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# "Mucoadhesive Buccal Film for Drug Delivery"- An Overview

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**ABSTRACT:**
Now days, The goal of design and development of any novel dosage form is to improve patient complaince, safety and efficacy. Buccal film is a new film technology that meets all of these criteria. The buccal film is delivered via the buccal drug delivery system. Buccal film is more palatable and acceptable dosage than other buccal drug delivery systems such as wafers, lozenges, microparticles, gel, and tablets because it is small in size, dose, and easy to administer. As it bypasses first-pass metabolism, buccal film has become an effective dosage form that improves bioavailability. It adheres to the buccal layer of the oral cavity satisfactorily, making it more convenient than other dosage forms. It is more accepted dosage form by geriatric and paediatric patients because it is cost effective, biodegradable, fast absorption, elegant, easy to handle, non-irritating, and does not require swallowing of the drug. This review covers the advantages, manufacturing methods, formulation aspects of buccal film and evaluation parameters in depth.

**Key words:** Buccal film, Mucoadhesive, Bioavailability.

## I. INTRODUCTION

Back in 1947, when attempts were made to formulate a penicillin drug delivery system for delivering the bioactive agent to the oral mucosa using gum tragacanth, dental adhesive powders for the use of mucoadhesive polymers were used for the development of pharmaceutical formulations. Improved results were reported when carboxy methyl cellulose (CMC) and petrolatum were used for the development of formulation. Subsequent research resulted in the development of a mucoadhesive delivery vehicle which consisted of finely ground sodium CMC (SCMC), pectin, and gelatin. The formulation was later marketed as OrahesiveR. Another formulation which entered into the clinical trials is OrabaseR which is a blend of polymethylene/mineral oil base. Over the years, various other polymers, for example, sodium alginate, SCMS, guar gum, hydroxy ethyl cellulose, karya gum, methyl cellulose, polyethylene glycol, and tragacanth have been found to exhibit mucoadhesive properties. During the 1980s, poly acrylic acid, hydroxypropyl cellulose, and SCMC were widely explored for the development of formulations having mucoadhesive properties. Since then, the use of acrylate polymers for the development of mucoadhesive formulations has increased many folds. After rigorous research, the researchers are of the view that a polymer will exhibit sufficient mucoadhesive property if it can form strong intermolecular hydrogen bonding with the mucosal layer, penetration of the polymer into the mucus network, easy wetting of mucosal layer, and high molecular weight of the polymer chain. The ideal character of a mucoadhesive polymer matrix includes the rapid adherence to the mucosal layer without any change in the physical property of the delivery matrix, minimum interference to the release of the active agent, biodegradable without producing any toxic byproducts, inhibits the enzymes present at the delivery site, and enhances the penetration of the active agent.

Several buccal adhesive delivery devices were developed at the laboratory scale by many researchers either for local or systemic actions.
They are broadly classified into:

- Solid buccal adhesive dosage forms
-Tablets, microparticles, wafers, lozenges
- Semi-solid buccal adhesive dosage forms
-Gels, Patches or films
- Liquid buccal adhesive dosage forms.
-Solutions, suspensions, Gel-forming liquids

Present review is on mucoadhesive buccal film for drug delivery which comes under Semi-solid Buccal adhesive dosage forms.

The demand for patient convenience and compliance-related studies is on the rise these days. The buccal film is a drug delivery device that has quickly gained recognition as a novel method of drug administration with increased drug molecule safety and efficacy, as well as a rapid beginning of

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action. It relies on the ability to bind to biological surfaces that are mucus-covered. Buccal film that dissolves on the patient's buccal mucosa is a novel method. The above delivery of drugs aims for those medications that have a high first-pass metabolism and are utilized to increase bioavailability while lowering dosage frequency to enhance plasma peak levels, reducing undesirable consequences. In elderly and paediatric patients, it is also made cost-efficient and effective. Furthermore, when compared to lozenges and tablets, films have improved patient compliance due to their tiny size and reduced thickness. Films have acquired popularity in the pharmaceutical business as new, patient-friendly, and convenient dosage forms[1].

The buccal and sublingual mucosas are the two areas of the oral mucosa where drugs are administered. Sublingual> buccal > palatal is the sequence of permeability of the oral cavity. The buccal film is well recognized for allowing medicinal substances to be absorbed directly from the oral mucosa into systemic circulation via the jugular vein[2].

Buccal film is made up of active pharmaceutical ingredients (API), multiple polymers, plasticizers, saliva stimulating agents, permeability enhancers, sweeteners, flavouring agents, preservatives, and colour. The buccal film is applied to oral mucosal tissues, which are instantly moistened by saliva in the mouth. The film is rapidly hydrated and adheres to the application site. The fundamental advantage of buccal film is that, due to its wide surface area, it enables for fast wetting of the film, which increases medication absorption more rapidly than tablets. The buccal mucosa has an abundant blood supply, making it an ideal and quick site for medication absorption[1, 2].

**Advantages of buccal film [3, 4]**

- Avoids first pass metabolism.
- Avoids exposure to GIT fluids.
- Direct drug administration into systemic circulation in less time.
- Film can be administered without water, anywhere.
- Dose accuracy.
- Palatable.
- It's stable for long duration.
- Because it is flexible and portable, it is easy to transport all through consumer handling and storage.

**Mechanism of buccal absorption [3, 5]**

When the delivery system is actually positioned on a patient's buccal mucosal tissue, saliva immediately wets it. Because hydrophilic polymers and other additives are present, the films quickly adhere, hydrate, dissolves, and release the medicaments, resulting in a rapid onset of action and ensuring medication absorption. The buccal mucosa, like many other mucosal membranes, has been described as a lipoidal barrier to drug passage; the more lipophilic the drug molecule, the more readily it is absorbed. The primary transport mechanism is the passive transport of non-ionic species throughout the lipid membrane of the buccal cavity.

The following is the linear relationship between salivary secretion and time:

$dm/dt = Kc/V_iV_t$

m is the mass of the drug in the mouth at time t, and K is the proportionality constant.

c - Drug concentration in the mouth at the time

$V_t$ - Salivary secretion rate

$V_i$- Volume of solution placed in mouth cavity

**BUCCAL FILM FORMULATION ASPECTS [1, 6]**

**Active Pharmaceutical Ingredient**

Any pharmaceutically active substance that can be administered orally or through the buccal mucosa can be used as an active pharmaceutical substance for eg, antiepileptic, anti-asthmatics, anti-ulcers, expectorants, antihistaminic, antitussive etc. The drug dose should be in mgs (less than 20 mg per day) for effective formulation. Buccal film can typically contain active pharmaceutical ingredients ranging from 5% to 30% by weight. It's difficult to incorporate a high dose of molecules into a film.

**Plasticizers [7]**

It is an essential component of oral films. The type of plasticizer chosen is determined by its compatibility with polymer as well as the solvent used throughout the film casting process. It increases the film's flexibility while decreasing its brittleness. They can be used at a concentration of 1 to 20% by weight of dry polymer. Glycerol, propylene glycol, low molecular weight polyethylene glycols, and others are used as plasticizers also citrate and phthalate derivatives can also be used.

**Coloring Agent [1, 8]**

When some of the formulation ingredients or drugs are present in insoluble or suspension

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form, pigments such as Titanium dioxide or FDC approved coloring agents are incorporated (not exceeding concentration levels of 1% w/w) in buccal film formulation**.**

**Mucoadhesive agents [1]**

Depending on the dosage form, different situations for buccal mucoadhesion may arise. Polymer hydration and swelling properties are likely to play a major role in dry or least in part hydrated formulations. Swelling must aid polymer chain flexibility and polymer-mucin chain interpenetration. As a result, different polymers with different properties must be capable of determining on the type of formulation. Polyacrylic acid (PAA), polyvinyl alcohol (PVA), sodium carboxymethyl cellulose (NaCMC), hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), and sodium alginate are the most common polymers used in buccal dry or partially hydrated dosage forms.

**Flavoring agent [8]**

The flavouring agent plays a significant role in taste preference. Flavoring agents, synthetic flavor oils, oleo resins, and extracts derived from various parts of plants such as leaves, fruits, and flowers are used.

**Saliva Stimulating Agents [1]**

This ingredient is important in the formulation because it increases saliva production, allowing the film to disintegrate and dissolve quickly in the buccal cavity. Acids that are commonly used in food preparation can be used as salivary stimulants. The most popular among them is citric acid.

**Cooling Agent [8]**

Monomethyl succinate is used as a cooling agent. It also greatly enhances the film's flavor strength and mouth feel effect. Many cooling agents which can be used with flavors include WS3, WS23, and Utracoll II.

**Surfactant [8]**

Surfactants are used as a wetting or solubilizing agent. Surfactant dissolves the film in seconds, allowing the drug to be released immediately. Surfactant can help improve the solubility of poorly soluble drugs in the mouth. Polaxamer 407, sodium lauryl sulphate, benzalkonium chloride, benzethonium chloride, tweens and spans, and others are examples.

**Stabilizing and thickening agents [8]**

To improve the viscosity and consistency of the dispersion or solution of the film preparation before casting, stabilizing and thickening agents must be added. Stabilizing and thickening agents include natural gums such as xanthan gum, locust bean gum, carrageenan, and cellulosic derivatives.

**FDA APPROVED BUCCAL FILMS[9]**

| Drug | Year of approved | Company | Use |
|---|---|---|---|
| Suboxone | 31/08/2010 | Reckitt Benckiser Pharmaceutical Inc | Psychological support and patient counseling |
| Zuplenz | January 2010 | PharmFilm technology | Prevention of nausea and vomiting before and after of Cancer Chemotherapy |
| Ondansetron | 23/03/2010 | APR Applied Pharma Research s.a. and Labtec | Prevention of nausea and vomiting before and after of Cancer Chemotherapy and radiotherapy |
| Zelapar | October | Valent Pharmaceuticals | Parkinson's |

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| | | | |
|---|---|---|---|
| | 2005 | International Inc. | Disease |

Table 1. List of FDA Approved Buccal films

**MANUFACTURING METHODS OF BUCCAL FILM**

Buccal film formulation is primarily accomplished using three methods.

1. Hot Melt Extrusion Method
2. Solvent Casting Method
3. Direct Milling Method

**1. Hot Melt Extrusion Method[10,11]**

The drug and other excipients are melted in the hot melt extrusion method. The material is then forced through an orifice to produce a more homogeneous material in various shapes such as granules, tablets, or films. It is used in the delivery of transdermal drugs.

**Steps in the Hot Melt Extrusion Process**

In solid form, the drug is combined with carriers

The mixture is melted in an extruder with heaters.

Finally, dies shape the melted mixture into films.

**Palem CRet al., [34]**Designed and investigated in vivo characterization of domperidone (DOM) **hot-melt extruded (HME**) controlled release films by central composite design (CCD) for buccal delivery. Concentration of PEO N750 (X1) and HPMC E5 LV (X2) as independent variables and tensile strength (Y1), percent drug release at 6 h (Q6, Y2) and percent drug permeated at 6 h (Y3, P6) as responses. In total, 13 formulations were prepared and studied. HME films were evaluated for drug excipient compatibility, physico-mechanical properties, drug content, in vitro drug release, bioadhesion, swelling and erosion, ex vivo permeation. Furthermore, statistically optimized formulation was subjected for bioavailability studies in healthy human volunteers. Results: Statistically optimized formulation exhibited a tensile strength (3.86 kg/mm2 ), 93.62 ± 2.84% of drug release and 63.36 ± 2.12% of drug permeated in 6 h. HME films demonstrated no drug excipient interaction and excellent content uniformity. Furthermore, optimized formulation exhibited elongation at break (38.6% mm2 ), peak detachment force (1.75 N), work of adhesion (3.21 mJ), swelling index (240.4%) and erosion (8.5%). Bioavailability from the statistically optimized buccal films was 3.2 times higher than the oral dosage form (p50.05). The ex vivo–in vivo correlation was found to have biphasic pattern and followed type A correlation.

**2. Solvent Casting Method[12]**

In this method the required amount of polymer is added and dissolved in distilled water. To this solution a small amount of active pharmaceutical ingredient is added. Plasticizer is then added to the solution and thoroughly mixed. The solution is then cast on petridish and dried in a hot air oven at 400°C. After drying, cut it from the petriplate with a blade and place it in a desiccator for 24 hours. Cut to size and shape as needed.

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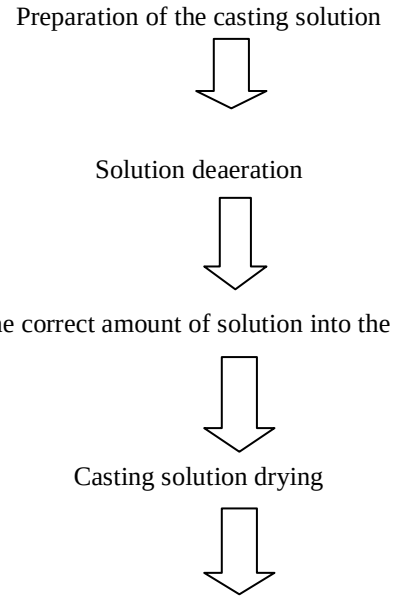
**Steps in the Solvent casting method**




**Lodhi M et al.,**[32]formulated and evaluated buccal film of Ivabradine hydrochloride for the treatment of stable angina pectoris, A combination of basic polymer **hydroxypropyl methyl cellulose (HPMC), K15M and K100M with carbopol 940, PEG 6000** gave promising results. The films were prepared by **solvent casting method**. Further, the drug content of all the formulations was determined and was found to be uniform. All the formulations were subjected to in vitro release study using phosphate buffer pH 6.6. Patches exhibited drug release in the range of 90.36% ± 0.854 to 98.37% ± 0.589 at the end of six hrs.

**3. Direct milling method**[10, 11]

This method does not use any solvents. Direct milling or kneading method is used to mix the drug and excipients in the absence of liquid. The finished product is then rolled onto a release liner until it reaches the desired thickness. This method is usually preferred because there is no risk of residual solvent and no link between solvent and health problems.

**Ahmed TAet al.,**[35] designed and developed simvastatin ex vivo permeation from mucoadhesive buccal films loaded with dual drug release carriers by **kneading method or direct milling method**. Two SMV carrier systems, namely, polymeric drug inclusion complex (IC) and mixed micelles (MM) nanoparticles, were developed and loaded into mucoadhesive buccal films to enhance SMV bioavailability. The two carrier systems were characterized and their permeation across human oral epithelial cells (OEC) was studied. The effect of IC to MM ratio (X1) and the mucoadhesive polymer concentration (X2) on the cumulative percent of drug released, elongation percent and the mucoadhesive strength, from the prepared mucoadhesive films, were optimized. Ex vivo permeation across bovine mucosal tissue was investigated. The permeation parameters for the in vitro and ex vivo release data were calculated.Complexation of SMV with hydroxypropyl beta-cyclodextrin (HP β-CD) was superior to all other polymers as revealed by the equilibrium saturation solubility, stability constant, complexation efficiency and thermodynamic potential. SMV-HP β-CD IC was utilized to develop a saturated polymeric drug solution. Both carrier systems showed enhanced permeation across OEC when compared to pure drug. X1 and X2 were significantly affecting the characteristics of the prepared films. The optimized mucoadhesive buccal film formulation loaded with SMV IC and drug MM nanoparticles demonstrated superior ex vivo permeation when compared to the corresponding pure drug buccal film, and the calculated permeation parameters confirmed this finding.

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## EVALUATION PARAMETERS OF BUCCAL FILM

**Weight of the film**[13]

A calibrated weighing balance is used to weigh buccal film. Each film's weight is calculated individually. The weighed film is calculated and analyzed.

**Thickness**[14]

A calibrated micrometer screw gauge is used to determine the thickness of the buccal film. The thickness of the film is analyzed five times and a mean value is determined. This test done to ensure uniformity in the film thickness, which is directly related to the accuracy of the dose in the film and continues to support the reproducibility of the formulation method.

**Surface pH of the film** [15]

The films are allowed to swell for 2 hours at room temperature after being in interaction with 1 ml of distilled water, and the pH is measured by placing the electrode on the film's surface and allowing it to equilibrate for 1 minute.

**Folding Endurance** [16]

Folding endurance is measured by folding the film repeatedly in the same spot until it breaks. The value of folding endurance is determined by the number of times the film can be folded at the same location without breaking.

**Tensile strength** [17]

The tensile strength of a film is the property that requires a load to cause deformation failure. Film strips of a specific size are held between two clamps at a specific distance. The following equation is used to calculate tensile strength by applying a load at rupture and the cross sectional area of a fractured film.

**Tensile strength (N/mm2 ) = breaking force (N)/ cross sectional area of sample**

**Percentage moisture loss** [18]

It is used to ensure the quality of films. The film is cut out and then weighed. Then, place it in a desiccator with fuse anhydrous calcium chloride. It is removed and weighed after 72 hours. The formula below is used to calculate the average percentage moisture loss.

**Percentage Moisture Loss = (Initialfilm weight-Final film weight)×100/Initial weight**

**Drug content uniformity** [19]

Buccal film is dissolved separately in 100 mL of pH 6.8 buffer and diluted appropriately. At 242 nm, the amount of drug in the film is measured by absorbance spectrophotometry. Average drug content is determined.

**In vitro disintegration time**[14]

It's measured visually in a petriplate containing 2 mL distilled water, with 10 seconds of swirling. The in vitro disintegration time is the time at which the film began to break or disintegrate.

**In vitro drug release**[2]

Franz diffusion cell assembly was used for in vitro drug release studies. It consists of two compartments, one of the receptor chambers containing a buffer solution of pH 6.8 and other donor compartment containing preparation. A dialysis membrane which was previously soaked for 2 h in receptor medium was placed in between these compartments to separate it from each other. To avoid disruption in the ongoing process, it was ensured that no air bubbles were seen between the membrane and liquid surface. During the entire process, the temperature was maintained at 37°C by circulating water bath. At a specific time interval till 8hours, 0.5 ml of the sample was withdrawn from the receptor chamber and filled with fresh buffer. Suitable dilution was carried out and the amount of drug release was spectroscopically analyzed.

The flux value was identified by the following formula

**Flux = Amount of drug released (mg)/Time (hr) × Area ($cm^2$)**

**Dissolution kinetics study** [22]

It is accomplished by determining the mathematical model that best fits the formulations. The values of R and k for various mathematical models are determined by putting the dissolution data into the appropriate mathematical models. The model with the highest R value is considered the best fit model for the given formulation. The n value for the best fit model is recorded and used to determine whether the formulation follows a fickian or non-fickian diffusion pattern.

**A. Zero-order kinetic**:

$$Qt = Qo + k_0t$$

Where, Qt is amount of drug release at time t, $K_0$ is zero order release rate constant, $Q_0$ is amount of drug present initially at t = 0

**B. First-order kinetic**:

$$\ln (100 - Q) = \ln Q_0 - k_1t$$

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Where, Q = amount of drug release at time t, $Q_0$ = amount of drug present initially. $k_1$ = first order release rate constant

### C. Higuchi equation

**$Q = kH\ t_{1/2}$**

Where, Q = amount of drug release at time t, kH = Higuchi dissolution constant

**Swelling index [23]**

A digital balance is used to determine the film's initial weight ($W_0$).The films are then allowed to swell on the petri plate's surface before being kept in an incubator at 37°Cfor 5 minutes. The weight of the swollen film (Wt) is determined at predetermined time intervals. The percentage of swelling (% S) is calculated using the following equation.

**% S= (Wt-Wo)*100 /Wo**

Where Wt is the weight of swollen patch after time t, $W_0$ is the initial weight of patch at t=0.

**Ex-vivo diffusion study[24, 25]**

The goat buccal mucosa membrane is used as a barrier membrane in the study, with phosphate buffer (pH 6.8) as the medium. Franz diffusion cell is used to assess drug release from film. Between the donor and receptor compartments is a buccal mucosa membrane. The mucosal membrane is covered with the film.The diffusion cell is submerged in 37±2°C simulated saliva. The receptor compartment is filled with 50 mL phosphate buffer (pH 6.8) and stirred at 50 rpm with a magnetic bead to maintain hydrodynamics. To keep the sink condition, 1 mL sample is withdrawn and replaced with 1 mL fresh medium. A UV spectrophotometer is used to analyze the samples at a specific wavelength.

**Stability study [26]**

A pharmaceutical product's stability can be defined as a formulation's ability to stay within its physical, chemical, microbiological, therapeutic, and toxicological specifications in a specific container / closure system. The stability of all the formulations should be carried out at different temperatures as per ICH guidelines.

Stability study is carried out at storage conditions; one at normal room conditions i.e 40°C/75% RH for 6 months and another at 30°C/75% for 24 to 36months. Film is packed in packing material like aluminum foil and then evaluated for the DSC, FTIR, Folding endurance, disintegration time, drug content and in vitro drug release [27]

## II. CONCLUSION

The present review concludes that the buccal film is the most accurate and acceptable dosage form, due to higher patient compliance, faster drug delivery system, and bypasses the hepatic first-pass effect and shows enhance bioavailability. Buccal films will replace the conventional dosage forms, as well as fast disintegrating tablets due to its advantages over the conventional dosage forms, and they can be manufactured at a low cost. Buccal films are more feasible formulation because of its simplicity in preparation, drug loading, and characterization. Buccal films will be a more robust choice to optimize the therapeutic efficacy of various API in the future. The oral mucoadhesive dosage forms can continue to be an exciting research focus. Thus it can be concluded that buccal drug delivery is most promising drug delivery in mucoadhesive system. Range of dosage forms can be incorporated in buccal drug delivery and also new functionalization strategies to modify the surface of nanoparticles could transport different types of drugs efficiently through the buccal route. First pass metabolism prone drugs can be administered by this non-invasive drug delivery system of buccal film.

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