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Review Article

Advances in Mucoadhesive Oral Drug Delivery: Mechanisms, Polymers, and Therapeutic Applications

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ABSTRACT

Mucoadhesive buccal drug delivery systems have emerged as a promising alternative to traditional routes of administration due to their ability to provide controlled drug release, improved bioavailability, and enhanced patient compliance. This review explores the fundamental principles, mechanisms, and theories underlying mucoadhesion, emphasizing its application in buccal drug delivery. The anatomy and physiology of the oral mucosa are discussed in relation to permeability and drug absorption, highlighting the significance of the mucosal environment and the role of mucin. A detailed evaluation of bio adhesive polymers and formulation strategies is provided, along with an overview of permeation enhancers used to improve mucosal drug transport. The advantages of this delivery route—such as avoidance of hepatic first-pass metabolism and ease of administration—are critically assessed. The review also identifies challenges associated with buccal systems, including formulation stability and limited surface area for absorption. By integrating current research and formulation approaches, this paper offers a comprehensive understanding of buccal mucoadhesive drug delivery systems and their potential in achieving effective therapeutic outcomes.

INTRODUCTION

Introduction to Bioadhesion and Mucoadhesion

Bioadhesion refers to the ability of a material—typically a natural or synthetic polymer—to adhere to a biological surface. This interaction may occur between two biological tissues or between a biological surface and a synthetic material. In the context of drug delivery, bioadhesion facilitates the retention of dosage forms at the site of application, enhancing therapeutic outcomes and patient compliance. A more specific form of bioadhesion is mucoadhesion, which involves adhesion to mucosal surfaces that are lined with a mucus layer. Mucoadhesion is defined as the

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prolonged interaction between a polymeric drug carrier and the mucin layer covering mucosal epithelia, maintained by physical and chemical interfacial forces such as hydrogen bonding, van der Waals forces, and electrostatic interactions (1,2). It typically occurs in two stages: the initial contact stage, involving polymer wetting and swelling, followed by the consolidation stage, where interpenetration and entanglement of polymer chains with mucin glycoproteins strengthen the adhesive bond (2,3). Mucoadhesive drug delivery systems (MDDS) are particularly advantageous for transmucosal routes such as buccal, sublingual, nasal, vaginal, and rectal administration. These systems can bypass hepatic first-pass metabolism, improve local and systemic bioavailability, and provide sustained or controlled drug release at the site of application (3,4). The selection of suitable mucoadhesive polymers is crucial for system performance. Commonly used materials include carbomers, polyacrylic acid derivatives, chitosan, sodium alginate, hydroxypropyl methylcellulose (HPMC), and other cellulose-based derivatives, all of which have demonstrated effective interaction with mucus glycoproteins (4,5). Advanced formulation approaches such as mucoadhesive hydrogels, films, microspheres, and nanoparticles have significantly improved the efficiency and versatility of mucoadhesive systems in recent years 5.

Mechanism of Mucoadhesion

Mucoadhesion refers to the process by which a drug delivery system, typically combined with a polymeric carrier, adheres to the mucosal surface, thereby enhancing drug residence time and absorption. This is a multifaceted process that involves several sequential steps, primarily categorized into two main phases: the **contact phase** and the **consolidation phase**.

During the initial contact phase, the mucoadhesive polymer comes into close proximity with the mucosal surface. This often involves wetting and swelling of the polymer, which increases its surface area and allows it to establish intimate contact with the mucus layer 6,7. The presence of biological fluids facilitates this process by promoting polymer hydration and spreading over the mucosal surface. The consolidation phase follows, in which polymer chains begin to interpenetrate with the glycoprotein chains of mucin. This interpenetration forms a semi-permanent adhesive bond primarily due to the entanglement of macromolecules and the establishment of non-covalent interactions such as hydrogen bonding, van der Waals forces, and electrostatic attractions (7,8). These forces work synergistically to stabilize the mucoadhesive interaction and extend the residence time of the dosage form at the site of absorption. Typically, mucosal residence times are short—often less than one hour. However, incorporating mucoadhesive polymers into a formulation can significantly enhance localization and prolong contact duration, thereby improving drug absorption and therapeutic efficacy (9). While the exact molecular mechanism of mucoadhesion remains an area of ongoing investigation, the widely accepted theory involves two sequential steps:

(1) formation of intimate contact and hydration of the polymer, and

(2) interpenetration and physical entanglement with mucin chains (8,10).

The strength and duration of mucoadhesion depend on several factors, including polymer structure, molecular weight, degree of cross-linking, and environmental conditions such as pH and ionic strength.

Theories of Mucoadhesion

Various theories have been proposed to explain the mechanisms by which mucoadhesion occurs between a polymeric drug carrier and the mucosal surface. Each theory highlights a different aspect of the adhesion process, ranging from molecular interactions to mechanical properties. The major theories include:

Wettability Theory,

Electronic Theory,

Fracture Theory,

Adsorption Theory,

and Diffusion Theory (11).

Wettability theory

The ability of bioadhesive or mucus to spread and develop intimate contact with its corresponding substrate is an important factor in bond formation. The wetting theory was developed predominantly in regard to liquid adhesives, uses interfacial tensions to predict spreading and in turn adhesion (12).The study of surface energy of polymers and tissues to predict mucoadhesive performance has been given considerable attention (13).

The contact angle (Q) which should ideally be zero for adequate spreading is related to interfacial tensions (g) as per the Youngs equation,

$$g\,tg = g\,bt + gbg \cos Q$$

Where the subscripts t,g and b represent tissue, gastrointestinal contents and bioadhesive polymer respectively, for spontaneous wetting to occur (14-15)

$$gtb \geq gbt + gbg$$

the spreading coefficient, Sb/t can be given by,

$$Sb/t = gtg - gbt - gbg$$

For the bioadhesion to take place the spreading coefficient must be positive, hence it is advantageous to maximize the interfacial tension at the tissue-GI contents interface and minimizing the surface tension at the other two interfaces. The interfacial tension can be measured by methods like the Wilhelmy plate method(16-17). It has been shown that the BG-tissue interfacial tension can be calculated as,

$$g\,bt = gb + gt - 2F(gbgt)1/2$$

Where the values of F (interaction parameter) can be found in published papers (18-19) thus by the wetting theory it is possible to calculate spreading coefficients for various bioadhesives over biological tissues and predict the intensity of the bioadhesive bond.

Electronic theory

The electronic theory depends on the assumption that the bioadhesive material and the target biological material have different electronic surface characteristics. Based on this, when two surfaces come in contact with each other, electron transfer occurs in an attempt to balance the Fermi levels, resulting in the formation of a double layer of electrical charge at the interface of the bioadhesive and the biologic surface. The bioadhesive force is believed to be present due to the attractive forces across this double layer (20).

Fracture theory

This is by-far the most accepted theory on bioadhesion. It explains the forces required to separate the two surfaces after adhesion has taken place. It measures the maximum Tensile stress(sm) produced during detachment as follows (21)

$$s\ m = Fm/Ao$$

Where Fm and Ao represent the maximum force of detachment and the total surface area respectively. In a uniform single-component system, fracture strength (sf), which is equal to the maximum stress of detachment(sm), is proportional to the fracture energy (gc), Youngs modulus of elasticity (E) and the critical crack length (c) of the fracture site as follows (19),

$$s\ f = (gcE/c)1/2$$

fracture energy can be obtained by the sum of the reversible work of adhesion, Wr (work done to produce new fracture surfaces) and the irreversible work of adhesion, Wi (work of plastic deformation),

$$g\ c = Wr + Wi$$

Adsorption theory

This theory states that the bioadhesive bond formed between an adhesive substrate and the tissue is due to the weak van der waals forces and hydrogen bond formation. It is one of the most widely accepted theories of bioadhesion (20).

Diffusion theory

The concept of the interpenetration and entanglement ob the bioadhesive polymer chains and mucous polymer chains is supported by the diffusion theory. The bond strength increases with the increase in the degree of the penetration. This penetration is dependent on the concentration gradients and the diffusion coefficients. It is believed that interpenetration in the range of 0.2-0.5µm is required to produce effective bond strength. The penetration depth (l) can be estimated by (22),

$$l = (tDb)1/2$$

where t is the time of contact and Db is the diffusion coefficient of the bio adhesive material in the mucus.

Advantages of Oral Mucoadhesive Drug Delivery

1. **Prolonged Residence Time**

Mucoadhesive systems remain attached to the mucosal surface for extended periods, enhancing drug contact with the absorption site and enabling sustained release (23).

2. **Enhanced Drug Absorption and Efficacy**

The increased residence time leads to improved drug absorption and overall therapeutic efficacy due to more consistent drug levels at the target site (24).

3. **Rapid Absorption Due to Rich Vascularization**

The buccal mucosa is highly vascularized, allowing drugs to be quickly absorbed into the systemic circulation, resulting in faster onset of action (25).

4. **Avoidance of First-Pass Metabolism**

Drugs administered through the oral mucosa bypass hepatic first-pass metabolism, increasing bioavailability and reducing dose-related side effects (26).

5. **Protection from Gastrointestinal Degradation**

Mucoadhesive delivery protects drugs from enzymatic degradation and the acidic pH of the gastrointestinal tract, which is particularly beneficial for acid-labile drugs (27).

6. **Improved Patient Compliance**

These dosage forms are non-invasive, easy to administer, and generally painless, enhancing patient compliance—especially among children and the elderly (28).

Oral Mucosa and Mucin

Oral Mucosa

The buccal region within the oral cavity presents a promising route for systemic drug delivery due to its rich vascularization and relatively high permeability (29).

Oral Histology

The oral mucosa consists of multiple layers: an outermost layer of stratified squamous epithelium, a basement membrane, a lamina propria, and the submucosa. The epithelium, like that found elsewhere in the body, has a basal cell layer with mitotic activity and differentiates through intermediate layers to the superficial layer, from which cells are sloughed off. The buccal epithelium is approximately 40-50 cells thick, while other areas like the sublingual epithelium are thinner. The turnover time for the buccal epithelium is around 5-6 days, which is typical for the oral mucosa (30).

1. **Keratinization and Mucosal Composition** The thickness of the mucosa varies across the oral cavity, with the buccal mucosa measuring 500-800 µm. Areas like the gingivae and hard palate have keratinized epithelia, while non-keratinized epithelia are found in the soft palate, sublingual region, and buccal mucosa. Non-keratinized epithelia are more permeable to water compared to their keratinized counterparts (31).

Permeability

The permeability of oral mucosae varies by region, with the buccal mucosa being considerably more permeable than skin. The permeability of the mucosa follows the pattern: sublingual > buccal > palatal, depending on the thickness and keratinization of the tissues. The permeability barrier is primarily located in the outer 200 µm of the epithelium, where intercellular material derived from membrane coating granules (MCG) provides resistance to permeation. The basement membrane may also contribute to resistance, but the superficial epithelial layers are considered the main barrier to drug penetration (32).

List of Compounds Used as Oral Mucosal Permeation Enhancers(33)

1. 23-lauryl ether
2. Aprotinin
3. Azone
4. Benzalkonium chloride
5. Cetylpyridinium chloride
6. Cetyltrimethylammonium bromide
7. Cyclodextrin
8. Dextran sulfate
9. Lauric acid
10. Lauric acid/Propylene glycol
11. Lysophosphatidylcholine
12. Menthol
13. Methoxysalicylate
14. Methyloleate
15. Oleic acid
16. Phosphatidylcholine
17. Polyoxyethylene
18. Polysorbate 80
19. Sodium EDTA
20. Sodium salicylate
21. Sodium taurodeoxycholate
22. Sulfoxides

Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principal components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association, or some may be attached to certain regions on the cell surfaces. This matrix may play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another (34). Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems (35). In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus-secreting cells like the goblet cells. However, in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva (36). Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands. At physiological pH, the mucus network carries a negative charge (due to the sialic acid and sulfate residues), which may play a role in mucoadhesion. At this pH, mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and chemicals. It allows for the continuous mineralization of tooth enamel after eruption and helps in the remineralization of the enamel in the early stages of dental caries (37). Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate, which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation (38). The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase, leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 liters, and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water-rich environment of the oral cavity.

Buccal Routes of Drug Absorption

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility in this environment. The cell membrane, however, is rather lipophilic in nature, and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to the permeation of lipophilic compounds, and the cell membrane acts as the major transport barrier for hydrophilic compounds (39).

Buccal Mucosa as a Site for Drug Delivery

Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for an oral transmucosal delivery system. The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva, making it difficult for device placement. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action, making it appropriate for drugs with short delivery period requirements and infrequent dosing regimens. Due to two important differences between the sublingual mucosa and the buccal mucosa, the latter is a more preferred route

for systemic transmucosal drug delivery (40, 41). First, the permeability characteristics of the region: the buccal mucosa is less permeable and is thus not able to give a rapid onset of absorption (i.e., more suitable for a sustained release formulation). Second, the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa, which makes it a more desirable region for retentive systems used for oral transmucosal drug delivery. Thus, the buccal mucosa is better suited for sustained delivery applications, delivery of less permeable molecules, and perhaps peptide drugs. Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well. One of the major disadvantages associated with buccal drug delivery is the low flux, which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration enhancers to increase the flux of drugs through the mucosa (42).

Permeation Enhancers

Since the buccal epithelium is similar in structure to other stratified epithelia of the body, enhancers used to improve drug permeation in other absorptive mucosae have been shown to work in improving buccal drug penetration (43). Drugs investigated for buccal delivery using various permeation/absorption enhancers range in both molecular weight and physicochemical properties. Small molecules such as butyric acid and butanol (44), ionizable low molecular weight drugs such as acyclovir, propranolol, and salicylic acid, large molecular weight hydrophilic polymers such as dextrans, and a variety of peptides including octreotide, luteinizing hormone-releasing hormone (LHRH), insulin, and interferon have all been studied. A series of studies (45) on buccal permeation of buserelin and fluorescein isothiocyanate (FITC)-labelled dextrans reported the enhancing effects of di- and tri-hydroxy bile salts on buccal penetration. Their results showed that in the presence of the bile salts, the permeability of porcine buccal mucosa to FITC increased by a 100-200 fold compared to FITC alone. The mechanism of penetration enhancement of FITC-labelled dextrans by sodium glycocholate (SGC) was shown to be concentration-dependent (46). Below 10 mM SGC, buccal permeation was increased by increasing the intercellular transport, and at 10 mM and higher concentrations by opening up a transcellular route. Gandhi and Robinson (47) investigated the mechanisms of penetration enhancement of transbuccal delivery of salicylic acid. They used sodium deoxycholate and sodium lauryl sulfate as penetration enhancers, both of which were found to increase the permeability of salicylic acid across rabbit buccal mucosa. Their results also supported that the superficial layers and protein domain of the epithelium may be responsible for maintaining the barrier function of the buccal mucosa.

Mucin

Mucin is a family of high molecular weight, heavily glycosylated proteins produced by many epithelial tissues. Some mucins remain membrane-bound, while others are secreted to the mucosal surface or as part of saliva (48).

Structure

Mucins are composed of two regions: the amino acid and carbonyl terminal regions, which are rich in cysteine, and a large central region composed of 10-80 residue sequences made up of serine or threonine (48).

Secretion

Mucin is secreted upon stimulation of MARCKS (myristylated alanine-rich C kinase substrate), which coordinates the secretion from vesicles

within the epithelial cells. The fusion of the vesicles with the plasma membrane causes the release of mucin, a viscoelastic product that combines with other secretions to form mucus (48).

Role of Mucus

The surface epithelium of the stomach and intestines is exposed to highly acidic concentrations of HCl and proteolytic enzymes like pepsin. Despite this, it retains its integrity due to the mucus secreted by goblet cells located in the stomach, duodenum, and transverse colon. This mucus contains mucin, an oligosaccharide with terminal sialic acid (pKa = 2.6), which neutralizes HCl and withstands the effect of pepsin. These surface adhesive properties of mucin are being utilized in the development of mucoadhesive drug delivery systems.

Mechanism

Drugs coated with a mucoadhesive polymer bind to the mucus and hence are retained on the surface epithelium for an extended duration. The drug molecules are continuously released from the polymer over an extended period.

Polymers Used for Mucoadhesive Drug Delivery (49)

The rheology of mucoadhesion is a typical topic and it deals with several forces, factors of the components, the state of the material, and its derived properties. Based on the rheological aspects, we can categorize mucoadhesive polymers into two broad categories: materials that undergo matrix formation or hydrogel formation by either a water-swellable material or a water-soluble material. Mucoadhesive drug delivery systems are based on the adhesion of a drug or carrier to the mucous membrane. To promote this adherence, a suitable carrier is required. These carriers, typically polymers, are classified as follows:

Hydrophilic Polymers

These contain carboxylic groups and possess excellent mucoadhesive properties. Examples include PVP (polyvinylpyrrolidone), MC (methyl cellulose), SCMC (sodium carboxymethyl cellulose), and HPC (hydroxypropyl cellulose) (49).

Hydrogels

Hydrophilic polymers swell when in contact with water and adhere to the mucus membrane. These are further classified according to their charge:

- **Anionic Polymers**: Carbopol, polyacrylates
- **Cationic Polymers**: Chitosan
- **Neutral/Non-Ionic Polymers**: Eudragit analogues (50)

These can also be classified as:

- **Synthetic Polymers**: Cellulose derivatives, carbopols, etc.
- **Natural Polymers**: Tragacanth, pectin, gelatin, sodium alginate, acacia (50).

Ideal Mucoadhesive Polymer Characteristics

A mucoadhesion-promoting agent or polymer is added to the formulation to help adhere the active pharmaceutical ingredient to the oral mucosa. This agent can have additional properties, such as swelling, to promote disintegration when in contact with saliva. As various physical and chemical factors affect polymer/mucus adhesion, the polymer should be carefully selected based on the following properties:

1. The polymer must have a high molecular weight, up to 100,000 or more. This is necessary to promote adhesiveness between the polymer and mucus (51).

2. Long chain polymers—chain length must be long enough to promote interpenetration but not too long that diffusion becomes a problem (52).

3. High viscosity.

4. Degree of cross-linking: It influences chain mobility and resistance to dissolution. Highly cross-linked polymers swell in the presence of water and retain their structure, which favors controlled release of the drug and increases polymer/mucus interpenetration. However, as cross-linking increases, chain mobility decreases, which reduces mucoadhesive strength (52).

5. Spatial conformation.

6. Flexibility of polymer chains: This promotes the interpenetration of the polymer within the mucus network (53).

7. Concentration of the polymer: An optimum concentration is required to promote mucoadhesive strength. For solid dosage forms, the adhesive strength increases with the increase in polymer concentration. However, in the case of semi-solid dosage forms, an optimum concentration is essential beyond which the adhesive strength decreases (54).

8. Charge and degree of ionization: The effect of polymer charge on mucoadhesion was clearly shown by Bernkop-Schnurch and Freudl. In this work, various chemical entities were attached to chitosan, and the mucoadhesive strength was evaluated. Cationic chitosan HCl showed marked adhesiveness compared to the control. The attachment of EDTA, an anionic group, significantly increased the mucoadhesive strength. DTPA/chitosan systems exhibited lower mucoadhesive strength than cationic chitosan and anionic EDTA chitosan complexes due to a lower charge. Thus, the mucoadhesive strength can be attributed as: anion > cation > nonionic (55).

9. Optimum hydration: Excessive hydration leads to decreased mucoadhesive strength due to the formation of a slippery mucilage (56).

10. Optimum pH: Mucoadhesion is optimum at low pH conditions, but at higher pH values, a change in conformation occurs into a rod-like structure, making those more available for inter-diffusion and interpenetration. At very elevated pH values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces (57).

11. High applied strength and initial contact time.

Polymers used for oral mucoadhesive drug delivery (69-74)

PAA derivatives carbomer- carbopol 934 noveon-polycarbophil These are polymers of acrylic acid cross linked with polyalkenyl ethers or divinyl glycol. They are produced from primary polymer particles of about 0.2 - 0.6 micron diameter. Each primary particle exists as a network structure of polymer cahains interconnected by cross links. Carbopol polymers along with pemulen and noveon polymers are all cross linked. They swell in water upto 1000 times their original volume to form a gel when exposed to a pH of 4.0 to 6.0. The glass transition temperature is about 105c. Due to presence of carboxylate group and a pka of 6.0 to 0.5, repulsion between the negative charges occurs

leading to increased swelling and hence increased mucoadhesive strength of the polymer. Today, a large number of companies are using carbopol polymers because of the following merits

- Good tabletting formulation flowability. –
- Long drug release profiles
-Can give drug releases profiles similar to carbopol 971oNF, with better handling characterstics.
- Are safe and effective for oral administration
- Arebioadhesive bioavailability - and providing increased
-Are approved by many pf the world pharmacopoeias
- Protect protien and peptides from degradation and hence increase the bioavailability of proteins or peptide based formulations

Related research on mucoadhesive polymers and delivery systems

Bioadhesive Polymer(s) Studied and its Investigation Objectives

HPC and CP

Preferred mucoadhesive strength on CP, HPC, and HPC-CP combination.

1. HPC and CP

Measured bioadhesive property using a mouse peritoneal membrane.

3. CP, HPC, PVP, CMC

Studied interpolymer complexation and its effects on bioadhesive strength.

4. CP and HPMC

Formulation and evaluation of buccoadhesive controlled-release delivery systems.

5. HPC, HEC, PVP, and PVA

Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer.

7. HPC and CP

Used HPC-CP powder mixture as peripheral base for strong adhesion and HPC-CP freeze-dried mixture as core base.

7. CP, PIP, and PIB

Used a two-roll milling method to prepare a new bioadhesive patch formulation.

8. Xanthan gum and Locust bean gum

Hydrogel formation by combination of natural gums.

9. Chitosan, HPC, CMC, Pectin, Xanthan gum, and Polycarbophil

Evaluate mucoadhesive properties by routinely measuring the detachment force from pig intestinal mucosa.

10. Hyaluronic acid benzyl esters, Polycarbophil, and HPMC

Evaluate mucoadhesive properties.

11. Hydroxyethyl cellulose

Design and synthesis of a bilayer patch (polytef-disk) for thyroid gland diagnosis.

12. Polycarbophil

Design of a unidirectional buccal patch for oral mucosal delivery of peptide drugs.

13. Poly (acrylic acid) and Poly (methacrylic acid)

Synthesized and evaluated crosslinked polymers differing in charge densities and hydrophobicity.

14. Number of Polymers including HPC, HPMC, CP, CMC

Measurement of bioadhesive potential and mechanical deformation on the structural requirement for bioadhesion.

15. Poly (acrylic acid-co-acrylamide)

Adhesion strength to the gastric mucus layer as a function of crosslinking agent, degree of swelling, and carboxyl group density.

16. Poly (acrylic acid)

Effects of PAA molecular weight and crosslinking concentration on swelling and drug release characteristics.

17. Poly (acrylic acid-co-methyl methacrylate) Effects of polymer structural features on mucoadhesion.

18. HEMA copolymerized with Polymeg® (polytetramethylene glycol)

Bioadhesive buccal hydrogel for controlled release delivery of buprenorphine.

19. Poly (acrylic acid-co-butylacrylate)

Relationships between structure and adhesion for mucoadhesive polymers.

20. CMC, Carbopol 974P, Carbopol EX-55, Pectin (low viscosity), Chitosan chloride Mucoadhesive gels for intraoral delivery.

21. CMC, CP, Polyethylene oxide, Polymethylvinylether/Maleic anhydride (PME/MA), and Tragacanth

Buccal mucoadhesive device for controlled release anticandidal device – CMC tablets yielded the highest adhesive force.

23. HPMC and Polycarbophil (PC)

Buccal mucoadhesive tablets with optimum blend ratio of 80:20 PC to HPMC yielding the highest force of adhesion.

23. PVP, Poly (acrylic acid)

Transmucosal controlled delivery of isosorbide dinitrate.

24. Poly (acrylic acid-co-poly ethyleneglycol) copolymer of acrylic acid and poly ethyleneglycol monomethyl ether monomethacrylate

To enhance the mucoadhesive properties of PAA for buccal mucoadhesive drug delivery.

25. Polyacrylic acid and Polyethylene glycol

To enhance mucoadhesive properties of PAA by interpolymer complexation through template polymerization.

26. Drum dried waxy maize starch (DDWM), Carbopol 974P, and sodium stearyl fumarate Bioadhesive erodible buccal tablet for progesterone delivery.

Chitosan

Chitosan is a cationic polysaccharide polymer derived from the deacetylation of chitin. It is gaining popularity in mucoadhesive drug delivery systems due to its excellent biocompatibility, biodegradability, and non-toxic properties. Chitosan adheres to the mucosal surface through ionic bonds between its amino groups and the carboxyl residues of salicylic acid. Its linear structure contributes to its flexibility, which

enhances mucoadhesion. Chitosan and its metabolized derivatives are quickly cleared by the kidneys [58].

Newer Second-Generation Polymers

Second-generation mucoadhesive polymers have several advantages:

- Site-specific drug delivery (also referred to as cytoadhesives).
- Minimal effect by mucus turnover rates.
- Improved controlled drug release capabilities [59].

Lectins

Lectins are naturally occurring proteins with carbohydrate-binding properties. These proteins bind reversibly to specific carbohydrate residues on the cell surface. Upon binding, lectins may either remain on the surface or be internalized via endocytosis, enabling targeted and controlled drug delivery. However, one major limitation of lectins is their immunogenic nature [60].

Thiolated Polymers

Thiolated polymers (thiomers) are derived from hydrophilic polymers such as polyacrylates, chitosan, or deacetylated gellan gum. The presence of a thiol group enhances mucoadhesion by forming covalent bonds with cysteine residues in mucus. This bonding also increases the rigidity and cross-linking of the polymer, potentially altering the release mechanism of drugs. Examples include chitosan-iminothiolane, PAA-homocystiene, and alginate-cysteine complexes [61].

Polyox WSR

Polyox WSR (water-soluble polyethylene oxide) is a class of high molecular weight polymers with hydrophilic properties. These polymers are biocompatible, non-toxic, and capable of hydrogen bonding. They are useful in the formulation of a variety of dosage forms, including tablets, films, gels, microcapsules, and syrups [62].

Novel Polymers

- Tomato lectin has shown binding selectivity to small intestine epithelium.
- Shojaei and Li developed a copolymer of PAA and PEG monoethylether mono-methacrylate (PAA-co-PEG) for optimized buccal adhesion.
- Lele et al. investigated PAA-PEGylated drug conjugates for novel mucoadhesive applications.
- Corplex, a class of hydrophilic pressure-sensitive adhesives (PSA), has been developed by Corium Technologies. These adhesives are formed via non-covalent hydrogen bonding between a film-forming hydrophilic polymer and a short-chain plasticizer with reactive OH groups [63].

Methods of Evaluation

Mucoadhesive polymers can be evaluated through various in vitro and in vivo tests.

In Vitro/Ex Vivo Tests

These tests focus on understanding the mechanisms of bio adhesion. Common methods include:

- Tensile strength determination
- Shear stress measurement
- Adhesion weight method
- Fluorescent probe method

- Flow channel method
- Mechanical spectroscopic method
- Falling liquid film method
- Colloidal gold staining method
- Thumb method
- Electrical conductance method
- Swelling property analysis
- In vitro drug release studies
- Mucoretentability studies [64].

In Vivo Methods

- Radioisotope tracing
- Gamma scintigraphy
- Pharmacoscintigraphy
- Electron paramagnetic resonance (EPR) oximetry
- X-ray imaging
- Isolated loop technique [65] [66].

Recent Applications in Oral Mucoadhesive Drug Delivery

Oral mucoadhesive drug delivery systems are increasingly used to improve the bioavailability of drugs that are poorly absorbed or rapidly degraded in the gastrointestinal tract. These systems provide advantages such as high patient compliance, easy administration, and reduced enzymatic degradation. The use of hydrophilic polymers like SCMC, HPC, and polycarbophil was previously common for treating periodontal diseases, but now these systems are also employed for peptide, protein, and polysaccharide drug delivery [67].

Various mucoadhesive dosage forms have been developed, including:

- **Single-layer devices**: Drugs are released multidirectionally.

- **Double-layered devices**: The bioadhesive layer is backed by an impermeable layer, preventing loss of the drug from the surface.

- **Unidirectional release devices**: The drug is released only from the side in contact with the mucosa.

Orabase, a first-generation mucoadhesive paste, is used for mouth ulcers. Additionally, buccal tablets such as Buccostem, an antiemetic tablet containing prochlorperazine, are formulated with a mucoadhesive layer and are designed to be kept under the upper lip to avoid clearance by the salivary glands [68].

CONCLUSION

Buccal mucoadhesive drug delivery represents a significant advancement in the field of pharmaceutical sciences, combining the benefits of localized and systemic drug delivery through a non-invasive route. The mucoadhesive approach ensures prolonged contact with the mucosal membrane, thereby enhancing drug absorption and therapeutic efficacy. This delivery system bypasses first-pass metabolism, enables rapid onset of action, and caters well to patient populations with swallowing difficulties. The design of an effective buccal formulation requires a thorough understanding of oral mucosal histology, the physicochemical properties of drugs, and the selection of suitable mucoadhesive polymers. Furthermore, the use of permeation enhancers and advanced formulation techniques can overcome the barriers posed by the mucosal membrane and ensure optimal drug release profiles. Despite certain limitations, such as the relatively small surface area and the need for retention in the oral cavity, continued innovation in polymer science and drug delivery technologies holds great promise for overcoming these challenges. In conclusion, mucoadhesive buccal drug delivery systems offer a versatile platform for both systemic and local therapies. With ongoing research into novel polymers, permeation enhancers, and formulation technologies, this

route is poised to play a critical role in the future of patient-centric drug delivery.

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