International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Mucoadhesive Buccal Drug Delivery Systems: An Updated Review

Nisvi C[1], Siva S[2], Mathew Keran k[3], Perumal Samy M[4], Aswin M[5], Dr. Ariya Mol R[6]

[1,2,3,4,5]B.Pharm student, Immanuel Arasar College of Pharmacy, Nattalam, Tamil Nadu 629165.
[6]Pharm.D, Assistant Professor, Department of pharmacy practice, Immanuel Arasar College of Pharmacy, Nattalam, Tamil Nadu 629165.

ABSTRACT

Mucoadhesive buccal drug delivery systems are gaining popularity as an alternative to conventional oral dosage forms because of their ability to increase drug bioavailability, sustain drug release, and enhance patient compliance. These systems stick to the buccal mucosa for direct absorption of the drug into systemic circulation; hence avoiding first-pass hepatic metabolism and degradation in the gastrointestinal tract. This makes them very attractive for use with drugs that have poor bioavailability through the mouth, or have short biological half-lives. This review presents an updated overview of recent advances in mucoadhesive buccal drug delivery, with emphasis on formulation strategies, polymer selection, and the mechanisms of mucoadhesion. Commonly used polymers such as chitosan, Carbopol, hydroxypropyl methylcellulose, and sodium alginate are discussed in terms of their mucoadhesive properties, biocompatibility, and ability to control drug release. The major theories of mucoadhesion are wetting theory, diffusion theory, and electronic theory which will be described briefly here since these theories explain polymer-mucosal interactions. This review also discusses key factors that affect drug permeation across buccal mucosa by highlighting physiological barriers like limited surface area available for absorption due to small size of mouth cavity compared to other routes of administration plus salivary flow dilution effect and rapid turnover rate of mucosa. The challenges faced by formulations such as irritation on the mucosa variability in residence time stability of drugs are also discussed. Emerging technologies along with future research directions supporting safe effective non-invasive development are highlighted

KEYWORDS: Mucoadhesive buccal drug delivery; Buccal films; Polymers; Bioavailability enhancement; Controlled drug release; Non-invasive drug delivery.

1. INTRODUCTION

The oral route of drug administration has been the most favoured by patients and clinicians because of its convenience and non-invasiveness. Many drugs, however, undergo pre-systemic clearance in the liver resulting in poor bioavailability. Alternative routes such as transmucosal delivery are being actively pursued to overcome this problem. The buccal mucosa offers some advantages like easy access, smooth muscle underneath, and relatively immobile mucosa; hence it can be considered for immediate release as well as controlled release dosage forms. Pharmaceutical industries have brought significant innovations

towards treating several diseases which have enhanced the quality of life for patients. To circumvent the problems associated with oral route administration, alternative routes through IN administration, buccal/sublingual, pulmonary and transdermal are being explored to avoid hepatic first-pass metabolism, local gastrointestinal toxicity as well as enzymatic degradation within the gastrointestinal tract.[1, 2, 3, 4,6,]

1.1. DEFINITION:

A buccal dosage form is a drug delivery system to be placed in the buccal cavity (the space between cheek and gum) of the mouth. (It is shown in figure no:1) It delivers drugs locally or systemically through the buccal mucosa.[3, 4]

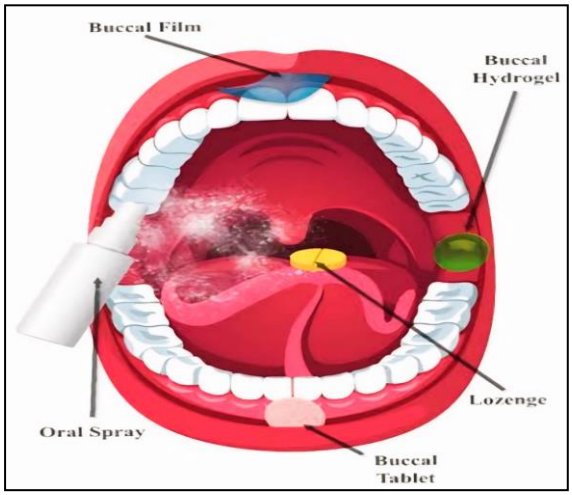


Figure no: 1 (Buccal Drug Delivery System)

1.2. Advantages:

- It is non-invasive, easy, and pain-free; hence, it is very patient compliant.
- The dosage form can be removed from the buccal mucosa whenever there are any adverse reactions or toxicity.
- The patient can apply the dosage form by himself without any medical help.
- Drug delivery through this route permits faster penetration than other mucosal or enteral routes.
- This route of delivery can also be given without swallowing; hence very useful in patients who are under sedation or have difficulty in swallowing. [17,18]

1.3. Disadvantages:

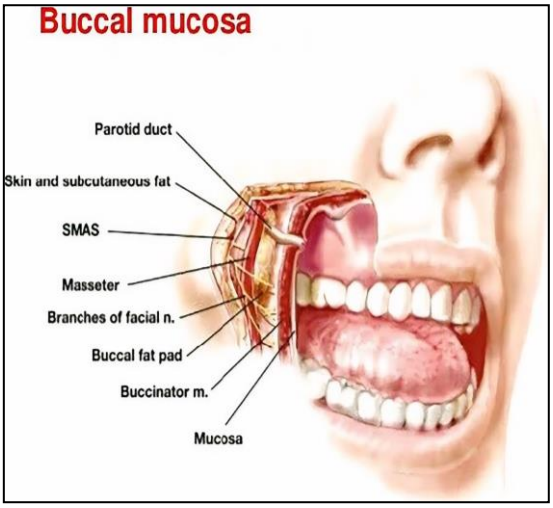
- Only small doses of drugs can be administered due to limited absorption.
- There are restrictions on eating and drinking.
- Some formulations may possess a bitter taste or an undesirable smell which will lead to poor patient compliance.
- The formulation and manufacturing of Mucoadhesive buccal systems would be more expensive as compared to conventional oral dosage forms.
- The mucous membrane can act as a barrier, limiting drug permeation especially for high molecular weight or hydrophilic drugs. [17,18]

1.4. Anatomy of the Buccal Mucosa:

Anatomically, the buccal cavity is defined by its borders. Lateral and anterior borders are formed by Anatomically, the buccal cavity is defined by its borders. Lateral and anterior borders are formed by che-

eks and lips, while posterior and medial borders are comprised of teeth or gums. The buccal gland lies between the mucous membrane and the buccinator muscles; it is like a labial gland but smaller. Its blood supply comes from branches of the maxillary artery, (which are shown in figure no :2) with relatively high perfusion rates of 2-4 ml/min/cm². Buccal mucosa thickness ranges from 500 to 800 µm, hence suitable for retentive drug delivery systems. Buccal mucosa has been reported to be 4-4000 times more permeable than skin epidermis but less than intestinal mucosa permeability.[1,5,17,13,18,22]

Figure no: 2 (Buccal Mucosa)



1.4.1. Three Distinctive Layers of the Oral Mucosa:

The oral mucosa is a unique tissue that covers the inside of the mouth. It has three clear layers: the outer layer (epithelium), the thin layer beneath it (basement membrane), and the layer of connective tissue underneath that (lamina propria). Together, these layers provide mechanical protection, maintain tissue integrity, and regulate permeability.

Epithelium: The mucosa of the mouth is covered by stratified squamous epithelium over its whole surface. This epithelium serves a protective function and has a thickness of approximately 40-50 cell layers. The epithelium lining the inside of the cheek is renewed quickly, with turnover taking about 5-6 days. Its matrix contains abundant carbohydrate-protein complexes that help lubricate the mucosal surface. This epithelial layer serves as the major barrier to drug diffusion, thus limiting molecular transport through the tissue. [1,17,18,22]

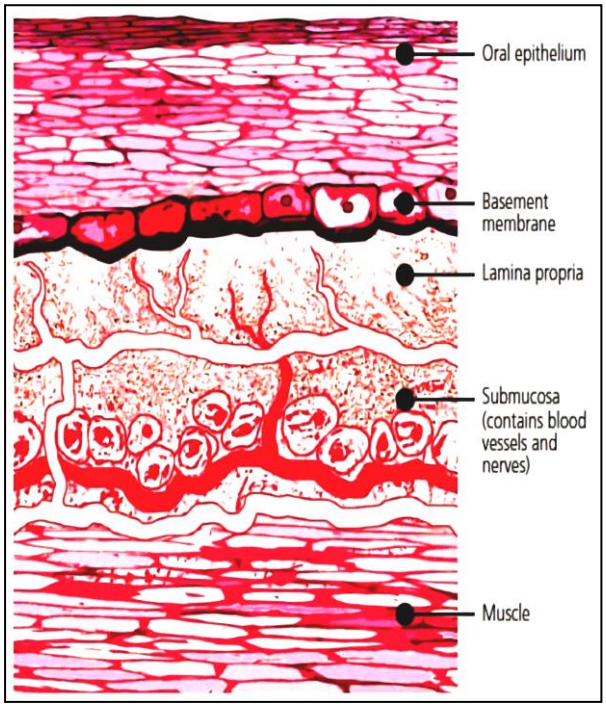


Figure No: 3 (Layers of the Oral Mucosa)

Types of Epitheliums in the Oral Cavity:

Keratinized Epithelium: Keratinized Epithelium has a greater quantity of neutral lipids like ceramides and acyl ceramides; hence it is relatively impermeable to water.

Non-keratinized epithelium: non-keratinized epithelium can be found in areas such as the soft palate, ventral side of the tongue, floor of the mouth, lips, and cheeks; this type contains smaller amounts of neutral but polar lipids mostly cholesterol sulfate and glucosylceramides making it more permeable than keratinized epithelium. [2,13,17,13,18]

Basement Membrane: The basement membrane is a trilaminar structure located between the epithelium and the connective tissue beneath it. It consists of lamina lucida which is an upper amorphous layer together with lamina densa that has collagen for structural support plus a sublayer fibrous material giving general architecture support to all three components; mechanical stability, adhesion function barrier property to select permeability. [1,17,18,22]

1.4.2. Mucus Layer: The mucus layer is an important part of the mucoadhesive system; it is a gel-like secretion produced by goblet cells that coat epithelial surfaces made up of water plus mucin proteins lipids mucopolysaccharides electrolytes (as in Table No:1). The thickness usually varies from 30-40 µm This layer helps protect mucosa against hydrophobic substances and acidic environments also works as a barrier by limiting molecular diffusion which will affect drug absorption.[1]

Table No: 1(Composition of mucus)

S.NO	COMPOSITION	% AMOUNT
1.	WATER	95
2.	GLYCOPROTEINS &LIPIDS	0.5-5.0
3.	MINERAL SALTS	1
4.	FREE PROTEINS	0.5-1.0

1.5. Mechanism of Bioadhesion:

Mucoadhesion typically occurs in two main stages:

- Contact stage
- Consolidation stage (it is shown in figure no:4)

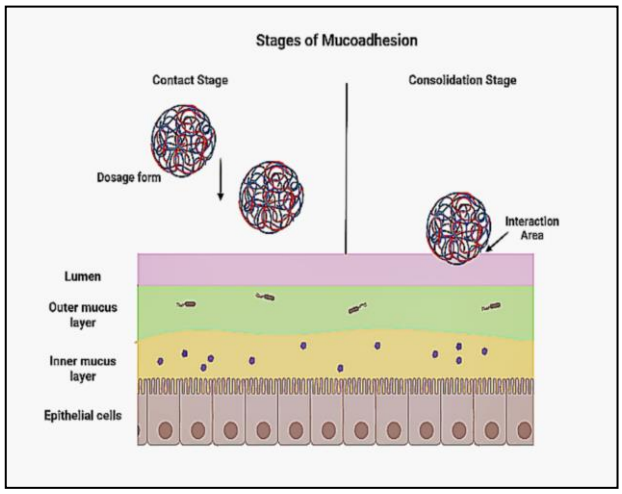


Figure No: 4 (Mechanism of Bioadhesion)

1.5.1. Contact Stage:

This involves the initial interaction between the mucoadhesive polymer and the mucus membrane. [10, 11, 13, 14, 15] It occurs either through good wetting of the polymer on the mucosal surface or by swelling of the polymer, which enhances the surface area available for interaction. [14] It begins to spread and swell, leading to close and intimate interactions with the mucus layer. [15]

1.5.2. Consolidation Stage:

The consolidation stage follows, during which moisture plays a crucial role. Moisture acts as a plasticizer, softening the mucoadhesive system and allowing the polymer chains to become mobile. This mobility facilitates the formation of weak intermolecular interactions, such as van der Waals forces and hydrogen bonds, between the mucoadhesive and mucin. These interactions strengthen and stabilize the adhesive bond, resulting in prolonged adhesion of the polymer to the mucosal surfaces. [10, 11, 13, 14, 15]

Two primary theories explain the consolidation stage.

(a) Diffusion Theory:

This theory suggests that mucoadhesive polymers and mucin glycoproteins interpenetrate at the molecular level. Their chains diffuse into each other and form secondary bonds, stabilizing the adhesive interaction. [10, 13]

(b) Dehydration Theory:

According to the dehydration theory, when a water-soluble mucoadhesive comes into contact with mucus in an aqueous environment, water migrates from the mucosal layer into the formulation owing to a concentration gradient. This water movement causes swelling or gelation of the dosage form, thereby increasing the contact time and enhancing adhesion, primarily through dehydration rather than polymer chain interpenetration. Polymers with hydrogen-bonding functional groups (e.g., –OH, –COOH), anionic surfaces, high molecular weights, flexible chains, and surface activity show improved mucoadhesion owing to enhanced chemical and physical interactions with mucus

1.6. Theories of Mucoadhesion:

Mucoadhesion is a multifaceted phenomenon, and various theories have been proposed to explain its underlying mechanisms. The most widely accepted theories include mechanical interlocking, electrostatic interactions, diffusion interpenetration, adsorption, and fracture mechanics. (Which are shown in **figure no: 5**) [10, 13, 16, 18, 19, 22]

1.6.1. Wetting Theory:

This theory primarily applies to liquid or semi-solid bio adhesive systems. It focuses on how the adhesive spreads over the biological surface. Adhesion occurs when the adhesive material adequately wet and spread on the biological surface.

The work of adhesion (WA) is defined by the Duprés equation:

$$WA=\gamma A+\gamma B-\gamma AB$$

γA: Surface tension of the biological membrane

γB: Surface tension of the bio adhesive

γAB: Interfacial tension between A and B

The work of cohesion (Wc) is given by:

$$WC=2\gamma A \text{ or } 2\gamma B$$

The spreading coefficient (S_{B/A}) is calculated as:

$$SB/A=\gamma A\text{-}(\gamma B+\gamma AB)$$

For successful adhesion,

SB/AS

B/A

Must be positive.

The contact angle (Φ) between the adhesive and surface also plays a role, with lower contact angles indicating better spread ability and stronger adhesion. Ideal contact angle is close to zero, signifying perfect wetting. [10, 13, 16] Effective mucoadhesion is achieved by minimizing interfacial tension and maximizing wetting. [10]

1.6.2. Diffusion Theory:

This theory focuses on the interpenetration of polymer and mucin chains at the interface, forming a semi-permanent bond. The degree of chain penetration is directly related to adhesion strength. The interpenetration depth depends on factors such as: Polymer chain mobility and flexibility, contact time, Diffusion coefficient, chemical compatibility, Molecular weight between crosslinks, Cross linking density (higher density reduces diffusion)

The depth of interpenetration (l) is estimated by:

$$l = (t \times Db)\ ½$$

Where:

l = depth of interpenetration

t = contact time

Db= diffusion coefficient of the Mucoadhesive in mucus

Depth of interpenetration is critical and typically ranges between 0.2–0.5 µm. Optimal mucoadhesion requires structural compatibility and mutual solubility between the adhesive and mucus. [10, 13, 16]

1.6.3. Electronic Theory

This theory explains mucoadhesion through electron transfer between the Mucoadhesive and mucus, caused by differences in their electronic structures. This transfer leads to the formation of an electrical double layer at the interface of the electrode. Electrostatic attractive forces in this layer contribute to adhesion strength. [10,13,16]

1.6.4. Fracture Theory:

This theory relates mucoadhesion to the mechanical separation of the adhesive bonds. It assesses the force required to separate an adhesive from the mucosal surface.

The fracture strength (G) is calculated using:

$$G = (E\varepsilon L)\ 1/2$$

Where:

E: Young's modulus of elasticity

ε: Fracture energy

L: Critical crack length

This theory is independent of molecular interactions and is based solely on mechanical strength. [13, 16]

Adhesion strength (σm) is calculated as:

$$\sigma m = Fm/A0$$

Where:

Fm= maximum detachment force

A0 = contact area

This model is particularly suitable for rigid or semi-rigid polymers, where diffusion into the mucus is minimal. [10]

1.6.5. Adsorption Theory:

According to this theory, when two surfaces come into contact, atoms or molecules on both surfaces form bonds due to surface forces, leading to adhesion. Two types of bonding involved:

Primary Bonds (Strong Bonds):

These include covalent bonds. Although strong, they are typically undesirable in bio adhesion because they are irreversible or permanent.

Secondary Bonds (Weak Bonds):

These include hydrogen bonds, Van der Waals forces, electrostatic interactions, and hydrophobic interactions. These weaker, reversible bonds dominate Bio adhesion owing to their low energy requirements and semi-permanent nature. Among all bonding types, secondary interactions are most commonly involved in Mucoadhesive systems because of their semi-permanent nature and energy efficiency. [10,13,16] These theories collectively help in understanding the complex phenomenon of mucoadhesion and are often complementary rather than mutually exclusive.

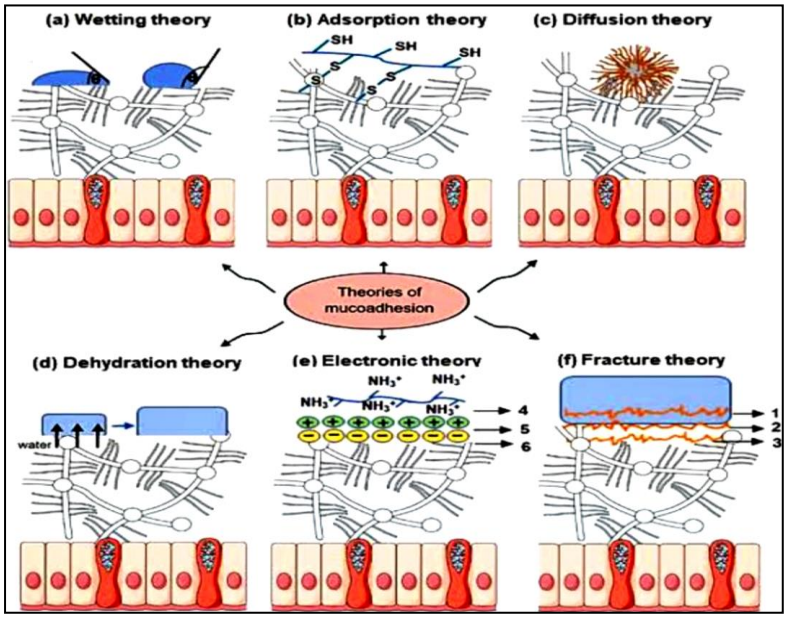


Figure No: 5 (Theories of Mucoadhesion)

1.7. Factors affecting Mucoadhesion:

1.7.1. Polymer –Related Factors

1. Molecular Weight:

The Mucoadhesion strength of linear polymers increases with molecular weight. Polyethylene glycols (PEGs) show greater mucoadhesion in the following order: $2\times10^4 < 2\times10^5 < 4\times10^5$. High molecular weight polymers provide more substantial physical entanglement with the mucus layer, while low molecular weight ones can penetrate through the mucus layer more effectively due to their small size.[13, 14]

2. Flexibility of Polymer Chains:

Chain flexibility is very important for proper interpenetration and bonding with mucin. More flexible chains mean that a polymer can diffuse deeper into the mucus network which helps create better mucoadhesion. The flexibility of a polymer is usually related to its viscosity and diffusion characteristics.[13] Highly cross-linked water-soluble polymers have reduced mobility; therefore, it will be more difficult for the chains to get into the mucus layer and this reduces bio adhesive strength.[14]

3. Polymer Concentration:

The concentration of polymer greatly affects the adhesive strength; at low concentrations not, enough chain is present to interact with mucus hence there will not be strong adhesion. At very high concentrations, however, the polymers are thought to exist in a coiled "unperturbed" state reducing solvent accessibility and hence limiting chain penetration into the mucus.[13] Also at very high concentrations more entanglement occurs among the chains leading to reduced flexibility which reduces adhesive strength.[14]

4. Polymer Chain Length:

An adequate length of chain is required for effective interpenetration and entanglement with a mucin network; very short chains will not interact sufficiently while very long ones may be less mobile.[14]

5. Hydrogen Bonding Capacity:

Hydrogen bonding is a very important aspect in mucoadhesion.[13] For effective mucoadhesion, the pol-

ymers must have functional groups that can form hydrogen bonds.[14] Polymers that have hydroxyl (-OH) and carboxyl (-COOH) functional groups are able to make hydrogen bonds with mucin. The higher the hydrogen bonding capacity, which is usually increased by the flexibility of the polymer, the stronger will be Mucoadhesive interaction.[13]

6. Cross-Linking Density and Swelling:

Cross-linking degree determines how much a polymer can swell and interact with mucin. Based on Flory's theory, increased cross-linking density lowers swelling because of limited water diffusion. This results in less interpenetration between the polymer and mucin, leading to weaker mucoadhesion.[17,18]

7. Charge:

The Mucoadhesive charge of polymers affects their relationship with mucus. Usually, anionic polymers have stronger mucoadhesion compared to non-ionic ones. For example, chitosan is a cationic polymer that demonstrates great Mucoadhesive properties in neutral or slightly alkaline conditions due to electrostatic interactions with negatively charged mucins; however, the charge of the mucus membrane itself has little effect. [13,14]

1.7.2. Environment-Related Factor

1. Hydrophilicity:

Mucoadhesive polymers are hydrophilic by nature and possess functional groups capable of forming hydrogen bonds with mucin. These polymers swell in aqueous environments, thereby increasing their surface area and exposing more adhesive sites. The swollen, disentangled chains increase flexibility and penetrate the mucus to enhance adhesion. [13,18]

2. pH:

pH affects the ionization of both polymer and mucin functional groups, thus influencing the adhesion process. For example, polycarbophil exhibits maximum Mucoadhesive strength at pH 3; adhesion decreases with increasing pH above 5 because of loss of hydrogen bonding capacity through ionization of carboxyl groups. [14,18]

1.7.3. Physiological Factors:

Certain biological conditions can impact mucoadhesion effectiveness, such as:

- **Mucus Turnover:** The rate at which mucus is continuously secreted and shed from the mucosal surface will affect how long a Mucoadhesive can stay attached.
- **Diseases or Conditions:** Different medical conditions may change the properties of the mucosal lining and hence possibly affect mucoadhesion effectiveness. [17,27]

1.8 Formulation Considerations for Buccal Delivery Systems:

1.8.1 Active Pharmaceutical Ingredients (APIs): Active pharmaceutical ingredients (APIs) typically make up about 5–30% of the total weight of a buccal film. Water-soluble APIs dissolve homogeneously in the film matrix, while water-insoluble APIs are dispersed in the film. For controlled drug release and uniform distribution, APIs can be processed by milling or micronization or formulated as nanocrystals or particulate systems.

1.8.2. Mucoadhesive Polymers: Mucoadhesive polymers are used to help the film stick to mucous membranes and increase its residence time at the site of application. Hydrophilic polymers such as polyvinyl alcohol (PVA) and hydroxypropyl methylcellulose (HPMC) are common examples. In

addition, hydrogel-forming polymers like Carbopol and other polyacrylates have strong mucoadhesive properties; therefore, they are widely used.

1.8.3. Plasticizers: Plasticizers are used to increase flexibility in buccal films and decrease brittleness for better handling and comfort for patients; common plasticizers include glycerol propylene glycol polyethylene glycols usually at levels of 1–20% based on dry polymer weight.

1.8.4. Sweetening Agents: Sweetening agents improve taste which is very important for pediatric and geriatric patients; these may be natural sweeteners like sucrose and dextrose or artificial sweeteners such as aspartame.

1.8.5. Saliva Stimulating Agents: Saliva-stimulating agents such as citric acid and malic acid enhance saliva secretion to hydrate and dissolve a buccal film more quickly; they are generally used at about 2–6% concentrations of total film weight.

1.8.6. Flavoring Agents: Flavoring agents can enhance the taste and overall acceptability of the buccal film. Natural or artificial flavorings like peppermint and different fruit flavors may be used at concentrations up to 10% of the weight of the film.

1.8.7. Coloring Agents: Coloring agents improve the appearance of the film and help to mask any unpleasant coloration due to either the drug or excipients used in making it. Common colorants are titanium dioxide and colors approved by FD&C, generally not more than 1% of total film weight.

1.8.8. Cooling Agents: Cooling agents sometimes added for mouth feel improvement and flavor enhancement include monomethyl succinate as well as other related compounds.[20,21]

1.9. Penetration Enhancers in Buccal Drug Delivery Systems:

1.9.1. Surfactants: Penetration enhancers surfactants are commonly used in buccal formulations; some examples include sodium lauryl sulfate and Tween 80 surfactants which enhance drug absorption by disrupting lipid bilayers of buccal epithelium increasing membrane fluidity facilitating transcellular transport of drugs through these membranes surfactants have been frequently incorporated into gels films patches for this purpose surfactant penetration enhancers improve absorption properties by lowering surface tension between two immiscible phases improving wetting properties thereby enhancing permeability through biological membranes.

1.9.2. Bile Salts: Sodium deoxycholate, sodium taurocholate, and sodium glycocholate are examples of bile salts that improve drug permeation through the buccal mucosa by solubilizing the membrane lipid barrier and opening tight junctions between epithelial cells temporarily. This mechanism supports both transcellular and paracellular pathways for drug transport. Bile salts are commonly used in formulations such as buccal films, gels, and tablets.

1.9.3. Fatty Acids: Oleic acid and lauric acid are examples of fatty acids that can enhance penetration by interacting with lipid domains within the buccal mucosal membrane reducing resistance to diffusion across membranes thus enhancing drug transport across epithelial barriers suitable for formulation into buccal films as well as patches.

1.9.4. Solvents: Solvents like ethanol and propylene glycol are used to enhance drug permeation by extracting lipids from the epithelial membrane and improving drug solubility. By increasing drug diffusion across the buccal mucosa, these solvents contribute to enhanced bioavailability and are commonly included in buccal films and gels.

1.9.5. Chelating Agents: Chelating agents are known to enhance paracellular drug transport by chelating calcium ions that maintain the integrity of tight junctions. The loosening of tight junctions due

to chelating agents increases the passage of drugs between epithelial cells. Examples include EDTA which is used in buccal films and gels.

1.9.6. Cyclodextrins: Cyclodextrins like β-Cyclodextrins and hydroxypropyl-β-Cyclodextrins enhance buccal drug delivery through solubilization of poorly water-soluble drugs and changing membrane permeability properties; their presence in formulations as part of the composition for buccal films helps stabilize and enhance absorption properties for the active ingredients therein.

1.9.7. Enzyme Inhibitors: Aprotinin, bestatin, and similar enzyme inhibitors are found in buccal formulations to inhibit mucosal enzymes that may destroy the drug prior to its absorption; these agents work by reducing enzymatic degradation hence maintaining stability for therapeutic effectiveness particularly in buccal tablets and films.

1.9.8. Cationic Polymers: Low molecular weight chitosan is included under cationic polymers since it supports absorption by temporarily opening tight junctions for paracellular transport plus its mucoadhesive nature prolongs residence time at the site of absorption making them very suitable for formulation into buccal films and gels.[32,33]

1.10. Polymers Used in Buccal Drug Delivery Systems:

1.10.1. Chitosan: Chitosan is widely used in drug delivery through the buccal route because of its strong mucoadhesive properties and ability to enhance drug permeation. It acts as a matrix-forming polymer that can transiently open tight junctions, thus increasing the paracellular transport of drugs. Chitosan is typically used in the form of buccal films, tablets, gels, and patches.

1.10.2. Carbopol (Carbomer): Carbopol is a highly mucoadhesive polymer with a high swelling capacity when it is hydrated. It forms viscous gels that adhere well to the buccal mucosa, making it suitable for prolonging the drug residence time. It is used in gels, films, and tablets for buccal drug delivery.

1.10.3. Hydroxypropyl Methylcellulose (HPMC): HPMC is a multifunctional polymer that can serve as a mucoadhesive agent, film former, and controlled-release matrix. It creates smooth and even films and offers predictable drug-release profiles. HPMC is frequently used in buccal films, tablets and patches.

1.10.4. Sodium Carboxymethyl Cellulose (CMC-Na): Sodium carboxymethyl cellulose is a hydrophilic polymer with decent mucoadhesive and swelling properties; it alters drug release by creating a gel layer when it gets wet, which then controls the diffusion of the drug. This polymer has wide applications in buccal tablets, films, and gels.

1.10.5. Polyvinyl Alcohol (PVA): Polyvinyl alcohol is mainly known as a film-forming polymer but also exhibits moderate mucoadhesive characteristics. It forms flexible, transparent films with good mechanical strength and can be used for buccal films and patches.

1.10.6. Polyvinylpyrrolidone (PVP): This plays the role of a mucoadhesive polymer as well as enhancing the flexibility of the buccal films besides improving solubility and uniformity of drugs in the formulation; therefore, it is widely used in buccal films and tablets.

1.10.7. Sodium Alginate: This is an organic polymer that is hydrophilic by nature with properties for mucoadhesion as well gel formation; when exposed to saliva, it creates a viscous gel helping keep the dosage form at its place upon administration, thus being popular amongst users of gels and films for buccal applications!

1.10.8. Guar Gum: It natural polysaccharide with very strong mucoadhesive and swelling properties. It can take up water to develop into a gel matrix, making it useful for sustained drug release from buccal tablets and films.

1.10.9. Xanthan Gum: This mainly acts as a mucoadhesive along with increasing viscosity; hence, it becomes thicker formulation stability aiding in extending contact time with the mucous membrane inside the mouth; therefore, it is mostly used in gels for oral application and pills.

1.10.10. Eudragit® RL: Eudragit®RL is a permeable polymer used to modify drug release from buccal dosage forms. Its relatively high permeability allows controlled drug diffusion while maintaining the film integrity. It is frequently incorporated into buccal films and patches for this purpose.

1.10.11. Eudragit® RS: Eudragit® RS is a low-permeability polymer designed to provide sustained drureleaseea that ipH-independentse. It forms rigid matrices that slow drug diffusion, making it suitable for buccal films and tablets that require prolonged release.

1.10.12. Ethyl Cellulose: Ethyl cellulose is a hydrophobic polymer used primarily as a film former and sustained-release agent. It provides mechanical strength and controls drug release by limiting the penetration of water. This polymer is commonly used in buccal films and patches to enhance drug delivery.

1.10.13. Polyethylene Oxide (PEO): Polyethylene oxide is a swelling polymer that forms a gel upon hydration, enabling controlled drug release. Its high molecular weight and hydrophilicity make it suitable for buccal tablets and films.

1.10.14. Carboxymethyl Cellulose (CMC): Carboxymethyl cellulose acts as a swelling agent and release modifier in buccal formulations. It enhances hydration and drug diffusion control and is commonly used in buccal tablets and films.

1.10.15. Gelatin: Gelatin is a natural bioadhesive polymer with good film-forming properties. It produces smooth, flexible films and enhances patient acceptability, making it suitable for buccal films and patches.

1.10.16. Pectin: Pectin is a natural polysaccharide that exhibits bioadhesive and gel-forming properties. It readily hydrates in the buccal cavity to form a viscous gel, aiding drug retention and release, and is commonly used in buccal gels and films.

1.10.17. Dextran: Dextran is a bioadhesive polymer that serves as a matrix former in buccal drug delivery systems. It supports sustained drug release and is typically used in buccal tablets and films.

1.10.18. Pullulan: Pullulan is a natural polymer with excellent film-forming and bioadhesive properties. It produces clear, flexible films with good mechanical strength and is widely used in buccal-film formulations.[1,6,9]

1.11. Formulation of Buccal Dosage Forms:

1.11.1. Buccal tablets are one of the most widely studied solid dosage forms for buccal drug delivery because of their simplicity, stability, accurate dosing, and ease of manufacture. They are small, flat, and designed to adhere to the buccal mucosa in the presence of saliva, allowing patients to speak and drink with minimal discomfort while remaining in place until drug release is complete. Buccal tablets can be formulated as monolithic or bilayer systems using direct compression or wet granulation, with sufficient hardness to resist erosion. Unidirectional drug release can be achieved by coating non-mucosal surfaces with water-impermeable materials, whereas modified drug forms can be incorporated to enhance activity or prolong release. An ideal buccal tablet should be elegant, mechanically strong, chemically and

physically stable, and capable of delivering the drug in a predictable and reproducible manner for local or systemic therapies.

1.11.1.1. Methods used to prepare buccal tablets

1. **Direct compression:** The formulation of mucoadhesive buccal tablets is typically achieved using techniques such as direct compression, wet granulation, and melt granulation, which are chosen based on the characteristics of the drug and polymers. In the direct compression method, the requisite amounts of the drug, mucoadhesive polymer, and diluents are initially sieved to achieve a uniform particle size and subsequently blended to ensure homogeneous mixing. Lubricants such as magnesium stearate are incorporated at the final stage to enhance flow and prevent adhesion. The blended powder is then compressed using a tablet press to produce uniform buccal tablets, rendering this technique suitable for drugs that are sensitive to moisture and heat.
2. **Wet granulation method:** Another prevalent technique is the wet granulation method, which enhances the flow and compressibility of powder mixtures. In this approach, the drug and selected mucoadhesive polymers are initially blended, followed by the addition of a binder solution, commonly containing PVP or HPMC, to transform the powder into moist, cohesive granules. These granules are dried at controlled temperatures, sieved to achieve a uniform size, and finally mixed with lubricants before compression. Wet granulation offers improved mechanical strength and uniformity, making it suitable for polymers that do not compress effectively in the dry state.
3. **Melt granulation method:** The melt granulation method is favored when low-melting carriers are used to enhance mucoadhesion or modify drug release. In this method, the drug and polymer mixture is combined with a molten or softened binder, such as PEG or Glacier, allowing granulation without the use of water or solvents. Following thorough mixing, the mass was cooled and screened to obtain granules of consistent size, which were subsequently lubricated and compressed into tablets. This method circumvents potential hydrolytic degradation and is advantageous for drugs that are unstable in aqueous environments. Overall, these techniques offer flexibility in formulating mucoadhesive buccal tablets with desired adhesion strength, mechanical integrity, and release characteristics.[36]

1.11.2. Buccal patches or films are laminated dosage forms composed of an impermeable backing layer, a drug-loaded reservoir layer that enables controlled drug release, and a bioadhesive surface that facilitates attachment to the buccal mucosa. These flexible systems are commonly prepared using solvent casting or hot-melt extrusion techniques and are designed to deliver drugs directly to the mucosal membrane. Compared with conventional semisolid formulations, such as creams and ointments, buccal patches and films provide improved dosing accuracy, prolonged residence time, and localized, controlled drug delivery.

1.11.2.1. Methods used to prepare buccal patches or films:

Solvent Casting Method

In the solvent casting method, the required amount of polymer was dissolved in distilled water. The active pharmaceutical ingredient is then incorporated into the polymer solution, followed by the addition of a suitable plasticizer. The mixture was thoroughly stirred to ensure uniformity. The prepared solution was poured onto a flat casting surface (such as a baking plate) and dried in a hot-air oven at 40 °C. After complete drying, the film was carefully removed from the plate and placed in a desiccator for 24 h. It is then cut into the desired size and shape for further processing.

Steps in the Solvent Casting Process:

1. Preparation of the casting solution:

2. Deaeration of the prepared solutions.
3. The appropriate volume of solution was poured into the mold.
4. The cast solution was dried.
5. The final dosage form was cut to the required dimensions.
6. Hot-Melt Extrusion Technique

Hot-melt extrusion (HME) is a solvent-free method used for the preparation of buccal films, in which polymers are heated and processed into films. In this technique, a dry mixture of the active pharmaceutical ingredient and suitable solid carriers is fed into the hopper of a hot-melt extruder, where it is conveyed, mixed, and melted under controlled temperature. The molten mass is then extruded through dies and cast into films that solidify upon cooling. The extrusion and casting steps are critical for obtaining uniform films with consistent drug distributions.

Direct Milling Method

The direct milling method is a solvent-free technique used for preparing buccal films. In this approach, the drug and excipients are blended by direct grinding or kneading without using any solvents. The resulting mass was then rolled onto a release liner to obtain films of the desired thickness. This method is preferred because of the complete absence of residual solvents, thereby eliminating solvent-related safety and health concerns.

Inkjet Printing Method for Buccal Films

Inkjet printing is a non-contact and highly precise technique employed to deposit active pharmaceutical ingredients onto buccal film substrates. In this method, a pharmaceutical ink is first prepared by dissolving or dispersing an API in a suitable liquid medium. The formulated ink was then loaded into the inkjet printer cartridge and accurately printed onto a preformed film or substrate. Drug deposition is achieved using either thermal inkjet printing, in which localized heating generates vapor bubbles that expel ink droplets through the nozzle, or piezoelectric inkjet printing, where pressure pulses produced by a piezoelectric crystal eject controlled droplets of ink. This technique enables accurate dose control and uniform drug distribution in buccal films.

Three-dimensional (3D) printing is an advanced method for creating buccal films by building them layer-by-layer using digital designs.

Process Overview:

A computer-aided design of the buccal film was created.

A drug-loaded material (e.g., a polymer or ink) is prepared.

Using 3D printing methods, such as

1. Fused Deposition Modeling (FDM)– melts and extrudes drug-polymer filament,
2. Inkjet Printing– deposits drug solution in droplets form,
3. Semi-solid extrusion _ it involves layer-by-layer deposition of semi-solid materials through a syringe-based tool head.

Finally dried to obtain desired film with accurate size and shape.[20, 28, 29]

1.12. Evaluation of Buccal Drug Delivery Systems

1.12.1. Drug–Excipients Interaction Studies:

Drug–excipients interaction studies play a crucial role in formulation development to ensure compatibility and stability of the dosage form. Such interactions can be studied with various analytical techniques, Differential Scanning Calorimetry (DSC) for thermal changes, X-ray Diffraction (XRD) for crystallinity, Fourier Transform Infrared Spectroscopy (FTIR) for chemical interactions, and Thin Layer Chromatography (TLC) as a method to identify degradation or interaction products.

1.12.2. Physical Evaluation: The physical evaluation shall comprise determining uniformity of content and weight and thickness measurements. Weight variation will be determined by comparing individual weights of ten randomly selected patches with their mean weight. Film thickness is determined at five different positions (center and four corners), and mean thickness calculated from those values; samples with any physical defect such as nicked edges, tears, air bubbles, or variation in thickness greater than 5% shall be excluded from further analysis.

1.12.3. Surface pH Measurement: Surface pH is measured to evaluate the risk of irritation to the buccal mucosa. Buccal patches are placed in contact with 1 mL of purified water (pH 6.5 ± 0.05) and allowed to swell at room temperature for two hours. The pH electrode is then gently placed on the surface of the patch, and the pH is recorded after stabilization to ensure mucosal compatibility.

1.12.4. Swelling Studies: Swelling behaviour is studied by placing a 1 × 1 cm^2 drug-loaded patch on a pre-weighed cover slip and immersing it in 50 mL of phosphate buffer (pH 6.6). The weight is recorded at five-minute intervals for up to thirty minutes; increase in weight reflects extent of water absorption and swelling of patch

1.12.5. Ex Vivo Mucoadhesive Strength: Ex vivo mucoadhesive strength is determined by a modified balance method. Fresh buccal mucosa of goat or sheep is used without any cleaning and equilibrated with phosphate buffer (pH 6.8). The mucosal tissue was mounted on a glass vial containing buffer and kept at 37 ± 1 °C. The force required for the tablet to detach from the surface of the mucosa after a predetermined contact time is measured and expressed as mucoadhesive strength in grams.

1.12.6. Ex Vivo Mucoadhesive Time: This test is carried out on freshly excised buccal mucosa placed between two glass slides. The formulation (mucoadhesive tablet/patch) was premoistened with phosphate buffer (pH 6.8) before application onto the tissue under slight pressure. The whole assembly was then placed inside a beaker containing phosphate buffer maintained at 37 ± 1 °C while stirring at 50 rpm, simulating oral conditions, until complete detachment of the formulation occurred; this was noted as mucoadhesive time.

1.12.7. In Vitro Drug Release Studies: Drug release studies in vitro are performed using the USP paddle method. The dissolution medium comprises phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C with a paddle rotation speed of 50 rpm. Samples are withdrawn at predetermined time intervals, filtered, and analyzed on a UV spectrophotometer after proper dilution.

1.12.8 In Vitro Drug Permeation Studies: In vitro permeation studies were carried out through Franz or Keshary–Chien diffusion cells using freshly excised buccal mucosa from goat or sheep. The mucosa was mounted in between donor and receptor compartments; phosphate buffer (pH 6.8) filled the donor compartment and phosphate buffer (pH 7.4) filled the receptor compartment. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically for drug permeation [1,2,34,35]

1.13. Application of Mucoadhesive Buccal Dosage Forms

1. Systemic Drug Delivery

- Membrane permeation of drugs through the buccal mucosa.
- Avoidance of hepatic first-pass metabolism.
- Increased bioavailability of drugs.
- Small-molecule drugs, peptides, proteins, and vaccines are applicable.

2. Local Drug Delivery

- Targeted drug delivery to the oral cavity.
- Sustained and controlled release of the drug at the site of action is possible.
- Oral diseases (e.g., ulcers, infections) can be effectively treated with it.
- Dental conditions and periodontal disorders can be managed with this.

3. Emerging and Advanced Applications

- Potential use in gene delivery systems
- Application in probiotic administration for oral and systemic health
- Development of theranostic systems combining therapy and diagnosis
- Support advancements in personalized medicine

4. Overall Advantages

- Improve drug efficacy
- Enhance patient compliance
- Broaden therapeutic options[36]

1.14. Challenges and Future Perspectives of Mucoadhesive Drug Delivery Systems

1. Challenges

Mucoadhesive drug delivery systems have a number of challenges that are quite significant and restrict their extensive use. A significant problem is that mucoadhesion varies greatly between subjects, and therefore, it may cause variations in the retention and absorption of drugs among individuals. This inconsistency usually leads to uncontrollable and unpredictable therapeutic outcomes. Besides, there are great technical challenges associated with the upscaling of the formulations developed in the laboratory to the production in the industry, especially in the stability and performance of the formulations. The economic limits also pose a risk to big-time production because of the higher production costs and process specialization. It is also difficult to ensure consistent quality of products in the scaling up period, because consistency between batches and between batches should be preserved. In addition, there are regulatory challenges due to the absence of endorsed and consistent guidelines that are related to mucoadhesive systems. Lastly, it is time consuming and resource intensive because the development process takes a considerable amount of time before a regulatory approval is obtained.

2. Future Perspectives

Development of new mucoadhesive materials with better adhesive and functional properties Research to overcome variability and performance limitations Integration of mucoadhesive systems with advanced drug delivery technologies to improve targeting efficiency as well as controlled drug release profiles Personalized design buccal drug delivery systems according to individual patient characteristics for the optimization of therapeutic efficacy with minimum inter-patient variability.[37]

CONCLUSION:

The mucoadhesive buccal dosage forms offer various advantages like increased drug bioavailability, prolonged residence time at the site of absorption, and better patient compliance due to their non-invasive and easy administration. Recent developments in this area have given rise to advanced formulations that use new polymers and technologies for optimizing adhesion, drug release, and stability. These dosage forms have a large potential to change the practice of pharmaceuticals since they allow for targeted controlled drug delivery with reduced systemic side effects which would enhance patient outcomes; however, further research is needed to solve problems such as variability in mucosal conditions, scalability of manufacturing processes, and complete clinical evaluations before one can fully benefit clinically and commercially from them.

REFERENCES

1. Walia C, Arya A. Review on Buccal Drug Delivery System. International Journal of Information Systems & Management Science. 2023 Oct 10;8(2456-4184)
2. Montero-Padilla S, Velaga S, Morales JO. Buccal dosage forms: general considerations for pediatric patients. AAPS PharmSciTech. 2017 Feb;18(2):273-82.
3. RathboneM, SenalS, patherI. Oral mucosal drug delivery and therapy. Springer, 2015.
4. SenelS, Rathbone MJ, Cansiz M, pather I. Recent developments in buccal and sublingual delivery systems, Expert opin Drug Deliv. 2012;9: 615-28
5. ShramikaA.chore,Dr.SachinJ.Dighade.An review on buccal drug delivery system International journal of pharmaceutical sciences Review and Research, 2020; 65(2):140-148
6. Chinna Reddy p, ChaitanyaK.S.C, Madusudan Rao Y.A review on bioadhesive buccal drug delivery systems Current Status of formulation and evaluation methods. DARU journal of pharmaceutical Sciences, 2011;19:385-399
7. Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: the next generation. Journal of pharmaceutical science, 2000;13:43-74
8. ShojaeiAH, Chang RK, Guo X. Systemic drug delivery through the buccal mucosal route. Journal of pharmaceutical technology, 2001; 25(6): 70-81
9. Sonia Barua, Hyeongminkim, Kanghee Jo, Chang won sea,Tea Jun park, Kyung Bin Lee, Gyiaeyun, Kyungsoo oh, Jaehwi lee. Drug delivery techniques for buccal route: formulation strategies and recent advances in dosage form design. journal of pharmaceutical Investigations, 2016
10. Boddupalli BM, Mohammad ZNK, Nath RA, Banji D. An overview on mucoadhesive drug delivery, journal Adv pharmaceutical Technology Research, 2010;1:381-381
11. M.N.L. Aishwarya, V. Prudhvi Raj, SubhashisDebnath, M.NiranjanBabu. A review on buccal drug delivery System. Research journal of pharmaceutical Dosage forms and Technology, 2017; 9(3)
12. Lewis shipp, fang Liu, Laxmikerai-Varsani, Tochukwu C. Okwuosa. A review of therapeutic opportunities, formulations & relevant evaluation approaches. Journal of Controlled release (Elsevier), 2022; 1071-1092
13. Vasu chauhan, Abhinavagrawal, Umesh Kumarsingh. Mucoadhesive drug delivery. A Comprehensive review on Journal of drug delivery and therapeutics, 2023
14. Ashish Budhrani, Ajay k. shadija. A Review on mucoadhesive buccal drug delivery system. American journal of pharmtech research, 2020; 275-276

15. SurenderVarma, MahimaKaul, ArunaRawat, Sapnasaini. buccal drug delivery system. International journal of pharmaceutical sciences and Research, 2011; 2(6):1303-1321
16. Krishnarajan D, jithinTG, NikhilV, ArchanaM.Nair, AsminaSherin, Sneha Thomas, M. purushothaman. Recent trend and approaches of buccal drug delivery System 2016; 7(5):246-268
17. ReenaSheoran.Buccal drug delivery system: A Review. International journal of pharmaceutical Sciences Review and Research, 2018; 50(1):40-46
18. Mohit, Md. Sadique Hussain. A Brief review on buccal drug delivery system. world journal of pharmaceutical research,2021; 10(5): 558-516
19. BadepaliRaddaiah Reddy, Divya S Kumar, Gururaj S Kulkurani, padmaa M paarakh, Muthukumar A. Mucoadhesive buccal formulation for anti-migraine agents: A Comprehensive review. International journal of Research in pharmacy and pharmaceutical science,2024;9(3)81-87
20. S.M Shahidulla, Ayesha Begum, Aafreenfatima. Buccal film: an updated overview. International journal for innovative in Research in multidisciplinary field, 2022; 8(11): 132-188
21. Javier O. Morales, Jason T. Mc Conville. Manufacture and Characterization of mucoadhesive buccal films. European Journal of pharmaceutics and biopharmaceutics [Elsevier], 2011; 77:187-199
22. Bruno Fonseca-Santos, Marluschorilli. An overview of polymeric dosage forms in buccal delivery: State of art, design of formulation and their in vivo performance evaluation. Materials science & engineering [Elsevier], 2018; 86:109-143
23. Dina Kottke, ArdLura, Dominique Jasmin Lunter, Jong Breitkreutz. Manufacturing and characterization of a novel Composite dosage form for buccal drug administration. International journal of pharmaceutics (Elsevier),2020
24. R. Khanna, sp. agarwal, Alka Ahuja. Mucoadhesive buccal dung delivery: A potential alternative to Conventional therapy. Indian journal of pharmaceutical sciences 1998; 60(1): 1-11
25. Anikumar J. Shinde, Deepti S. Waghmare, Rahul S. Dalvi, harinath N. formulation, Design and characterization of mucoadhesive buccal film of Nebivolol using factorial design. International journal of pharmaceutical Sciences and Research, 2018; 9(5):1797-1805
26. A. Zvonar, K.Bolko, M. Gašperlin. Microencapsulation of self-micro emulsifying systems: optimization of shell-formation phase and hardening process. International Journal of pharmaceutics (Elsevier), 2012; 437:294-302
27. P.V.V. Siva Krishna, p. SrinivasaBabu, T. Kumar sai, k.MuniRajyalakshmi, Ch.Apparao. Advances and Challenges in mucoadhesive drug delivery systems. A Comprehensive Review. Asian journal of pharmaceutics, 2024; 18(2)
28. SumayyaHaneef, Mariya Sultana, S.M. Shahidulla. An overview on buccal films. European journal of pharmaceutical and medical research, 2024; 11(5)
29. VishakhaDhananjayJagtap. Buccal film- A Review on Novel drug delivery system. International journal of Researchand Review, 2020; 7(6): 21-22
30. Christopher A. Squier, Mary T. Kremer. Biology of oral mucosa and Esophagus. Journal of the National Cancer Institute Monographs, 2001
31. Gerard J Tortora, Bryan Derrickson. The digestive System: Oral mucosa. principles of anatomy & physiology (Wiley), 2017; 905-911
32. Okur, N. Ü., Bülbül, E. Ö., Yağcılar, A. P., &Siafaka, P. I. (2021). Current Status of Mucoadhesive Gel Systems for Buccal Drug Delivery. *Current Pharmaceutical Design*, *27*(17), 2015–2025. https://doi.org/10.2174/1381612824666210316101528

33. Dhiman, M. K., Dhiman, A., & Sawant, K. K. (2009). Transbuccal Delivery of 5-Fluorouracil: Permeation Enhancement and Pharmacokinetic Study. *AAPS PharmSciTech*, *10*(1), 258–265.https://doi.org/10.1208/s12249-009-9203-8
34. Eval Kumria, R., Nair, A. B., Goomber, G., & Gupta, S. (2014). Buccal films of prednisolone with enhanced bioavailability. *Drug Delivery*, *23*(2), 471–478. https://doi.org/10.3109/10717544.2014.920058
35. Eval Obeidat, W. M., &Lahlouh, I. K. (2025). Chitosan Nanoparticles: Approaches to Preparation, Key Properties, Drug Delivery Systems, and Developments in Therapeutic Efficacy. *AAPS PharmSciTech*, *26*(5). https://doi.org/10.1208/s12249-025-03100-z
36. Puri, V., Sharma, A., Maman, P., Rathore, N., & Singh, I. (2019). OVERVIEW OF MUCOADHESIVE BIOPOLYMERS FOR BUCCAL DRUG DELIVERY SYSTEMS. *International Journal of Applied Pharmaceutics*, 18–29. https://doi.org/10.22159/ijap.2019v11i6.35438
37. Future Barua, S., Kim, H., Jo, K., Seo, C. W., Park, T. J., Lee, K. B., Yun, G., Oh, K., & Lee, J. (2016). Drug delivery techniques for buccal route: formulation strategies and recent advances in dosage form design. *Journal of Pharmaceutical Investigation*, *46*(7), 593–613. https://doi.org/10.1007/s40005-016-0281-9