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"BUCCAL DRUG DELIVERY SYSTEMS: CURRENT ADVANCES, FORMULATION STRATEGIES, AND FUTURE PERSPECTIVES"

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Abstract:

Buccal drug delivery systems have gained considerable attention as an alternative route for drug administration due to their ability to bypass hepatic first-pass metabolism and improve drug bioavailability. The buccal mucosa offers a highly vascularized surface that enables rapid drug absorption and provides both local and systemic therapeutic effects. Buccal dosage forms such as tablets, films, patches, and gels have been widely explored for their advantages including non-invasive administration, improved patient compliance, and controlled drug release. This review summarizes the anatomy and physiological characteristics of the buccal mucosa, mechanisms of buccal drug absorption, and factors influencing drug permeation through the mucosal membrane. Various bioadhesion mechanisms and theories, including electronic, wetting, diffusion, adsorption, and fracture theories, are discussed to explain the interaction between mucoadhesive polymers and mucosal surfaces. The review also highlights the basic components and different types of buccal dosage forms along with conventional and advanced preparation techniques such as solvent casting, hot-melt extrusion, electrospinning, freeze-drying, and 3D printing. Furthermore, important evaluation parameters including surface pH, swelling index, mucoadhesive strength, drug content uniformity, in-vitro drug release, and ex-vivo permeation studies are described. Recent advancements and future perspectives in buccal drug delivery systems, including nanotechnology-based approaches and personalized medicine, are also discussed. Overall, buccal drug delivery represents a promising and patient-friendly strategy for improving therapeutic efficacy and drug delivery performance.

Index Terms- Buccal drug delivery system, Mucoadhesion , Buccal films, Drug permeation, Oral mucosa.

INTRODUCTION

Traditionally we use lots of herbal ingredients for mouth rinse via the buccal route, placing herbs, but not the exact amount of drug, into the systematically absorbed area. We shift to allopathic medicine, isolate a main drug, and prepare a formulation. According to their bioavailability, we choose a route to deliver a drug to obtain maximum effect. The buccal route of drug delivery is one of the easiest routes in which we simply place a drug only to get a quick pharmacological effect.[1,2]

The buccal drug delivery system involves placing a dosage form such as a film, patch, tablet, or gel inside the cheek, where it can provide both local and systemic effects. This method is considered an advanced oral delivery technique because it helps bypass the liver's first-pass metabolism and reduces issues like drug breakdown in the gastrointestinal tract, ultimately enhancing the drug's bioavailability. Buccal delivery is noninvasive and convenient, with the added benefit that the dosage can be easily removed if adverse effects occur. However, it does have some drawbacks, including limited absorption area, dilution of the drug by saliva, and the risk of the drug being swallowed.[3]

Buccal delivery is one type of oral mucosal drug administration, alongside sublingual and local oral methods. It is particularly useful for drugs that require rapid onset or controlled release without going through the digestive system. Modern buccal systems often use mucoadhesive polymers to help the formulation stick to the mucous membranes for extended periods. Additionally, recent innovations incorporate nanocarriers, multilayer structures, and 3D printing to enhance drug loading, stability, and compatibility.[3]

In recent years, researchers have also explored buccal delivery for drugs that are poorly soluble, as well as certain proteins and peptides. Techniques such as permeation enhancers, enzyme inhibitors, and polymer blends are being used to improve the effectiveness of these formulations. Furthermore, patient compliance is often improved with buccal drug delivery systems due to their ease of administration and noninvasive nature. This route is especially advantageous for patients who have difficulty swallowing tablets or capsules, such as pediatric, geriatric, or unconscious patients.[4,5]
The buccal mucosa's rich vascularization allows for rapid absorption directly into the bloodstream, which can lead to faster therapeutic effects compared to traditional oral routes. However, formulating drugs for buccal delivery requires careful consideration

of factors such as taste masking, irritation potential, and the mechanical properties of the dosage form to ensure comfort and effectiveness during use.[5]

ADVANTAGES :

- Buccal delivery can bypass first-pass metabolism and may increase bioavailability for suitable drugs.[5]
- It can reduce exposure to gastric acid and digestive enzymes, so it is useful for drugs that degrade in the GI tract.[5]
- It is non-invasive and painless, which improves patient acceptance compared to injections.[1]
- Therapy can be stopped quickly because the film or patch can be removed easily.[4]
- It may provide faster onset because the oral mucosa has good blood supply.[4]
- It is helpful for patients who have difficulty swallowing tablets, such as pediatric, geriatric, and bedridden patients.[4]
- It can be used for both local treatment in the oral cavity and systemic drug delivery through mucosal absorption.[4]
- Mucoadhesive polymers can increase residence time and support controlled or sustained drug release.[4]
- In some cases, a lower dose may be sufficient because absorption can be more direct into systemic circulation.[4]
- With proper taste-masking and thin flexible films, patient compliance can be improved in long-term therapy.[4]

DISADVANTAGES:

- Saliva flow can dilute the drug and wash it away, which may cause dose loss and variable effect.[5]
- There is a risk of unintentional swallowing of the drug or dosage form, reducing buccal absorption.[4]
- Talking, chewing, and swallowing can shorten residence time unless strong mucoadhesion is achieved.[5]
- The mucosal barrier restricts permeation, especially for hydrophilic drugs and large molecules like peptides and proteins.[5]
- Permeation enhancers may cause irritation or mucosal damage if not selected carefully.
- Consistent clinical performance can be challenging because oral conditions vary between patients.

I.OVERVIEW OF THE ORAL MUCOSA:

1.1 Structure

The oral mucosa consists of several layers. The outermost layer is the stratified epithelium, followed by the basement membrane and the lamina propria, while the submucosa forms the innermost layer. The epithelial layer is similar to stratified squamous epithelium present in other parts of the body. It contains a basal layer of cells that actively divide, and these cells gradually move upward through intermediate layers where they differentiate, finally reaching the superficial layer from which they are shed.[21]

The buccal mucosa epithelium is relatively thick, consisting of approximately 40–50 cell layers, whereas the sublingual mucosa is comparatively thinner.[4,21]epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingiva measures at about 100-200 μm]

Fig 1 anatomy of the oral mucosa

1.2 Layers of buccal mucosa.

1. **Epithelium** – stratified squamous layer; main barrier to drug transport.
2. **Basement membrane** – supportive layer separating epithelium from deeper tissues.
3. **Lamina propria** – connective tissue providing strength and support.
4. **Submucosa** – contains blood vessels; important for systemic absorption after crossing epithelium.[4]

1.3 Special importance of buccal mucosa.[7]

1. Buccal mucosa is usually non-keratinized, so it is more permeable than heavily keratinized regions such as hard palate and gingiva.
2. Because of this, the buccal site is commonly selected for mucoadhesive films and patches for controlled local or systemic delivery.[4]

1.4 Physiological factors affecting buccal delivery

1. **Saliva flow** can dilute drug and wash it away → reduces contact time and concentration.
2. **Mucin layer** may improve retention but can also act as an additional diffusion barrier.
3. **Enzymes in saliva/oral tissues** may degrade sensitive drugs (enzymatic degradation).
4. **Cheek movement** (talking, chewing, swallowing) can reduce residence time unless strong mucoadhesion is achieve.[5]

II. BUCCAL ABSORPTION

Buccal absorption means the absorption of a drug through the lining of the cheek (buccal mucosa)**.** When a drug is placed in the buccal area, it dissolves in saliva and passes through the mucosal membrane into the nearby blood vessels. Because this area has a rich blood supply, the drug can enter the bloodstream quickly. Drug transport across the buccal mucosa can take place for it to reach the local and systemic circulation by two pathways [6].

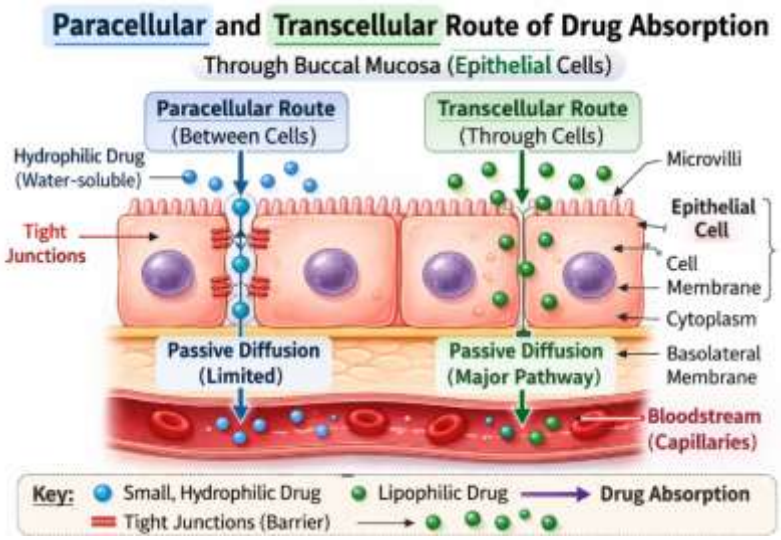


Fig 2. Drug Absorption routes

2.1 Transcellular route – In this pathway, the drug passes directly through the epithelial cells of the buccal mucosa. This route is more suitable for lipophilic (fat-soluble) drugs because the cell membranes are lipid in nature.[7]

2.2 Paracellular route – In this pathway, the drug moves between the cells through the intercellular spaces. This route is generally used by hydrophilic **(**water-soluble**)** drugs, but the absorption is usually slower due to tight cell junctions.[6,7]

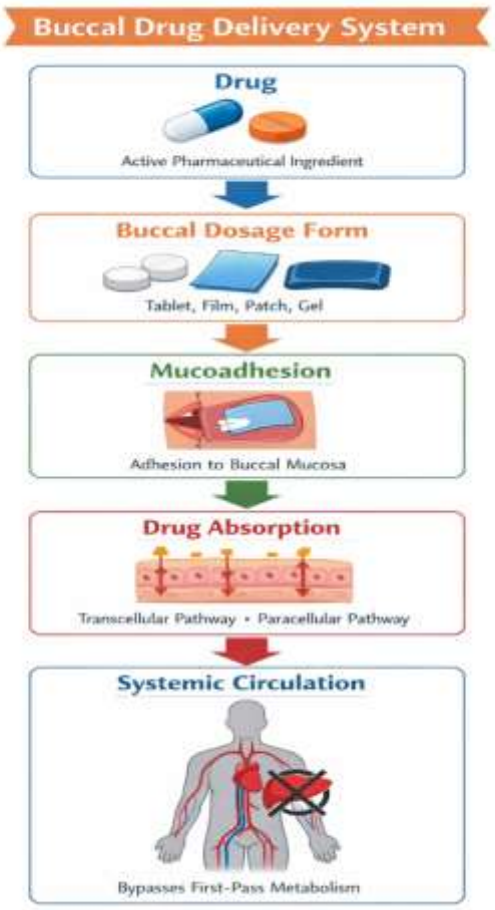


Fig. 3: Schematic representation of the buccal drug delivery process.

III . FACTORS AFFECTING BUCCAL ABSORPTION:

3.1 Permeability Barrier of Oral Mucosa

The permeability barrier of the oral mucosa mainly arises from intercellular lipid materials produced by membrane coating granules (MCGs). These granules contain intracellular lipids that migrate toward the apical surface of epithelial cells. When they reach the surface, their membranes fuse with the cell membrane and release lipid components into the extracellular spaces, forming a barrier that restricts drug penetration.[7,8]

Studies have shown that cultured oral epithelium lacking MCGs becomes highly permeable, allowing compounds to pass that normally cannot penetrate the oral mucosa. Permeation experiments using tracer molecules of different sizes demonstrated that these molecules were unable to pass through intact epithelium. However, when the tracers were introduced beneath the epithelium, they moved through the intercellular pathways, confirming that the barrier corresponds to the region where MCGs are present. This permeability pattern is observed in both keratinized and non-keratinized oral epithelium, indicating that keratinization does not significantly influence the barrier function.[7]Another important limitation for drug transport across the buccal mucosa is enzymatic degradation.

Saliva contains enzymes such as esterase, carbohydrates, and phosphatases, though proteases are generally absent. In contrast, the buccal epithelium contains several proteolytic enzymes, including aminopeptidases. Among them, aminopeptidase N, aminopeptidase A, and aminopeptidase B act as significant enzymatic barriers, particularly affecting the delivery of peptide drugs through the buccal route.[8]

3.2 Physio-chemical characteristics of the drug:

Molecular weight: ions are low penetrate than molecules. Smaller molecules more rapidly penetrate than larger molecules. [9]

Degree of ionization: The pH of saliva is on an average of 6.4. pKa of the drug plays an important role in absorption. If the pKa is greater than 2 for an acid and pKa less than 10 for a base adequate absorption occurs. [9]

Lipid solubility: For optimal drug absorption the partition coefficient between 40-2000 is necessary.[9]

3.3 Environmental factors:

Saliva: Environmental factors in the oral cavity can influence drug absorption through the buccal mucosa. One important factor is saliva. A thin layer of saliva, known as a salivary film, covers the buccal mucosa. The thickness, composition, and movement of this film can affect how quickly a drug dissolves and is absorbed through the mucosal membrane[9,10]

Movement of buccal tissues: the buccal region shows relatively limited movement compared to other parts of the mouth, activities such as eating, drinking, and speaking can still disturb the dosage form. Therefore, mucoadhesive polymers are often incorporated into buccal formulations to help the dosage form remain attached to the mucosal surface for a longer duration.[10]

IV. STRATEGIES TO IMPROVE BUCCAL DRUG DELIVERY

The buccal mucosa acts as a protective barrier that limits the passage of many therapeutic agents into systemic circulation. Therefore, various formulation approaches are employed to improve drug permeation across the buccal membrane. Among these approaches, the use of penetration enhancers and solubility modifiers is widely explored in buccal drug delivery systems.[11]

4.1 Penetration enhancers

Penetration enhancers are substances incorporated into formulations to temporarily increase the permeability of the buccal epithelium. These agents facilitate drug transport by altering the lipid organization of epithelial cell membranes, increasing membrane fluidity, or widening the intercellular spaces. As a result, drug molecules can diffuse more easily through the mucosal barrier. Common penetration enhancers used in buccal formulations include surfactants**,** fatty acids, bile salts, and certain chelating agents. The effectiveness of these agents depends on their ability to enhance drug permeation without causing irritation or permanent damage to the mucosal tissue.[4,11,12]

Another approach to improve drug absorption is the use of solubility modifiers**.** Many drugs intended for buccal delivery exhibit limited aqueous solubility, which can restrict their dissolution and subsequent permeation across the mucosa. Solubility modifiers improve the drug's dissolution rate and maintain an adequate concentration gradient at the absorption site. This can be achieved through the use of cyclodextrins, co-solvents, hydrophilic polymers, or pH-adjusting agents**.** By enhancing the solubility and availability of the drug at the mucosal surface, these modifiers can significantly improve drug transport through the buccal membrane.[13]

The careful selection of penetration enhancers and solubility modifiers plays an important role in optimizing buccal formulations, as these strategies help improve drug absorption while maintaining mucosal safety and patient comfort.

Table 1 : Penetration Enhancers Used in Buccal Drug Delivery Systems

Category	Examples	Mechanism of Action
Surfactants	Sodium lauryl sulfate, Tween 80, Polysorbates	Disrupt lipid structure of epithelial membrane and increase membrane fluidity, enhancing drug diffusion[10]
Bile Salts	Sodium deoxycholate, Sodium taurocholate, Sodium glycocholate	Interact with membrane lipids and proteins to increase mucosal permeability
Fatty Acids	Oleic acid, Lauric acid, Capric acid	Modify lipid packing in cell membranes and enhance intercellular drug transport[7]
Chelating Agents	EDTA, Citric acid	Bind calcium ions and open tight junctions between epithelial cells
Alcohols	Ethanol, Propylene glycol	Increase drug solubility and improve drug partitioning into the mucosal membrane

4.2 Solubility Modifiers

Solubility modifiers are incorporated into buccal formulations to improve the dissolution and availability of poorly water-soluble drugs at the site of absorption. Many drugs used in buccal delivery exhibit limited aqueous solubility, which may reduce their permeation through the mucosal membrane. By improving the drug's solubility, these modifiers help maintain a sufficient concentration gradient across the buccal epithelium, which facilitates drug absorption.[14]

Solubility enhancement can be achieved through different mechanisms such as

Complex Formation
Ph Modification
Co-Solvency
Hydrophilic Carriers

These approaches increase drug dissolution and promote uniform drug distribution within the buccal formulation. As a result, the therapeutic effectiveness of the drug can be improved while ensuring consistent drug release.[14]

Table:2 Solubility Modifiers Used in Buccal Drug Delivery

Category	Examples	Mechanism of Action
Cyclodextrins	β-Cyclodextrin, Hydroxypropyl-β-cyclodextrin	Form inclusion complexes that enhance drug solubility
Co-solvents	Ethanol, Propylene glycol, PEG 400	Improve drug dissolution by increasing solvent capacity
Hydrophilic Polymers	PVP, HPMC, PEG	Enhance drug dispersion and improve wettability
pH Modifiers	Citric acid, Sodium bicarbonate	Adjust microenvironmental pH to improve drug solubility
Surfactants	Poloxamer, Tween 80	Reduce surface tension and increase drug solubilization

V. BIOADHESION

Bioadhesion is the phenomenon between two materials, which are held together for extended periods of time by interfacial forces. It is generally referred as bioadhesion when interaction occurs between polymer and epithelial surface; mucoadhesion when occurs with the mucus layer covering a tissue. Generally bioadhesion is deeper than the mucoadhesion. However the, these two terms seem to be used interchangeably. It is interesting that the interaction between the layers adsorbed from whole saliva resembles the one previously reported between adhesion**:** layers of adsorbed gastric mucus, which points to a strong contribution to the interaction of high molecular weight glycoproteins.[15,16,19]

5.1 MECHANISM OF ADHESION

There are two phases involved in the mechanism of bioadhesion.

The contact stage

The consolidation stage

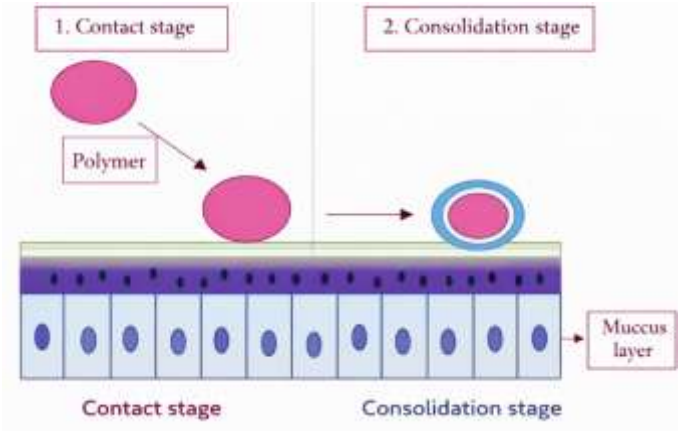


Fig 4: Mechanism of adhesion:

Step 1: The contact stage is the first point of interaction between the drug's two surface polymers and the mucus surface. Following the polymer's soaking and swelling, these two surfaces physically combine. [15]

Step 2: The stage of consolidation involves the bio adhesive polymer's interpenetration into the mucous membrane. The primary mechanism of attachment is the entanglement of the adhesive chemicals with the extended mucus chain, followed by the non-covalent interaction induced creation of secondary bonds. [16]

5.2 THEORIES OF BIOADHESION:

It is simple to expand the theoretical framework for polymer-polymer adhesion to explain the bioadhesion of polymeric substances having living surfaces. The electronic, adsorption, wetting, diffusion, and fracture theories are among the pertinent theories.[15]

Electronic Theory:

According to electrical theory, there is probably going to be electron transfer when the bio adhesive polymer and the Different electronic topologies of glycoprotein networks will result in the creation of two electrical charge layers at the bio adhesive interface [15]

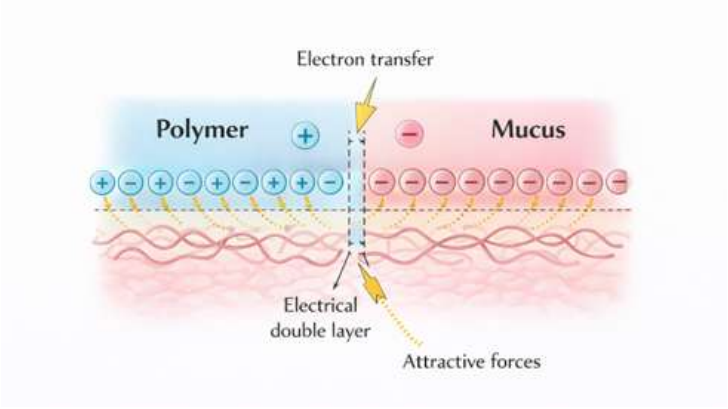


Fig 5: Electronic Theory:

Wetting theory

Wetting theory is mainly applicable to liquid and semi-solid mucoadhesive systems. It explains adhesion in terms of how effectively a formulation can spread over the biological surface, because spreading increases the area of contact. The thermodynamic work of adhesion can be described by[15]

Dupree's equation:

$WA = \gamma A + \gamma B - \gamma AB$
where A is the biological membrane and B is the mucoadhesive formulation.The work of cohesion is expressed as

$Wc = 2\gamma A$ or $2\gamma B$.

For a formulation to spread on a biological surface, the spreading coefficient is:

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

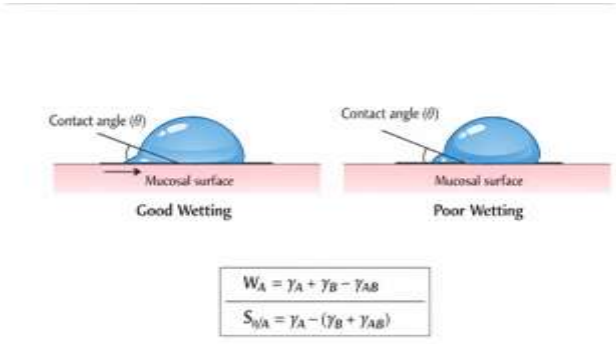


Fig 6: Wetting theory

Diffusion theory

Diffusion theory states that mucoadhesion occurs when the polymer chains and mucus chains mix to a sufficient depth to form a semi-permanent bond. The penetration depth depends on the diffusion coefficient and the contact time. The diffusion coefficient is influenced by polymer properties such as molecular structure and cross-linking characteristics, which can affect the mobility of polymer chains.[16]

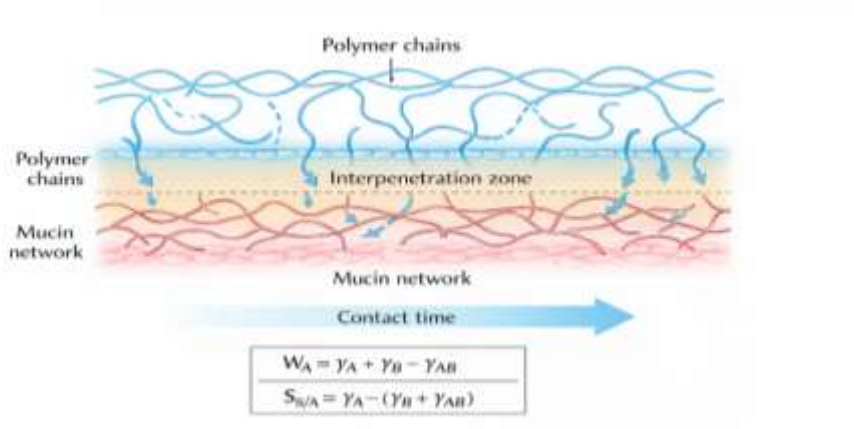


Fig 7: Diffusion theory

Fracture theory

Fracture theory relates mucoadhesion to the force needed to separate two adhered surfaces, which is why it is often linked to detachment-force based evaluation methods.

The fracture strength (G) is expressed as:
$G = (E\varepsilon / L)^{½}$
where E is Young's modulus of elasticity, ε is fracture energy, and L is the critical crack length at separation.[15]

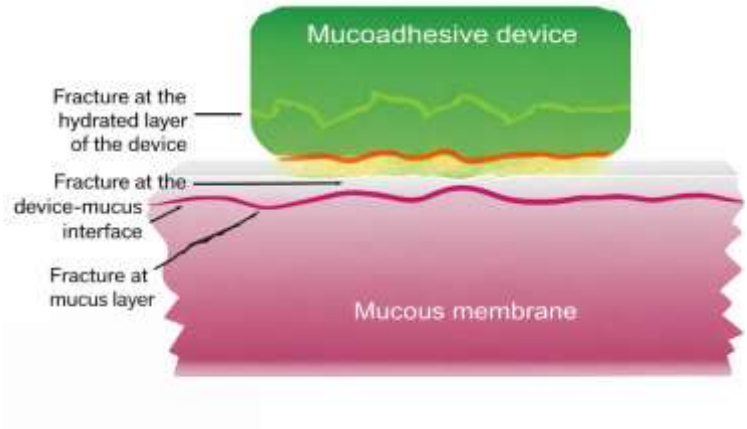


Fig 8: Fracture theory

Adsorption theory

Adsorption theory suggests that after initial contact, adhesion is maintained by surface forces acting between atoms and molecules at the interface. It describes involvement of both primary (covalent) bonds and secondary bonds, although secondary interactions such as electrostatic forces, van der Waals forces, hydrogen bonding, and hydrophobic interactions are most relevant in mucoadhesive drug delivery.[16]

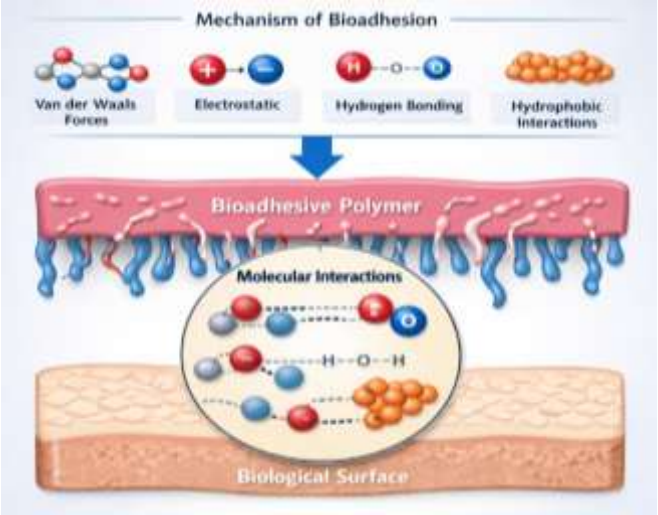


Fig 9: Adsorption theory

VI. BASIC COMPONENTS OF BUCCAL DRUG DELIVERY

A buccal drug delivery system is generally designed using a small number of essential components that work together to ensure retention on the mucosa**,** controlled drug release**,** and effective permeation. These components typically include the drug substance, a mucoadhesive polymer**,** an optional backing membrane, and permeation enhancers when required.[17]

6.1 Drug substance:

Selection of the drug is the first critical step and depends on whether the intended therapy requires rapid release **or** prolonged/controlled release**,** and whether the goal is local action in the oral cavity or systemic absorption through the buccal mucosa. Drugs are usually chosen based on pharmacokinetic suitability. Commonly recommended characteristics include a small conventional dose**, a** biological half-life around 2–8 hours for controlled delivery suitability, and oral administration issues such as variable/high Tmax**,** first-pass metabolism, or pre-systemic elimination.[17,18]

6.2 Mucoadhesive polymer:

The mucoadhesive polymer is considered the backbone of buccal dosage forms because it provides adhesion to the mucin/epithelial surface and helps the dosage form remain in place for a longer period.In many systems, the same polymer also acts as a matrix former, where the drug is embedded inside the polymer network and released gradually as the polymer hydrates, swells, and allows diffusion.The overall performance of buccal delivery (retention, release rate, comfort, and stability) depends strongly on choosing and characterizing an appropriate polymer or polymer blend. An ideal mucoadhesive polymer should be non-toxic, inert, compatible with the oral environment, stable during storage, economical, and capable of forming strong non-covalent interactions with mucin while allowing easy incorporation of the drug.[17,19]

6.3 Backing membrane:

Many buccal patches and films include a backing membrane to improve delivery efficiency. The backing layer helps the dosage form stay attached and, importantly, supports unidirectional release by preventing the drug from diffusing outward into saliva.For this reason, backing materials are selected to be inert and impermeable to the drug and permeation enhancers, so drug loss is minimized and a higher fraction of drug is directed toward the mucosa.[17]

Permeation enhancers:

When the drug has limited permeability across buccal epithelium, permeation enhancers may be included to improve transport through the mucosal barrier.Their role is to increase drug flux by altering the mucosal barrier temporarily or improving drug partitioning into the tissue. However, selection must be careful because strong enhancers can cause irritation; therefore, buccal systems aim to balance enhancement with safety and patient comfort.[18]

VII. TYPES OF BUCCAL DOSAGE FORMS

Buccal drug delivery systems are available in several dosage forms, and the choice mainly depends on the required drug release profile**,** retention time, and whether the aim is local or systemic therapy. The most commonly discussed forms include buccal tablets, films, patches, and semi-solid systems (gels/ointments)**. [**22**,**23]

7.1 Buccal tablets: Buccal tablets are small solid units designed to adhere to the buccal mucosa and release drug either rapidly or in a controlled manner.In many formulations, bilayer tablets are used, where one layer contains the drug and mucoadhesive polymer, while the second layer acts as **an** impermeable backing, helping to direct drug release toward the mucosa and reduce drug loss into saliva. Tablets are generally simple to manufacture, but patient comfort and the possibility of dislodgement due to mouth movements must be considered.[30]

7.2 Buccal films: Buccal films are thin, flexible polymeric strips that hydrate quickly and provide close contact with the mucosa. Films are widely studied because they are comfortable, easy to apply, and suitable for both fast and controlled release depending on polymer selection and film structure.Films can also incorporate taste-masking agents and plasticizers to improve acceptability. [30]

7.3 Buccal patches: Buccal patches are polymeric laminates designed to remain attached for longer durations and are particularly useful for sustained drug delivery. Patch systems can be designed as matrix or reservoir types. In matrix patches, the drug is dispersed throughout the polymer network. In reservoir patches, the drug is placed in a separate core compartment, and release is controlled through a rate-controlling membrane. Many patches include a backing membrane that is impermeable to drug and enhancer, which improves adhesion stability and promotes unidirectional release toward the mucosa.[27]

7.4 Semi-solid systems (gels/ointments): Gels and ointments are mainly intended for local therapy in the oral cavity and are useful when ease of spreading over lesions is needed. However, their retention time is often lower than films/patches because they can be diluted and removed by saliva and oral movements.

7.5 Lozenges and troches: Lozenges and troches solid dosage forms that dissolve slowly in the mouth, releasing the drug gradually in the buccal cavity. These are commonly used for local therapeutic effects in the oral cavity

VII. METHOD OF PREPARATIONS OF BUCCAL DRUG DELIVERY

Buccal films are thin, flexible polymeric dosage forms designed to adhere to the buccal mucosa and deliver drugs either locally or systemically. The method of preparation plays a crucial role in determining film thickness, drug uniformity, mechanical strength, mucoadhesive performance, and release characteristics. Several techniques have been developed for the preparation of buccal films, ranging from conventional solvent-based approaches to advanced solvent-free and digital manufacturing technologies. Among these, solvent casting remains the gold standard for laboratory-scale development, while hot-melt extrusion is increasingly adopted for industrial-scale production.[21,22,24]

8.1. Solvent Casting Method

The solvent casting technique is the most widely used method for preparing buccal films due to its simplicity, reproducibility, and suitability for thermolabile drugs. The method involves dissolving polymers and excipients in a suitable solvent system to form a homogeneous viscous solution, followed by casting, drying, and cutting into desired film sizes.Film-forming polymers such as hydroxyl propyl methylcellulose or polyvinyl alcohol are dissolved in aqueous or hydro alcoholic solvents. The polymer solution is prepared at 40–60°C under continuous stirring for 1–2 hours to obtain a viscous gel with viscosity ranging from 100 to 5000. [24]

8.2. Direct milling

Direct milling involves kneading drug and excipients without the use of organic solvents. The homogeneous mass is rolled into films of required thickness and laminated with backing material. This solvent-free technique eliminates risks associated with residual solvents and improves environmental safety during manufacturing.[24,25]

8.3 Hot Melt Extrusion Technique.

Hot melt extrusion is an advanced manufacturing approach in which drug and thermoplastic polymers are melted and forced through an orifice to produce films. This method offers improved homogeneity, continuous production capability, and suitability for controlled drug release systems. Although less frequently reported for buccal films, it represents a promising industrial scale technology. [25]

IX. ADVANCED METHODS FOR PREPARATION OF BUCCAL DRUG DELIVERY SYSTEMS.

Recent advancements in pharmaceutical technology have introduced several novel methods for the preparation of buccal drug delivery systems to improve drug release, mucoadhesion, and patient compliance. Techniques such as electrospinning, 3D printing, freeze-drying (lyophilization), and inkjet printing are increasingly being explored. Electrospinning produces nanofibrous films with a large surface area that enhances drug dissolution and absorption. 3D printing enables the fabrication of personalized buccal dosage forms with precise control over drug dose, shape, and release profile.

Freeze-drying creates highly porous and lightweight films that rapidly hydrate and dissolve in the buccal cavity, leading to faster drug release. Inkjet printing allows accurate deposition of drug solutions onto polymeric films, ensuring precise dosing and minimal drug wastage. These advanced techniques provide improved formulation flexibility and are considered promising approaches for the development of next-generation buccal drug delivery systems.[32,33,34]

9.1. Electrospinning Method

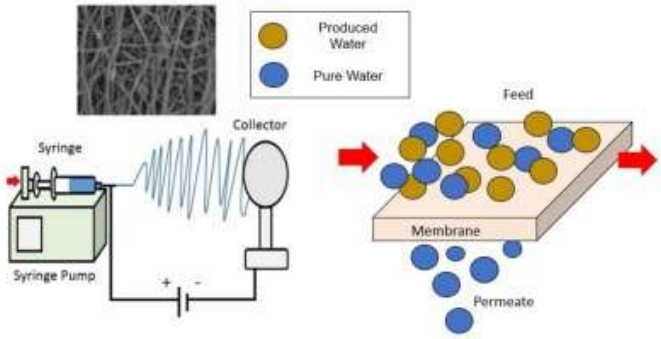


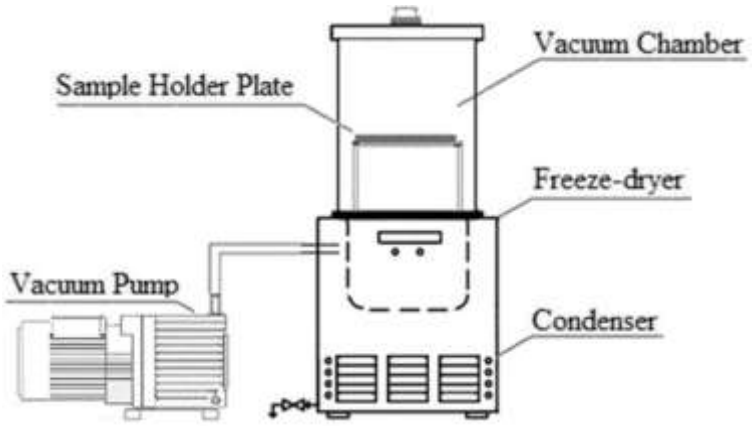
Fig 10: Electrospinning

Electrospinning is an advanced technique used to produce nanofibrous buccal films using a high-voltage electric field. This method generates ultrafine polymer fibers with a very high surface area, which enhances drug dissolution and absorption. Electrospun films show improved mucoadhesion, rapid drug release, and better bioavailability, making this technique promising for modern buccal drug delivery systems.[32]

9.2. 3D Printing Method

3D printing is an emerging pharmaceutical technology that allows the layer-by-layer fabrication of buccal films or patches with precise control over drug dose, shape, and thickness. This method supports personalized medicine, as drug formulations can be customized according to patient requirements. It also enables the development of complex dosage forms with controlled drug release properties.[33]

9.3. Freeze-Drying (Lyophilization) Method



Freeze-drying, also known as lyophilization, is a technique in which a drug–polymer solution is frozen and the solvent is removed by sublimation under vacuum. This process produces highly porous and lightweight buccal films that rapidly hydrate when placed in the oral cavity. The porous structure enhances drug dissolution, quick disintegration, and faster drug release.**[**34**]**

X. EVALUATION OF BUCCAL DRUG DELIVERY SYSTEM

Evaluation of buccal drug delivery systems such as films and patches is necessary to confirm that the formulation **is** safe for oral tissues, possesses uniform thickness and drug content, shows appropriate swelling behavior, adheres effectively to the mucosa, provides controlled drug release, and remains stable under physiological conditions of the oral cavity.[25]

Surface pH

Surface pH is determined to ensure that the buccal formulation does not cause irritation to the oral mucosa and remains compatible with the normal pH of saliva. For this study, buccal patches are placed on an agar plate and allowed to swell for approximately two hours**.** After swelling, the pH is measured by gently placing pH paper or a pH electrode on the surface of the hydrated patch. Ideally, the surface pH should be close **to** neutral salivary pH (about 6.5–7.0)**. [**26**]**

Swelling Study and Swelling Index

The swelling behavior of buccal formulations indicates their hydration capacity, polymer relaxation, and potential for mucoadhesion**.** In this method, individual buccal patches are initially weighed and recorded as W_1. The patches are then placed on 2% agar gel plates and incubated at 37 ± 1°C**.** At predetermined time intervals, the patches are removed and the excess surface moisture is carefully wiped off. The swollen patches are then reweighed and recorded as W_2**.**

The swelling index is calculated using the following equation:

$$\text{Swelling Index (SI)} = (W_2 - W_1) / W_1 \times 100$$

This parameter helps in understanding the water uptake capacity of the polymeric system**,** which influences mucoadhesion and drug release behaviour.

Folding Endurance

Folding endurance is determined to evaluate the flexibility and mechanical strength of buccal films or patches. In this test, a small section of the film is repeatedly folded at the same location until it breaks. The number of times the film can be folded without breaking is recorded as the folding endurance value. A higher folding endurance indicates that the film possesses good mechanical strength and flexibility, which is essential for handling and application in the oral cavity.[26]

Drug Content Uniformity

Drug content uniformity is measured to confirm that the drug is evenly distributed throughout the buccal formulation. For this study, a specified area of the buccal film or patch is dissolved in a suitable solvent such as phosphate buffer or methanol. The solution is then filtered and analyzed using UV–visible spectrophotometry or high-performance liquid chromatography (HPLC)**.** The amount of drug present is calculated to ensure uniform drug loading within the formulation.[25]

Mucoadhesive Strength

Mucoadhesive strength indicates the ability of the buccal formulation to adhere to the mucosal surface for a sufficient period of time. This parameter is generally measured using a texture analyzer or modified physical balance method with excised animal buccal mucosa (commonly porcine mucosa). The force required to detach the film or patch from the mucosal surface is recorded as the mucoadhesive strength. Adequate mucoadhesion helps in maintaining the dosage form at the site of application and enhances drug absorption.[27]

In-vitro Drug Release Study

In-vitro drug release studies are conducted to determine the rate and extent of drug release from the buccal formulation**.** The test is commonly performed using USP dissolution apparatus or Franz diffusion cells with phosphate buffer (pH 6.8) as the dissolution medium. Samples are withdrawn at predetermined time intervals and analyzed spectrophotometrically to measure the amount of drug released over time.

Ex-vivo Permeation Study

Ex-vivo permeation studies are carried out to determine the ability of the drug to penetrate through the buccal mucosal membrane**.** In this method, freshly excised buccal mucosa (commonly obtained from porcine or goat tissue) is mounted between the donor and receptor compartments of a Franz diffusion cell. The buccal formulation is placed on the mucosal surface in the donor compartment, while the receptor compartment contains phosphate buffer solution (pH 6.8) maintained at **37 ± 0.5°C** and continuously stirred. At

predetermined time intervals, samples are withdrawn from the receptor compartment and analyzed using UV–visible spectrophotometry or HPLC to determine the amount of drug permeated through the mucosa.[27]

Mucoadhesive Residence Time (In-vitro)

The mucoadhesive residence time test is performed to evaluate how long the buccal formulation remains attached to the mucosal surface under simulated oral conditions. In this test, buccal mucosa is fixed onto a glass slide and the buccal film or patch is attached to the mucosal surface. The slide is then placed in a phosphate buffer solution (pH 6.8) at 37°C and subjected to gentle agitation. The time required for the film to detach from the mucosa is recorded as the mucoadhesive residence time.[25,26,27]

Stability Studies

Stability studies are conducted to evaluate the physical and chemical stability of the buccal formulation during storage**.** The prepared buccal films or patches are stored under specified conditions such as 25°C/60% RH or 40°C/75% RH **f**or a defined period of time according to stability guidelines. During storage, parameters such as drug content, appearance, surface pH, and drug release profile are periodically evaluated to ensure that the formulation remains stable.[28,29]

XI. CHALLENGES IN BUCCAL DRUG DELIVERY SYSTEMS

Despite the numerous advantages of buccal drug delivery systems, several challenges limit their widespread application. One major limitation is the relatively small surface area of the buccal mucosa, which restricts the amount of drug that can be absorbed. Continuous saliva secretion can dilute the drug and reduce the residence time of the dosage form at the absorption site. Additionally, movements of the oral cavity during speaking, chewing, and swallowing may lead to displacement of the buccal formulation.

Another challenge is the permeability barrier of the buccal epithelium, which restricts the absorption of hydrophilic drugs and macromolecules such as peptides and proteins. Enzymatic degradation within the oral cavity can also reduce the stability of certain drugs. Furthermore, patient acceptability may be affected by factors such as unpleasant taste, irritation, or discomfort caused by the dosage form.

Therefore, the development of effective buccal drug delivery systems requires careful selection of polymers, permeation enhancers, and formulation techniques to overcome these limitations while ensuring patient safety and comfort.

XII . RECENT TRENDS AND FUTURE PERSPECTIVES IN BUCCAL DRUG DELIVERY SYSTEMS

Recent advancements in pharmaceutical technology have significantly improved the development of buccal drug delivery systems. Modern research is focusing on the use of advanced polymeric materials, nanotechnology-based carriers, and innovative manufacturing techniques to enhance drug permeation and mucoadhesion. Nanoparticles, nanoemulsions, and nanofibrous systems are increasingly being incorporated into buccal formulations to improve drug solubility, stability, and bioavailability. Techniques such as electrospinning enable the production of nanofibrous buccal films with high surface area, which enhances drug dissolution and absorption. In addition, three-dimensional (3D) printing technology has emerged as a promising approach for the fabrication of personalized buccal dosage forms with precise control over drug dose, size, and release characteristics.

Looking toward the future, buccal drug delivery systems are expected to play an important role in the delivery of macromolecules such as peptides, proteins, and vaccines, which are normally degraded in the gastrointestinal tract. The development of novel mucoadhesive polymers, permeation enhancers, and stimuli-responsive drug delivery systems may further improve the effectiveness of buccal formulations. Furthermore, the integration of nanotechnology and personalized medicine is likely to expand the therapeutic potential of buccal drug delivery systems. Continuous research in formulation design and advanced drug delivery technologies will contribute to the development of safer, more efficient, and patient-friendly buccal drug delivery platforms.

In addition to technological innovations, increasing attention is being given to the development of multifunctional buccal drug delivery systems that combine mucoadhesion, controlled drug release, and enhanced permeation. Researchers are exploring the use of smart polymers and stimuli-responsive materials that can respond to changes in pH, temperature, or enzymatic activity in the oral cavity, thereby providing more precise control over drug release. Moreover, hybrid systems that incorporate nanoparticles within polymeric buccal films are being investigated to improve drug stability and targeted delivery. Such advanced approaches may help overcome current limitations associated with drug permeability and residence time on the buccal mucosa. With ongoing progress in material science and pharmaceutical engineering, buccal drug delivery systems are expected to become an important platform for the delivery of both conventional drugs and complex biological therapeutics

CONCLUSION

Buccal drug delivery systems have emerged as an important alternative route for drug administration due to their ability to bypass hepatic first-pass metabolism and enhance drug bioavailability. The buccal mucosa provides a well-vascularized surface that allows rapid drug absorption and offers both local and systemic therapeutic effects. Various buccal dosage forms such as tablets, films,

patches, and gels have been developed using mucoadhesive polymers to improve drug retention and controlled release at the site of absorption. The success of buccal drug delivery largely depends on several factors including drug physicochemical properties, polymer selection, and formulation design.

Recent advances in pharmaceutical technology, including nanotechnology, electrospinning, and three-dimensional (3D) printing, have significantly improved the development of buccal drug delivery systems. These technologies enable the formulation of more efficient, patient-friendly, and personalized dosage forms. However, certain challenges such as limited absorption area, saliva dilution, enzymatic degradation, and mucosal irritation still restrict the widespread application of this delivery system. Continuous research focusing on novel mucoadhesive polymers, permeation enhancers, and advanced formulation strategies is expected to overcome these limitations. Overall, buccal drug delivery systems represent a promising platform for future drug delivery, particularly for drugs with poor oral bioavailability and for the delivery of peptides, proteins, and other sensitive therapeutic agents.

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