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Page: 1-15

MUCOADHESION: A PROMISING STRATEGY FOR SITE-SPECIFIC AND TARGETED DRUG DELIVERY

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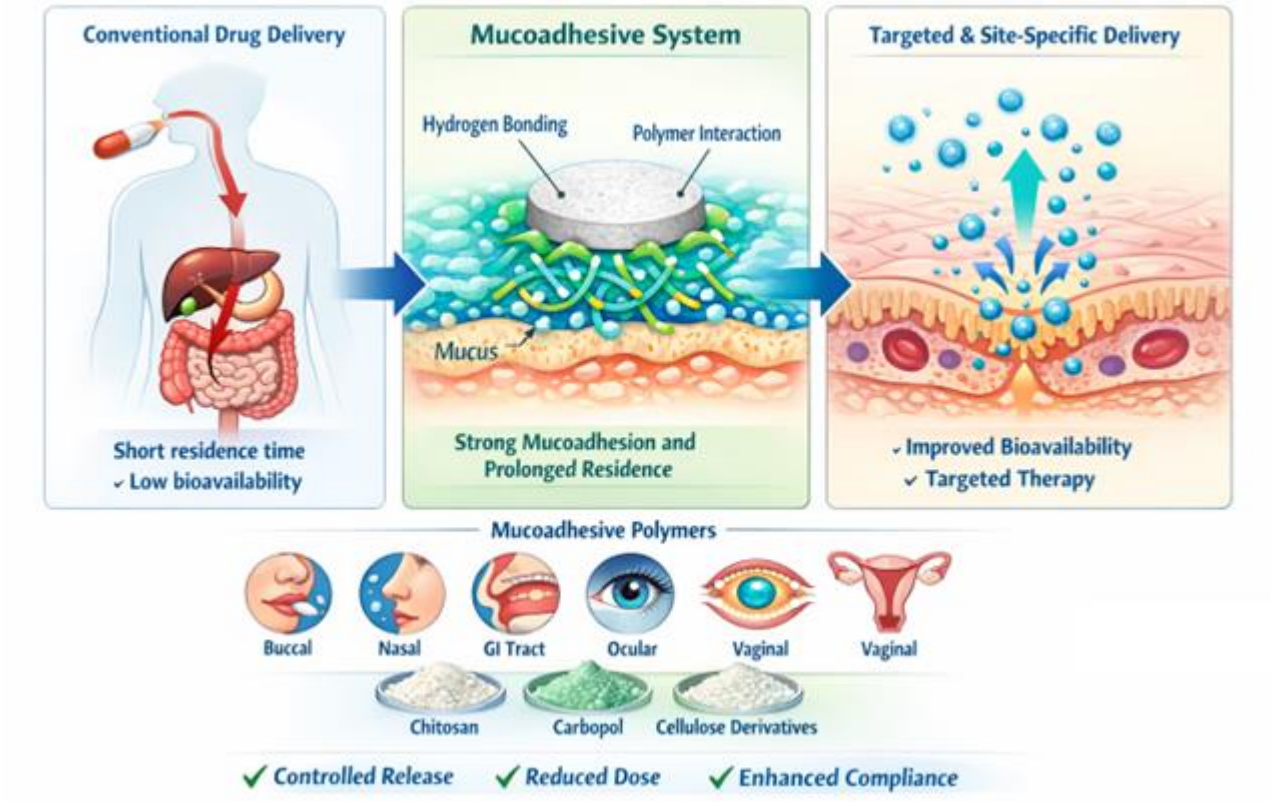
ABSTRACT

Mucoadhesion has emerged as a promising and versatile approach in site-specific and targeted drug delivery, offering significant advantages over conventional dosage forms. Mucoadhesive drug delivery systems are designed to adhere to mucosal surfaces such as the gastrointestinal tract, buccal cavity, nasal mucosa, ocular surface, vaginal, and rectal tissues, thereby prolonging the residence time of the formulation at the site of absorption. This prolonged contact enhances drug localization, improves bioavailability, and enables controlled and sustained drug release while minimizing systemic side effects. The mechanism of mucoadhesion involves complex physicochemical interactions, including hydrogen bonding, electrostatic forces, polymer chain interpenetration, and wetting phenomena between the polymer and mucus layer. Advances in polymer science have led to the development of a wide range of natural, semi-synthetic, and synthetic mucoadhesive polymers, such as chitosan, carbopol, polyvinyl alcohol, and cellulose derivatives, which can be tailored to achieve desired adhesive strength and release profiles. Mucoadhesive systems play a crucial role in targeted drug delivery by bypassing first-pass metabolism, reducing dosing frequency, and improving patient compliance. Furthermore, integration of mucoadhesion with novel drug delivery platforms, including nanoparticles, microspheres, hydrogels, and films, has expanded its application in the delivery of peptides, proteins, vaccines, and anticancer agents. Despite its advantages, challenges such as mucus turnover, variability in mucosal physiology, and formulation stability remain critical considerations. Overall, mucoadhesive drug delivery represents a potential and effective strategy for site-specific and targeted therapy, contributing significantly to improved therapeutic outcomes and the advancement of modern pharmaceutical drug delivery systems.

KEYWORDS: Mucoadhesion; Site-specific drug delivery; Targeted drug delivery; Mucoadhesive polymers; Controlled drug release; Bioavailability enhancement; Mucosal drug delivery

Graphical Abstract



INTRODUCTION

The development of advanced drug delivery systems has gained significant momentum in recent years with the aim of improving therapeutic efficacy, patient compliance, and safety. [1, 2] Conventional dosage forms often suffer from limitations such as poor bioavailability, frequent dosing, and non-specific drug distribution, which may lead to reduced therapeutic outcomes and increased systemic side effects. [3, 4] To overcome these challenges, site-specific and targeted drug delivery approaches have been extensively explored, among which mucoadhesive drug delivery systems (MDDS) have emerged as a promising strategy. [5]

Mucoadhesion refers to the phenomenon in which a drug delivery system adheres to the mucosal surface for a prolonged period through physical and chemical interactions with mucus or epithelial tissues. [6] The concept of mucoadhesion was first introduced to enhance the residence time of dosage forms at the site of absorption, thereby improving drug bioavailability and localized therapeutic action. Mucosal surfaces such as the oral, buccal, nasal, ocular, gastrointestinal, vaginal, and rectal membranes are highly vascularized and offer an attractive route for both local and systemic drug delivery due to their high permeability and avoidance of first-pass hepatic metabolism. [7]

Mucoadhesive systems utilize polymers capable of forming strong interactions with mucin glycoproteins present in the mucus layer. These interactions may involve hydrogen bonding, electrostatic attraction, van der Waals forces, or polymer chain

interpenetration, resulting in prolonged adhesion at the target site. The extended residence time provided by mucoadhesion allows for controlled drug release, enhanced absorption, and improved therapeutic efficiency, particularly for drugs with a narrow absorption window or poor aqueous solubility.[8, 9]

In the context of site-specific and targeted drug delivery, mucoadhesive systems play a crucial role by ensuring localized drug action at the desired site while minimizing systemic exposure. This approach is particularly beneficial in the treatment of chronic diseases, infections, inflammatory conditions, and cancers, where maintaining a high drug concentration at the target site is essential. Additionally, mucoadhesive drug delivery systems can enhance patient compliance by reducing dosing frequency and improving ease of administration. [10, 11]

Recent advances in polymer science and nanotechnology have further expanded the scope of mucoadhesive drug delivery by enabling the development of mucoadhesive nanoparticles, microspheres, films, tablets, and gels. These novel formulations offer improved stability, precise targeting, and better control over drug release profiles. Consequently, mucoadhesion has become an integral component of modern pharmaceutical research focused on designing efficient and patient-friendly targeted drug delivery systems. [12, 13]

Advantages of MDDS

- Increases bioavailability by extending the dosage form's residence time at the absorption site.
- Fast absorption due to a large blood supply and high rate of perfusion
- Decreased frequency of dosing
- An alternative to oral administration in which the drug has been protected from deterioration in the GIT's acidic environment.
- Increased compliance patients. [14, 15]
- **Disadvantages**
- This type of delivery cannot be used to deliver drugs that irritate the oral mucosa, or unpleasant taste, or have an unpleasant odour.
- Drugs with low dosage is the only kind that can be administered.
- Consumption of food and drinking may become restricted.
- In ocular delivery, the formulation might make you feel uneasy or blur your vision.16,17]

MECHANISM OF MUCOADHESION

Mucoadhesion is a complex, multistep process by which a drug delivery system adheres to the mucus layer or epithelial surface of mucosal tissues, resulting in prolonged residence time and controlled drug release at the target site. In gastric drug delivery, mucoadhesive systems adhere to the gastric mucosa, enabling localized drug action, enhanced absorption, and improved therapeutic efficacy, particularly for drugs requiring prolonged gastric retention.

1. Contact Stage (Wetting and Swelling)

The initial step in mucoadhesion involves intimate contact between the mucoadhesive dosage form and the gastric mucosal surface. Upon oral administration, the dosage form reaches the stomach and comes into contact with the mucus layer lining the gastric epithelium. Hydrophilic mucoadhesive polymers such as carbopol, chitosan, hydroxypropyl methylcellulose (HPMC), and poly (acrylic acid) absorb gastric fluid and undergo swelling. This swelling allows the polymer chains to spread and wet the mucus surface, creating favorable conditions for adhesion. [18]

2. Interpenetration and Diffusion Stage

Following wetting, polymer chain interpenetration occurs between the swollen mucoadhesive polymer and mucin glycoprotein chains present in gastric mucus. The degree of interpenetration depends on polymer molecular weight, flexibility, and mucus viscosity. This diffusion-based interaction enhances physical entanglement between the polymer and mucus network, forming a semi-permanent adhesive bond that anchors the drug delivery system to the gastric mucosa. [19]

3. Consolidation Stage (Bond Formation)

The consolidation stage involves the formation of chemical and physical bonds that stabilize mucoadhesion. These include hydrogen bonding, electrostatic interactions, van der Waals forces, and hydrophobic interactions. In the acidic gastric environment, polymers such as chitosan exhibit strong electrostatic attraction toward negatively charged mucin, significantly improving adhesion strength. The formation of these bonds ensures prolonged retention of the formulation at the gastric site despite peristaltic movements. [20]

4. Drug Release and Absorption

Once firmly adhered to the gastric mucosa, the drug is released in a controlled or sustained manner from the mucoadhesive matrix. The close proximity of the delivery system to the mucosal surface maintains a high local drug concentration gradient, enhancing drug permeation through the gastric epithelium. This mechanism is particularly advantageous for drugs with narrow absorption windows, local gastric action (e.g., anti-ulcer agents), or poor intestinal stability. [21]

5. Detachment and Mucus Turnover

Eventually, the mucoadhesive system is removed due to mucus turnover, enzymatic degradation, or gradual erosion of the polymer matrix. However, the residence time achieved is significantly longer than that of conventional dosage forms, resulting in improved bioavailability and therapeutic outcomes. [22]

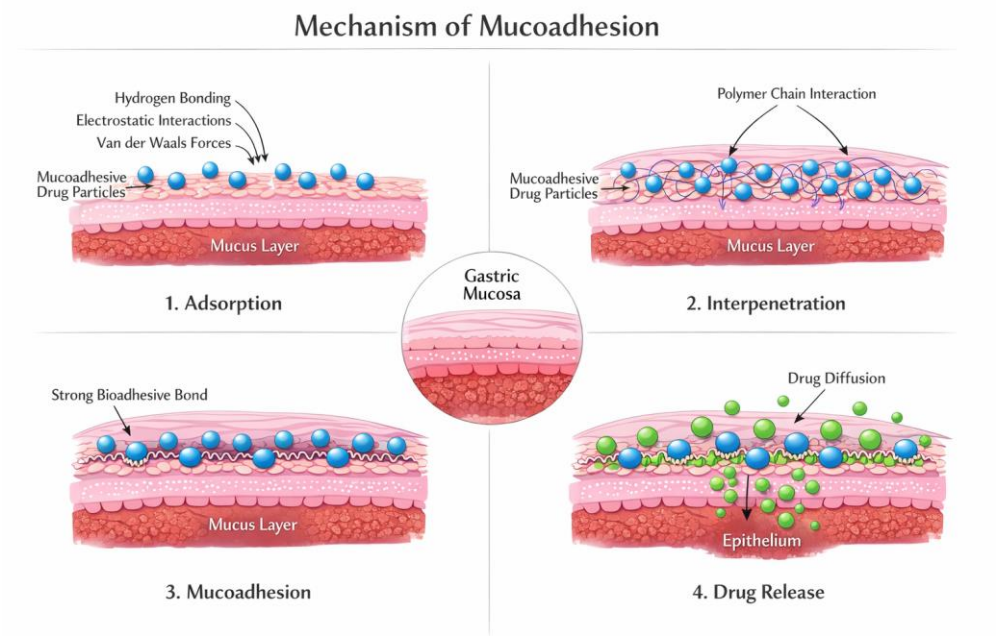


Fig 1: Mechanism of mucoadhesion

THEORIES OF MUCOADHESION

Mucoadhesion is governed by several physicochemical theories that explain the interaction between a mucoadhesive drug delivery system and the mucosal surface. These theories collectively describe the mechanisms responsible for adhesion, retention, and controlled drug release at mucosal sites such as the gastric mucosa.

1. Wetting Theory

The wetting theory is primarily applicable to liquid or semi-solid mucoadhesive systems such as gels, films, and suspensions. According to this theory, mucoadhesion occurs when the formulation spreads efficiently over the mucosal surface, allowing close contact between the polymer and mucus.

The degree of adhesion depends on the contact angle (θ) formed between the dosage form and the mucus surface. A lower contact angle indicates better wetting and stronger mucoadhesion.

Key data concept:

- $\theta \rightarrow 0^\circ \rightarrow$ maximum adhesion
- $\theta > 90^\circ \rightarrow$ poor adhesion

Application

Gastric mucoadhesive gels and floating tablets rely on this theory for initial adhesion. [23]

2. Diffusion Theory

The diffusion theory explains mucoadhesion through interpenetration of polymer chains with mucin glycoproteins. When the mucoadhesive polymer comes into contact with the mucus layer, polymer chains diffuse into the mucus network and form entangled structures.

Critical parameters:

- Polymer molecular weight
- Chain flexibility
- Contact time
- Mucus viscosity

Typical interpenetration depth: ≈ 0.2–0.5 µm (2)

Application

Widely applicable to gastric, buccal, and intestinal mucoadhesive systems using polymers like carbopol and HPMC. [24]

3. Electronic Theory

According to the electronic theory, mucoadhesion occurs due to electron transfer between the mucosal surface and the polymer, resulting in the formation of an electrical double layer at the interface.

This leads to electrostatic attraction between oppositely charged surfaces.

Example:

- Positively charged chitosan
- Negatively charged sialic acid residues of mucin

Application

Highly relevant for gastric mucoadhesion, as chitosan shows strong adhesion in acidic gastric pH. [25]

4. Adsorption Theory

The adsorption theory states that mucoadhesion results from secondary chemical bonding between the polymer and mucus surface after initial contact.

Types of interactions involved:

- Hydrogen bonding
- Van der Waals forces
- Hydrophobic interactions
- Ionic bonding (strongest)

These bonds are strong enough to maintain adhesion but weak enough to allow eventual detachment without tissue damage.

Application

Common in solid dosage forms such as mucoadhesive tablets and microspheres. [26]

5. Mechanical Theory

The mechanical theory describes mucoadhesion as a result of physical entrapment of the polymer into the irregularities of the mucosal surface.

Gastric mucosa contains folds and crevices, allowing polymers to lodge within them and resist removal by peristaltic movements.

Application

Relevant for microspheres, nanoparticles, and rough-surfaced dosage forms. [27]

6. Fracture Theory

Fracture theory focuses on the force required to detach the mucoadhesive system from the mucosal surface. It does not explain molecular interactions but quantifies adhesive strength. [28]

Key parameter:

- Maximum detachment force (N or dyne/cm²)

This theory is widely used in texture analyzer–based mucoadhesion testing.

Application

Important for evaluating gastric retention strength of mucoadhesive tablets.

Table 1: Summary of Theory their mechanism [29]

Theory	Key Mechanism	Major Polymers	Gastric Relevance
Wetting	Surface spreading	HPMC, Carbopol	High
Diffusion	Chain interpenetration	PAA, HPMC	Very high
Electronic	Electrostatic attraction	Chitosan	Excellent
Adsorption	Secondary bonding	Carbopol	High
Mechanical	Physical interlocking	Microspheres	Moderate
Fracture	Detachment force	All polymers	Evaluation tool

Mucoadhesion is complex phenomenon and numerous theories have been proposed to explain the mechanisms. These theories can be broadly categorized into two types (fig 2).

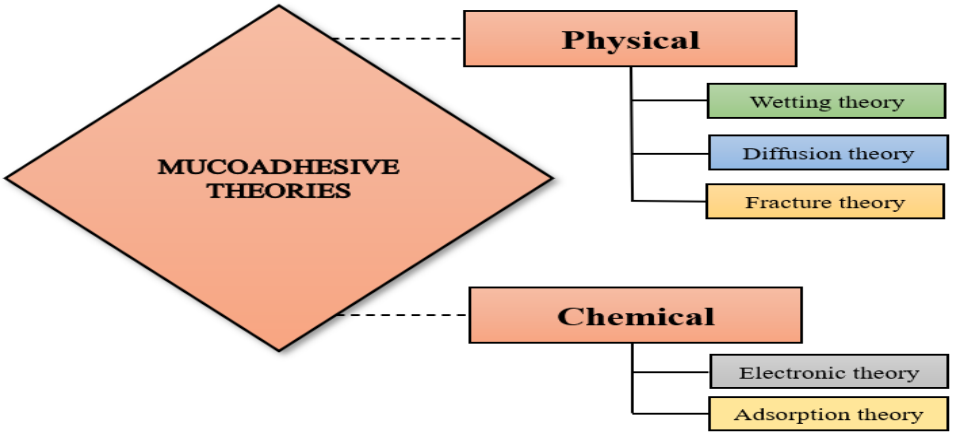


Fig 2: Classification of mucoadhesive theories

MUCOADHESIVE MATERIAL

Mucoadhesive polymers have hydroxyl, carboxyl, amide, and sulphate moieties, among other hydrophilic functional groups. These groups adhere to cell membranes or mucus through several interactions, including electrostatic attractions, hydrophobic interactions, and H-bonding. These hydrophilic substances also cause the polymer to

swell in water, which increases the exposure of adhesive sites for optimal performance. [30]

An ideal polymer (Fig 5) for a MDDS should possess the following attributes. The polymer, along with its degradation products, should be non-toxic and non-absorbable.

- It must not cause irritation upon contact with biological tissues.
- Ideally, it should form strong, non-covalent bonds with mucus or epithelial cell surfaces.
- It should facilitate easy incorporation of the drug while allowing unhindered release.
- Stability over the storage period and throughout the shelf life of the dosage form is crucial; any decomposition should be avoided.

The cost of the polymer should be reasonable to ensure the overall affordability of the prepared dosage form. [31]

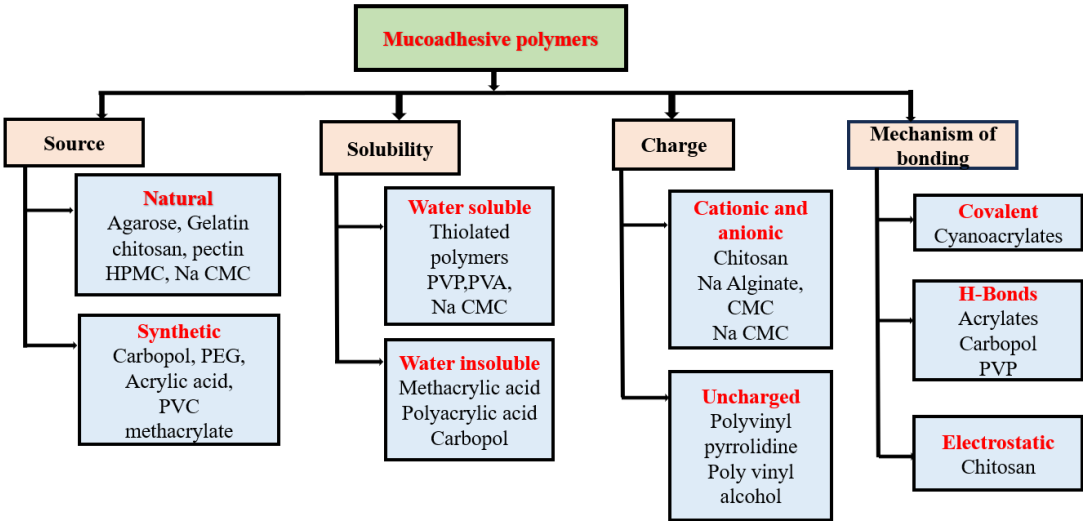


Fig 5: Classification of mucoadhesive polymers

Mucoadhesive drug delivery systems:

MDDSenhance the drug's ability to perform therapeutically by facilitating close contact between the dosage form and the underlying absorption surface thus improving its bioavailability and promoting local or systemic effects at the application or absorption site[18].This approach can be available in different dosage forms like Tablets, Patch, Film, Nanosuspension, Nanoemulsion*In-situ* gel, Microspheres, Insert, Nanocapsules (Table 2).

Table 2: Recent advancements on different MDDS

Route of administration	Dosage form	Drug used	Polymers used	Applications
Buccal	Tablet	Candesartan	Carbopol 934, HPMC	Management of hypertension and heart failure [32]

			K4M, sodium CMC	
	Film	Ondansetron	Gelatin Hpmc Sodiumhyaluronate chitosan	To treat nausea and Vomiting [33]
	Patch	Metoprolol succinate	Chitosan,pvpk 30	Treatmentof hypertension, angina, and heart failure [34]
	Tablet	Aceclofenac	Carbopol 934, HPMC, Na CMC	Relieving pain and inflammation associated with conditions like arthritis and musculoskeletal disorders [35]
	Film	Propranolol Hydrochloride	Polyvinyl alcohol, chitosan and Carbopol	Management of hypertension, angina, arrhythmias, anxiety disorders [36]
Nasal	Nanosuspension	loratadine	Sodium hyaluronate	Relieve symptoms of allergic rhinitis and chronic idiopathic urticaria [37]
	In-situ gel	Almotriptan malate	Carboxymethyl Chitosan	To treat migraines [38]
	Microspheres	Metoclopramide HCL	Chitosan	To treat gastroparesis and gastroesophageal reflux disease (GERD) [39]
	Microspheres	ziprasidone hydrochloride	Chitosan	To treat schizophrenia and bipolar disorder [40]
	Insert	Rivastigmine tartrate	Gelatine, HPMC	To treat Alzheimer's disease and Parkinson's disease [41]
Vaginal	Tablets	Fluconazole	HPMC K15, Carbopol 934	To treat fungal infection [42]
	Tablets	Voriconazole	Chitosan, HPMC k 100	To treat invasive aspergillosis and candidiasis. [43]
	In -situ gel	clotrimazole	HPMC K 100	To treat candidiasis [44]
Ophthalmic	Nano emulsion	Moxifloxacin	HPMCK4M, PVP	To treat bacterial infections such as sinusitis, pneumonia, and skin infections [45]
	Film	Moxifloxacin	Eudragit RL-	Treat bacterial infections such

		and Prednisolone	100 PVA sodium alginate	as sinusitis, pneumonia, and skin infections [46]
	Nanocapsules	Brinzolamide	Pectin, chitosan	To treat glaucoma [47]
	Film	Erythromycin	Eudragit Polyvinyl Alcohol	To treat respiratory and sexually transmitted diseases [48]
	In-Situ gel	Chloramphenicol	poloxamer 407 HPMC	To treat conjunctivitis [49]

Marketed Formulations of MDDS

Marketed formulations represent a significant advancement in drug delivery technology, catering to various therapeutic need for local to systemic applications. Complying with the regulatory guidelines is important for the successful development of commercial formulation. Commercially available mucoadhesive formulations are shown in table 2.

Table 3: Marketed products of MDDS [50, 51]

Drug	**Dosage forms**	**Polymer used**	**Marketed as**	**Manufacture**
Hydrocortisone	Oral mucosal pellets	Acacia gum	Corlan pellets	Celltech
Glyceryl trinitrate	Buccal tablets	HPMC, PVP, Xanthum gum	Suscard	Forest pharmaceuticals
Chlorhexidine di gluconate	Oral mucosal gel	HPMC	Corsodyl gels	Ekr therapeutics
Fentanyl	Film	CMC, HEC	onsolis	Meda pharmaceuticals
Testosterone	Buccal tablet	HPMC, PVP	Striant	Columbia laboratories
Buprenorphine and Naloxine	film	CMC, HEC	Suboxone	Reckitt Benckiser pharmaceuticals
Triamcinolone acetonide	Tablet	HPC, Carbopol 934	Ledercort	Pfizer

CONCLUSION

Mucoadhesion has emerged as a highly promising strategy for site-specific and targeted drug delivery, particularly for mucosal tissues such as the gastric mucosa. By enabling prolonged residence time at the site of administration, mucoadhesive drug delivery systems significantly enhance drug bioavailability, therapeutic efficacy, and patient compliance while minimizing systemic side effects. The ability of mucoadhesive polymers to interact with mucin through physical, chemical, and electrostatic mechanisms forms the foundation of this targeted approach.

The various theories of mucoadhesion—including wetting, diffusion, electronic, adsorption, mechanical, and fracture theories—collectively explain the complex interactions governing adhesion and retention on mucosal surfaces. Each theory contributes to understanding specific aspects of mucoadhesive behavior, from initial contact and polymer chain interpenetration to bond formation and detachment strength. In gastric drug delivery, these mechanisms are particularly advantageous due to the acidic environment, continuous mucus turnover, and peristaltic movements that typically limit drug retention.

Advances in polymer science and formulation technologies have further expanded the scope of mucoadhesive systems through the development of mucoadhesive tablets, microspheres, nanoparticles, gels, and films. The integration of mucoadhesion with novel drug carriers, such as nanotechnology-based systems, offers enhanced control over drug release profiles and improved targeting efficiency. Despite these advantages, challenges such as mucus turnover, variability in mucosal physiology, and long-term safety of polymers must be addressed through continued research.

Overall, mucoadhesion represents a robust and versatile platform for site-specific and targeted drug delivery. Continued advancements in material design, mechanistic understanding, and in vivo evaluation are expected to further optimize mucoadhesive systems and expand their clinical applications in the management of gastric and other mucosal disorders.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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