illum, 2000).

2.1.5. Adsorption (Van der Waals and Hydrophobic Interactions)

Adsorption is a secondary mechanism of mucoadhesion in which polymers adhere to the mucosal surface via weak, non-covalent interactions. These include van der Waals forces, hydrophobic interactions, and dipole–dipole interactions. While weaker than hydrogen bonding or electrostatic interactions, adsorption contributes cumulatively to the overall adhesive strength of a mucoadhesive system (Boddupalli and Suryanarayana, 2010; Raza, Singh and Sharma, 2021). Hydrophobic polymers, such as certain modified cellulose derivatives or amphiphilic polymers, can associate with nonpolar regions of mucin glycoproteins, enhancing residence time. Similarly, van der Waals interactions allow close contact between the polymer and the mucosal surface, stabilizing adhesion even in the presence of mucus turnover or fluid flow. Adsorption often works synergistically with other mucoadhesive mechanisms, such as hydrogen bonding, electrostatic interactions, chain interpenetration, and physical entrapment, producing a stronger and more durable mucoadhesive effect (Hua, 2014; Sonaje, Lin, Wey and Juang, 2011). This mechanism is particularly relevant for oral, buccal, nasal, vaginal, and gastrointestinal drug delivery applications, where maintaining prolonged contact with the mucosal tissue is crucial for effective drug absorption.

2.1.6. Mucoadhesive Polymers

A wide variety of polymers are employed in the design of Mucoadhesive Drug Delivery Systems (MDDS). Natural polymers such as chitosan, alginate, hyaluronic acid, pectin, and gelatin offer excellent biocompatibility and biodegradability (Illum, 1998) Synthetic polymers such as Carbopol, polyacrylic acid, Hydroxypropyl methylcellulose (HPMC), and Polyvinylpyrrolidone (PVP) provide greater mechanical strength and formulation versatility (Grabovac et al., 2005). Some polymers—particularly chitosan and its derivatives—not only facilitate mucoadhesion but also act as permeation enhancers by transiently opening epithelial tight junctions, improving paracellular transport (Thanou et al., 2001).

3. Limitations of Mucoadhesive Drug Delivery Systems (MDDS)

Despite the significant promise of mucoadhesive drug delivery systems, several biological and physicochemical limitations restrict their overall effectiveness. One major challenge is the inherently low permeability of hydrophilic and high-molecular-weight therapeutic agents such as peptides, proteins, and nucleic acids across mucosal epithelial layers. These macromolecules often struggle to penetrate the tight junctions and lipid-rich cellular membranes, resulting in suboptimal absorption and limited systemic availability (Ensign et al., 2012). This barrier significantly limits the success of MDDS designed for non-parenteral delivery of biologics. In addition to permeability issues, enzymatic degradation presents another substantial obstacle. Mucosal tissues are rich in proteases, nucleases, and other metabolic enzymes that rapidly break down vulnerable drug molecules before they can reach systemic circulation. This phenomenon, combined with pre-systemic metabolism, further compromises the stability and bioavailability of drugs administered via mucosal surfaces (Hameed et al., 2023). Such degradation is particularly problematic for peptide- and protein-based therapeutics that are naturally susceptible to enzymatic cleavage. Mucus turnover dynamics also play a critical role in limiting the performance of MDDS. Mucus is continuously secreted and cleared as part of the body's natural protective mechanisms. In tissues with high mucus turnover—such as the gastrointestinal tract, where mucus is replaced every 4–6 hours, or the nasal cavity with clearance occurring within minutes, mucoadhesive formulations may be rapidly removed from the site of absorption. This reduction in residence time significantly decreases the contact between the drug and the mucosal epithelium, thereby lowering absorption efficiency (Lai et al., 2009). Variations in mucus rheology, hydration, and thickness across individuals further contribute to inconsistent drug delivery outcomes. Together, these limitations highlight the complexity of designing effective MDDS. Overcoming these barriers requires advanced formulation strategies, such as incorporating permeation enhancers to transiently loosen epithelial tight junctions, enzyme inhibitors to protect sensitive molecules from degradation, and nanocarrier-based systems engineered for

improved mucoadhesion, mucus penetration, or controlled release. These innovations aim to maximize drug retention, enhance permeability, and ultimately improve therapeutic efficacy.

4. Role of Bioenhancers in Mucoadhesive Drug Delivery Systems (MDDS)

The incorporation of bioenhancers into mucoadhesive drug delivery systems (MDDS) has emerged as a promising strategy to improve drug absorption, bioavailability, and stability. Bioenhancers are natural or synthetic compounds that enhance the absorption, distribution, or metabolic stability of co-administered drugs without exerting significant pharmacological effects at their administered dose (Atal and Bedi, 2010). Their use is particularly valuable for hydrophilic, high-molecular-weight, or enzymatically labile drugs, such as peptides, proteins, and nucleic acids, which typically have low permeability across mucosal epithelia.

4.1. Synergistic Potential of MDDS and Bioenhancers

The integration of bioenhancers into mucoadhesive drug delivery systems (MDDS) offers a synergistic approach to improve the therapeutic performance of drugs that otherwise exhibit poor absorption or rapid metabolism. In this strategy:

4.1.1. Mucoadhesive Component

The mucoadhesive component of a drug delivery system significantly enhances drug absorption by ensuring prolonged intimate contact between the dosage form and the mucosal surface. Mucoadhesive polymers interact with the mucus layer through hydrogen bonding, electrostatic forces, and polymer–mucin interpenetration, which anchors the formulation at the site of absorption and prevents rapid washout (Ensign et al., 2012; Smart, 2005). This prolonged residence time allows the drug and any co-administered bioenhancer to remain in proximity to the epithelial tissue long enough for efficient uptake rather than being cleared by mucus turnover or physiological movement (Lai et al., 2009). Because the formulation remains localized, it maintains high concentrations of both the therapeutic agent and the bioenhancer at the absorption site, increasing the driving force for permeation, whether via passive diffusion or facilitated transport (Ensign et al., 2012). By resisting mucus clearance mechanisms, mucoadhesive systems minimize drug loss that commonly limits the effectiveness of conventional dosage forms (Hua, 2014). Additionally, mucoadhesive systems enable site-specific and controlled drug release, which can reduce dosing frequency and improve patient compliance (Peppas et al., 2000). This feature is particularly important for drugs with narrow absorption windows, poor permeability, or susceptibility to enzymatic degradation. Overall, the mucoadhesive component acts as a strategic platform, anchoring the formulation at the mucosal surface, maintaining local drug and bioenhancer concentrations, and reducing clearance, thereby enhancing bioavailability and therapeutic efficacy.

4.2. Mechanisms of Action

4.2.1. Inhibition of Drug-Metabolizing Enzymes

One of the key mechanisms by which bioenhancers improve drug absorption in mucoadhesive drug delivery systems (MDDS) is through the inhibition of drug-metabolizing enzymes. Many orally or mucosal administered drugs undergo pre-systemic (first-pass) metabolism in the intestinal mucosa and liver, primarily mediated by cytochrome P450 enzymes (CYPs) and UDP-glucuronosyltransferases (UGTs). This metabolism often reduces the active drug reaching systemic circulation, limiting therapeutic efficacy. Bioenhancers help reversibly inhibit these enzymes, allowing more of the active drug to be absorbed without altering its pharmacological effect.

Table 1 Roles and mechanisms of bioenhancers in mucoadhesive drug delivery systems (MDDS)

Mechanism	Description	Examples	Effect on Drug Delivery	References
Inhibition of drug-metabolizing enzymes	Bioenhancers inhibit pre-systemic metabolism, increasing systemic drug levels.	Piperine	Enhances bioavailability of co-administered drugs by inhibiting CYP3A4 and UGT enzymes.	Bhutani et al., 2009
Modulation of drug efflux transporters	Block or modulate transporters like P-glycoprotein (P-gp), preventing drug efflux from epithelial cells.	Piperine, Quercetin, Verapamil	Increases intracellular drug retention and systemic availability.	Challa et al., 2005
Transient opening of epithelial tight junctions	Permeation enhancers temporarily disrupt tight junctions, facilitating paracellular transport of hydrophilic drugs.	Sodium caprate, Bile salts, Chitosan	Enhances paracellular drug transport across mucosal barriers; reversible effect.	Bernkop-Schnürch and Dünnhaupt, 2012 Maher et al., 2019
Solubilization and stabilization of poorly soluble or labile drugs	Enhances solubility and protects drugs from degradation; improves absorption.	Cyclodextrins, SNAC	Improves solubility, protects hydrophobic or labile molecules, and enhances transcellular absorption.	Loftsson and Duchêne, 2007 Buckley et al., 2013

5. Common Bioenhancers Used with Mucoadhesive Formulations

Bioenhancers are natural or synthetic compounds that improve the absorption, bioavailability, and therapeutic efficacy of drugs when co-administered, without exerting significant pharmacological effects at the administered dose (Atal and Bedi, 2010). In mucoadhesive drug delivery systems (MDDS), bioenhancers are critical for overcoming physiological and biochemical barriers such as poor epithelial permeability, enzymatic degradation, rapid mucus clearance, and low solubility (Ensign et al., 2012). By integrating bioenhancers into mucoadhesive formulations, the drug remains localized at the mucosal surface for extended periods, while the bioenhancer facilitates enhanced transport across the epithelial barrier.

Chitosan and its derivatives (e.g., trimethyl chitosan, thiolated chitosan) perform a dual function in mucoadhesive drug delivery systems. First, they act as strong mucoadhesive polymers, adhering to mucosal surfaces and prolonging the residence time of the drug at the absorption site, which helps maintain high local drug concentrations and reduces loss due to mucus turnover (Ensign et al., 2012). Second, they transiently open epithelial tight junctions, facilitating paracellular transport of hydrophilic and macromolecular drugs that normally exhibit low permeability across mucosal barriers. This property makes chitosan particularly effective for delivering peptides, proteins, and other high-molecular-weight compounds, improving bioavailability without causing permanent disruption of epithelial integrity (Maher et al., 2019).

Herbal bioenhancers, including piperine, quercetin, and curcumin, are widely used in mucoadhesive drug delivery systems to improve systemic drug exposure. These compounds primarily function by inhibiting key drug-metabolizing enzymes, such as CYP3A4 and UDP-glucuronosyltransferases (UGTs), which are responsible for the pre-systemic metabolism of many orally administered drugs (Bhutani et al., 2009). In addition, they can modulate efflux transporters, including P-glycoprotein (P-gp), reducing the active pumping of drugs back into the lumen and thereby increasing intracellular drug retention (Challa et al., 2005). By simultaneously targeting metabolism and efflux pathways, these herbal bioenhancers enhance the bioavailability of co-administered drugs, lower the effective therapeutic dose required, and improve pharmacokinetic profiles without exhibiting significant pharmacological activity themselves at the administered dose. Their integration into mucoadhesive formulations further ensures prolonged contact with the mucosal surface, maximizing absorption and therapeutic efficacy.

Bile salts and fatty acids, such as sodium caprate, sodium glycocholate, and oleic acid, are widely used as bioenhancers in mucoadhesive drug delivery systems. These compounds interact with the lipid components of epithelial membranes,

increasing membrane fluidity and permeability, which facilitates transcellular transport of both hydrophilic and lipophilic drugs (Maher et al., 2019). Additionally, they can enhance the solubilization of poorly soluble drugs in the mucosal environment, improving their stability and absorption. When incorporated into mucoadhesive formulations, bile salts and fatty acids prolong the drug's residence time at the absorption site while simultaneously promoting enhanced drug penetration across epithelial barriers, making them particularly effective for delivering drugs with low oral bioavailability, such as peptides, proteins, and lipophilic small molecules

Table 2 Common Bioenhancers Used with Mucoadhesive Formulations

Bioenhancer	Primary Function in MDDS	Examples / Notes	Application Route	References
Chitosan and its derivatives	Adheres to mucosal surfaces and temporarily opens tight junctions → promotes paracellular drug transport	Trimethyl chitosan, thiolated chitosan	Buccal, nasal, gastrointestinal	Maher et al., 2019;
Plant-derived compounds	Reduce metabolism and inhibit efflux pumps → improves systemic absorption	Piperine, quercetin, curcumin	Oral, buccal, nasal	Bhutani et al., 2009; Challa et al., 2005;
Bile salts and fatty acids	Increase membrane permeability and solubilize lipophilic drugs → enhances transcellular uptake	Sodium caprate, sodium glycocholate, oleic acid	Buccal, nasal, intestinal	Maher et al., 2019;
Cyclodextrins	Encapsulate hydrophobic or unstable drugs → improves solubility and protects from degradation	β-cyclodextrin, hydroxypropyl-β-cyclodextrin	Oral, nasal, buccal	Loftsson and Duchêne, 2007; PMID: 17475336
SNAC (Sodium N-[8-(2-hydroxybenzoyl) amino] caprylate)	Facilitates peptide transport across epithelial cells and prevents enzymatic degradation	Used in oral semaglutide formulations	Oral	Buckley et al., 2013;
Chelators and chemical enhancers	Temporarily loosen tight junctions via calcium chelation → enhances paracellular absorption	EDTA, citric acid, salicylates	Buccal, nasal, GI	Maher et al., 2019;

Cyclodextrins, including β-cyclodextrin and its derivatives such as hydroxypropyl-β-cyclodextrin (HP-β-CD), are widely employed as bioenhancers in mucoadhesive drug delivery systems. They function by forming inclusion complexes with hydrophobic or chemically labile drugs, thereby stabilizing the drug molecules in the mucosal environment and protecting them from enzymatic degradation and chemical hydrolysis (Loftsson and Duchêne, 2007). This complexation not only improves the solubility of poorly water-soluble drugs but also enhances their bioavailability by maintaining higher local concentrations at the absorption site. When incorporated into mucoadhesive formulations, cyclodextrins act synergistically with the polymer, prolonging the residence time of the drug at the mucosal surface while facilitating efficient transport across epithelial barriers, making them especially valuable for peptides, proteins, and lipophilic small molecules.

Chelators and chemical permeation enhancers, including EDTA, citric acid, and salicylate derivatives, are commonly used in mucoadhesive drug delivery systems to improve the absorption of hydrophilic macromolecules and poorly permeable drugs. These agents transiently modulate epithelial tight junctions by chelating calcium ions, which are essential for maintaining tight junction integrity, thereby facilitating paracellular transport across mucosal barriers (Maher et al., 2019). When combined with mucoadhesive polymers, chelators, and chemical permeation enhancers, extend the residence time of the drug at the mucosal surface while simultaneously increasing epithelial permeability, resulting in enhanced bioavailability of macromolecules, peptides, and other hydrophilic drugs that typically exhibit

low absorption. Their transient action ensures that tight junctions return to normal integrity after drug absorption, minimizing potential epithelial damage.

5.1. Formulation Strategies for Mucoadhesive Drug Delivery Systems with Bioenhancers

5.1.1. Co-formulation in a single mucoadhesive matrix

Co-formulation in a single mucoadhesive matrix involves blending the active drug and a bioenhancer directly into a mucoadhesive polymer system, such as films, patches, gels, or hydrogels. This approach ensures uniform distribution of the bioenhancer throughout the matrix, enabling sustained local release alongside the drug, while the mucoadhesive polymer prolongs contact with the mucosal surface, maximizing absorption and reducing pre-systemic metabolism (Ensign et al., 2012; Maher et al., 2019). Recent advances over the past seven years have significantly enhanced this strategy. Functionalized polymers, such as thiolated, methacrylated, or acrylated derivatives, have improved mucoadhesion, stability, and controlled drug release, while natural polymers like chitosan, alginate, and cellulose-based matrices have been optimized for biocompatibility and biodegradability, particularly for buccal and oral delivery (MDPI, 2021). Modern formulations increasingly embed nanoparticles or nanomicelles within mucoadhesive matrices, providing targeted transport, controlled release, and localized delivery of both drugs and bioenhancers. For example, mucoadhesive gels containing drug-loaded nanoparticles have demonstrated prolonged retention on mucosal surfaces and improved permeation, particularly for hydrophilic or labile molecules (ScienceDirect, 2020; MDPI, 2021). This co-formulation strategy is versatile, applicable across various mucosal routes including buccal, sublingual, nasal, and gastrointestinal delivery, while also improving patient compliance by offering noninvasive, easy-to-use dosage forms. The integration of bioenhancers within mucoadhesive matrices facilitates paracellular or transcellular transport, inhibits pre-systemic metabolism, modulates efflux transporters, and stabilizes poorly soluble or labile drugs, effectively enhancing systemic bioavailability. Overall, co-formulation of drugs and bioenhancers in mucoadhesive systems represents a robust and evolving platform, capable of delivering small molecules, macromolecules, peptides, and hydrophobic phytochemicals more efficiently and with sustained therapeutic effect.

5.1.2. Layered systems

In layered mucoadhesive systems, the formulation is designed with multiple layers, each performing a distinct role to optimize drug absorption. Typically, the inner layer contains a bioenhancer, which is released first upon contact with the mucosal surface. This layer transiently modulates epithelial tight junctions, inhibits metabolizing enzymes, or blocks efflux transporters, thereby priming the mucosa for enhanced drug uptake. The outer mucoadhesive layer then adheres firmly to the mucosal surface, prolonging residence time and ensuring controlled, localized release of the drug. This sequential design allows sensitive drugs to be protected during the initial phase and to be released under optimized conditions, reducing enzymatic degradation and improving bioavailability. Layered systems are particularly advantageous for macromolecules, peptides, or labile compounds that require precise timing of absorption or activation. Recent advances have integrated nanocarriers, hydrogels, and functionalized polymers into layered designs, improving both mucoadhesion and permeability while enabling more sophisticated control over release kinetics and site-specific delivery. By combining bioenhancer priming with prolonged mucoadhesion, layered systems represent a promising strategy to overcome mucosal barriers and enhance therapeutic efficacy.

5.1.3. Nanoparticles or nanomicelles embedded in mucoadhesive hydrogels

Incorporating drug-loaded nanoparticles or nanomicelles within a mucoadhesive hydrogel represents an advanced strategy for mucosal drug delivery, combining the benefits of nanotechnology with prolonged mucosal residence. In this approach, nanoparticles or nanomicelles serve as protective carriers that shield the drug from enzymatic degradation, chemical instability, or premature clearance, while the hydrogel matrix ensures firm adhesion to the mucosal surface. Bioenhancers can be co-encapsulated within the nanocarriers or dispersed throughout the hydrogel, providing localized enhancement of drug permeation by modulating tight junctions, inhibiting metabolizing enzymes, or blocking efflux transporters. This dual-function system allows for targeted delivery and controlled release, optimizing both the rate and extent of drug absorption. Such formulations are particularly suitable for peptides, proteins, and hydrophobic small molecules, which traditionally face challenges in oral or mucosal delivery due to poor stability and low permeability (Buckley et al., 2013). Recent studies have also explored functionalized nanoparticles, such as chitosan- or lipid-based nanocarriers, integrated into mucoadhesive hydrogels to further enhance mucoadhesion, permeability, and bioavailability, demonstrating promise for next-generation mucosal drug delivery platforms (MDPI, 2022). By combining nanocarrier protection, bioenhancer activity, and prolonged hydrogel residence, this approach provides a versatile and effective system for the delivery of challenging therapeutic molecules.

5.1.4. Mucoadhesive tablets with site-directed erosion

Mucoadhesive tablets with site-directed erosion are specifically engineered to release drugs and bioenhancers at targeted mucosal sites, such as the gastric, intestinal, or buccal mucosa. These systems are formulated with polymers that erode or dissolve in a controlled manner under specific physiological conditions, ensuring that both the drug and the bioenhancer are delivered precisely where absorption is optimal. By maintaining localized high concentrations at the absorption site, these tablets reduce premature drug loss and improve bioavailability. For example, SNAC-type bioenhancers are frequently incorporated into oral peptide formulations to protect labile molecules from enzymatic degradation while promoting transcellular uptake at the site of absorption, thereby enabling oral delivery of otherwise poorly bioavailable peptides like semaglutide (Buckley et al., 2013). Recent advances over the past 5–7 years have focused on combining mucoadhesive polymers with pH-sensitive or enzyme-responsive excipients, allowing more precise site-directed erosion and tunable release profiles. Additionally, researchers have explored multi-layered or hybrid tablet designs that integrate nanoparticles or microcarriers to further protect the drug and optimize release kinetics, making this approach increasingly versatile for challenging molecules such as peptides, proteins, and other labile therapeutics (MDPI, 2022). Overall, site-directed mucoadhesive tablets provide a robust platform for enhancing targeted drug absorption, minimizing systemic degradation, and improving therapeutic outcomes.

5.2. Evaluation Methods

Evaluating mucoadhesive formulations (especially those combining bioenhancers) requires a multi-tiered approach — from in vitro assays to in vivo and clinical studies to ensure effectiveness, safety, and reproducibility. Over the past five years, there have been important methodological refinements and emerging best practices.

5.2.1. In Vitro Methods

In vitro methods remain the first line of evaluation for mucoadhesive formulations. Mucoadhesion tests such as tensile, shear, and peel-strength assays are commonly used to quantify adhesion to mucin or mucus-simulating gels, and recent studies highlight the need for strict control of hydration, mucin type, contact force, and detachment speed to avoid variability across laboratories (Sogias et al., 2019; Wlodarczyk et al., 2022). Beyond bulk adhesion tests, mucin-binding and mucin-penetration assays help determine polymer–mucus interactions at the molecular level, offering insight into diffusion and residence time within the mucus layer (Menchicchi et al., 2021). Epithelial cell permeability models, especially Caco-2 and MDCK monolayers, remain essential for predicting drug transport pathways and evaluating the impact of bioenhancers on tight-junction modulation or efflux inhibition; updated permeability studies increasingly incorporate mucus-coated or co-cultured models to better mimic physiological conditions (Melero et al., 2020). Additionally, enzyme-stability assays are used to evaluate protection of peptides and labile drugs from mucosal enzymes, a key consideration in enhancer-containing systems; recent work uses simulated mucosal fluids and recombinant enzymes to assess formulation-mediated inhibition or shielding effects (Vllasaliu et al., 2020).

5.2.2. Mucoadhesion Testing

Mucoadhesion testing typically involves standard tensile, shear, or peel-strength measurements to quantify the adhesion of formulations to mucin or mucus-simulating gels, and these methods remain the most widely used in early formulation screening. Recent research, however, emphasizes that variations in test conditions—such as mucin source, level of hydration, contact time, substrate type, and temperature—can significantly influence measured adhesion strength, leading to poor interlaboratory reproducibility. To address these issues, several studies have proposed standardized protocols and improved characterization of mucus-like test media to ensure more physiologically relevant and comparable results (Sogias et al., 2019; Włodarczyk et al., 2022; Doppalapudi et al., 2020).

5.2.3. Mucin binding / penetration assays

To more realistically simulate the mucosal barrier in vitro, many recent studies now employ artificial mucus media or reconstituted mucin-based hydrogels, rather than simple mucin solutions, when performing mucin-binding or penetration assays. These mucus-mimicking hydrogels reproduce the viscoelasticity, mesh-like structure, and pore architecture of native mucus, all of which critically influence particle diffusion and transport behavior (Zou et al., 2024). For example, a newly developed synthetic mucus barrier array used a mucin-based hydrogel engineered to mimic in vivo mucus rheology and successfully screened nanoparticle formulations for their ability to penetrate the barrier, showing that smaller, PEG-coated particles exhibited significantly higher penetration efficiency through the gel (Zou et al., 2024). Similarly, studies on mucus-penetrating nanoparticles demonstrated that PEG-grafted or non-ionic surface–modified particles diffused more effectively through reconstituted mucin gels and ex vivo mucosa than strongly mucoadhesive, unmodified particles, emphasizing the importance of realistic mucus models for predicting in vivo transport (Higashi et al., 2019; Yu et al., 2023).

Thus, the use of artificial mucus media or mucin-based hydrogels in binding and penetration assays provides more physiologically relevant insight into how a formulation may behave in vivo, particularly regarding its ability to traverse the mucus barrier and reach the epithelial surface for effective absorption.

5.2.4. Epithelial cell models for permeability

Epithelial cell models are fundamental for evaluating drug permeability in mucoadhesive and bioenhancer-based delivery systems. Traditional Caco-2 and MDCK monolayer models remain widely used because they form tight junctions and provide standardized measurements of transcellular and paracellular transport. However, these simple monolayers do not fully replicate the complexity of the human mucosal barrier. To address this limitation, recent research increasingly utilizes advanced systems such as 3D epithelial cultures, co-culture models (e.g., Caco-2 with mucus-secreting HT29-MTX cells), and tissue-engineered mucosal constructs, which more accurately reproduce mucus secretion, barrier heterogeneity, and physiological tight-junction dynamics (Martínez-Maldonado et al., 2023). Additionally, organ-on-chip platforms, such as gut-on-chip and nasal-on-chip systems, have emerged as powerful tools that incorporate fluid flow, mechanical stimulation, and multi-cellular interactions, enabling a more realistic assessment of drug permeation and enhancer effects under dynamic conditions (Kim et al., 2021; Poças et al., 2020). These advanced models better reproduce in vivo tissue architecture, mucus turnover, and barrier responses, making them significantly more predictive of clinical absorption outcomes than traditional monolayers.

5.2.5. Enzyme-stability assays

Enzyme-stability assays play a crucial role in evaluating peptide- and protein-based mucoadhesive formulations, especially when bioenhancers are incorporated to protect drugs from enzymatic degradation. Traditionally, enzyme-stability studies relied mainly on simple buffer systems containing isolated enzymes such as trypsin, chymotrypsin, or peptidases. However, these conditions often fail to reflect the complex enzymatic environment present on real mucosal surfaces. Recent research increasingly uses mucus, simulated mucus, or mucosal homogenates (e.g., intestinal, nasal, or buccal homogenates) to provide a more physiologically relevant degradation profile (Bhat et al., 2020). These complex matrices contain a broad spectrum of proteases, glycosidases, esterases, and mucin-associated enzymes that more accurately mimic in vivo conditions. Studies on oral peptide delivery systems have shown that including mucus in enzyme-stability assays significantly improves the prediction of in vivo proteolytic susceptibility and allows better assessment of bioenhancer-mediated protection, such as enzyme inhibition or steric shielding effects (Maher et al., 2019; Hwang et al., 2021;). Furthermore, advanced methods such as LC–MS-based degradation profiling and real-time fluorescence assays have been adopted to quantify degradation kinetics with higher sensitivity (Zhang et al., 2022). Overall, using mucus- or mucosa-derived enzyme environments provides a far more realistic evaluation of how well a bioenhancer-containing mucoadhesive system can protect labile drugs during mucosal delivery.

5.2.6. Ex Vivo Methods

Tissue-based permeation studies remain a gold standard for evaluating mucoadhesive and bioenhancer-formulated drug delivery systems. In this approach, excised mucosal tissues such as oral, nasal, intestinal, or vaginal mucosa are mounted in diffusion chambers or Ussing chamber systems under near-physiological conditions to assess drug permeation, retention of mucoadhesion, and the effects of permeation enhancers or bioenhancers. For instance, a viable excised porcine intestine mounted in a Ussing chamber has been shown to predict human in vivo absorption: apparent permeability coefficients measured ex vivo correlated strongly with known human effective permeability values, and the system was able to discriminate regional differences along the gut as well as demonstrate active metabolism (e.g., CYP3A4 activity) and efflux transporter (e.g., P-glycoprotein, P-gp) effects (Arnold YE 2019 Mar 21). Because this ex vivo models preserve the structural and functional complexity of real mucosa including mucus layer, epithelial architecture, enzyme and transporter expression, and tissue viability they remain among the most physiologically relevant preclinical methods before in vivo or clinical testing. They are thus particularly valuable for evaluating whether a mucoadhesive-bioenhancer formulation can (a) adhere to mucus/tissue appropriately, (b) release drug and enhancer in a controlled manner, and (c) facilitate realistic absorption across mucosal barriers.

5.2.7. In Vivo (Animal) Studies

Pharmacokinetics and biodistribution studies after mucosal administration are essential for evaluating the in vivo performance of mucoadhesive formulations combined with bioenhancers. Animal models, particularly rodents, are widely used to assess systemic absorption, bioavailability, and pharmacodynamic outcomes. For example, intranasal mucoadhesive gels loaded with drugs or nanoparticles have been investigated in rats to enhance brain delivery and systemic uptake. The mucoadhesive component prolongs residence time in the nasal cavity, while bioenhancers or permeation enhancers improve epithelial transport, reduce enzymatic degradation, and increase drug absorption. Studies have demonstrated significantly higher brain concentrations and systemic exposure compared to conventional

formulations, highlighting the translational potential of mucoadhesive- bioenhancer systems for targeting difficult-to-reach tissues or improving overall bioavailability (Nair AB2022 May 30; Tanna V, 2024 Sep 5; Singh M. 2025 Jun 11).

Local tolerability and mucosal integrity testing are critical components of evaluating mucoadhesive formulations containing bioenhancers or permeation enhancers. Since agents such as tight-junction modulators and enzyme inhibitors can transiently alter mucosal barrier function, modern studies routinely perform histological analyses of treated mucosal tissues to detect any signs of irritation, inflammation, or structural damage **(**Masoodi Khabar P, 2023 May 2**).** These assessments are particularly important for repeated or chronic dosing regimens, as prolonged exposure may compromise epithelial integrity or trigger immune responses. Common evaluations include hematoxylin–eosin staining, assessment of epithelial thickness, and measurement of inflammatory markers, providing a comprehensive picture of both short- and long-term safety **(**Wu Y2025 Apr 29). Recent research has emphasized combining these histological studies with functional assays, such as transepithelial electrical resistance (TEER) measurements, to correlate structural changes with barrier function and ensure safe formulation design (Masoodi Khabar P2023 May 2**;** Hoson T2023 Sep 26).

5.3. In-situ gelation and mucoadhesion duration in vivo

In situ gelling mucoadhesive systems are designed to undergo sol-to-gel transition upon contact with the mucosal surface, triggered by physiological stimuli such as temperature, pH, or ions. Evaluating these formulations in vivo allows determination of gelation time, mucoadhesive strength, and residence duration, which are critical parameters influencing drug absorption and therapeutic efficacy. For instance, intranasal or buccal in-situ gelling formulations are administered as liquids that rapidly gel upon contact with the mucosa, prolonging retention at the absorption site and minimizing clearance by mucus or saliva. Animal models are typically employed to assess in vivo gelation kinetics, adhesion to mucosal tissues, and duration of residence, often using techniques such as fluorescence labeling, gamma scintigraphy, or pharmacokinetic monitoring of drug absorption. These studies help optimize polymer composition, crosslinking density, and bioenhancer incorporation to maximize local drug concentrations and systemic uptake before clinical translation (Kumar et al., 2021; Patel et al., 2020; Fujihara FMF 2020 Jun 15).

5.4. Clinical / Translational Evaluation

Randomized PK/PD trials for mucoadhesive formulations incorporating bioenhancers that advance to clinical testing, randomized pharmacokinetic (PK) and pharmacodynamic (PD) trials are essential to evaluate human performance. PK studies measure parameters such as absorption rate, maximum plasma concentration (Cmax), area under the curve (AUC), and bioavailability, providing quantitative insight into systemic exposure achieved via mucosal delivery. PD studies assess the therapeutic effect, onset and duration of action, and dose-response relationship, revealing whether the formulation achieves the desired clinical outcome. These trials also evaluate safety endpoints, including mucosal tolerability, irritation, and structural integrity, particularly for systems containing permeation enhancers or enzyme inhibitors. Data from these studies help optimize dosing regimens, confirm translational relevance of preclinical models, and support regulatory approval of mucoadhesive-bioenhancer drug delivery systems (Buckley et al., 2013; Maher et al., 2019; Cousyn L 2018).

Safety endpoints Given the potential risks associated with repeated use of permeation enhancers—including tight junction modulation, local irritation, or enzyme inhibition safety endpoints have become a critical aspect of clinical evaluation for mucoadhesive-bioenhancer systems. Trials increasingly incorporate mucosal integrity assessment through histological examination, biomarker analysis, and imaging to detect epithelial disruption or inflammation. Local tolerability is monitored for signs of erythema, edema, or discomfort at the administration site. Furthermore, long-term safety studies are emphasized, particularly for chronic-use formulations, to ensure that the mucosa fully recovers between doses. Recent reviews and regulatory guidance recommend incorporating mucosal repair studies, confirming that epithelial structure and function return to normal following repeated administration, thereby minimizing risk of cumulative damage and supporting safe translational use (Maher et al., 2019; Ensign et al., 2012).

Patient compliance and acceptability metrics are increasingly recognized as key evaluation parameters for mucoadhesive formulations, particularly for films, gels, or patches. Early clinical studies now systematically assess adhesion time, comfort during wear, ease of application or removal, and sensory characteristics such as taste or texture for oral products. Local irritation or discomfort is monitored to ensure the formulation is well-tolerated over repeated use. These acceptability metrics are critical because even highly effective mucoadhesive-bioenhancer systems can fail in real-world use if patients find them uncomfortable, inconvenient, or unpleasant, thus directly influencing adherence and therapeutic outcomes (Ensign et al., 2012; Maher et al., 2019).

6. Conclusion

Combining mucoadhesive drug delivery systems with bioenhancers provides a multidimensional strategy to overcome key barriers such as poor epithelial permeability, rapid enzymatic degradation, and limited residence time at mucosal surfaces. By prolonging drug–mucosa contact while simultaneously modulating membrane fluidity, tight junctions, or enzymatic activity, these hybrid systems can significantly improve the bioavailability of poorly absorbed therapeutics. Clinical successes including SNAC-enabled oral semaglutide for peptides and piperine-augmented anti-tubercular therapy underscore the translational potential and real-world impact of bioenhancer-mediated formulations. However, broader clinical adoption demands meticulous attention to safety, mechanistic clarity, and rational formulation design. Factors such as mucoadhesive polymer selection, optimal bioenhancer concentration, localized versus systemic effects, and long-term mucosal tolerance must be thoroughly characterized. Rigorous preclinical studies, physiologically relevant in vitro models, and well-controlled clinical trials are essential to validate efficacy, safety, and reproducibility. With continued innovation in polymer engineering, molecular enhancer discovery, and advanced characterization tools, bioenhancer-assisted mucoadhesive delivery systems are poised to emerge as a powerful platform for improving the therapeutic performance of molecules traditionally limited by poor absorption.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclsoed.

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