Review Article

Recent Trends and Advances in Buccal Film Drug Delivery System: An Innovative Pharmaceutical Dosage Form Technology

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ABSTRACT

Nowadays, extensive research is being done on the design and production of a new drug delivery system to improve safety, efficiency and compliance issues. The only delivery system that complements all of the above-mentioned methods is Buccal Film Technology. If planning of any appropriate drug delivery, buccal drug delivery system is considered to be the best amongst all. A buccal drug delivery system directly enters systemic circulation. It uses a jugular vein pass to deliver drugs from hepatic first pass metabolism, which boosts their bioavailability. All in all, the buccal mucosa has excellent accessibility, muscle elasticity, and smooth mucosa which is why it is ideal for controlling the final dose forms. Buccal films release drugs orally in a slow and predetermined dose that provides well-defined benefits in addition to standard dosage forms for the prevention and treatment of certain diseases. Buccal films share certain features like reduced size, volume, dynamic control, which is why they taste better and more acceptable forms than other buccal drug delivery systems such as gels, pills, lozenge, microparticles, etc. is more appropriate than the others. In addition, certain factors such as non-irritability, natural flexibility, painless management, easy drug withdrawal choose the buccal drug delivery system as a promising method for further research. It is very expensive and there are no medicines to be swallowed, which is why it is so convenient and friendly to pediatric patients and Geriatrics patients. This article provides a detailed review of the introduction, benefits, limitations, buccal film types, composition, preparation methods, estimates and sales arrangements and their capabilities of these formulation forms as pharmaceutical formulation forms.

Keywords: Buccal films, buccal drug delivery system, polymers, buccal mucosa, bioavailability.

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INTRODUCTION

The current article mainly concentrates on the Bucco adhesive drug delivery systems established on cohering mucus membranes. Today, increasing need for patient ease, comfort and observance related research. Moreover, buccal film technology is the advanced method which leads to dissolution in patient's buccal mucosa. The buccal area of the oral mucosa offers an appealing route of administration for regulated systemic medication distribution. The administration of medications is occurred through the mucosal membrane lining the cheeks which is known as buccal delivery. The sublingual mucosa is more permeable compared to buccal mucosa, even though the buccal mucosa is chosen for systemic transmucosal medication administration. Due to the presence of larger span of smooth muscles, buccal mucosa becomes the most appropriate in terms of retentive systems. As a result, the buccal mucosa is better suited to delivering less permeable molecules and peptide medicines over time. The body possesses unique and distinctive features, hence buccal mucosa is considered to be the absolute route of mucoadhesive drug delivery system.[1-2] Oral use membrane space as drug control centers has become a topic interest rate increase over the last decade. It is known that the absorption of therapeutic compounds into the oral mucosa provides direct administration of the drug to the circulatory system, thereby ignoring it. Primary Hepatic Metabolism and gastrointestinal dysfunction, both associated with peroral management.[3-5] Buccal, sublingual, rectal and nasal mucosa (Mucoadhesive drug delivery system) can be a quick and systematic mode of non-interactive drug administration to circumvent the inceptive metabolism of passage. Rapid delivery of medications and improved drug availability are the results than can be obtained in mucoadhesive administration. Buccal films, on the other hand, have the greatest obstacle in terms of developing excellent quality, which is also required for ongoing evaluation and comprehension of performance.

Oral mucosa

The mouth possessing the lining of mucous membrane is defined as oral mucosa.

Classification of oral mucosa

Depending on the function and histology, the oral mucosa can be split into three primary categories: Nonkeratinized stratified squamous epithelium lining mucosa, which can be found practically wherever else in the oral cavity, including the: The lining between the buccal and labial

mucosae which is called alveolar mucosa. It has a stronger red color, is smooth and shiny, and has numerous blood vessels. The lining mucosa and the floor of the mouth appearing inside of the cheeks designated as buccal mucosa. The inside lining of the lips and a part of the mucosa lining is specified as labial mucosa. Keratinized stratified squamous epithelium together formed are specified as masticatory mucosa that remains safe due to the dorsum of the tongue, the hard palate, and the connected gingiva. Nerve endings for general sensory reception and taste perception are found in specialized mucosa, notably in the areas of the taste buds situated on lingual papillae at the dorsal surface of the tongue.

Structure of human oral mucosa:

Oral mucosa = Surface stratified squamous epithelium + deeper lamina propria.

The epithelium of keratinized oral mucosa is composed of the following layers:

1) Stratum Basale (Basal Stratum) (basal layer)

2) Spinosum stratum (prickle layer)

3) Granulosum stratum (granular layer)

4) Corneum stratum (keratinized layer)

The two deep layers (Basale and spinosum) stay the same in nonkeratinized epithelium, however the outer layers are referred to as the intermediate and superficial layers. The epithelium of the mouth: 1) Nonkeratinized 2) Keratinized.

1) Nonkeratinized squamous epithelium composed of the soft palate, inner lips, inner cheeks, the floor of the mouth, and the ventral surface of the tongue.

2) Keratinized squamous epithelium: The gingiva and hard palate, along with parts of the tongue's dorsal surface. [6]

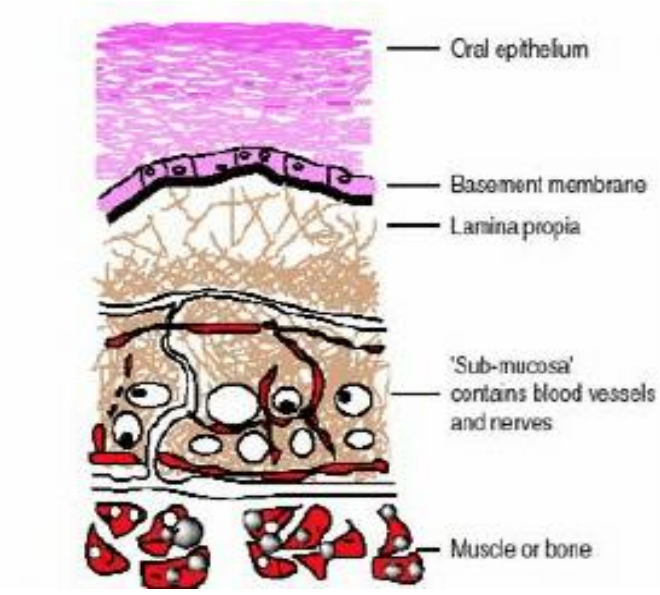


Figure 1: Structure of human oral mucosa

The oral cavity adheres and acts as a lubricant, allowing cells to move more freely than others with minimal abrasion. The oral cavity provides a therapeutic route for both local and systemic circulation, to prevent first pass metabolism and GI degeneration. The oral cavity is easily accessible to control, drug withdrawal is possible if necessary, and the drug is safe, so patients receive it. Bio adhesive polymers have attracted a lot of attention as buccal-controlled delivery platforms to avoid the introduction of volume forms or volume disposal. The addition of drug-containing particles to the mucous membrane due to mucous adhesion will result in more time to stay in the suction area or action, proper treatment system at its site of action as well as particular work area, and the development of drug concentration due to rapid contact of particles with mucosal surface.[7] In addition, Oral mucosal drug delivery systems possess two categories: buccal and sublingual. The buccal cavity is widely used in drug administration through the mucosa, and the small tongue canal is used to quickly initiate action, as in the case of angina pectoris. The inner cheek is attached to the buccal mucosa.[6] The administration of medications into the oral mucosa is divided into three categories:[8]

1. Sublingual Delivery

2. Delivery of Buccal

3. Local Delivery

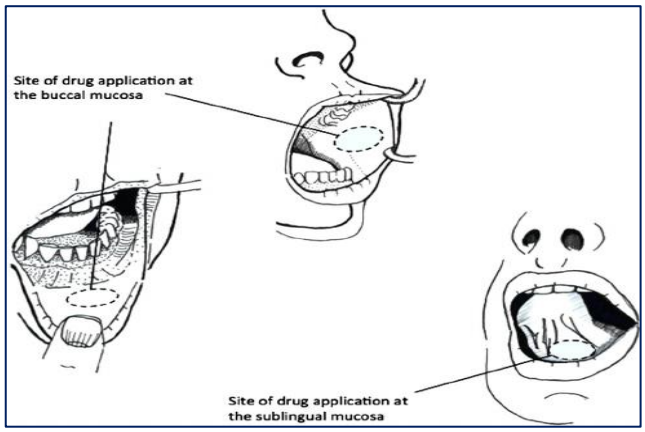


Figure 2: Site of application in buccal cavity

Buccal Mucosa Environment:

The oral cavity is distinguished by the presence of saliva generated by salivary glands and mucus secreted as part of saliva by the main and minor salivary glands.

Role of Saliva:

- Salivary fluid is a water-based exocrine secretion in the form of liquid consisting of a wide range of electrolytes such as sodium, potassium, calcium, magnesium, phosphate, etc. and proteins like immunoglobulins, enzymes and other antimicrobial factors, mucosal glycoproteins, traces of albumin, and some polypeptides and oligopeptides that are essential as well as important to oral health, as they help in rapid administration of drugs. [9,10]

- No tissues of the oral cavity get harm as saliva acts as a protective fluid hence prevents from toxicity.
- Continuous mineralization and demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.
- Lubrication.

Role of Mucus:

- Negatively charged and containing mucins, which are giant glycoproteins referred to as mucus Mucin is made up of a protein core that's high in O-glycosylated serine and threonine and has a lot of helix-breaking proline residues. Saliva has a pH range of 5.8 to 7.4.6
- Composed of proteins and carbohydrates.
- Cell-cell adhesion
- Lubrication
- Bio adhesion of mucoadhesive drug delivery systems

Buccal drug delivery system:

Buccal controlled drug delivery system is considered to be the most appropriate amongst other drug delivery systems in terms of oral cavity due to highest tendency and potency. The continuous saliva secretion is the only parameter which is responsible for the drug release of buccal film. The mucin film situated in the oral mucosa helps in the innovation of a mucoadhesive system, which is holding mucoadhesion at the absorption site for a longer period of time. The medicine is absorbed more quickly when it comes into close touch with the absorption membrane. With the correct dosage form design and composition, the pH of the buccal cavity does not pose a difficulty for the medicine. In order to accommodate medication penetration, the buccal mucosa's permeability and local environment can be adjusted and altered.[11]

Novel buccal dosage forms:

The novel buccal dosage forms include:

buccal adhesive tablets,

patches,

films,

semisolids (ointments and gels) and

powders.

A. Tablets with mucoadhesive properties for the buccal mucosa:

Buccal mucoadhesive tablets are dry tablets that get wet when they come into touch with the buccal mucosa. A double-layer tablet, for example, with an HPC and polyacrylic acid sticky matrix layer and a cocoa butter inner core containing insulin and a penetration enhancer (sodium glycocholate).

B. Films and Patches:

Buccal patches are made up of two laminates: A sticky polymer solution is and an impermeable backing sheet, which are mocked up and further cut into the necessary shapes of oval form.

C. Preparations that are semisolid (Ointments and Gels):

Patients do not take bio adhesive gels or ointments as well as other solid bio adhesive dosage forms as they are used mostly in local medications.

D. Powders:

When HPC and beclomethasone both are taken certain dosage form like powder forms and then sprayed on the oral mucosa of rats, they show a considerable increased results in residence duration compared to an oral solution, with 2.5 percent beclomethasone remaining on the buccal mucosa for nearly 4 hours, which shows that it possesses quite good properties. Hence above-mentioned powders are considered essential for better effects.[12]

Characteristics: Buccal drug delivery System: [13-15]

- Non-poisonous and safe
- Patient cooperation is necessary like no interfering with basic activities such as talking, eating, and drinking
- Strong mechanical properties
- Adherence to the buccal mucosa right away
- Release of drugs under strict regulation
- Absorption of drugs to their maximum potential

Buccal Drug Delivery System: Benefits: [16-17]

- As compared to other drug delivery system, a medicine reaches directly into the systemic circulation without taking more time i.e., in shorter duration.
- Avoids first-pass metabolism and GIT fluid exposure.
- Longer contact time with the mucosa increases bioavailability.
- Patient compliance is higher when compared to other non-oral medication delivery methods.
- To allow better transportation of molecules having higher molecular weight, permeability enhancers and protease inhibitors are added like peptides, proteins, and ionized species, however this does not cause any complex issues.

Buccal Drug Delivery System: Drawbacks: [18-20]

- Surface area is reduced.
- Mucosal lining
- Due to continual saliva flow, the medication is diluted or lost.

Introduction to buccal film:

Buccal film is a non-dispersible thin type of spreadsheet modified release dosage form made up of one or more polymer matrix or coverings that holds the medicine and/or additional excipients. When relative to other dosage forms, the buccal film is an exquisite and effective dosage form with enhanced

bioavailability since it skips hepatic first pass metabolism. Due to its tiny size, modest dose, and film thickness, it is the most agreeable and appetizing dosage form. Oral mucosa, teeth or gingiva may get adhered due to the presence of mucoadhesive polymers in the film. This enhances oral cavity getting appropriate medication release leading to produce better therapeutic effects which is defined as unidirectional release, individually in the oral cavity by unidirectional release or the two of them together i.e., bidirectional release. After a set amount of time, the patch is removed from the mouth and discarded.[21}]

Buccal Dosage Form Structure and Design:[22]

Buccal Dosage Forms include:

1)Matrix type (Bi-directional):

A buccal patch with medication, adhesive, and additives combined together in a matrix format.

2.Reservoir type **(**Unidirectional):

A reservoir system buccal patch has a chamber for both medicine and additives but not adhesives. To regulate the direction of medication distribution, decrease patch deformation and disintegration while in the mouth, and avoid drug loss, an impermeable backing is used.

Mechanism of buccal absorption:

A slow dispersion of non-isolated or individual species results in better buccal absorption of drugs. Concentration gradient plays a wide role in regulation of the entire process through intertwined epithelium spaces. Transmission of non-ionic species throughout the buccal lipid membrane is the primary mode of transport. The buccal mucosa is said to be a lipoidal barrier to drug overdose, as it does in many other mucosal pores and where the drug molecule is lipophilic, it is where it is most easily absorbed.[23] The dynamics of buccal drug absorption can be adequately explained by the first dose procedure. Dearden and Tomlinson (1971) have shown that saliva begins to change buccal absorption kinetics from drug solution by doing significant changes and alterations of the drug overload in the mouth. The correspondence between saliva and time is given as follows:

$dm/dt = Kc/V_iV_t$

where,

M - Mass of drug in mouth at time t

K - Proportionality constant

C - Concentration of drug in mouth at time

V_i - The volume of solution in the mouth cavity and

V_t - Salivary secretion rate [24-25]

Consequences of Buccal Films:

- Buccal delivery can be used to deliver drugs that are not able to tolerate stomach's acidic environment.
- Passive diffusion is a method of drug absorption.
- Physical condition, shape, size, and surface flexibility.
- Absorption rate is increased.
- Action takes place quickly.
- If therapy must be stopped, the formulation can be withdrawn.
- The oral cavity's large contact surface aids in quick and thorough medication absorption.
- Because the extent of perfusion is greater, absorption is faster and more effective.
- Nausea and vomiting are reduced to a minimum.
- Stratum corneum is absent in mucosal surfaces, while they are present in TDDS. As a result, with transmucosal routes of administration, the primary barrier layer to transdermal drug transport is not a problem. As a result, transmucosal systems have a faster start and stop time than transdermal patches. [22,26-30]

Downsides of buccal films:

- When compared to transdermal patches, transmucosal administration is less variable amongst patients, resulting in lower inter subject variability.
- Smooth muscle and somewhat immobile mucosa are present, making it suited for the administration of retentive dose forms.
- Drugs or excipients present in the film may cause adverse effects by causing irritation to the mucosa hence must be determined first before processing.
- Thinner the film better is the dose accuracy than liquid formulations since each strip is produced to contain a specific amount of medicine, making it more stable, robust, and quick to dissolve.

Factors that influence medication distribution through the buccal route: [27]

Any of the drug delivery may get affected due to some of the factors. Buccal drug delivery system also includes some factors which may affect drug absorption, distribution, metabolism or elimination processes. These factors are mentioned below.

1. Membrane Factors:

The degree of cellular proliferation, the surface area accessible for absorption, the mucus coating of the salivary pellicle, epithelial intercellular lipids, the basement membrane, and the lamina propria are all factors to consider. Furthermore, the thickness of the absorptive membrane, blood sourcing discharge, cell reproduction, and enzyme composition are all other factors that contribute to lowering the rate and amount of medication entering the systemic circulation.

2. Environmental Factors:

A. Saliva: Salivary pellicle or film is a thin film of saliva that covering the whole lining of the buccal mucosa. The salivary film thickness should be from 0.07 to 0.10 mm The rate of buccal absorption is affected by the thickness, content, and mobility of this film.

B. Salivary glands: Salivary glands are found in the buccal mucosa's epithelium or deep epithelial area but are smaller in size. Secretion of mucus occurs continually on the buccal mucosa's surface. Mucus aids in the retention of mucoadhesive dose forms, but it can also act as a barrier to medication penetration.

C. Buccal tissue movement: The buccal portion in mouth cavity does not cause forceful or vigorous motions. The bio adhesive polymers will be used to retain the dose form in the buccal area for lengthy periods of time, and exert its effect for longer duration, allowing it to tolerate tissue movements while talking and, if feasible, eating or swallowing.

3. Formulation related factors:[27]

A. Molecular size: Smaller the molecules (75-100 Da) more and quickly the movement through the mucosa, including penetration declining as molecular size rises. Absorption enhancers have been utilized to successfully change the permeability of buccal epithelium for hydrophilic biomolecules like peptides, making this route more suited for delivery of bigger molecules.

B. Partition coefficient: A important tool for determining a drug's absorption capability is the partition coefficient. In general, boosting a drug's polarity by ionization or adding hydroxyl, carboxyl, or amino groups increases the drug's water solubility and lowers the lipid water partition coefficient. Increasing the polarity of a drug (by adding methyl or methylene groups, for example) results in a higher partition coefficient and lower water solubility.

C. pH: The pH at the location of medication absorption has an impact on the partition coefficient. Both are interdependent on each other. The partition coefficient of acidic medications decreases as pH rises, while the partition coefficient of basic pharmaceuticals rises. Partition coefficient helps in calculating the amount of drug present in adipose tissue. Obese people acquire lot of lipid soluble drugs which are in the fat storage. These medicines are dissolved in lipid and act as a slow-release storage in these fat deposits.

D. pKa: pKa and pH are the two parameters resulting in the drug ionization and they both are proportional to each other at the mucosal surface. Many weak acids and weak bases only have considerable lipid solubility and hence the capacity to pass lipoidal membranes in their nonionized state. Hence it has been discovered that peak absorption of these chemicals occurs at the pH at which they are unionized, with absorbability decreasing as ionization rises.

FORMULATION OF BUCCAL FILMS

1.Drug: [22-27]

The molecular weight, chemical functionality, and melting point of the drug are all critical factors that determine its absorption through the patch and buccal. While formulating the buccal drug delivery system, pharmacokinetic features consideration is necessary.

Buccal Mucoadhesive Drug Delivery: Essential criteria: [22,27]

• The conventional medicine should have smaller single dose hence easy to administer and quick absorption.

• The medication may display a first pass effect or pre systemic drug clearance when taken orally.

• The drug should not possess detrimental effect on the mouth cavity containing microbes.

• The drug should not have a foul taste and should be devoid of irritancy, allergenicity, discolorations, or tooth erosion.

• Drugs with a biological half-life of 2-8 hours are suitable controlled drug delivery options.

• When taken orally, the drug's T_{max} has larger variations or higher values.

• When taken orally, drug absorption should be passive, hence need not require any kind of energy for the drug absorption.

Any class of pharmaceutically active chemicals that may be delivered orally or through the buccal mucosa can be used as an active pharmacological agent. Antiulcers, antiasthmatics, antitussives, antihistaminics, expectorants, antianginals, and other antiepileptics, the medicine dose should be measured in milligrams (less than 20 milligrams per day) for the most effective formulation. Buccal film can usually include 5 percent w/w to 30 percent w/w active medicinal substances. It's tough to include a high dose of molecules into a film.

2.Polymers:

Polymers with mucoadhesive properties:

To choose proper mucoadhesive polymer is the foremost criteria for emerging mucoadhesive drug delivery system, as they play major role in appropriate manufacturing of buccal films. These polymers should adhere rapidly, be

stable, inert, nonirritant means not causing any irritation, nontoxic without any toxic effect, affordable as well as be medication compatible.[31]

The following kinds of mucoadhesive polymers are available: [32-35]

Table 1: Types of Mucoadhesive Polymers

Type	Example
Natural	Tragacanth, Sodium alginate, Guar gum, Xanthan gum, Soluble starch, Gelatin, *Lectins (*naturally occurring proteins), Antigen K99-fimbriae, an attachment protein derived from E. coli
Synthetic	Polyacrylic acid (PAA), Polyvinyl alcohol (PVA), Hydroxypropyl methyl cellulose (HPMC), Hydroxyethyl cellulose (HEC), Hydroxypropyl cellulose (HPC) and Sodium alginate, glyceryl monooleate (GMO), chitosan or deacetylatedgellan gum

3.Plasticizers: [36]

Plasticizers are highly useful for improving the flexibility, fluidity, and strength of mucoadhesive films as well as reducing their embrittlement. Plasticizer, like polymer, is an important component of the film formulation, with a ratio of 0–20 percent w/w of dry polymer composition. Plasticizers are chosen based on stability, polymer type, and solvent absorption. Plasticizers used in abundance or in the wrong combination can cause film breaking, cracking, and peeling. Examples include glycerol, propylene glycol, low molecular weight polyethylene glycols, phthalate derivative products such as citrate derivatives such as tributyl, triethyl, acetyl citrate, and castor oil, and phthalate derivatives such as dimethyl, diethyl, and dibutyl phthalate.

4.Penetration or permeation enhancers: [34-35,37]

Penetration or permeation enhancers enhances proper mixing of the drugs with mucosal layer, which allows the drugs to enter systemic circulation. Table 3 lists a few penetration enhancers as examples. Although the mode of action of these compounds is unknown, experts have proposed the following assumption:

• Low viscosity of mucus and saliva are two primary obstacles responsible for the penetration or permeation.

• Interacting with and disturbing desmosomes, which are constituents at stiff junctions, to increase the flexibility of the lipid bilayer membrane by disrupting intracellular lipid or protein packing

• By suppressing peptidase and protease enzymes in the buccal mucosa and breaking through the enzymatic barrier.

Table 2: List of Permeation Enhancers

No.	Permeation Enhancer	No.	Permeation Enhancer
1	Aprotinin	11	Polyoxyethylene
2	Azone	12	Polysorbate 80
3	Benzalkonium chloride	13	Phosphatidylcholine
4	Cetylpyridinium chloride	14	Sodium EDTA
5	Cetyltrimethyl ammonium	15	Chitosan
6	Bromide	16	Sodium glycocholate
7	Cyclodextrin	17	Sodium glycodeoxycholate
8	Dextran sulfate	18	Sodium lauryl sulfate
9	Glycol	19	Sodium salicylate
10	Lauric acid	20	Sodium taurocholate

5.Inhibitors of enzymes:

The existence of a large number of enzymes is a main hindrance to medication delivery from the oral mucosa, but when a drug is given in combination with enzyme inhibitors or thiol derivatives of polymers, it helps boost buccal absorption. By interacting with co-factors, most enzyme inhibitors produce confirmational changes in enzymes, resulting in a reduction of enzymatic function. E.g.: Bestatin, puromycin, aprotinin, carbomer derivatives like polyacrylic acid and chitosan derivatives.

6. Agent that stimulates saliva:

The goal of utilizing saliva stimulating compounds is to raise the rate of saliva production, which will help the quick dissolving film formulations dissolve faster. Acids that are often used in food preparation can be employed as salivary stimulants, as they help in the secretion of saliva. Moreover, certain salivary stimulants are available which are beneficial and effective include citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid, with citric acid being the most commonly used inducing saliva secretion and exerting the effect of the drug. Between 2 and 6% w/w of the film's weight, these ingredients are employed alone or in combination.

Salivary stimulants are also present in other buccal film substances, such as sweets. Salivary stimulants such as food-grade sugars and synthetic sugars, as well as acidulants, are beneficial. Sweeteners including glucose, fructose, xylose, maltose, and lactose are just a few examples. The quantity of resting and induced flow at the same time under the same conditions can be used to determine salivation stimulation. Sweeteners' stimulating effect is determined by their sweetness level. Fructose has a sweetness rating of 1.1, whereas glucose has a value of 0.7 and sucrose has a value of 1.0. Artificial sweeteners are

chosen over natural sugars since they demand less focus and do not induce tooth cavities in persons.

7.Sweetening agents: [38]

Sweetener is a chemical substance that has a sweet flavor. Traditional sweetening agents/sweeteners can be added for masking the taste which are available in the form of low molecular weight carbohydrate and, in particular, sucrose.

Sucrose has the benefits of being colorless, having a high-water solubility, and being stable across a wide pH range, as well as imparting a pleasing texture and a fast, clean, and short-lived sweet flavor. However, because sucrose metabolism and its fermentable metabolites have been linked to diabetes, obesity, and even tooth damage, there is a significant need for healthy, natural sweeteners. Between 2 and 6 percent w/w of the film's weight, sweeteners are employed alone or in combination. The following is a list of alternative sweeteners:

Table 3: list of alternative sweeteners

Nutritive sweeteners	Compared to sugar, less sweet and calorie-free but does not possess many of the sugar's desirable chemical and physical properties e.g., sorbitol, mannitol, xylitol, maltitol, lactitol, fructose
Non-nutritive sweeteners	Potently sweet and required in minute quantities. e.g., fruit sugars, aspartame, saccharin, cyclamate, acesulfame, glycyrrhizin
Artificial sweeteners	These are prepared synthetically and most preferred sweeteners. e.g., Aspartame, saccharin, sorbitol, mannitol
Natural sweeteners	Sources from plant or animal sources e.g.: Plant: Glycyrrhizin, Neohesperidin, Stevioside, Thaumtin Animal: Honey, Lactose from cow milk.

8. Flavoring agents: [39]

In the case of oral dissolving systems, the flavoring agents are crucial for easy intake of drug and suppress bitter taste of the drug. The flavor's quality and the duration of the flavor for how long does it lasts and exerts its effects are the two essential criteria for the patient's approval of an oral disintegrating formulation. Certain flavoring agents are available in the form of flavor oils which include peppermint, cinnamon, spearmint, and nutmeg oil, while other agents in the form of fruity tastes include vanilla, cocoa, coffee, and chocolate. Fruit essences include apple, raspberry, cherry, and pineapple, to name a few. Flavors can be added in the drug and mixed alone as well in the form of mixtures. The proportion of flavor required to cover the taste is determined by the kind and concentration of the flavor. In the compositions of buccal films, up to 10% w/w tastes are preferred. Cooling additives like monomethyl succinate can be used to boost taste strength and increase the mouth-feel impact of the product, also induce cooling effect in the mouth also suppresses bad taste.

9.Agent of Color:

When some of the active ingredients or medications are present such that they are not soluble or are not able to dissolve, pigments such as Titanium dioxide or FD&C approved coloring agents only to be used whose concentration levels should not surpass 1% w/w in buccal film formulation. [40-41] Hence approved coloring agents only to be added in the formulation.

10.Surfactants:

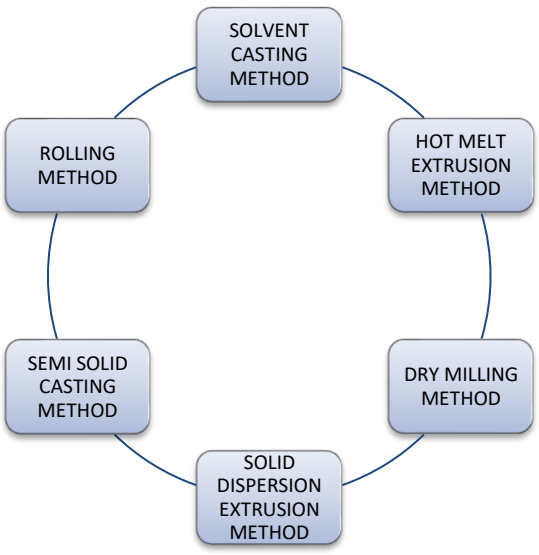
Surfactants are utilized as a wetting or solubilizing agent. Surfactant dissolves the film in seconds, allowing the medicine to be delivered quickly. Surfactant are mainly used for increasing the solubility property of the drugs in the mouth which are weakly/poorly soluble. Poloxamer 407, sodium lauryl sulphate, benzalkonium chloride, benzethonium chloride, tweens and spans, and others are examples.[41]

11.Agents for thickening and stabilizing:

Thickening agents and stabilizing agents play major role in in the improvement of fluency and uniformity properties of the dispersion or solution in preparing the film before the casting process. Stabilizing and thickening agents include natural gums such as xanthan gum, locust bean gum, carrageenan, and cellulosic derivatives. They're employed at concentrations of up to 5% w/w. [41]

MANUFACTURING METHOD FOR BUCCAL FILMS

Buccal film formulation can mostly be accomplished using below mentioned six methods.



1.Solvent casting method:

The needed amount of polymer is introduced and dissolved in distilled water in the solvent casting procedure. This solution should include a small amount of

active medicinal ingredient. Plasticizer is allowed to mix uniformly with the solution. The solution is then mocked up on Petri dish. Further it is parched in a hot air oven at 400°C to remove any moisture or humidity if present. After drying, cut it off the Petri plate with a blade and place it in a desiccator for 24 hours. Cut in the necessary size and form from now on.

The Solvent Casting Method performing steps:

Step 1: Preparation of the casting solution

Step 2: Deaeration of the solution

Step 3: Cascade the mould with the correct amount of solution

Step 4: Allow the casting solution to dry.

Step 5: Cut the finished dosage form so that the desired amount of medicine is contained as per the requirement. [42-43]

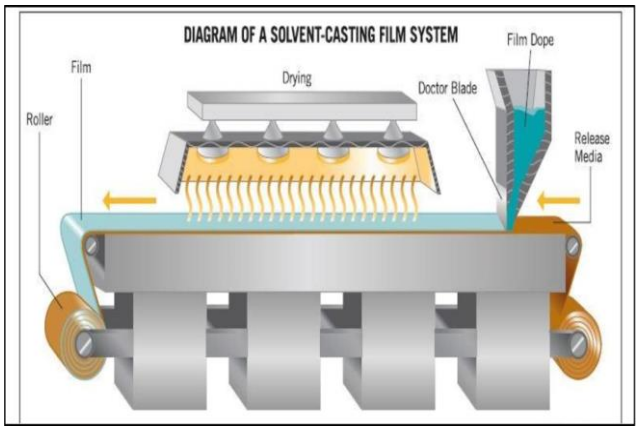


Figure 3: Solvent casting film system [44]

2. Hot melt extrusion method:

Hot melt extrusion process includes the medication and other excipients to be molten. The material is then pressed through an aperture to produce a more homogeneous substance in various shapes such as granules, tablets, or films. It is utilized in the administration of transdermal drugs. [21,42]

Steps in the Hot Melt Extrusion Process:

Step 1: In solid form, the medication and carriers are added together in this process.

Step 2: Through heating, the mixture is allowed to get liquified and to obtain in fluid form.

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

Advantages:

- There are minimal operation units.
- Improved content consistency
- A process that is devoid of water

Disadvantages:

- Thermal processing may cause some harmful errors which may lead to instability.
- Appropriate flow characteristics of polymers are essential as they play vital role in formulation of buccal films.
- There are just a few polymers available.

3. Direct Milling:

Direct milling or kneading are used to mix the medicine and excipients in the absence of liquid. The resulting material is then rolled on a release liner until it reaches the desired thickness, as thickness of the film plays major role for proper administration and absorption. If the solvents are not present in this solution, although it would not affect much to this procedure. This procedure is frequently used because there is no risk of leftover solvent and no link between solvent and health problems. [21,42]

4. Solid dispersion extrusion:

This process involves extruding immiscible components with the medication. Further based on above process solid dispersions are prepared. Finally, dies are used to mould the solid dispersions into films.[30]

5. Semisolid casting:

A solution of water-soluble film forming polymer is created initially in the semisolid casting procedure in order to enhance faster absorption of the medication. The resultant solution is allowed to get mixed with an ammonium or sodium hydroxide solution of acid insoluble polymer (cellulose acetate phthalate, cellulose acetate butyrate) for the formulation of buccal films. The appropriate amount of plasticizer is then added, resulting in a gel mass. Finally, heat-controlled drums are used to diffuse the gel mass and convert it into films or ribbons. The film is around 0.015-0.05 inches thick. The acid insoluble producing polymer should be used in a 1:4 ratio.[30]

6. Rolling Method:

A drug-containing solution or suspension is rolled on a carrier in the rolling method. Water and water-alcohol mixtures are the simplest solvents to be used in this particular method. The film is cut into suitable shapes and sizes after removing moisture by drying on rollers.[30]

EVALUATION OF BUCCAL FILMS

1.Organoleptic properties:

The desired organoleptic qualities such as color, flavor, and taste can be determined by visual inspection of the created film composition. E-tongue software is helpful in determining the flavor of a composition as we come to know the amount of flavor added or if further required Color and aroma uniformity, as well as acceptable taste improves patient acceptance.[45]

2. The film's weight:

A calibrated weighing balance is used to weigh buccal film. Each film's weight is computed individually. [46]

3. Measurements of thickness: [47]

An instrument known as electronic digital micrometer is used in order to measure the how much the film is (thickness). The data is expressed on the basis of mean ± standard deviation of five different determinations.

4. Morphological characteristics of the surface:[48]

Scanning electron microscopy is the equipment used to after the formulation to assess the cross section of the films (SEM). After drying the films, they were allowed to get enveloped with a compound called gold sputter and examined or investigated under a scanning electron microscope.

5. Tensile resistance:

The tensile strength of a film is the quality that requires a load to cause deformation failure. Film strips of a certain size are kept in place by two clamps spaced at a specific distance. The following equation is mentioned to calculate tensile strength by applying a load at rupture and the cross-sectional area of a shattered film. [49]

Tensile strength (N/mm2) = breaking force (N) / sample cross sectional area (mm^2)

6. Permeation studies:

The mucosal surface should be kept in touch with a film specimen moistened with a few drops of simulated saliva. Hence the results can be observed about the reaction between film and saliva. 1 mL of simulated saliva fluid with a pH of 6.8 should be placed in the donor compartment. Samples are taken out at regular intervals and replaced with the same amount of new medium. The proportion of drug penetrated can be determined using a proper analytical approach. [45]

7. Percentage moisture loss:

This is used to ensure the quality of films by observing the moisture and humidity as no incompatibility arises. The film is cut out and then weighed. After that, the film is allowed to place it in a desiccator with fuse anhydrous calcium chloride. Further, it is weighted and removed after 72 hours. The formula mentioned below is used to compute the average % moisture loss. [50]

Moisture Loss as a Percentage (%) = (Initial weight-film weight) * 100/Initial weight.

8.Swelling studies:

The samples were collected and allowed to put in an incubator for swelling on the surface of an agar plate at 370°C after the original patch weight and diameter were calculated and determined. At predetermined time intervals (1–5 h), the weight and diameter of the patches (n = 5) were measured. Below equation examines % swelling studies:

$\% S = (X_t - X_o/X_0)\ 100$, where X is the swelled patch's weight or diameter at time t, and Xo is the patch's initial weight or diameter at zero time.[51]

9. Drug-excipients interaction studies: [52,53]

When the drug ingredient and excipient are mixed together, it may cause problem in stability. Hence assessment of these incompatibilities is necessary. To analyze probable drug excipient interactions, Fourier Transformer Infrared Spectrum (FTIR), Differential scanning calorimeter (DSC), thin layer chromatography, and X-Ray Diffraction (X-RD) can be utilized. Because it indicates changes in appearance, shifts in melting endotherms and exotherms, and variations in the accompanying reaction enthalpies, DSC is responsible for a quick assessment of potential incompatibilities. [52,53]

10. Folding endurance:

The test is performed by folding the films numerous times repeatedly until the films begin to crack or break. The test is occasionally limited to a maximum of 300 folds, and the value is stated as the number of folds the film can withstand before rupturing. [54,55]

11. Surface pH:

In order to evaluate the probability of any negative effects in vivo, the surface pH of the films was assessed. We tried to keep the surface pH as close to neutral as possible because an acidic or alkaline pH may produce irritation to the buccal mucosa and it may get damaged rather than producing therapeutic effects. The films were initially allowed to swell for 2 hours in specially built glass tubes by submerging them in 1.0 ml of distilled water (pH 6.5 0.05). After that, the surface pH was measured by placing a combination glass electrode near the film's surface and allowing it to equilibrate for 1 minute. [56]

12.In-vitro Disintegration studies:

It's measured visually in a petri plate holding 2 mL distilled water, with 10 seconds of whirling. The film when gets broken or disintegrated is the time specified as disintegration time. [57]

13.In-vitro dissolution studies:

Dissolution experiments are necessary to estimate the amount of active drug released into the dissolution medium per unit time under controlled circumstances of liquid/solid interface, concentration, and evaluated the rate of drug dissolved at particular time at 37±0.5°C, and rotational speed of 50 rpm.

Permeation experiments should be performed despite the fact that the permeability of the mouth mucosa is 4-1000 times greater than that of the skin. A modified Franz diffusion cell and porcine. The two compartments namely a donor and a receptor compartment make up the Franz diffusion cell. Mucosa is mounted between the two

compartments, and the size of the mucosa should be the same as the head of the receptor compartment. [58]

14.Stability studies:

A pharmaceutical product's stability can be defined as a formulation's capacity such that it can tolerate its physical, chemical, microbiological, therapeutic, and toxicological parameters in any specified container / closure system. All of the formulations were tested only to be determine stability at various temperatures in accordance with ICH recommendations.[59] The storage settings for the stability study were as follows: one was regular room conditions at 40°C/75 percent RH for 6 months, and the other was 30°C/75 percent for 24 to 36 months. DSC, FTIR, Folding endurance, disintegration time, drug content, and in vitro drug release are all tested after the film being placed in packing material such as aluminum foil or any other. [60]

15.Packaging:

Buccal films can be packaged in a variety of ways, including single pouches, blister cards containing several units, multiple-unit dispensers, and continuous roller dispensers. For films, single packaging is required. The most popular packing system is an aluminum pouch. For oral films, there are a few patented packing solutions. Rapid card is a patented packaging method by Labtec, and Core-peel is a patented packaging technology by Amcor Flexibilities.

Applications of Buccal Films

1.It is feasible to make multilayer drug films, also known as an emerging field possessing immediate applications. Two or more medications might be integrated in one structure, and the layers could be designed to dissolve at the same rate or at different speeds.

2.The dissolving rates of the medications might range from minutes to hours depending on how the films are made.

3.Films can be employed as gastro retentive dosage forms, with dissolution initiated by the pH or enzyme secretions of the gastro intestinal tract, and could be utilized to treat gastro intestinal illnesses.

FDA approved buccal films: - [49]

Table 4: List of FDA Approved Buccal Films [49]

Drug	Year of Approved	Company	Use
Suboxone	August 2010	Reckitt Benckiser Pharmaceutical Inc.	Psychological support and patient counseling.
Zuplenz	January 2010	Pharm Film technology	Nausea and vomiting can be suppressed before and after of Cancer Chemotherapy
Ondansetron	March 2010	APR Applied Pharma Research s.a. and Labtec	Nausea and vomiting can be suppressed before and after of Cancer Chemotherapy and radiotherapy.
Zelapar	October 2005	Valent Pharmaceuticals International Inc.	In Parkinson's Disease.

Buccal Film: Future Aspects

- Potent drugs that meet the parameters for buccal film as a drug delivery technology can be included into buccoadhesive buccal films. [42]
- For drug release profile investigations, we can assess the dissolution of buccal film.
- In-vivo research can be enhanced for the preparation of buccal film.
- For buccal film, we can do a stability study.

CONCLUSION

The current study reveals that the buccal film is the most precise and tolerable dosage form since it avoids the hepatic first pass effect and has high bioavailability. This has proven that it is the most effective, novel and emerging technology available, and it is beneficial as well as applicable to the patients of all ages, particularly pediatric and geriatric patients, moreover to those having problems in swallowing. Due to more advantages as compared to other dosage forms, buccal films acquire tendency in replacing traditional dosage forms, including rapid disintegrating tablets, due to their benefits over traditional dosage forms and their low cost of manufacture. This technique is a useful amongst all other techniques for maintaining the therapeutic and pharmacoeconomic value of drugs.

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