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## Drug Delivery System Using a Buccal Film

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### Recommended Citation

Salih, Zainab Thabit; Al-Mahmood, Asia; and Al-Mahmood, Sumayah (2023) "Drug Delivery System Using a Buccal Film," *Maaen Journal for Medical Sciences*: Vol. 2 : Iss. 2 , Article 3.

Available at: <https://doi.org/10.55810/2789-9136.1021>

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## REVIEW

# Drug Delivery System Using a Buccal Film

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## Abstract

The pharmaceutical industry has recently adopted a revolutionary strategy concerning the dosage form's composition and delivery methods, it is necessary to generate unique dosage forms in order to increase patient compliance, safety, and effectiveness. Enzymes are responsible for both the first-pass digestion and subsequent degradation of common oral dosage forms, although mucoadhesive films can prevent this issue, so, the creation of the buccal film is just one of the cutting-edge technologies that serve as an alternative to the conventional oral solid dosage form particularly for young children and elderly patients who have trouble swallowing. The buccal film is easier to use, visually appealing, and more suitable than alternative buccal drug administration since it is non-irritating, simple to use, quickly absorbed, elegant, and biodegradable (1). The buccal mucosa offers a direct pathway into the bloodstream while eliminating an acidic environment. The most popular method for producing a buccal film is called film casting for delivering proteins and personal care items. This article provides a thorough analysis of the buccal film's advantages, drawbacks, evaluation criteria, and formulation.

**Keywords:** Buccal film, Solvent casting, Mucoadhesive polymers, Buccal mucosa

## 1. Introduction

In recent years, mucoadhesive systems for drug delivery have attracted a lot of attention in the delivery of pharmaceuticals. The study of mucosal drug delivery has increased due to recent developments in drug delivery, and oral, buccal, ocular, nasal, and pulmonary routes are some examples of this type of route. Systems for delivering drugs that adhere to mucous membranes are known as mucoadhesive drug delivery systems, they become adhesive on hydration, therefore, have significant value for both regional and systemic delivery of drugs since they. It can be used to continuously supply the body with drugs for longer [1].

Buccal films are an unconventional and creative method of administering drugs to reach the blood instead of any swallowing [2], easy to use and painless, and patients report no feeling of a foreign body as shown in Fig. 1. As a result, they could provide significant benefits over oral tablets and

suppositories in the fields of pediatrics and geriatrics. In addition, less API can be utilized in comparison to the mentioned dosage forms [3,4].

Buccal drug delivery, the drug may reach the blood more quickly from the buccal mucosa, leading to higher drug availability, attributable to the mucoadhesive properties of non-invasive drug administration, in addition to that avoiding the liver's first-pass action. In buccal medication administration, due to the fact that the drug and gastric acid have no contact, the stomach is shielded against the drug as well as the opposite is true [5], additionally, the smallish stature and lower film thickness result in an improve in the patient care compared to tablets and lozenges [6]. In the pharmaceutical industry, films as dosage forms have become more significant as "unique," patient-friendly "amiable, and practical products. and this less friable dosage forms than most manufactured tablets that dissolve in the mouth, which typically need to be packaged specifically. Additionally, due

Received 2 May 2023; revised 13 June 2023; accepted 19 June 2023.  
Available online 16 August 2023

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<https://doi.org/10.55810/2789-9136.1021>

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Fig. 1. Buccal Film.

to its attachment to the buccal tissue, it can be used to show confined or systemic action [7].

### 1.1. Buccal films' benefits

Buccal films have a number of advantages compared to oral tablets, swallowed tablets, and oral liquids [8–10].

1. Rapid disintegration and dissolution due to the larger surface area provided by buccal films and promote systemic absorption.
2. Lack of chewing, swallowing, and choking prevention.
3. Bypasses the hepatic first-pass metabolism, result in an increase of bioavailability.
4. Drugs are protected from the gastric environment and enzymes of the gastrointestinal tract.
5. Rapid onset of action.
6. Precise dose in comparison with liquid dosage formulations.
7. Prolong the time at which the drug is spent at the absorption site.
8. Simple administration for those younger or elderly, intellectually challenged, physically impaired, or uncooperative patients.
9. Acceptable oral sensation
10. The simplicity of handling, storage, and shipping.

### 1.2. Disadvantages of buccal drug delivery [11,12]

The following are some drawbacks of buccal medication delivery system.

1. Very little medication at the surface of the absorbing membrane since saliva continuously

generates in the mouth cavity, resulting in diluting drugs there.

2. Possibility to be swallowed
3. The candidate list of drugs for the buccal route may be restricted by irritation, taste, allergy, and unfavorable discoloration or tooth erosion.
4. Eating and drinking may be restricted
5. Limited amount of loaded drug
6. Less stable than tablets and capsules
7. More expensive compared to conventional oral dosage form
9. Variable drug absorption
10. Affected by mouth wounds and ulcers
11. Hard to mask undesirable test
12. Can be used only for small MW highly lipophilic drugs
13. May cause mouth irritations
14. Thickness of film is critical
15. Absorption is affected by saliva volume
16. Manufacture is not suitable for heat sensitive materials
17. Permitted for medications that are absorbed through passive diffusion only.

## 2. The buccal mucosa

The lip, tongue, cheek, delicate palate, solid palate, and mouth floor make up the oral cavity. Three layers make up the oral mucosal layer: the epithelium which is the outer layer, the middle layer which is the basement, and the inner layer which is made of connective tissues as shown in Fig. 2. The oral cavity has an epithelial thickness of 0.5 mm thickness epithelium [13].

Drug delivery can fall into one of three types inside the oral cavity.

1. Sublingual Route
2. Buccal Route
3. Local Route

## 3. Buccal absorption

The passive diffusion of non-ionized species, which is mainly affected by the difference in the concentration, through the epithelium's intercellular spaces results in drug absorption in the buccal cavity. There are two main routes for drug transport through the buccal mucosa: transcellular and paracellular pathways. The main pathway for large molecules to pass through stratified epithelium is the intercellular spaces, where there is a barrier to penetration due to the intercellular substance's alterations in the surface layers. It is widely accepted

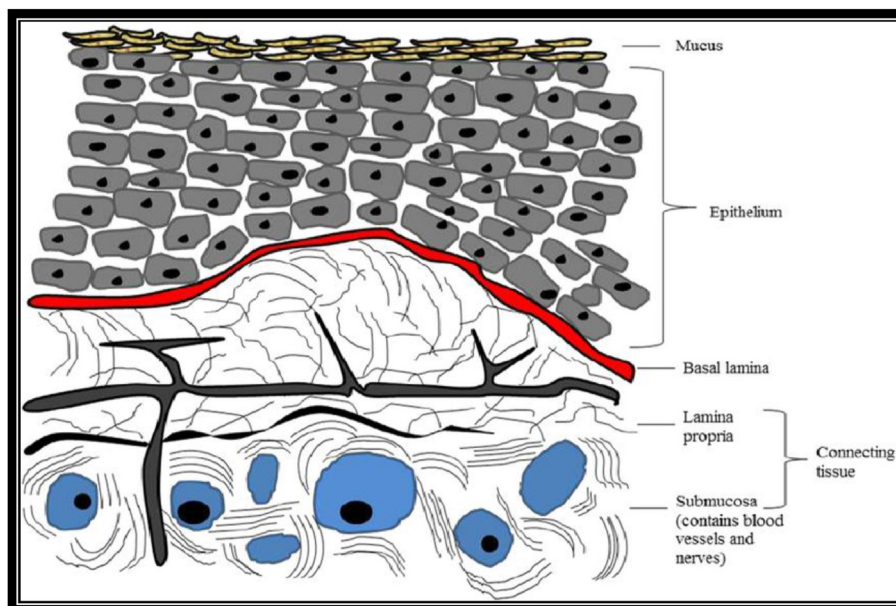


Fig. 2. Structure of oral mucosa [14].

that the lipid matrix of the extracellular space plays a significant role in the barrier function of the paracellular route, especially when the substances, like peptides, are hydrophilic and have a large molecular weight [15].

The lipid solubility and molecular weight of the diffusant have an impact on the buccal mucosa's capacity for absorption. It has been discovered that some medications absorb more readily via the buccal mucosa when the carrier pH is lowered and less readily when the carrier pH is raised [16].

#### 4. Aspects of buccal films' formulation

Buccal films generally consist of a number of ingredients like polymer, plasticizer, drug, sweetener, and necessary additives. Recently, mucoadhesive films using polymers have been vastly used.

##### 4.1. Active pharmaceutical ingredient

The buccal film can typically incorporate active medicinal components ranging from 5% w/w to thirty% w/w of total weight of polymer. Dose of drug in mgs (less than 20 mg/day) is required for effective formulation [8]. The water-soluble drugs can be found in the buccal film in a dissolved condition or as a solid solution, hydrophobic medications are evenly distributed throughout the film or complexation with different cyclodextrins can increase the drug's solubility. According to the necessary drug release pattern, API can be mixed as milled, nanocrystalline, micronized, or in the form

of particles. The film texture will be enhanced by the usage of micronized API, as well as for improved dissolving and homogeneity [9]. It is possible to use every kind of medicinally active substance that can be ingested orally and administered through buccal mucosa such as drugs used for ulcer and antiallergic drugs [18].

##### 4.2. Water soluble polymers

Polymers that are water-soluble considered as a film former and its use in medical and nutraceutical applications has drawn significant attention since it gives the films quick disintegration, a pleasant mouthfeel, and strong mechanical qualities. Higher molecular weight polymers have led to a slower rate of polymeric disintegration. Methyl cellulose A-3, A-6, and methyl cellulose A-15 are a few of the water-soluble polymers utilized as film formers, along with K-3 Pullulan [19,20].

##### 4.3. Plasticizers

The use of plasticizers in the creation of a buccal medication delivery system is absolutely essential since they aid by enhancing the buccal film's mechanical qualities, including its tensile strength and elongation, while also offering other benefits including a decrease in the film's brittleness and increased flexibility as well as a higher degree of the polymer's flow characteristic and a lower glass transition temperature [21]. Glycerin, sorbitol,

propylene, and polyethylene glycol are a few examples of plasticizers, as are tri-acetin, dibutyl phthalate, tri-ethylcitrate, acetyl tri-ethyl-citrate, and various citrate esters. The amount of plasticizer to be used can be 20% or less of the total dried polymer's weight [21]. The choice of plasticizers is influenced by polymer type, solvent solubility, and compatibility. Plasticizers used in excess or with the wrong materials can result in film that peels, splits, and cracks [22].

#### 4.4. Mucoadhesive polymers

Muco-adhesion was thought to be mainly generated by the polymer hydrating and expansion caused by the diffusion of water and the resulting dehydration of mucin and expansion ought to boost the flexibility of the polymeric molecule and interchain penetration, strengthening the mucoadhesive strength. The features of polymer to be utilized for buccal formulation depend on extent of spreading capacity and capacity to create various kinds of molecule and molecule bonds at distinct stages of water absorption [23]. Various mucoadhesive polymers have been researched recently for extending dose form or active retention in specified locations of the oral mucosa. Acrylic acid polyethylene glycol (PEG) and monomethyl ether copolymer, are the polymers that usually find their way in the formulation of buccal dosage forms, in addition to that varieties of cellulose, such as sodium carboxymethyl cellulose (NaCMC), are among other frequently used polymers. Chitosan is a natural polymer that is positively charged, biocompatible, and biodegradable. Because of its electrostatic interaction with mucin's negatively charged O-linked oligosaccharide chain, chitosan has been widely used as a mucoadhesive polymer. Chitosan's limited solubility at the physiological pH of the buccal mucosa and compatibility concerns with anionic medicines and excipients are what restrict its widespread use. Many chitosan derivatives are now being researched to improve chitosan's solubility and permeability at various pH levels without any precipitation caused by drug-polymer complexation [23].

#### 4.5. Penetration enhancers

Improving drug penetration through buccal mucosa was achieved by using penetration enhancers. The use of water is one of the straightforward penetration enhancers examples, their effects should be reversible and not irritating. Surfactants (like Tween), fatty acids (like oleic acid), terpenes (like eucalyptus), and solvents (like ethanol) are just

a few of the chemicals that might increase penetration. Additionally, polymers with the mucoadhesion property, bile salts, azone, and presently chitosan, its derivatives, and have the potential to increase penetration. Chitosan is viewed as a possible penetration enhancer for hydrophilic macromolecular medicines that are absorbed transmucosally [24].

#### 4.6. Saliva stimulating agent

Fast-dissolving film preparations dissolve quickly because more saliva is produced when using them. As a result, these dosage forms may include saliva enhancers such as citric acid and tartaric acid [25].

#### 4.7. Cooling agent

Using monomethyl succinate as cooling agents contributes to the enhancement of the mouthfeel and flavor intensity of the film. In addition to agents including WS3 is a menthol derivative, it is virtually nonvolatile, odorless, and tasteless in contrast to menthol and considered as one of the most popular cooling agents on the market, WS23, and Utracoll II can be utilized [7].

#### 4.8. Sweetening agents

Sweeteners are essential in pharmaceutical products wanted to dissolve or disintegrate in the mouth. Traditional sweetener sources include sucrose, dextrose, glucose, liquid glucose, and fructose. For the purpose of developing oral medications, polyhydric alcohol like mannitol is important because, they are free of a bitter aftertaste and have a lesser risk of causing cancer [26]. For people with diabetes, the use of naturally occurring sugars is limited in these formulas. Artificial sweeteners, such as aspartame and saccharin, are consequently most frequently employed in food products and pharmaceutical items [27].

#### 4.9. Surface active agents

Surfactants are used as wetting, dispersing, and solubilizing agents to melt the film quickly and release the active ingredient. Furthermore, surfactants make drugs that are not soluble more soluble in rapidly dissolving buccal films, examples include polaxamer407, sodium lauryl sulfate, benzalkonium chloride, tweens, and spans [8,21].



#### 4.10. Agents for stabilizing and thickening

The solution or dispersion used for preparing the film for casting has better consistency and viscosity by the addition of stabilizing and thickening agents before casting. Cellulose derivatives and carrageenan are some examples of naturally occurring stabilizers and thickeners in a 5% w/w concentration [28].

#### 4.11. Buccal film production techniques

The manufacturing procedures used to create buccal films are solvent casting, hot melt extrusion, and direct milling [17].

##### 4.11.1. Solvent casting method [29,30]

The solvent-extraction process is mainly utilized for preparing the oral film. According to this method, the required amount of polymer is dissolved in distilled water. A small amount of the active medicinal ingredient is then added to this solution, then, plasticizer is added and thoroughly combined with the solution. After applying the mixture on a Petri dish, it dried out at 40 °C in the oven with hot air. Once it has dried, it should be removed with a blade from the Petri dish and place it in a desiccator for 24 h. It should be cut and shaped as needed. Ivabradine hydrochloride buccal film formulation and evaluation for the treatment of stable angina pectoris according to study done according to Lodhi M et al., positive results were obtained by combining the basic polymers K15M and K100M of HPMC and carbopol 940. Additionally, the medication content of each formulation was assessed and confirmed to be consistent. Utilizing phosphate buffer pH 6.6, an in vitro release study was conducted on all formulations and a drug release from films in the range of 90.36% ± 0.854–98.37% ± 0.589 was obtained at the end of 6 h [31].

##### 4.11.2. Hot melt extrusion method [32]

The solvent casting method can be replaced by hot melt extrusion (HME). In the HME procedure, the unprocessed components are transported through rotating screws at a high temperature through a die to produce a product with a uniform structure, including dietary supplements, pharmaceutically active ingredients, polymers, and plasticizers. There are four steps in the hot-melt extrusion process. Mixing, chopping, and kneading bioactive substances and the formulation ingredients before feeding them through a hopper to the extruder. The molten material is transferred to the rotating screw,

then it is extruded through the die to form the desired shape [33]. Central composite design was used to prepare domperidone film using hot melt extrusion method and controlled release films are intended for buccal administration [34].

#### 4.12. Parameters for evaluating buccal film

##### 4.12.1. The Film's weight [35]

Using an adjusted weighing balance, the buccal film is weighed; the weight of each one has been determined individually.

##### 4.12.2. Film thickness [36]

This test is carried out with a calibrated micrometer screw gauge to measure the uniformity of how thick the film is since it has a substantial impact on the film's dosing precision and maintains the production process's predictability. A mean value is calculated after five analyses of the film's thickness.

##### 4.12.3. pH of the Film's surface [37]

After the films have interacted with 1 ml of distilled water for 2 h at 25 °C, the pH can be measured by placing the electrode on the film's surface and letting it equilibrate for 1 min.

##### 4.12.4. Folding endurance [30]

The film is continuously folded in the same spot till it breaks to assess how long it can withstand folding. The number of folds a film can endure in a specific area before rupturing is known as its folding tolerance.

##### 4.12.5. Tensile strength [30]

A film's tensile strength is the amount of force needed to cause deformation failure. In between two clamps that are spaced apart by a certain amount, film strips of a particular size are held.

"Tensile strength (N/mm<sup>2</sup>) = breaking force (N) / cross sectional area of sample".

##### 4.12.6. In-vitro disintegration time [38]

A Petri plate filled with two milliliters of distilled water measures the in vitro disintegration time by rotating it each 10 s while visually observing how long it takes to disintegrate. This time is then recorded as the period during which the film disintegrates.

##### 4.12.7. Homogeneity of the drug content [37]

Homogeneity determination was assessed by taking 5 films that had been previously weighed, and dissolved in 100 ml of isotonic phosphate

buffer, pH 6.8, then allowing the mixture to stand for 2 h using a magnetic stirrer, then, the resulting liquid was filtered employing Whatman filter paper, and after the correct dilution, the medication was assessed using a spectrophotometer.

#### 4.12.8. Test for percent moisture loss [39]

The percentage of moisture loss was determined by putting two films measuring  $2 \times 2 \text{ cm}^2$  with anhydrous calcium chloride in a desiccator for three days. After removing and weighing the film sheets, an equation was employed to calculate the percentage of moisture lost.

"Percentage Moisture Loss = [(Initial weight – Final weight) / Initial weight] X 100%"

#### 4.12.9. Percentage moisture uptake [39]

Films were dried out in a desiccator for 24 h at 25 °C with a saturated potassium chloride solution and 84% relative humidity level. The short films were taken off after a full day and weighed. The percentage of moisture uptake can be determined by employing the formula below.

"Percentage moisture uptake = [(Final weight – Initial weight) / Initial weight] X 100%"

#### 4.12.10. Swelling index [40]

Each buccal film was individually weighed (W1) and put in a petri plate containing phosphate buffer pH 6.8. Buccal films were dried with filter paper to separate the excess surface water and reweigh it (W2).

Swelling index (SI) was calculated using the formula:

"SI=(W2 – W1) / W1";  
where; SI = Swelling index, W2 = Final weight.  
W1 = Initial weigh.

#### 4.12.11. In-vitro drug release [37]

Two chambers Franz diffusion cell was utilized, one of which contains a buffer solution with a pH of 6.8 and the other of which has 10 mg of the medicine as a donor. Between these sections, a dialysis membrane (Mol. Wt. 12,000–14000Da) that had previously been soaked for 2 h in receptor media was used to create a barrier. The flowing water bath kept the temperature at 37 °C throughout the entire procedure. For up to 8 h, 0.5 ml of the sample was taken out of the receptor compartment and replaced with a new buffer at predetermined intervals. The appropriate dilution was done, and spectroscopic analysis was carried out to find how much

medication was released. The following formula was used to determine the flux value:

Flux = Amount of drug released (mg)/Time (hr) × Area (cm<sup>2</sup>)

#### 4.12.12. Ex-vivo muco-adhesion time [26]

The buccal film is put to the fresh buccal mucosa of sheep or rabbit, which is tied to a glass slide, to measure the muco-adhesion time using fingertips and a drop of phosphate buffer pH 6.8 to moisten the buccal film, then, the buccal mucosa is covered for 30 s. The glass slide is kept at 37 °C ± 1 °C in a beaker containing phosphate buffer with a pH of 6.8. After 2 min, a 50-rpm stirring speed is introduced, and film adherence for 24 h to mimic the buccal cavity environment. Along with the film's time collapsing, a timer records how long it takes for shape and color changes to become apparent.

#### 4.12.13. Ex-vivo permeation studies [31]

The adapted Franz diffusion cell comprised of two sections: a donor chamber and a receptor chamber, each having a 25 ml capacity, was implemented to carry out permeation investigations. In order to control the environment of the test at 37 °C, a water jacket comprised of 23 ml of pH 6.6 phosphate buffer was inserted within the compartment that holds the receptors. The dissected buccal epithelium was installed between the two chambers, and a Teflon-coated magnetic bead was used to suspend the complete assembly on a magnetic stirrer. After the buccal film was set aside to stabilize, 1 ml of the sample was taken out at regular intervals and properly diluted for spectrophotometric analysis.

#### 4.12.14. Stability studies [41]

Stability tests are carried out for the purpose of examining any changes that may occur while storing any formulation. All of the formulations were stored in stability chambers for three months in triplicate at 40–42 °C and 75 °C + 5% RH. Stability experiments were analyzed for folding durability, drug content, and in vitro drug release.

## 5. Conclusion

The current review has determined that buccal film is the most attractive and appealing dosage form due to its unique characteristic properties compared to other innovative buccal drug delivery systems, it skips first-pass metabolism and also increases the bioavailability of the active component. Buccal drug administration is an interesting alternative for the non-invasive delivery of potent

peptide and maybe protein therapeutic molecules as well as a potential field for systemic delivery of medications that are ineffective when taken orally. However, a key element for a bright future in the field of buccal medication delivery is the requirement for safe and efficient buccal permeation and absorption enhancement. Research on buccal film is expected to continue with the goal of systematically delivering medications that are ineffective when taken orally.

### Conflict of interest

There is no conflict of interest.

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