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MUCOADHESIVE BUCCAL FILMS: ENHANCING DRUG DELIVERY THROUGH MUCOSAL SURFACES

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ABSTRACT

Mucoadhesive buccal films are innovative drug delivery systems designed for effective local and systemic therapeutic action via the oral mucosa. This review explores anatomical, physiological, and formulation factors that influence their performance. Key advantages include bypassing hepatic first-pass metabolism, enhanced bioavailability, patient compliance, and controlled drug release. The article details mechanisms of mucoadhesion, polymers, plasticizers, and manufacturing techniques such as solvent casting and hot-melt extrusion. Evaluation parameters, including mechanical strength, drug content, and in vivo residence time, are outlined. Despite formulation challenges, recent advances in nanoformulations and hybrid films offer promising prospects for commercial and clinical applications.

KEYWORDS: Mucoadhesive films, Buccal film, Buccal drug delivery, Oral physiology, Mucoadhesion.

INTRODUCTION

The development of novel approaches in drug delivery system for the drug molecules which are already existed in market not only improves the performance of the drugs in terms of safety and efficacy but it also improves the patient compliance along with other therapeutic benefits. There are several routes of drug administration and each route has its own disadvantages. As compared to injectable and oral delivery of drugs the buccal delivery is mostly preferred routes of drug delivery. Oral drug delivery is more convenient, but it can also lead to issues such hepatic first pass metabolism, enzymatic drug degradation in gastrointestinal disorders, and low bioavailability, which can result in insufficient drug absorption.[1] Mouth dissolving or mucoadhesive buccal film is a new and promising dosage form with significant benefits because of its ability to distribute drugs.[2]

Buccal drug delivery is defined as the administration of drugs to the buccal mucosa, located on the inside of the cheek within the mouth, and has capability of facilitating both local and systemic drug delivery.[3] This route avoids hepatic first-pass metabolism, enzymatic drug degradation, and it provides effective therapy to patient groups which unable to swallow or with swallowing difficulties.[4] The delivery systems that use the bioadhesion of specific polymers—which become sticky when hydrated—to target a medicine to a specific area of the body for a prolonged amount of time are known as mucoadhesive drug delivery systems. Limited absorption area, salivary restoration cycle, masticatory effects during eating, and mucosal membrane barrier layers are the primary formulation issues encountered when creating buccal drug-delivery systems for systemic action.[5]

This review was focused on mucoadhesive buccal films, and discusses the patient-related physiological, pathological and pharmacotherapeutic factors which underpin their development.

ANATOMICAL AND PHYSIOLOGICAL FEATURES OF BUCCAL MUCOSA

Structure of oral mucosa

Lips, cheeks, hard and soft palates, and the floor of the mouth are all parts of the buccal/oral cavity (figure 1). There are two areas in the oral cavity. The cheeks, lips, teeth, and gingival (gums) form the outer oral vestibule. The hard and soft palates make up the roof of the oral cavity proper, which stretches from the teeth and gums back to the fauces, which lead to the pharynx. The tongue protrudes from the cavity's floor.[6]

The oral cavity can be divided into specific regions, including:

- Gingiva
- Hard palate
- Soft palate
- Tonsil
- Tongue

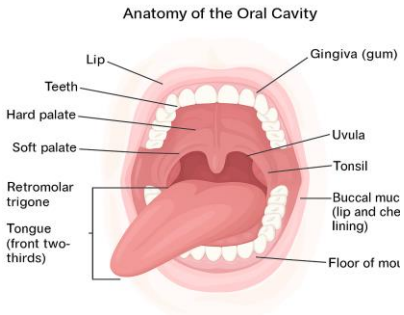

Figure 1: Mucosal region of mouth.

The oral cavity is divided into four layers: keratinized, granular, prickle-cell, and basal layer (figure 2).[7]

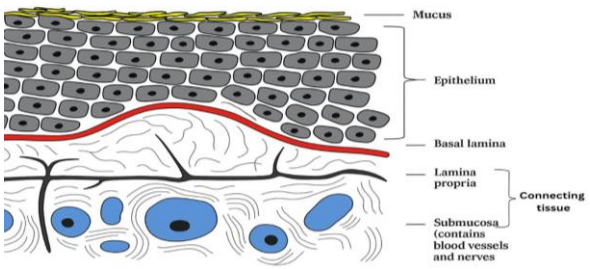

Figure 2: Structure of oral mucosa.[8]

Role of Saliva and Mucus

A variety of electrolytes and proteins, including enzymes, immunoglobulins and other antimicrobial factors, mucosal glycoproteins, traces of albumin, and certain polypeptides and oligopeptides important to oral health, are present in salivary fluid, an exocrine secretion that is composed of about 99% water.[9,10]

Functions of Saliva

- Buffer capacity
- Dilution and cleaning
- Integrity of tooth enamel
- Protection and Lubrication
- Digestion
- Dilution and Cleaning
- Buffer capacity

Role of mucus

Mucus is negatively charged and contains large glycoproteins called as mucins. Mucins consist of a protein core, rich in O glycosylated serine and threonine, containing many helix-breaking proline residues. The pH of Saliva is 5.8-7.4.[11]

Functions of Mucus[12,13]

- Protective in nature due to hydrophobicity
- Cell-cell adhesion
- Lubrication
- Bioadhesion of mucoadhesive drug delivery system

Characteristics of oral environment influencing buccal drug delivery system:

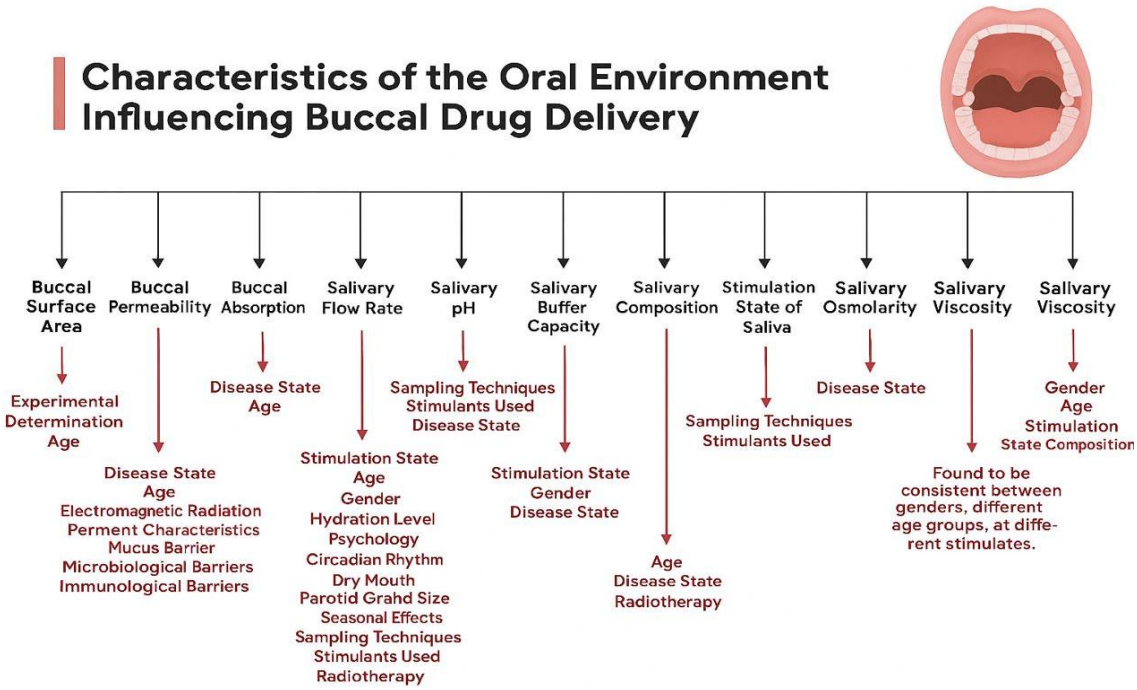

Figure 3: Overview of the characteristics of the oral environment relevant to buccal drug delivery (black) and the factors that influencing them (red).[14,15,16]

Mucoadhesion

Mucoadhesion, which causes medication to stick to our body's mucous membranes, can be used to distribute medication. This increases the length of time the drug acts, which may enhance absorption and treatment effectiveness.[17]

Mechanism of mucoadhesion

Mechanism of mucoadhesion is divided into two steps:

1. Contact stage
2. Consolidation stage

The contact stage involves close contact between a mucoadhesive polymer and a membrane by wetting and swelling process. Consolidation stage requires penetration of the mucoadhesive into cleft of the tissue or into the surface of the mucus membrane.[18,19]

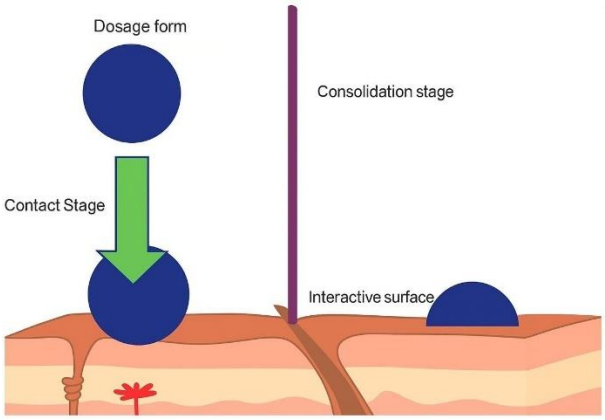

Figure 4: The process of consolidation.

Factors affecting mucoadhesion

i. Hydrophilicity
ii. Spatial orientation
iii. pH
iv. Cross-linking and Swelling.[20]

Theories of mucoadhesion

Following are theories that have been considered for the complete understanding of the mechanism of mucoadhesion or bio adhesion.[21]

1. Wetting theory
2. Diffusion theory
3. Electronic theory
4. Fracture theory
5. Adsorption theory
6. Dehydration theory

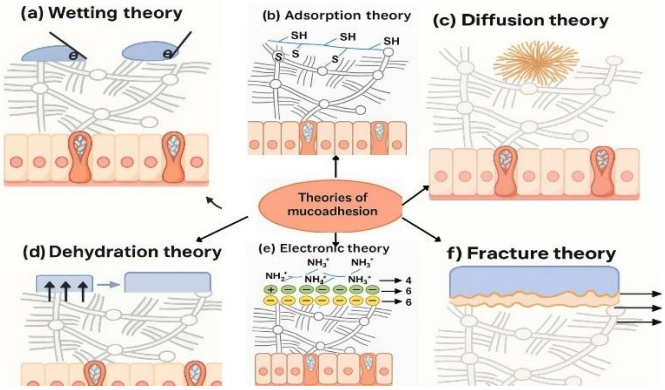

Figure 5: Theories of mucoadhesion.[22,23]

BIOADHESIVE

The ability of a drug delivery system to adhere to a biological substrate for an extended period of time is known as bioadhesive. Organs that contain mucus could be the biological substrate. When it comes to drug delivery systems, bioadhesion is essential for maximizing systemic or local delivery for various administration routes.[24]

1. Increase the duration of communication
2. Any drug delivery's localization

Type 1 (adhesion between two biological phases): interactions between proteins that include thrombin and fibrinogen, avidin and biotin, and disulphide bonds.[25]

Type 2 (Biofilm formation on prosthetic implants and devices): Biological Phase Adhesion to an Artificial Substratum).[25]

Type 3: (Adhesives for tooth enamel and synthetic hydrogels for connecting tissues).[25]

In drug delivery, "bioadhesion" refers to the way a drug transporter system clings to a particular biological site. Biological surfaces include the mucous lining of a tissue and epithelial tissue. Mucoadhesion is the term for the sensation of sticky attachment to a mucus lining. The distinction between bioadhesion and mucoadhesion must be made.

Characteristics that are ideal

1. It must not be bothersome.
2. It should ideally establish a solid, non-covalent connection with the surface of the epithelial cells.
3. It should adhere to moist tissue right away and be site specific.
4. It should remove any obstacles to the drug's release and make its inclusion simple.
5. Throughout the dosage form's storage period, the polymer must not break down.[26]

Different Bioadhesive Mechanism Types

1. Physical bioadhesion forces including electrostatic interaction and Van der Waals forces are the foundation of physical bioadhesion.
2. Chemical bioadhesion: The bioadhesive and the tissue interact covalently.
3. Mechanical bioadhesion: This is based on the tissue and bioadhesive locking together mechanically.[27]

Mechanism of Action (MOA) of Bioadhesive's:

Wounds, mucous membranes, and skin are among the biological tissues that bioadhesives form a strong, intimate bond with. The following important steps are included in the MOA:

1. Wetting: The bioadhesive's surface energy allows it to moisten the surface of biological tissue upon contact.
2. Penetration: By putting itself through the tissue's surface, the bioadhesive forms a strong bond with it.
3. Adhesion: The bioadhesive forms a strong adhesive contact with the tissue covalent connection through a number of mechanisms, including as hydrogen bonding, electrostatic interactions, and hydrophobic interactions.
4. Retention: The bioadhesive's ability to hold its adhesive properties over time allows for wound healing, tissue repair, or prolonged medication administration.

The following variables affect the bioadhesive mechanism:

1. Surface energy affects how the bioadhesive wets and spreads.
2. Tissue characteristics: These affect how well the bioadhesive adheres and stays in place.
3. The strength and adhesion mechanism are influenced by the bioadhesive formulation.
4. Environmental elements: Impacting the bioadhesive's efficacy and stability. Developing and refining bioadhesive systems for a range of medical applications requires an understanding of the MOA of bioadhesives.[25]

Table 1: Polymer used as bioadhesive in drug delivery.

Polymer	Sensitive toward bio adhesive
Poly(acrylic acid/divinyl benzene)	+ + +
Carboxymethyl cellulose	+ + +
Caropol934	+ + +
Hydroxyl ethyl cellulose	+ + +
Tragacanth	+ + +
Thermally modified starch	+
Guar gum	+ +
Polycarbophil	+ + +
Polyvinyl pyrrolidone	+
Acacia	+
Poly ethylene glycol	+

MUCOADHESIVE BUCCAL FILMS

The administration of medications to the buccal mucosa, which is found inside the mouth on the inside of the cheek, is known as buccal drug delivery. This process can support both local and systemic drug delivery.[28] By avoiding first pass metabolism and enzymatic drug degradation, this approach offers patients who are incapable of swallowing an efficient course of treatment.[29] Among the few dosages forms available in these field, buccal tablets are the most widely used in the commercial sector because of their greater flexibility, which improves comfort and their adjustable size, mucoadhesive buccal films are seen to be preferred dosage form among patients when compared to buccal tablets.[28]

These films are primarily recommended for sustained medication release within the oral cavity and are made up of several layers.[30] The lack of translation from published study into the commercial sector indicates that the buccal route of administration is underutilized despite its therapeutic potential. A particular type of pharmaceutical formulation known as mucoadhesive buccal films (MBF) uses a water-dispersible polymer to quickly hydrate, attach, and dissolve when applied to the tongue or oral cavity, enabling effective systemic drug release.[31]

These films, which provide better safety and a quicker commencement of action, have rapidly become recognized as a unique administration route. Compared to other buccal dose forms such as buccal tablets, lozenges, and the like, buccal films are a sophisticated and effective dosage form that offer greater bioavailability. This is accomplished by avoiding the first-pass metabolism in the liver. These films disintegrate in the buccal mucosa of the patient after administration. Drug delivery takes place on the oral mucosa, which is further separated into buccal and sublingual mucosa.[32]

Mucoadhesive films are ideal for both local and systemic therapy because they adhere firmly to the mucosal membrane, distribute over a larger surface area, provide precise dosing, and enhance overall drug absorption. The most preferred dosage form for buccal application is biocompatible and biodegradable mucoadhesive films because of their adaptability, versatility, physical flexibility, comfort, light weight, acceptability, resistance to mechanical stress, and scalability.[33]

Characteristics of ideal buccal film[34-38]:

- Compatible with medicament
- High degree of safety and no toxicity
- No irritation occurs
- pH that is biocompatible
- More adaptability or enhanced pilability
- Instant adherence to the mucosa of mouth
- Long-term retention
- Optimal medication absorption rate and extent
- Controlled or regulated drug distribution

Table 2: Physical Characteristics of buccal films.[39]

Property	Flash release wafers	Mucoadhesive melt away wafers	Mucoadhesive sustained release
Area(cm^2)	2-8	2-7	2-4
Thickness (µm)	20-70	50-500	50-250
Structure (film)	Single	Single or multilayer	Multilayer
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution

Merits of mucoadhesive buccal film

1. Accurate dosage as opposed to liquid dosage. It is possible to disguise your taste. Both mouth feel and stability are good. Using less excipient is required.
2. Easy handling by consumers, storage, and transportation.
3. The same goes for patients who are uncooperative, disabled, or intellectually challenged.
4. Enhances the dosage form's duration of stay at the absorption site. Hence, bioavailability is enhanced.
5. The medication is protected from deterioration in the acidic environment and gastrointestinal tract. Because buccal film has a wide surface area, it dissolves and disintegrates quickly in the mouth cavity.[40]

Demerits of mucoadhesive buccal film

1. Drug concentrations are low at the surface of the absorbing membrane because saliva is constantly produced into the oral cavity, diluting medications at the site of absorption. The greatest amount of dissolved or suspended

released medication eliminated from the site of absorption when saliva is instinctively swallowed. Furthermore, there is a chance that the delivery system will be ingested.

2. The properties of the medicine can determine the limits of using the oral cavity as a drug delivery site. The choice of potential drugs via the buccal route may be restricted by taste, irritability, allergies, and side effects such tooth discoloration or erosion. The patient was unable to eat, drink, or converse at the same time with traditional buccal drug administration devices.[41]
3. The buccal drug delivery method has several restrictions, including the inability to provide medications that are unstable at mouth pH.
4. This method is incompatible with drugs that irritate the mucosa, have an offensive odor, or have a bitter or unpleasant taste.
5. Only this method is suitable for administering medications that are absorbed by passive diffusion.[42]

Therapeutic application

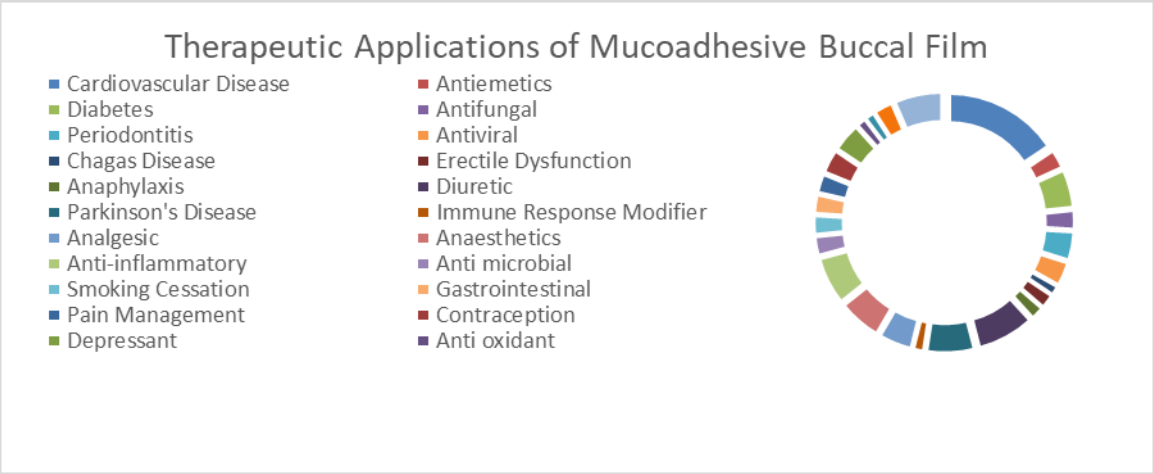

Figure 6: Diagram Illustrating the Therapeutic Areas and Diseases where the use of Mucoadhesive Buccal Films have been demonstrated.[43-45]

Design & formulation aspects of buccal films

The intended drug concentration level is usually not maintained by conventional buccal dose forms, either in the systemic circulation or on the targeted mucosal location. Salivary refurbishment cycle and mechanical stress from masticatory action are the main formation obstacles.[46,47]

Drug substance/API

When designing mucoadhesive drug delivery systems, the right drug should be chosen based on its pharmacokinetic characteristics. Medications with a biological half-life of two to eight hours make excellent choices for regulated drug administration.[48] Usually, 5–30% (w/w) of the medication can be utilized to make the buccal film. Medications that are hydrophilic are in the form of dissolved substance or solid solution, whereas medications that are hydrophobic are uniformly distributed across the buccal film.[49]

Mucoadhesive Polymers

Mucoadhesion is primarily driven by polymer hydration and swelling caused by water diffusion and subsequent mucin dehydration. Swelling should encourage interpenetration between mucin chains and the polymer chain's flexibility,

strengthening the mucoadhesive power. The polymer's spreadability and capacity to create distinct kinds of intermolecular interactions at different hydration stages dictate which properties are best suited for buccal formulation. There are numerous ideas that explain the mechanisms of adhesion between the polymer and mucin, including wetting, fracturing, diffusion, electrical, adsorption, and dehydration. Using a contact angle goniometer to quantify a material's wetness, one can use wetting theory to calculate the mucoadhesion. Molecular mass, viscosity, elasticity, crosslinking density, hydrogen bonding ability, charge, solubility, hydration, swelling, and contact time are only a few of the variables that affect the polymer's diffusion coefficient.[50]

Polyacrylic acid and its copolymers, including acrylic acid polyethylene glycol (PEG), monomethyl ether copolymer, polyvinyl alcohol (PVA), chitosan, sodium alginate, gelatin, carrageenan, and hyaluronic acid[51,52], as well as cellulose derivatives, including sodium carboxymethyl cellulose (NaCMC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), and eudragit RS 100, are the most commonly used polymers in buccal dosage forms. Due to its electrostatic interaction with the negatively charged O-linked oligosaccharide chain of mucin, chitosan, a naturally occurring positively charged, biocompatible, and biodegradable polymer, has been extensively used as a mucoadhesive polymer.[53]

Table 3: Commonly used bioadhesive polymers in pharmaceutical applications.

Criteria	Categories	Examples
Source	Semi natural/Natural	*Agarose*, *chitosan*, *gelatin*, *Hyaluronic acid*, Various gums (guar gum, xanthan, gellan, *carrageenan*, pectin, and *sodium alginate*.)
	Synthetic	Cellulose derivatives: CMC, thiolated CMC, NaCMC, HEC, HPC, HPMC, MC
		Poly (acrylic acid)-based polymers: CP, PC, PAA, polyacrylates, poly(2-hydroxy ethyl methacrylate), copolymer of acrylic acid and PEG.
Aqueous solubility	Water soluble	CP, HEC, HPC, HPMC, PAA, NaCMC, sodium alginate.
	Water insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC.
Charge	Cationic	Aminodextran, chitosan, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, NaCMC, xanthan gum.
	Non-ionic	Hydroxy ethyl starch, HPC, poly(ethylene oxide), PVA
Potential	Covalent	PVP, scleroglucan
	Hydrogen bond	Cyanoacrylate
Bio adhesive forces	Electrostatic interaction	Acrylates[hydroxylated, methacrylate], CP, PC, PVA

Plasticizer

It is a component that the oral films require. The choice of plasticizer is based on how well it works with the polymer and what kind of solvent is utilized for film casting. This increases the film's pliability and decreases its brittleness. They are employed at concentrations ranging from 1 to 20% w/w of dry polymer weight.

Examples include castor oil, glycerol, propylene glycol, low molecular weight polyethylene derivatives, citrates such as triacetin and acetylcitrate, and phthalate derivatives such as dimethyl, diethyl, and dibutyl derivatives.[54]

Plasticizers: PEG-100, 400, propylene glycol, etc.

Penetration Enhancers

Table 4: List of penetration enhancers, transport mechanisms.

Category	Examples	Transport mechanism	References
Surfactants	Anionic: Sodium lauryl sulphate, sodium dodecanoate Cationic: Cetylpyridinium chloride	Disruption of intercellular lipids and integrity of protein Increase water solubility of drugs	55
	Non-ionic: Polyoxyethylene-9-lauryl ether, nonylphenoxy poly oxyethylene, polysorbates (Tweens), sorbitan fatty acid esters (Spans), macrogol ethers (Brijs), macrogol esters (Myrjs)	Hydrophobic interaction between surfactant and keratin fibrils causes swelling of epithelium	
	Bile salts: Sodium taurocholate, sodium cholate, sodium deoxycholate, sodium taurodihydrofusidate, sodium taurodeoxycholate	Penetration into intercellular regions, increase fluidity, solubilization and extraction of lipids Interaction with keratin leads to disruption of corneocytes	
Fatty acids and their esters	Capric acid, caprylic acid, lauric acid, linoleic acid, linolenic acid, oleic acid, 2-octyldodecyl myristate, 1-[(N,N dimethylamino)propan-2-yl]dodecanoate)	Interact with phospholipid domain and increase the membrane fluidity	56
Cyclodextrins	Alpha, beta, gamma cyclodextrins, methylated cyclodextrins	Disruption of intercellular lipids and integrity of protein	55
Polymers	Cationic: Chitosan, trimethyl chitosan, poly-L-arginine, L-lysine	Ionic interaction with negatively charged carboxyl and sulfate groups on mucin	57
Chelating agents	Ethylenediaminetetraacetic acid, polyacrylate, citric acid, salicylates	The chelators form complexes with Ca2+ ions	57

Taste masking & Sweeting Agent

Masking the harsh taste of medications is crucial to improving patient compliance. Taste masking agents are techniques that can be used to cover up the bitter taste, such as complex creation or salting-out technology (buccal film). Examples of artificial sweeteners include saccharin, aspartum, sucralose, and others, whereas examples of natural sweeteners include sucrose, dextrose, fructose, glucose, and maltose.

The common sweeteners are maltose, sucrose, glucose, fructose, dextrose, and liquid glucose. When fructose is sweeter than sucrose or dextrose, it is quickly absorbed by the mouth.[58]

Flavoring agents

Another material known as a flavoring agent may be included in an orodispersable system. Among the many different types of flavoring agents are peppermint oil, cinnamon oil, spearmint oil, nutmeg oil, vanilla, cocoa, coffee, chocolate, citrus, apple, raspberry, cherry, and pineapple, among others.[58]

Coloring Agents

Coloring chemicals are used to enhance buccal film's look. FD&C has approved a variety of coloring chemicals. For buccal film formulations where part of the formulation ingredients or medications are present in insoluble or suspension form, pigments such as titanium dioxide or FD&C-approved coloring additives are added at concentrations no more than 1%w/w.[58,59]

Saliva Stimulating Agent

These substances are used to increase saliva production, which aids in the buccal film's breakdown. Acids such as citric, tartaric, ascorbic, and malic acids are saliva-stimulating substances.

The incorporation of this chemical into the formulation is crucial because it speeds up the production of saliva, which causes the film to dissolve quickly and enter the buccal cavity. Typically, acids that are used to prepare food can also be used to stimulate saliva. Ascorbic acid, lactic acid, citric acid, malic acid, and tartaric acid are a few examples of salivary stimulants; citric acid is the most commonly used.[58]

Surfactant

As a solubilizing or wetting agent, surfactants are employed. Surfactant is used to breakdown the film quickly—within seconds—and release the medication instantly. Surfactant is a useful tool for increasing the solubility of poorly soluble medications in buccal fluid. Examples include sodium lauryl sulphate, Polaxamer 407, tweens and spans, benzoalkonium chloride, and benzoethonium chloride.[60]

PREPARATION METHOD / MANUFACTURE

Solvent Casting

The Solvent Casting Method's steps:

Step 1: Making the casting solution

Step 2: De-aeration of the mixture

Step 3: Fill the mold with the proper amount of solution.

Step 4: The casting solution is dried

Step 5: Cutting the final dosage form to include the required quantity of medication is step five.[61]

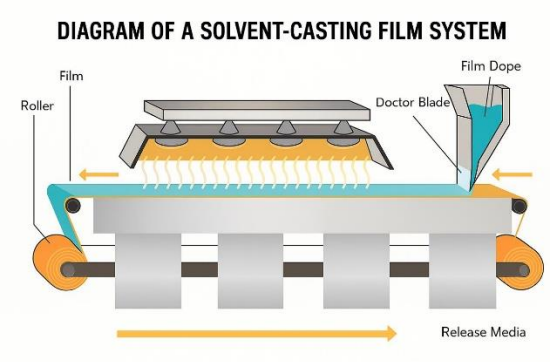

Figure 7: Solvent casting method.[62]

Table 5: Advantages and disadvantages of solvent casting method.[63]

Advantages	Disadvantages
1. Simple, reproducible, and established process	1. Drug re-crystallisation after production
2. Industrial solvent casting offers better control over film thickness & polymer concentrations	2. Difficult to achieve dose uniformity

Hot Melt Extrusion

The medication and other excipient mixture is melted in the hot melt extrusion process then pushed through a hole to produce a more uniform substance in various forms, such as films, tablets, or granules. The transdermal medicine

delivery system makes advantage of it.[61] Hot Melt Extrusion (HME) has a variety of uses in the pharmaceutical industry since it is a continuous, repeatable process that may be automated.[63]

The Hot Melt Extrusion Method's steps:

Step 1: A solid mixture of the medication and carriers is made.

Step 2: The mixture is melted by the extruder's heaters.

Step 3: The dies are used to finally form the melted substance into films.

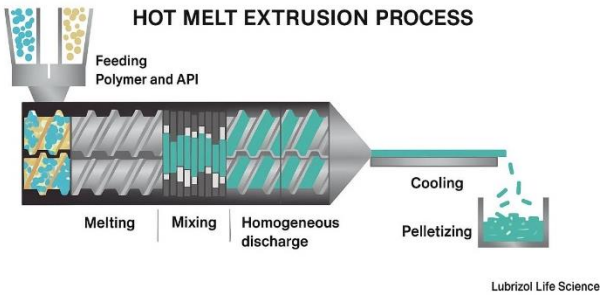

Figure 8: Diagram of Hot Melt Extrusion.

Table 6: Advantages and disadvantages of hot melt extrusion method.

Advantages	Disadvantages
1. Fewer operation units	1. Thermal process creates stability problem.
2. Better content uniformity	2. Flow properties of polymer are important to processing.
3. An anhydrous process	3. Limited numbers of polymers are available.

Direct Milling

In this process, patches are produced without the need for solvents. Next, as previously mentioned, the backing material is laminated. Although patches made using the two methods operate very slightly or not at all differently, the solvent-free method is recommended since there is no chance of leftover solvents and no related health risks related to solvents.[64] This technique does not need any solvents. Using either kneading or direct milling, the medication and excipients are combined without the use of liquid. After that, the final material is rolled on a release liner until it reaches the desired thickness. This approach is typically preferred since there is no chance of solvent residue and no link to any health problems associated with solvents.[61]

Semi-Solid Casting

Layer-by-layer deposition of semi-solid materials using a syringe-based tool-head is the process of semi-solid extrusion (SSE) 3D printing. In order to create a medium with the right viscosity for printing, polymeric components are combined with the suitable solvent or solvents.[65] The beginning material properties (semi solid vs. heated thermoplastic filament), the printing temperatures (room temperature vs. 180 degrees Celsius for polylactic acid filament), and the mechanical characteristics of the printed object (solid, but "wet" vs. rapidly solid, hard, and dry) are the main distinctions from the FDM process.[66]

EVALUATION PARAMETERS

Physical and Mechanical Properties

The evaluation methods for buccal films are quite like those for other pharmaceutical films and transdermal films. Standard tests for thickness, weight fluctuation, film endurance, flexibility, water absorption, surface morphology,

moisture content, etc. are used to assess the produced films. The mechanical properties of a buccal film are usually ascertained using the ASTM D882-01 technique. A regular stress–strain curve yields various values; however, the tensile strength, elongation at break, and elastic modulus, also referred to as Young's modulus, are most pertinent to the study of buccal films.[67,68] The assessment of the mechanical characteristics of a buccal film is typically conducted following the ASTM D882 standard[69] and evaluated. The tensile strength of a film refers to the material's resistance against a force that aims to pull it apart,[70–74] usually recognized as the peak stress on the stress–strain curve, which can be calculated according to Equation 1.

$$Tensile\ strength = \frac{Force\ at\ failure}{Cross\ sectional\ area\ of\ the\ film} \quad ----------1$$

The maximum deformation the film can withstand before breaking is measured by the elongation at break, which is computed using Equation (2):

$$Elongation\ at\ break = \frac{Increase\ in\ length\ at\ break}{Initial\ Film\ Length} \times 100 \quad ----------2$$

Typically, elongation (or strain) tends to rise as the quantity of appropriate plasticizing agents in a specific formulation increases.[75] Young's modulus measures the rigidity or the deformation of the film in the elastic range.[76] It is characterized in the initial elastic deformation phase and is calculated from the ratio of the applied stress and the related strain, which can be determined from the slope of the stress–strain curve using the equation 3.

$$Young's\ Modulus = \frac{Slope\ of\ stress - strain\ curve}{Film\ thickness \times Cross - head\ speed} \quad ----------3$$

It has been stated that weak and soft polymers possess low tensile strength, low Young's modulus, and low elongation at break, whereas a soft yet strong polymer shows moderate tensile strength, low Young's modulus, and high elongation at break.[77,78] Some examples of behaviors derived from stress–strain curves can be illustrated, as seen in Fig. 4.[75] The typical method for determining a film's tear resistance is to use stress-strain curves and relatively low loading rates (51 mm/min). The corresponding force is derived from the greatest stress value and is a complicated function of the film's final resistance to rupture.[79,80]

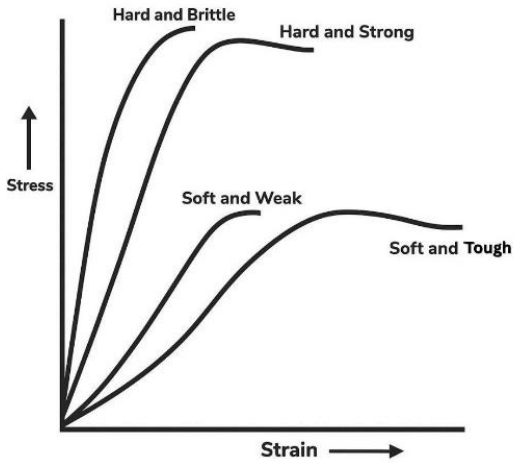

Figure 9: Examples of behaviours observed in stress-strain curves in polymeric films.

Thickness and weight variations

A well-calibrated electronic digital micrometer, screw gauge, vernier caliper, or SEM images are often used to measure the films' thickness. The thickness of the film must be measured to ascertain its uniformity because the thickness of the film is directly related to the accuracy of the dosage in the film. Moreover, adding plasticizer to the formulation may also have an impact on the film's thickness.[81,82] A buccal film should, in general, have a thickness of 50–1000 μm. The average weights are determined by weighing each patch separately to account for weight fluctuation. The unique weight of each patch is then deducted from the average weight of the patches. A significant weight variance suggests that the procedure used was ineffective and that the medication content was not consistent.

Tear resistance and porosity

A film's resistance to rupture determines its tear resistance, which is assessed by rate of deformation. The maximum stress required to tear the film is expressed in Newton's or pound-force.[83] The strength or resistance of the film to tearing is indicated by the area of the plot in a stress-strain curve. A larger region under the stress strain curve increases the film's toughness and the amount of energy that a portion of the material can absorb. A weaker material may therefore be more resilient than a stronger one. A material's porosity is defined as the number of pores per unit area; the higher the porosity, the weaker the material. The type and rate of drying have an impact on porosity, a surface characteristic.[84] The porosity and tear resistance of the film are influenced by the polymer's type, composition, content, and character.

Folding endurance

Buccal patches' flexibility is a crucial physical attribute required for simple application at the administration site. By repeatedly folding the film at a 180° angle of the plane at the same plane until it breaks or folds 300 times without breaking, the flexibility of the buccal patches may be quantitatively assessed in terms of folding endurance. The folding endurance value is calculated as the number of times the film can be folded without breaking.[85]

Water Absorption Capacity

Water absorption capacity or swelling capacity of the produced buccal film is critical for two reasons. The composition of the polymer matrix mostly determines the film's ability to absorb water, which is necessary for improved bioadhesion of the film with the buccal mucosa. Second, it makes it easier for the medication to be released from the films, mostly through two processes (erosive and diffusion). Guo has suggested that there is a strong link between medication dissolution and water absorption.[86] Following the application of the film to the buccal mucosa, a series of processes occur, including water molecule transport into the polymer, hydration, swelling, disentanglement, and polymer erosion. A disintegrating thin layer forms at the matrix's surface as a result of water diffusing into it. The medication diffuses out while matrix hydration takes place. The more aqueous medium penetrates the matrix, the more the drug escapes the matrix.[87] However, the swelling behavior of a buccal film is strongly influenced by its structure and content.[88] In the case of films made using hydrophobic polymers, the % hydration was often found to be very low. The simulated films are typically assessed for polymer erosion and water absorption capability.

Degree of hydration

The polymeric film's level of hydration is significant since it affects the mucoadhesive strength. Although excessive hydration often results in reduced mucoadhesion and/or retention because of the development of slippery mucilage, it is necessary for the relaxing and interpenetration of polymer chains.[89] The link that forms will be weak at first, but it gets

stronger with hydration. Excessive hydration causes the polymer molecules at the interface to become disentangled and distorted, which reduces adhesion.[90] The % hydration is typically used to assess the swelling characteristics of films. The percentage of hydration is computed as follows: *% Hydration = [(W2 –W1) × 100 / W1]*. Film pieces are weighed (W1), submerged in simulated saliva fluid for a predefined amount of time, removed, and wiped off to eliminate excess surface water.[91] In order to be sure that the percentage changes in weight during the sorption–desorption cycle were on a dry weight basis.

Moisture content

The degree of moisture has an impact on the buccal films' friability and brittleness. In essence, the product's ingredients control the amount of moisture in a given film. Typically, weighing, the Karl Fisher titration technique, or moisture content testing equipment are used to measure the quantity of moisture in the film. A preweighed film of a certain size is usually heated to between 100 and 120 degrees Celsius until its weight remains constant. The weight difference indicates the quantity or degree of moisture in the film. *% Moisture content = [(Initial weight – Final weight) × 100 / Initial weight]* is one way to determine moisture content. An optimal buccal film has a moisture level of 5%.

Surface Morphology

Using scanning tunnelling microscopy, electron microscopy, and SEM, one may ascertain the thickness, homogeneity, aggregated/scattered drug distribution, and other surface characteristics of prepared films. But according to the literature, SEM has been used in most of the research to evaluate the films' surface morphology. In order to achieve the desired enlarged pictures, the films are mounted on stubs, sputter coated with gold in an inert atmosphere, and then imaged using a scanning electron microscope. It has been shown that SEM may be used to determine the size, shape, and quantity of pores in buccal films as well as the potential impact of plasticizer.[92,93] The usefulness of SEM in evaluating the impact of the film's chemical composition on surface morphology, crystallinity, etc., has not been extensively documented in research.[94,95]

Surface pH

A film with an excessively acidic or basic pH affects the region of application and destroys the oral mucosal barrier, causing patient pain. After letting the prepared films expand by letting them come into touch with distilled water for about two hours at room temperature, the surface pH of the films was generally measured. The pH of the produced films is probably influenced by the chemical makeup of the medication and the excipients.[96] For example, Patel et al. found that the pH of the film lowers proportionately as the amount of polyvinylpyrrolidone increases.[97]

Crystallinity of the films

With the use of an X-ray diffractometer, X-ray crystallographic examinations may readily ascertain if the drug molecule within the film is crystalline or amorphous. With a certain X-ray source, the films may be put in the sample holder and the XRD transmission diffractograms can be obtained throughout a start-to-end diffraction angle, scan range, and scan speed.[94]

IN VIVO EVALUATION PARAMETERS

Residence Time

The measurement of the buccal patches' residence duration was one of the first methods used to gauge in vitro mucoadhesion. Instead of measuring the force of adhesion, this approach calculates the retention time. This is

accomplished by adhering the buccal films to a glass plate or the edges of a container, then applying mechanical stress by rotating the container, moving the plate, or swirling the media until the film separates or is totally eroded.[98-100]

Release studies

In order to scrutinize the DNA liberation from the fabricated formulations within SSF (n = 3), double-walled glass jars held 50 mL of SSF, then equilibrated at 37 °C. The selection of the SSF volume eased observation regarding the influence from a supporting layer's nature or existence. This determination confirmed the dissolving films were entirely immersed within the solvent material. Reported solubility data of DNA in purified water along with SSF validated that sink conditions were preserved during the research period.[101,102]

Table 7: Weight and dose uniformity data of the developed formulations in absence or presence of chitosan (0C or 1C) and absence or presence of a backing layer (X: absence, EC: ethyl cellulose, WAF: wafer).

Formulation	0C-X	1C-X	0C-EC	1C-EC	0C-WAF	1C-WAF
Film weight(mg)	112.8 ± 2.1	113.4 ± 1.9	151.9 ± 2.2	152.4 ± 2.5	181.9 ± 8.9	176 ± 9.6
Drug Content(mg)	9.10 ± 0.21	9.04 ± 0.26	8.92 ± 0.24	9.01 ± 0.26	9.05 ± 0.30	8.98 ± 0.25

EX-VIVO EVALUATION PARAMETERS

Mucoadhesion studies

The TA-XT texture analyzer (TA instruments, New Castle, DE) was used to assess the mucoadhesive qualities of the produced formulations (n=4). To be more specific, double-adhesive tape was used to mount the 3D printed and PET films, respectively, on the platform and device probe. Cyanoacrylate glue was used to adhere freshly removed (less than two hours) swine buccal mucosa to PET films. The probe was lowered at a speed of 0.5 mm/s after 0.1 mL SSF was placed onto the mucosa in order to keep the formulation in touch with the adjacent mucosa for 120 s (applied force 0.5g). The force-distance curves were then recorded when the probe was removed at a speed of 1 mm/s. While the work of adhesion (Wad) was determined from the area under the curve in the force-distance plot, the maximum detachment force (Fmax) was identified as the maximum force required to fully separate the formed film from the buccal mucosa.

Permeation Studies

In Franz diffusion cells (n=4), the penetration of the API through newly excised (<2h) swine buccal mucosa was examined at 37°C. The cells had a 20mL compartment capacity and a 4.9 cm2 diffusion area. Receptor PBS pH 7.4 was added to the chamber, and the pig epithelium was positioned between the donor and acceptor sections. The pig mucosa was meticulously coated with the 3D printed formulations, and then 2 mL of SSF was injected. 1 mL aliquots were taken out of the receptor chamber at 0.5, 1.0, 1.5, 2.0, 4.0, and 6.0 hours. They were then centrifuged for 20 minutes at 4000 rcf and passed through 0.45 μm polyvinylidene fluoride (PVDF) filters. The receptor compartment was immediately supplied with new, warmed PBS (37°C). To recover the accumulated amount of drug, the buccal tissue was submerged in 40 mL of HPLC mobile phase and sonicated for 30 minutes at the conclusion of the experiment. Using HPLC, the API was quantitatively measured. The slope of the cumulative mass-time plotted curve (linear fraction) was used to calculate the steady-state mass flow (Jss).

Nanoformulation

Adding nanoscale drug delivery systems (usually smaller than 1000 nm) to buccal films to improve the solubility, stability, and absorption of poorly bioavailable medications is known as nanoformulation.

Types of nanoformulations:

- Nanoparticles
- Solid lipid nanoparticles
- Nanoemulsions
- Nanocrystals
- Dendrimers
- Nanostructured lipid carriers

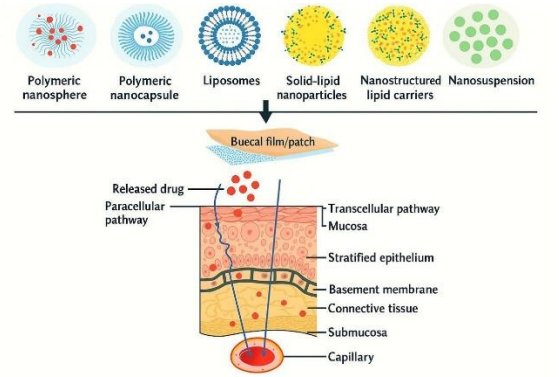

Figure 10: Transport process of diverse nanocarriers through the buccal epithelium.

Hybrid films

Hybrid buccal films are multipurpose devices that enhance medication delivery qualities by combining several polymers, drug carriers, or technology.

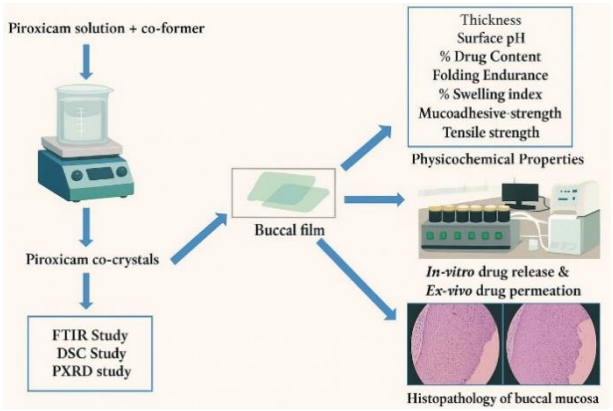

Figure 11: Process of developing mucoadhesive buccal films containing Piroxicam.

REGULATORY CONDITIONS AND COMMERCIAL PRODUCTS

Challenges in buccal drug delivery development[103,104]

When administering systemic medications, the oral environment poses significant challenges. For infections that are released from the formulation and delivered to the site of administration (such as the buccal or sublingual).

Saliva secretion creates the primary physiological environment of the mouth cavity in terms of pH, liquid volume, and content. Three main salivary glands—the mandibular, sublingual, and salivary glands—as well as smaller salivary glands that are situated on or beneath the mucous membrane, release saliva. The sublingual glands secrete viscous

saliva with little enzyme activity, whereas the parotid and mandibular glands secrete a watery fluid. Saliva serves a number of purposes, including reducing tooth calcification, encouraging swallowing, and lubricating the oral cavity.

The mouth's continuously present saliva volume is only about 1.1 ml, leaving a comparatively small amount of liquid available for medication release via delivery devices. If the oral cavity offers a physiological environment for drug transport that is comparatively stable and welcoming and is sustained by constant saliva production, then this barrier can be removed. Compared to GIT secretions, saliva is a fluid that is mobile, has little mucus, limited enzymatic activity, and hardly any proteases. Saliva has a pH of 5.5 to 7.0, making it an inadequate buffer. Depending on the high flow rate, it may rise slightly due to the higher percentage of salt and bicarbonate.

CONCLUSION

Mucoadhesive buccal films are an emerging and highly effective method for drug delivery, providing notable benefits over traditional oral and injectable routes. By adhering to the inner cheek lining, they avoid first-pass metabolism by the liver and degradation by digestive enzymes, thereby improving bioavailability and enabling faster therapeutic effects. Their adaptable structure, ease of use, and high patient acceptance make them ideal for individuals who have difficulty swallowing. The successful formulation of these films depends on several factors, including the anatomy and physiology of the buccal cavity, as well as the choice of excipients like mucoadhesive polymers, plasticizers, penetration enhancers, and taste-masking agents. Techniques such as solvent casting, hot melt extrusion, and 3D printing have enabled precise and scalable production of these dosage forms. Nevertheless, limitations such as dilution by saliva restricted drug-loading capacity, possible mucosal irritation, and taste or stability issues can limit their broader use. Still, advancements in nanotechnology and hybrid materials are driving progress toward more efficient and user-friendly drug delivery solutions. Overall, mucoadhesive buccal films hold great promise for both local and systemic drug administration. With ongoing research and development, they are poised to become a major advancement in pharmaceutical drug delivery.

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