A Review on Recent Developments of Mucoadhesive Buccal Films

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Abstract

Nowadays, there is a demand for the creation and development of innovative dosage forms in order to increase patient compliance, safety, and efficacy. Mucoadhesive buccal film is a unique film technology that meets all of these characteristics. Traditional oral dosage forms are susceptible to first pass metabolism and degradation caused by enzymes, but mucoadhesive films can avoid first pass metabolism and associated deterioration. Delivery through transmucosal products benefits the absorption 4 times than that of the skin. It provides greater patient compliance without the danger of choking in paediatric and elderly patients. The present paper intends to emphasize the basic methodologies, importance of transmucosal drug delivery and also highlights on the latest advancements in the field.

Keywords: Mucoadhesive buccal film, Mucoadhesion, Mucoadhesive polymer, Oral mucosa, Transmucosal, Buccal drug delivery.

1. Introduction

The current article mainly focuses on the mucoadhesive buccal films which binds to biological surfaces that are covered by mucus. Normally, drugs are administered via numerous routes and dosage forms. Although the oral route is the most desired way of drug delivery, drug solubility and first pass metabolism sensitivity are crucial characteristics that must be present for the drug to be absorbed by this route. Parental route is the most painful type of administration. Topical medications can only be used for local or topical therapy. Drugs with high molecular weight, low skin penetration, poor water solubility, and substantial first pass metabolism require alternate routes. Most drugs are increasingly being administered via mucoadhesive route. Mucoadhesive drug delivery systems via buccal, sublingual, rectal, and nasal mucosa may be a more rapid and systemic means of non-invasive administration. To avoid first pass metabolism, drugs are administered in a different manner. Faster medication delivery and increased bioavailability have been demonstrated through mucoadhesive administration[1].

Nowadays, the creation of buccal films, which dissolve on the patient's buccal mucosa, is unique technique. Due to their compact design and thinner thickness, films have also increased patient compliance when compared, for instance, to lozenges and tablets. The pharmaceutical industry has increased its focus on buccal films as dosage forms since they are patient-friendly, and practical[2].

Mucoadhesive drug delivery systems, which uses both natural and synthetic polymers, is a technique for controlled drug release that enables close contact between the polymer and a target tissue. Mucoadhesive drug delivery systems utilise the bioadhesion of certain polymers, which in turn adhesive during hydration and are therefore able to be used for targeted drug delivery to a specific area of the body for a prolonged length of time[3].

Mucoadhesive buccal films are an novel dosage form that avoids the first-pass metabolism, has a quick onset of action, and most significantly, has higher patient acceptability. These mucoadhesive buccal films have been formulated to release drug locally in order to treat fungal infections in the oral cavity such as oral candidiasis. mucoadhesive buccal films are seen to be the preferred dosage form by patients when compared to buccal tablets because of their higher flexibility, which increases comfort[4].

The mechanism involved here is Mucoadhesion. Early in the 1980s, the idea of mucoadhesion was developed in the context of controlled release medication delivery systems. It is well established that mucoadhesion lengthens and increases the closeness of contact between drug-containing polymer and a mucous surface. The mucoadhesive properties are known to extend the drug's duration in the body after administration. The direct drug absorption and the reduced excretion rate together have the effect of increasing the drug's bioavailability. Lower API concentrations may result from longer residence times and more adhesion[5].

Advantages of buccal drug delivery system [6]

Drug delivery through the buccal mucosa has a number of specific benefits:

- In compared to other mucosal tissues, the buccal mucosa is strong, rich in blood supply, and moderately permeable.
- Avoids the first-pass effect and the drug's lack of exposure to gastrointestinal fluid.
- API localisation at the disease site may also result in considerable cost savings and a decrease in dose-related adverse effects.
- Since many drugs are contacting the mucosa for extended periods of time, their effectiveness should be improved.
- Higher levels of patient acceptability compared to other non-oral drug delivery systems.
- Tolerance to possible sensitizers, as compared to the skin and nasal mucosa.
- A decrease in the frequency of administration may result from longer residency times combined with controlled API releases.
- The formulation remains longer at the distribution site, improving API bioavailability with lower API concentrations for disease therapy. This is because of adhesion and intimate contact.
- Buccal drug administration avoids the harsh environmental variables that might affect oral drug delivery.
- It does not need to be activated and offers a passive mechanism of drug absorption.
- Contrary to rectal or transdermal routes, the presence of saliva ensures a relatively substantial volume of water for drug breakdown.
- Provides the alternative route for delivery of different hormones, narcotic analgesics, steroids, enzymes, cardiovascular medications, etc.

- It permits localised changes to tissue permeability, protease activity suppression, and immunogenic response decrease. As a result, it is simple to transport therapeutic substances such peptides, proteins, and ionised species.

Disadvantages of buccal drug delivery [6]

The primary difficulties of buccal administration are

- Limited absorption area: The buccal membrane and other non-keratinized tissues make up around 50 cm^2 to 170 cm^2 total surface area of the oral cavity membranes that are accessible for drug absorption.
- Mucosal barrier properties.
- The medicine is subsequently diluted as a result of the continual salivation (0.5-2 l/day).
- There is a risk of choking if the delivery system is involuntarily swallowed.
- The loss of dissolved or suspended drug through swallowing of saliva may also result in the unintentional removal of the dosage form.

BUCCAL MUCOSA

The oral route is perhaps the one that is most frequently recommended to patients and doctors alike in novel drug delivery systems. However, oral drug delivery has restrictions, including hepatic first pass metabolism and GI tract enzymatic breakdown, which prevent oral administration of several pharmacological types, most notably peptides and proteins. As a result, different absorptive mucosae are taken into account as potential drug delivery sites. For systemic drug delivery, transmucosal routes i.e; the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities propose clear benefits over peroral administration[7]. The benefits may include avoiding pre-systemic clearance inside the GI tract, by-passing the first pass effect, and depending on the specific drug, a superior enzymatic flora for drug absorption. Oral mucosal drug delivery systems are separated into two classes: buccal and sublingual. The buccal cavity is often used for drug delivery through mucosa. Inner cheeks are lined by buccal mucosa. Drug delivery inside the oral mucosal cavity is divided into three categories[8].

1. Sublingual delivery
2. Buccal delivery
3. Local delivery

ANATOMY AND PHYSIOLOGY OF ORAL MUCOSA

The oral mucosa serves as a key channel for drug delivery. The oral cavity has been diagrammatically illustrated in (Fig.1). The oral cavity has a total surface area of around 100 cm^2 and is coated by mucus membranes. The mouth cavity is made up of around one-third of the buccal surface's 0.5 mm thick epithelium. The oral mucosal cavity is made up of stratified epithelial tissues that are also coated by mucus. A basal membrane is found here, extending into the epithelial layers. The lamina propria is a layer of connective tissue located within the basal membrane. The lamina propria serves as a mechanical support structure. Following then, the submucosal portion begins. It contains many blood vessels as well as nerves from the central nervous system (fig.2).

The submucosal region has the greatest vascularity, allowing for complete drug absorption. Both keratinized epithelium (found in the gingiva and portion of the hard palate) and non-

keratinized epithelium (found on the surface of the distensible lining mucosa, soft palate, floor of the mouth, lips, and cheek) are present in the human oral mucosa[9].

The buccal region is the area of the mouth that is bounded anteriorly and laterally by the lips and cheeks, posteriorly and medially by the teeth and gums, and above and below by mucosal imprints from the lips and cheeks to the gums. Buccal mucosa's essential role is similar to the skin, plays an important function in protecting underlying tissues from foreign agents. The permeability of the buccal mucosa is roughly 4-4000 times higher than that of the skin. Sublingual>buccal>palatal is the order of permeability of the oral mucosa, which is dictated by relative thickness and keratinization level[10].

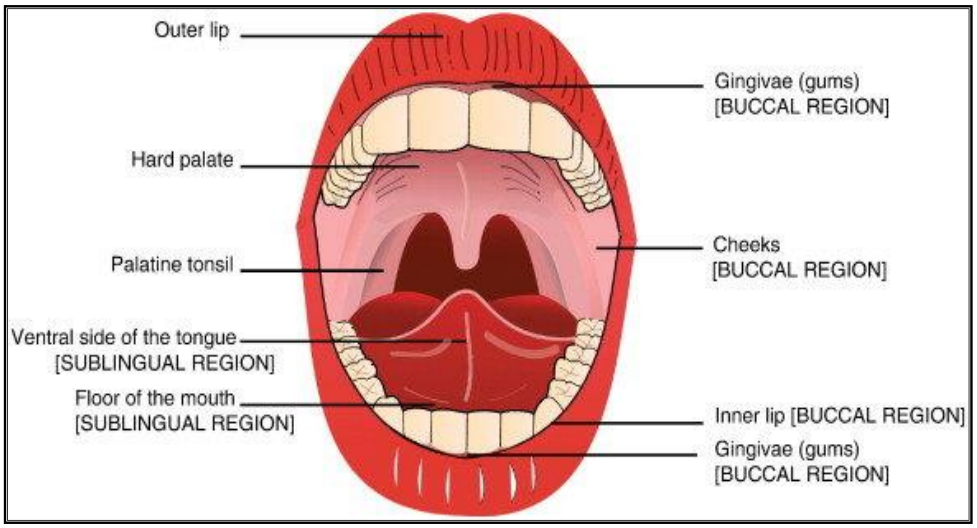

Fig 1: Anatomy of oral cavity[11]

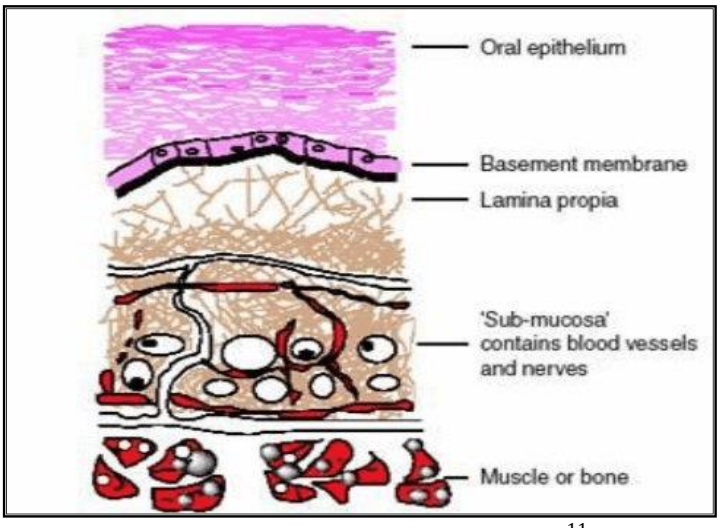

Fig 2: Structure of buccal mucosa[11]

MUCUS

Mucus, which is composed of glycol proteins and is found in many bodily compartments including the respiratory and gastrointestinal tracts, is a thin, continuous jelly layer of translucent and viscid discharge from epithelial surface. In humans, this mucus layer, which ranges in thickness from 50 to 450 micrometres, acts as an adhesive surface for drugs.

Mucus is continuously secreted to balance removal of mucus layer during digestion, solubilization, and bacteria-mediated breakdown[12].

COMPOSITION OF MUCUS[10]

Mucus composition changes depending on anatomical regions, however the overall composition remains as shown below (table 1):

Table 1: Composition of mucus

S.No	Components	Amount (%)
1.	water	90-95
2.	Lipids	0.5-6.0
3.	Minerals	1.0-1.5
4.	proteins	0.5-1.5

The following tasks are performed by this mucus layer:

- **Protective:** protects the epithelial surface from acid diffusion via lumen and permits selective transport.
- **Barrier:** enables drugs to be absorbed selectively**.**
- **Adhesion:** Molecular adhesion surfaces are made firm by a mucus layer with cohesive characteristics.
- **Lubrication:** Mucosal layer is kept lubricated by moisture in mucus.

MUCOADHESION[13]

Mucoadhesion is the condition in which two materials adhere to one another for a extended period of time with the aid of interfacial forces. In simple words, the process of binding a substance to the body's mucosal layer is known as mucoadhesion.

MECHANISM OF MUCOADHESION[14,15]

- Adhesion is the state in which two surfaces are bonded together due to valence interfacial forces, interlocking action, or both.
- Mucoadhesion is the attachment of a substance to mucus and/or an epithelial surface, whereas bio adhesion is the adhesion of a synthetic or natural material to a biological surface. Mucoadhesion happens in two stages (Fig 3), depending on the type of the dosage form and how it is administered:

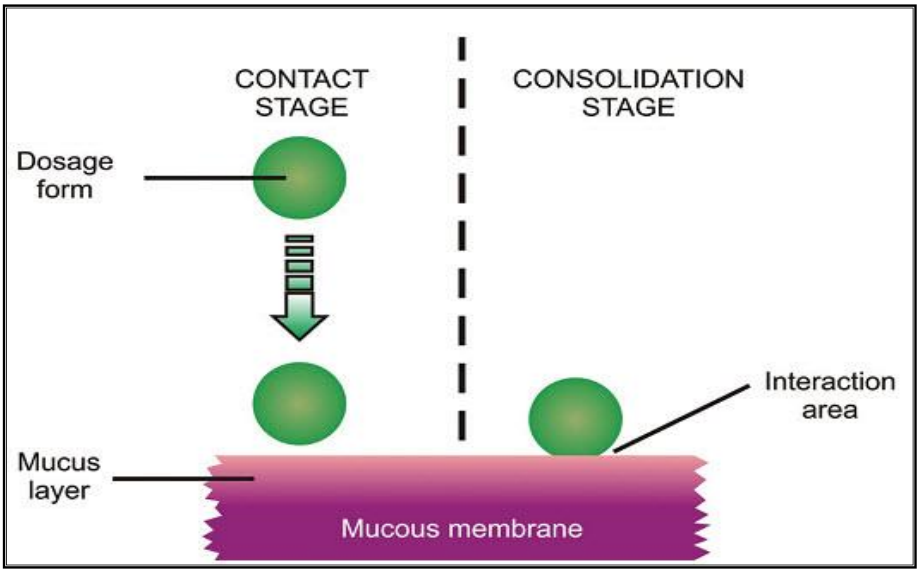

Fig 3: Two stages of mucoadhesion[14]

Stage-I (Contact Stage)

A bio adhesive and a membrane come into intimate contact as a result of wetting, spreading, and swelling of the bio adhesive surface. Additional forces, such as mechanical systems during vaginal delivery, aerodynamics during nasal delivery, and peristaltic movements during intestinal distribution of dosage forms, can occasionally be present.

Stage II (Consolidation Stage)

Hydrophobic interactions, hydrogen bonds, Vander Wall forces, and electrostatic interactions all contribute to the interpenetration or prevailing attractive connection between two surfaces that results when moisture breaks molecules. Attractive factors must prevail over repellent forces for full bioadhesion. Consolidation step is explained by two theories:

i. Diffusion theory

By interpenetrating their chains and establishing secondary bonds, mucus glycol proteins interact with the mucoadhesive compounds. This is a mechanical as well as chemical interaction.

ii. Dehydration theory

Substance undergoes dehydration after coming into contact with mucus until osmotic pressure balance and jelly mixture of mucus with mixture is obtained. According to this theory solid or hydrated formulation does not work.

THEORIES OF MUCOADHESION[16,17]

The phenomena of mucoadhesion is explained by five main theories (Fig 4).

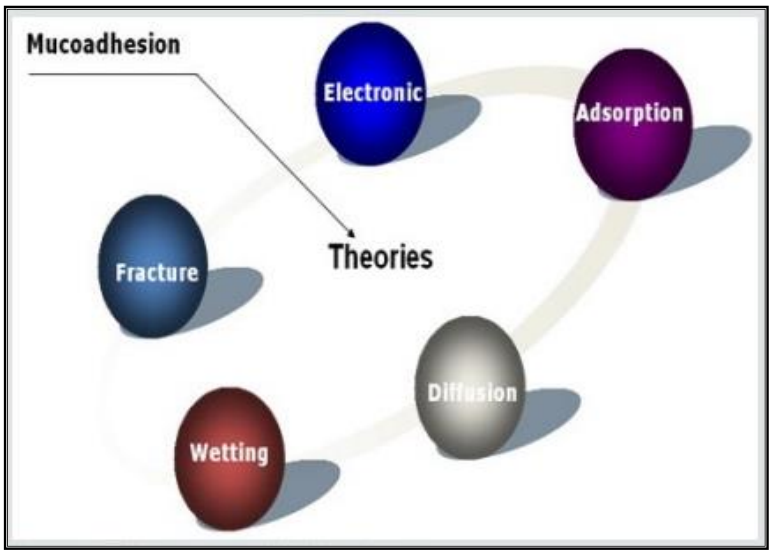

Fig 4: Theories of mucoadhesion[10]

i. Electronic theory

This theory is based on the observation that biological materials, including the mucus layer, have opposing electrical charges that can form a double electronic layer at the edge, which aids in determining the mucoadhesive strength.

ii. Wetting theory

Liquid or less viscous molecules penetrate the mucosal surface and stabilise themselves by reducing the surface tension. This characteristic relates to the molecule's contact angle, wetting, and spreading capabilities (Fig 5). Contact angle (θ) and interfacial tension (γ) can be determined from following equation:

$$\gamma SG = \gamma SL + \gamma LG\cos S = \gamma SG - (\gamma SL - \gamma LG)$$

Where, γLG is liquid–gas surface tension,
γSL is solid–liquid surface tension,
γSG is solid–gas surface tension.

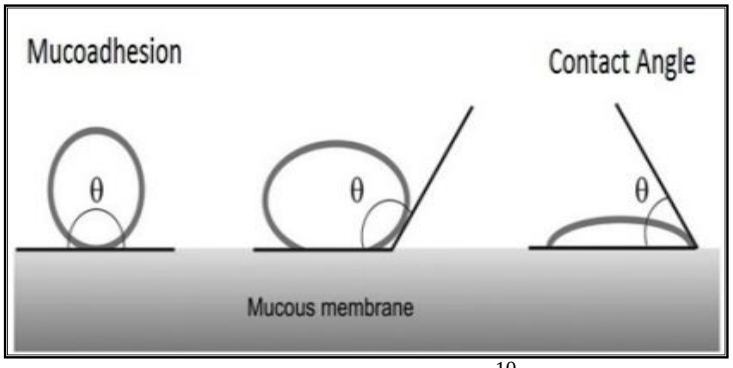

Fig 5: Wetting theory[10]

iii. Diffusion theory

The mucosal surface is penetrated by liquid or less viscous molecules, which stabilise by lowering the surface tension there. The contact angle, wetting, and spreading properties of the molecule are all covered by this property (Fig 6).

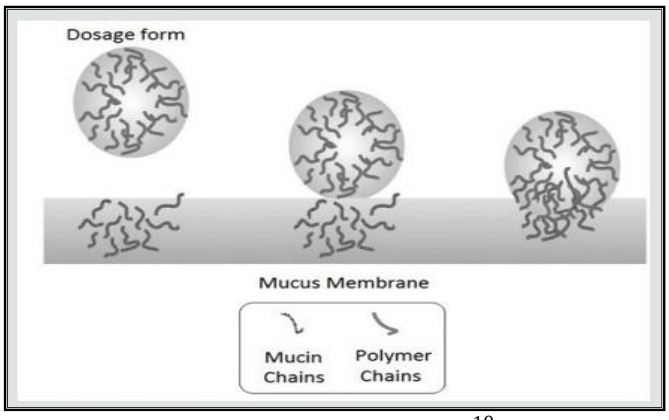

Fig 6: Diffusion theory[10]

iv. Adsorption theory

The most widely recognised adsorption theory of the mechanism of mucoadhesion involves weak vander waals forces and hydrogen bond mediated adhesion. It exhibits semi-permanent surface interactions through primary and secondary bonding.

v. Fracture theory

The forces needed to separate the two surfaces after adhesion are explained by this second-most widely accepted theory. This force is called as tensile stress as well as fracture strength. The following equation is used to determine this force:

$$m = Fm/Ao$$

Where, Fm: maximum force of detachment and
Ao: surface area

Every theory that attempts to explain the mucoadhesion process has equal importance. It is possible that the mucin will first be wetted, followed by the diffusion of the polymer into the mucin layer, which will break the layers and ultimately result in the perfect mucoadhesion by adhesion, electronic transfer, or simple adsorption.

BUCCAL FILM FORMULATIVE ASPECTS[18-20]

i. Active pharmaceutical ingredient (API)

In general, active pharmacological substances ranging from 5% w/w to 30% w/w can be added into the buccal film. Water soluble APIs can be found in the buccal film as a dissolved substance or as a solid solution. The water-insoluble drugs are distributed equally across the film. This includes the dispersion of water-insoluble molecules in a water-miscible polymer, or the drug's solubility can be increased by complexation with different cyclodextrins. APIs can also be added milled, micronized, or in the form of nano crystals or particles, depending on the desired release profile. The use of micronized API improves film texture as well as dissolution and homogeneity in the buccal film.

Buccal films are more useful in specific therapeutic conditions where rapid drug release is required for immediate alleviation. Cough, allergies, motion sickness, discomfort, and other local oral symptoms are examples of such clinical conditions.

ii. Mucoadhesive polymers

Polymers with various properties must be considered based on the kind of formulation. Depending on the dosage type, many circumstances for buccal mucoadhesion are feasible. Mucoadhesive polymers are divided into two categories: hydrophilic polymers and hydrogels. polyvinyl alcohol [PVA], sodium carboxy methylcellulose [NaCMC], hydroxyl propyl methyl cellulose [HPMC], hydroxyl ethyl cellulose, and hydroxypropyl cellulose [HPC] are the hydrophilic polymers most widely used in buccal drug or partially hydrated dosage forms. Hydrogels are composed of anionic polymers such as carbopol, polyacrylates, cationic polymers such as chitosan, and non-ionic polymers such as eudragit derivatives.

Ideal characteristics of mucoadhesive polymer

- To improve the adhesion between polymer and mucus, polymer must have a molecular weight of 10,000 or more.
- The length of the chain in the case of long chain polymers must be sufficient to encourage interpenetration.
- The polymer chain must be flexible.
- The polymer and its breakdown products must not be harmful and must not be absorbed by the digestive system.
- It must not aggravate the mucous membrane.
- It should bind firmly to the mucin-epithelial cell surfaces via non-covalent bonds.
- It should have some site-specificity and stick to the majority of tissues fast.
- Neither during storage nor the dosage form's shelf life may the polymer degrade.
- To maintain the competitiveness of the produced dosage form, the cost of the polymer shouldn't be too high.

iii. Plasticizers

Plasticizers are often employed in concentrations ranging from 0 to 20% w/w of dry polymer. Plasticizer is an important component of the film since it enhances flexibility and decreases bitterness by lowering the glass transition temperature of the film. The plasticizer chosen is determined by its compatibility with the polymer and the type of solvent used in film casting. Plasticizers should be carefully chosen since inappropriate application affects the mechanical

characteristics of the film. Plasticizers that are commonly used include PEG 400, propylene glycol, glycerol, and castor oil.

iv. Penetration enhancers

Excipients that improve penetration are also significant in the composition of buccal films. These are necessary when a drug must enter the systemic circulation in order to exert its effect. These must be non-irritant and have reversible action. After the drug has been absorbed, the epithelium should regain its barrier qualities. Fatty acids that break intercellular lipid packing, surfactants, bile salts, and alcohols are the most prevalent types of buccal penetration enhancers.

v. Sweetening agents

Sweeteners have emerged as critical excipients in the oral disintegrating medication delivery system. In the case of the paediatric population, the sweet flavour in the formulation is particularly significant. To increase the palatability of oral dissolving formulations, both natural and artificial sweeteners are employed. Sucrose, dextrose, fructose, glucose, liquid glucose, and maltose are examples of natural sweeteners. In comparison to sucrose and dextrose, the sweetness of fructose is sensed quickly in the tongue. If the dosage form is intended for diabetic people, artificial sweeteners should be employed. The first generation artificial sweeteners include saccharin, cyclamate, and aspartame, followed by acesulfame-K, sucralose, alitame, and neotame, which are classified as second generation artificial sweeteners.

vi. Taste masking agents

If the APIs have a bitter taste, flavour masking agents or taste masking procedures should be utilised in the formulation, since the bitter pharmaceuticals make the formulation unpleasant, especially for paediatric formulations. As a result, before inserting the API into the buccal film, the taste must be concealed. Complexation technology, salting out technology, and other techniques can be utilised to increase the palatability of the formulation.

vii. Coloring agents

When some of the formulation components or medications are insoluble or suspended, pigments such as Titanium dioxide or FD&C approved colourants are used (not exceeding concentration levels of 1%w/w) in buccal film formulation.

viii. Cooling agents

Monomethyl succinate is utilised as a cooling agent, which serves to improve the taste strength and mouthfeel of the film. Other cooling agents that may be used in combination with flavours include WS3, WS23, and Utracoll II.

ix. Saliva stimulating agents

The inclusion of this chemical in the formulation is crucial since it increases the rate of saliva production, resulting in quick disintegration and rapid dissolving of the film in the buccal cavity. Typically, acids employed in the preparation of food can be used as salivary stimulants. Salivary stimulants include citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid, with citric acid being the most popular. These chemicals are employed alone or in combination between 2 and 6%w/w of the film's weight.

x. Surfactants

Surfactants are solubilizing or wetting agents. Surfactant dissolves the film quickly within seconds, releasing the medication immediately. Surfactants can increase the solubility of poorly soluble drugs in buccal. Polaxamer 407, sodium lauryl sulphate, benzalkonium chloride, benzethonium chloride, tweens and spans are a few examples.

xi. Stabilizing or thickening agents

The use of stabilising and thickening agents is necessary to increase the viscosity and consistency of the film preparation dispersion or solution prior to casting. Stabilising and thickening agents include natural gums such as xanthan gum, locust bean gum, carrageenan, and cellulosic derivatives. They are employed at concentrations of up to 5%w/w.

METHODS TO MANUFACTURE BUCCAL FILMS[2,21,22]

i. Solvent casting method

The specified amount of polymer is introduced and dissolved in distilled water in the solvent casting procedure. This solution contains a tiny amount of active medicinal ingredient. Plasticizer is added to the solution and mixed well. The solution is then cast on petri dish and dried in a hot air oven at 40°C. After drying, cut it off the films in the petriplate with a knife and place it in the desiccator for 24 hours.

Steps involved in the solvent casting method

Step 1: Make the casting solution

Step 2: Solution deaeration

Step 3: Pour the necessary amount of solution into the mould.

Step 4: Allowing the casting solution to dry

Step 5: Cut the finished dosage form into suitable size whenever needed.

ii. Hot melt extrusion method

The drug and other excipients are molten in the hot melt extrusion process (Fig 7). The mixture is then pressed through an aperture to produce a more homogeneous substance in various forms such as granules, tablets, or films. It is employed in the transdermal drug delivery system.

The following steps are involved in hot melt extrusion method

Step 1: The drug is combined with solid carriers.

Step 2: A heated extruder melts the mixture.

Step 3: Finally, the dies mould the melted mixture into films.

Advantages

- fewer units of operation.
- An anhydrous procedure improves content uniformity.

Disadvantages

- The thermal process causes a stability issue.
- Polymer flow characteristics are critical in processing.
- There are only a limited amount of polymers accessible.

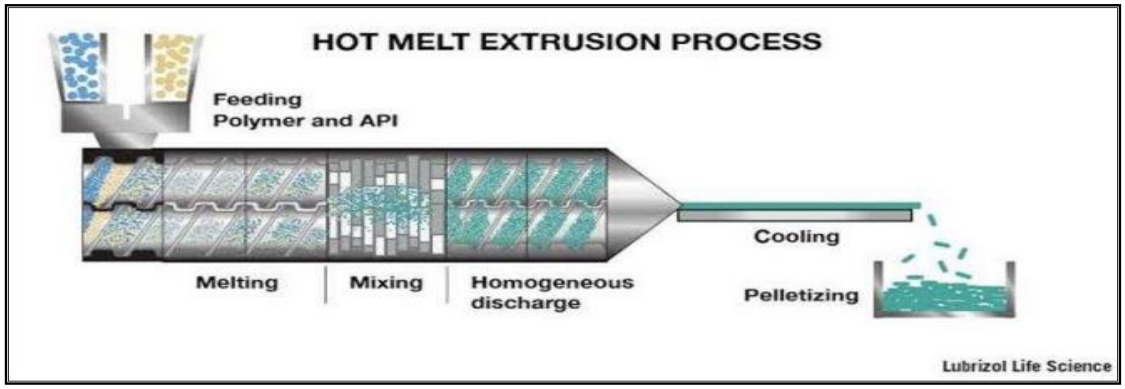

Fig 7: Hot melt extrusion method[2]

iii. Direct milling method

This is a solvent-free approach. Direct milling or kneading is used to combine the drug and excipients in the absence of liquid. The resultant material is then rolled on a release liner to achieve the desired thickness. This approach is frequently preferred since there is no leftover solvent and no connection of solvent-related health issues.

EVALUATIONS OF BUCCAL FILMS[11,23,24]

i. Weight variation

Buccal film is weighed using a calibrated weighing balance. Each film is weighed and calculated individually. The average weight of all films is calculated, and the film's actual weight is examined.

ii. Thickness

The thickness of the buccal film was measured using a calibrated micrometre screw gauge. The film is measured at five different points (four on the corners and one in the centre) and the mean thickness is calibrated. This step is important to ensure the uniformity of thickness as well as accurate dosing in the film due to their correlation.

iii. Surface pH

For determination of surface pH, 2% w/v agar in isotonic phosphate buffer pH 6.8 was dissolved and placed onto the Petri dish and is gelled at room temperature. Buccal films are put on the surface of the agar plate for 2 h until they swell completely. The surface pH is measured using pH indicator paper after a 90-second colour change is noticed and compared to a standard colour scale.

iv. Tensile strength

The property of film that demands load producing deformation and finally failure of a film is termed tensile strength. Two clamps spaced at equidistance are positioned in such a way that film strips are placed in between them. The following equation can be used to calculate a tensile film by applying a load at rupture and knowing the cross-sectional area of a fractured film.

Tensile strength (N/mm^2) = Breaking force (N)/Cross-sectional area of film (mm^2).

v. Folding endurance

Three films are trimmed to the proper size for the folding endurance test. Folding endurance may be measured by folding a single film repeatedly in the same location or up to 300 times until it breaks. When the film does not break after being folded several times, folding endurance is valuable.

vi. Drug content uniformity

A magnetic stirrer is used to dissolve previously weighed 5 films for 2 hours in 100 ml of isotonic phosphate buffer, pH 6.8. Further, this solution is filtered with Whatman filter paper, and after adequate dilution, drug is estimated analytically.

vii. Percentage moisture uptake

In order to maintain 84% relative humidity, films are kept in the desiccator for 24 hours at room temperature with saturated potassium chloride solution. After 24 hours, the films are removed and weighed. The following formula can be used to calculate the percentage of moisture uptake.

Percentage moisture uptake = [(Final weight – Initial weight) / Initial weight] × 100.

viii. Percentage moisture loss

Two 2×2 cm^2 films are put in a desiccator with anhydrous calcium chloride, and the % moisture loss is calculated. After 3 days, the films are taken out and weighed. The % moisture loss is estimated using the following formula.

Percentage Moisture Loss= [(Initial weight – Final weight) / Initial weight] × 100.

ix. Swelling index

Each buccal film is individually weighted (W1) and placed in a Petri plate containing phosphate buffer pH 6.8. Buccal films are collected from the petri plate and excess surface water is removed using filter paper and weighed again (W2). The swelling index (S1) is calculated using the following formula:

$$SI = (W2 - W1) / W1$$

Where, SI stands for Swelling Index.

W2 denotes the final weight.

W1 is Initial weight.

x. *In vitro* disintegration time[11]

Visual analysis may be performed in a Petri dish with 2 ml of distilled water by spinning every 10 seconds. The time required for the film to dissolve or break is recorded as the *in vitro* disintegration time.

xi. *In vitro* dissolution study

For dissolving investigations, a USP type II apparatus (Basket type apparatus) is used with pH 6.8 buffer (50 ml) as a dissolution medium at 37°C temperature and speed of 50 rpm. 1ml of the sample solution is removed and re-equilibrated with fresh dissolving medium. The buccal films are filtered using 0.45 m Whatman filter paper, and API is analysed spectrophotometrically at max.

xii. *In vitro* drug release

In vitro drug release investigations are conducted using the Franz diffusion cell assembly. It is divided into two compartments, one of which receptor compartment contains a buffer solution with a pH of 6.8 and the other which donor compartment contains 10 mg of the medicine. A dialysis membrane (Mol. Wt 12000-14000) previously soaked in receptor media for 2 hours is inserted in between these compartments to separate them. To prevent disrupting the current process, no air bubbles are allowed to form between the membrane and the liquid surface. The temperature is maintained at 37°C during the procedure by using a circulating water bath. 0.5 ml of the sample is removed from the receptor chamber and replaced with

new buffer at regular intervals until 8 hours. The amount of medication released is spectroscopically analysed after appropriate dilution. The flux value is determined using the following formula:

Flux = Amount of medication released (mg)/Time (hr)×Area (cm^2).

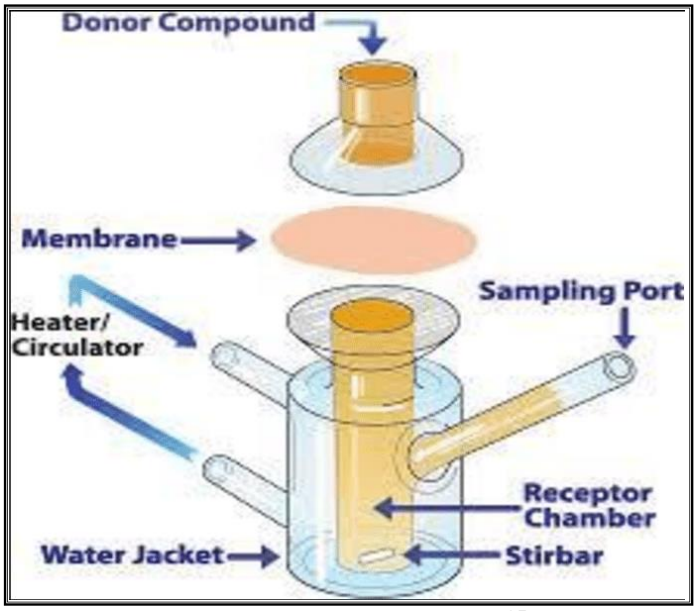

Fig 8: Franz diffusion cell[25]

xiii. *Ex vivo* mucoadhesion time

The fresh buccal mucosa of a sheep or rabbit is tied on a glass slide in order to apply the buccal film and measure the mucoadhesion time. Using fingertips, apply the buccal film to the buccal mucosa for 30 seconds while lightly pressing on it. The buccal film is moistened with a drop of phosphate buffer pH 6.8. The glass slide is maintained at 37°C ± 1°C in a beaker with 200 ml of phosphate buffer at pH 6.8. After two minutes, a 50 rpm stirring speed is introduced, and film adherence is controlled for 24 hours to stimulate the environment of the buccal cavity. Along with the film's collapse time, the time required for apparent changes in shape and colour is also noted.

xiv. *Ex vivo* permeation studies

A modified Franz diffusion cell is used for permeation investigations. Two compartments of 25 ml capacity are seen, one of which is a donor compartment and the other a receptor compartment. The receptor compartment is kept at 37°C by sealing it in a water jacket made of 23 ml of pH 6.6 phosphate buffer. The split or seperated buccal epithelium is sandwiched between the two chambers and the complete assembly is placed on a magnetic stirrer containing a Teflon-coated magnetic bead. The buccal film is set aside for stabilisation before withdrawing 1ml of the sample at regular intervals and diluting it appropriately for spectrophotometric analysis.

xv. Stability studies

Stability studies are conducted to analyse any changes that occur during the storage of any product. All formulations are stored in triplicate in stability chambers at 40°C ± 2°C and 75% ± 5% RH for three months. Stability studies are assessed by analysing their folding endurance, drug content, and *in vitro* drug release.

RECENT ADVANCES IN BUCCAL DRUG DELIVERY SYSTEM[26]

Vaccination against severe infectious illnesses has shown to be effective in disease prevention and has contributed greatly to an increase in life expectancy, particularly among children, in many regions of the world. Several variables can impact vaccination efficacy in order to provide optimal mucosal protection. The route of delivery and capacity for antigen processing by antigen-presenting immune cells, such as macrophages and dendritic cells, are the most important factors in mucosal vaccination efficacy. Most vaccinations are currently delivered by parenteral or other invasive ways. Invasive vaccine injection can elicit a systemic immune response but may not provide significant mucosal immune protection. Effective mucosal vaccines, on the other hand, not only provide greater local immune protection, but have also been demonstrated to elicit a systemic response similar to that of parenterally administered vaccination. As a result, it is crucial to investigate the development of mucosal vaccination techniques capable of eliciting both systemic and mucosal immunity. Mucosal vaccines are now being studied utilising a variety of nanocarrier systems, including multiple emulsions, liposomes, polymeric nanoparticles, dendrimers, immunostimulating complex (ISCOM), and others. Furthermore, mucosal distribution of nanocarrier antigens and vaccines can induce immunisation at various mucosal barriers, which is the body's critical first line of defence in addition to systemic immune response.

In the future, the development of vaccines utilising a combined strategic approach, such as nanocarriers administered via mucosal channel of administration, might play a significant role in the treatment of infectious illnesses.

The recent developments in buccal drug delivery systems are as follows[27,28]

- **Buccal delivery by means of iontophoresis**

To enable therapeutic drug distribution via the oral mucosal route, many chemical absorption enhancers and enzyme inhibitors have been utilised, and these enhancers have been extensively studied. Recently, physical approaches such as sonophoresis and electric fields have also been employed. An electric field can act as an extra driving force on drug ions (iontophoresis), push water (or physiological fluids) to flow with the dissolved medication or metabolites (electroporation), or temporarily change tissue architecture to make them more permeable (electroporation). Such techniques may have advantages in that they allow for greater quantities of pharmacologically active chemical to be transported across the buccal mucosa. Before we see widespread acceptance and use of this approach in the buccal drug delivery field, many technical issues must be resolved, patient acceptance of the final dosage form must be evaluated, and the potential improvement in patient compliance (particularly in paediatric and geriatric populations) must be established.

Iontophoresis has been studied for over a century and has been widely used in transdermal medication administration. It has also been studied in recent years for improving medication transfer over the buccal mucosa.

The combination of medication administration and metabolite collection in one device, with the same driving power, appears to be highly promising. Using pig skin and buccal tissues, researchers evaluated the effect of chemical enhancers and iontophoresis on the *invitro* transdermal and trans buccal transport of lidocaine hydrochloride, nicotine hydrogen tartrate, and diltiazem hydrochloride. Chemical enhancers like dodecyl 2-(N,N-dimethylamino)

propionate (DDAIP), dodecyl-2-(N,N-dimethylamino) propionate hydrochloride (DDAIP HCl), N-(4-bromobenzoyl)-S, Br-iminosulfurane, and azone (laurocapram) are used .

In recent years, a new type of delivery, particularly for chronic illnesses, based on highly miniaturised computerised delivery systems integrated within a dental device, has been reported. An intraoral electronic device (IntelliDrug) was created for the buccal administration of naltrexone, an opioid antagonist widely used in the treatment of opiate addiction, alcoholism, and smoking cessation. It is demonstrated to cause long-lasting, continuous, and regulated drug levels in pigs while avoiding the spikes seen with intravenous delivery. Galantamine, which is used to treat individuals with mild-to-moderate Alzheimer's-type dementia, is loaded into the IntelliDrug device for transbuccal administration, and the drug's penetration augmentation by iontophoresis is demonstrated in pigs *in vivo.*

- **Buccal mucosa and photodynamic therapy**

In this approach, photodynamic therapy (PDT) and photodynamic antimicrobial chemotherapy (PACT), involves the use of a photoactive dye (photosensitizer) that is activated by exposure to light of a specific wavelength in the presence of oxygen to kill target cells. PDT, which is accepted to be minimally invasive and minimally toxic, is used clinically to treat a wide range of medical conditions of oral mucosa including neoplastic and non-neoplastic conditions. PACT has been shown to eradicate a wide variety of pathogens of the oral cavity, thus this treatment is considered as an alternative for the management of infections that respond poorly to conventional antibiotics and antifungal therapy. In the future, this approach may play an important role in persistent infections.

The correct formulation for the distribution of the photosensitizer in the oral cavity has a significant impact on the success of the therapy. The size, pH, and lipophilicity of the photosensitizer molecule all influence its transit to the site of action. The molecule's solubility and diffusivity, as well as its chemical stability, are also crucial considerations in successful distribution.

However, the photosensitizers employed might be highly coloured, resulting in discoloration of teeth, lips, and buccal mucosa. Appropriate formulations that transport the photosensitizer to the site of infection are necessary.

In vitro, a wide range of species, from Gram-positive *Staphylococcus aureus* to Gram-negative *Pseudomonas aeruginosa*, have been found to be sensitive to PACT with a variety of photosensitizers.

RESEARCH ON BUCCAL ADHESIVE DRUG DELIVERY SYSTEMS[29,30,31]

Many researchers created several buccal adhesive delivery systems at the laboratory size for either local or systemic activities. They are basically classed as follows:

1. Solid buccal adhesive dosage forms
2. Semi solid buccal adhesive dosage forms
3. Liquid buccal adhesive dosage forms

i. Solid buccal adhesive dosage forms

Bioadhesion is achieved in dry formulations by dehydration of the local mucosal surface. These dosage forms are classified into

- Tablets
- Microparticles

- Lozenges
- Wafers

➢ **Tablets**

Several bioadhesive tablet formulations for local or systemic medication administration have been developed in recent years. The tablets are applied directly to the mucosal surface. In the presence of saliva, these tablets stick to the buccal mucosa. They are intended to deliver the medicine unidirectionally to the buccal mucosa or multidirectionally into the saliva. Some examples of drugs formulated into buccal adhesive tablets are given in table 2.

Table 2: Buccal adhesive tablets

Drug	**Bioadhesive polymer**
Nifedipine	Chitosan, polycarbophil, gellan gum, sodium alginate
Ketoprofen	Chitosan and sodium alginate
Propranolol	Hydroxypropyl methyl cellulose, Carbopol 934
Propranolol	Hydroxypropyl methyl cellulose, polycarbophil
Triamcinolone	Hydroxypropyl cellulose, Carbopol 934
Metronidazole	Carbopol 934, hydroxypropyl methyl cellulose.
calcitonin	Hakea gum
Ergotamine tartrate	Polyvinyl alcohol
Morphine sulphate	Carbomer, hydroxypropyl methyl cellulose

➢ **Microparticles**

These are usually given as an aqueous solution, but they can also be applied as an aerosol or mixed into a paste or ointment.

Microparticles have a higher mucosal surface area and can be given to less desirable areas such as the gastrointestinal tract (GIT) and upper nasal cavity. Its modest size lowers local irritation at the point of adhesion as well as the unpleasant sense of foreign objects within the mouth cavity. The main drawback is that the medication dose remains on the buccal mucosa and hence may not be constant in comparison to a single-unit administration form such as a buccal tablet or patch.

➢ **Lozenges**

Antimicrobials, corticosteroids, local anaesthetics, antibiotics, and antifungals are examples of medications that may be delivered via bioadhesive lozenges. The major advantage of using delayed release bioadhesive lozenges is that they provide sustained medication release with enhanced patient compliance. The disadvantages include significant initial drug release in the oral cavity that quickly declines to subtherapeutic levels.

➢ **Wafers**

Wafers are employed in a new periodontal medication delivery system to treat microbial infections associated with periodontitis. The delivery system is a composite wafer with sticky surface layers and a bulk layer composed of antibacterial agents, biodegradable polymers, and matrix polymers. Because of their thinness and flexibility, they are less conspicuous and more acceptable to patients. Due to the relative thinness of the film, it is sensitive to overhydration and loss of adhesive qualities.

ii. Semi-solid buccal adhesive dosage forms

Semi-solid buccal adhesive dosage forms are classified into

- Gels
- Films/Patches

Gels

Cross-linked polyacrylic acid has been utilised in gel-forming bioadhesive polymers to stick to mucosal surfaces for extended periods of time and offer regulated medication delivery. Drug delivery gels have been frequently employed in the oral cavity. Gels have the potential to make intimate contact with the mucosal barrier, resulting in fast drug release at the absorption site. They are unable to deliver a precise dosage of medication to the spot. As a result, they are only useful for medications with a small therapeutic window.

Films/Patches

These can be used to deliver medications directly to the mucosa. Buccal adhesive films and patches (e.g., zilactin) are currently commercially available for the treatment of canker sores, cold sores, and lip sores. Some examples of drugs and other agents formulated in the form of films/patches are given in table 3

Table 3: Buccal adhesive films/patches

Drug	**Bioadhesive polymer**
B-galactosidase	Noveon, eudragit S-100
Chlorhexidine gluconate	Chitosan
Chlorpheniramine maleate	Polyoxyethylene
Plasmid DNA	Noveon, eudragit S-100
Ipriflavone	Poly lactide co-glycolide, chitosan
Isosorbide dinitrate	Hydroxypropyl cellulose, hydroxypropyl methyl cellulosepthalate.
Lidocaine	Hydroxypropyl cellulose, Carbopol
Nifedipine	Sodium alginate
Buprenorphine	Carbopol 934, polyisobutylene

iii. Liquid buccal adhesive dosage forms

These are classified into solutions, suspensions and gel-forming liquids. Viscous liquids can be utilised to cover the buccal surface as a protectant or as a medicine delivery vehicle to the mucosal surface. Pharmaceutically approved polymers have traditionally been used to increase the viscosity of goods in order to facilitate retention in the oral cavity. They are used to make artificial saliva for the treatment of dry mouth. The fact that they are not easily retained or targeted to the buccal mucosa and can distribute relatively uncontrolled quantities of medication throughout the oral cavity is a significant disadvantage.

DELIVERY OF PEPTIDES AND PROTEINS[29]

- The buccal mucosa might be an essential target for the regulated distribution of macromolecular medicinal agents like peptides and protein medicines. It has several distinct benefits, such as avoiding hepatic first-pass metabolism, acidity, and protease activity in the GIT (gastro intestinal tract).

- Another intriguing benefit is its tolerance to possible sensitizers (in compared to nasal mucosa and skin).

CHALLENGES IN BUCCAL DRUG DELIVERY DEVELOPMENT[26,32]

The oral cavity environment provides some substantial problems for systemic medication administration. The medicine must be released from the formulation and delivered to the delivery site (e.g., buccal or sublingual region) before passing through the mucosal layers and entering the systemic circulation. Certain physiological features of the oral cavity, such as pH, fluid volume, enzyme activity, and oral mucosa permeability, play important roles in the process. The structure and turnover of the mucosal surface are also performance criteria for drug delivery systems designed for longer release in the oral cavity (e.g., mucoadhesive systems).

The main physiological environment of the oral cavity, in terms of pH, fluid volume, and composition, is shaped by saliva production. Saliva is released by three primary salivary glands (parotid, submaxillary, and sublingual) as well as tiny salivary or buccal glands located in or just under the mucosa. The parotid and submaxillary glands release watery secretions, whereas the sublingual glands secrete viscous saliva with minimal enzyme activity. Saliva plays different roles such as to lubricate the mouth cavity, aid swallowing, and prevent tooth demineralization. It also promotes carbohydrate digestion and modulates oral microbial flora by regulating mouth pH and enzyme activity.

The amount of total salivary secretion per day ranges between 0.5 and 2.0 L. However, the volume of saliva that is continually present in the mouth is around 1.1 ml, resulting in a relatively modest fluid volume accessible for drug release via delivery devices as compared to the GIT. This obstacle can be overcome if the oral cavity provides a somewhat stable and hospitable physiological environment for drug transport, which is maintained by continuous saliva production. Saliva is a mobile fluid with little mucus, minimal enzymatic activity, and almost no proteases as compared to GIT secretions. Saliva is a poor buffer, with a pH ranging from 5.5 to 7.0. Because of the greater percentage of salt and bicarbonate, this may somewhat rise depending on the high flow rate. The minimal enzymatic activity of saliva can overcome this barrier.

Saliva creates a water-rich environment in the mouth cavity, which can aid medication release from delivery systems, particularly those based on hydrophilic polymers. The temporal span of the released medicine at the delivery location, on the other hand, is determined by saliva flow. This flow can cause the medicine to be swallowed prematurely before efficient absorption occurs through the oral mucosa, and it is a well-accepted notion known as "saliva washout." However, the volume of saliva continually present in the mouth, which is around 1.1 ml, can overcome this barrier.

Another key physiological barrier for oral transmucosal drug administration is drug permeability through the oral mucosa (e.g., buccal/sublingual). The mucosa of mechanically stressed regions (the gingiva and hard palate) is keratinized in the same way as the epidermis is. The mucosa of the soft palate, sublingual area, and buccal region, on the other hand, is not keratinized. Neutral lipids such as ceramides and acyl ceramides have been linked to barrier function in keratinized epithelia. In contrast to nonkeratinized epithelia such as the floor of the mouth, these epithelia are generally impermeable to water, and the buccal epithelia lack

acylceramides and contain only trace levels of ceramides. They also have trace levels of polar but neutral lipids, primarily cholesterol sulphate and glucosyl ceramides. These epithelia have been discovered to be much more permeable to water than keratinized epithelia.

The primary penetration barrier within the oral mucosa resides in the outermost quarter to one-third of the epithelium. The oral mucosa's relative impermeability is attributed to intercellular components generated from membrane-coating granules (MCGs). They can be present in both keratinized and non-keratinized epithelial cells. To ensure epithelial cohesiveness in the superficial layers, MCGs release their contents into the intercellular space, and this discharge provides a barrier to the permeability of different substances. As the oral mucosa possess higher overall permeability than the other mucosa of the mouth, the buccal and sublingual routes, which are the emphasis for drug delivery via the oral mucosa, can overcome this difficulty.

APPLICATIONS OF BUCCAL FILM[11,33,34]

- **Controlled and sustained release**

Sustained-release buccal films are used in hospital preparations and different polymer excipients such as chitosan derivatives because they help with wound dressings, reduce toxicity, and have strong water resistance and adhesive characteristics.

- **Nicotine replacement therapy**

Nicotine in tobacco is a psychoactive chemical that contributes to the addictive characteristic of smoking. The mucosal mode of distribution is the most efficient in this therapy because it easily enters the mucosal barrier.

- **Antifungal infections**

Fluconazole, a systemic antifungal used to treat oral candidiasis, is often chosen for mucosal administration. By raising its oral concentration, its systemic side effects can be decreased. The contact period between the drug and pathogenic yeast is enhanced for a longer length using mucoadhesive buccal films with modest doses of fluconazole, which eventually boosted its efficacy.

- **Targeted therapy of oral cancer**

The most often prescribed treatment for oral cancer is targeted therapy, which strives for site-specific delivery with minimal toxicity and adverse effects. It has been established that by gaining nano delivery systems in the form of polymer films, an increase in solubility, stability, and bioavailability accrued even inside tumour cells.

- **Management of herpes**

Acyclovir, an antiviral medication, is the most often used treatment for oral herpetic lesions. Acyclovir's permeability in the oral mucosa is minimal, resulting in decreased effectiveness. As reported in the literature, strong mucoadhesive strength and excellent physicomechanical properties, as well as increased acyclovir oral bioavailability is achieved by employing in the form of nano particles.

- **Cardiovascular diseases**

Hypertension is one of the primary cardiovascular illnesses that requires long-term treatment. Because of their poor water solubility and rapid first-pass metabolism, antihypertensives such as carvedilol, propranolol, and metoprolol have a short half-life and limited oral bioavailability. To address this, the buccal mucoadhesive system was developed, which gives

a direct passage into the systemic circulation via the internal jugular vein while avoiding the first-pass impact and achieving high bioavailability. With extending contact duration and overcoming first-pass metabolism, a lower effective dosage of 3.125 mg of carvedilol generates better effectiveness[34].

- **Asthma**

The buccal patches are designed to provide sodium cromoglycate for the treatment of asthma. As the medicine is having short half-life, it has to be formulated in a controlled release mechanism. The inclusion of this medicine in buccal patches resulted in an increase in the time necessary to achieve maximum plasma concentration in the blood, as well as a decrease in the maximum plasma concentration in the blood. It also offered regulated drug release.

- **Hypoglycemic agents**

A buccal delivery system for hypoglycemic drugs such as glipizide and glibenclamide is recently introduced. Glipizide has a short biological half-life when taken at two or three dosages of 2.5-10 mg daily. When a water-insoluble drug is added, the uptake of water by the film is seen. For the preparation of glibenclamide mucoadhesive buccal films, several grades of HPMC with specified ratios are utilised. Finally, at low concentrations of HPMC3000, buccal drug administration can be beneficial in a regulated manner.

- **Antiemetic**

Ondansetron HCL possesses features such as low molecular weight and biphasic solubility, which are favourable for absorption through the buccal mucosa. The mucosal route may boost its bioavailability because its principal route of elimination is through hepatic Phase I metabolism. Patients who are vomiting during chemotherapy have a tough time swallowing a pill. As a result, it is claimed that buccal film improves patient compliance by eliminating the requirement for swallowing. Though the medications used may be the same, nausea and vomiting linked with cancer chemotherapy differ from regular nausea and vomiting that many individuals experience in their daily lives.

COMMERCIAL PRODUCTS[35]:

Different categories of the drugs are developed in the form of buccal film or patch for different treatments. Some commercially available products are given in the table 4.

Table 4: Commercial products

Product Name	Manufacturer	Active pharmaceutical ingredient (API)	Dosage form	Use of the Product
Listerine	Pfizer	cool mint	Film strip	Mouth freshener
Benadryl	Pfizer	Diphenylhydramine HCL	Film strip	Antiallergic
Orajel	Del	Menthol/pectin	Film strip	Mouth ulcer
Theraflu	Novartis	Dextromethorphan HBR	Thin film strip	Cough suppressant
Theraflu	Novartis	Diphenylhydramine HCL	Thin film strip	Cough suppressant
Theraflu	Novartis	Dextromethorphan HBR	Thin film strip	Cough suppressant
Theraflu	Novartis	Dextromethorphan HCL	Thin film strip	Cough suppressant
Sudafed PE	Wolters Kluwer Health Inc.	phenylephrine	Film strip	Relieving Congestion
Triaminic	Novartis	Dextromethorphan HBR	Thin film strip	Antiallergic
Triaminic	Novartis	Diphenylhydramine HCL	Thin film strip	Antiallergic

Triaminic	Novartis	Dextromethorphan HBR	Thin film strip	Antiallergic
Triaminic	Novartis	Hcl/Diphenylhydramine HCL	Thin film strip	Antiallergic
Chloraseptic	Prestige	Benzocaine/menthol	Film strip	Sore throat
Suppress	InnoZen Inc.	Menthol	Film	Cough supressant
Zuplenz	Galena biopharma	Ondansetron	Film	Nausea & Vomiting
Gas-X	Novartis	Simethicone	Film	Anti flatuating

2. Future Trend[36]:

A buccal adhesive system has several benefits in terms of cost, accessibility, administration, withdrawal and patient compliance. Traditional polymers are currently being investigated by researchers for innovative drug delivery methods. In the current global scenario, scientists are exploring several approaches to develop buccal adhesive dosage forms to increase the oral bioavailability of medications. It has been discovered that the second generation mucoadhesive polymers has considerable promise. A novel buccal adhesive delivery method has emerged, in which medication distribution is guided towards the buccal mucosa while taking the local environment of the oral cavity into account. Patients now accept solid dose forms, liquids, and gels administered through oral cavity commercially. The distribution of peptides and proteins, as well as vaccine formulations, is the future direction of buccal adhesive drug delivery. Bilayer buccal tablets, films, and patches are superior ways for developing buccal formulations for medication delivery in combination. Microparticulate or nanoparticulate bioadhesive systems are particularly appealing right now since they provide therapeutic entities with protection as well as better absorption due to extended contact time given by the bioadhesive component.

3. Conclusion

The current review concludes that buccal film is the most accurate and acceptable dosage form due to increased patient compliance, a quicker drug delivery method, bypassing the first-pass effect and demonstrating enhanced bioavailability. Buccal films will replace traditional dosage forms as well as rapid dissolving tablets due to their benefits over traditional dosage forms and their low cost of production. Buccal films, on the other hand, are a more viable formulation due to their ease of manufacture, drug loading, and characterisation. Buccal film is a non-invasive drug delivery technique that can be used to overcome first pass metabolism prone drugs. These will be a more robust alternative in the future to optimise the therapeutic effectiveness of diverse API. Oral mucoadhesive dosage forms have the potential to remain an intriguing research focus on enhancing drug absorption, particularly for the next generation of drugs. This review summarizes polymer based drug delivery systems for buccal administration. The use of these systems increasing the research and development of bio materials and buccal delivery systems. Such studies could be remarkable and will manifest themselves in new publications in future.

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