Formulation And Evaluation of Films For Buccal Drug Delivery System

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Abstract- *Buccal films represent a promising advancement in oral drug delivery, offering several benefits over conventional dosage forms. These thin, polymeric strips adhere to the buccal mucosa, facilitating direct absorption into systemic circulation and effectively bypassing first-pass hepatic metabolism, which enhances bioavailability and enables a rapid onset of action. Due to their ease of use, absence of a need for water during administration, and patient-friendly design, buccal films are particularly advantageous for paediatric, geriatric, and dysphagic populations. This study provides an overview of buccal film classification, advantages, limitations, packaging, and manufacturing methods, with a focus on solvent casting and hot-melt extrusion. The role of formulation components—such as film-forming polymers, plasticizers, sweeteners, and saliva stimulants—is discussed in detail. BetaxololHCl, a cardio selective β1-adrenergic blocker used in hypertension treatment, is explored as a model drug for buccal delivery. Evaluation parameters including film thickness, folding endurance, drug content uniformity, in vitro disintegration, and dissolution testing are described to assess film quality and performance. The findings affirm buccal films as an efficient and patient-compliant platform for non-invasive drug administration with significant clinical potential.*

Keywords- Buccal films, BetaxololHCl, bucal drug delivery, solvent casting method, bioavailability enhancement, antihypertensive drug, mucoadhesive film

I. INTRODUCTION

The buccal route of drug administration offers several notable advantages, including enhanced patient comfort, ease of use, and efficient drug delivery. This route bypasses the gastrointestinal tract, enabling faster onset of action and reducing the impact of hepatic first-pass metabolism, thereby improving the drug's bioavailability. Buccal films—thin polymeric sheets designed to adhere to the buccal mucosa—have emerged as a promising alternative to traditional oral dosage forms such as tablets and capsules [Arya, 2010].These films facilitate direct absorption of the active pharmaceutical ingredient (API) into the bloodstream through the buccal mucosal membrane, which is particularly advantageous for patients who experience difficulty swallowing or require rapid therapeutic effects. Additionally, buccal films do not necessitate water for administration, making them especially useful in settings with limited water availability.

The formulation of buccal films typically incorporates hydrophilic polymers that support rapid disintegration or dissolution upon contact with the buccal mucosa, allowing for immediate release of the drug [Liew, 2012]. Their ease of application, along with the potential to enhance patient adherence, makes them highly suitable for pediatric, geriatric, and dysphagic populations who may find conventional tablets or capsules challenging to ingest due to conditions such as nausea or swallowing difficulties.

Flavor-masking technologies and taste enhancers can further improve the acceptability of buccal films, especially for children and patients sensitive to the taste of certain medications [Liew, 2012]. These user-friendly and discreet dosage forms do not require water and are ideal in scenarios such as travel or emergency care where water might not be accessible [Ferlak, 2023].

The European Pharmacopoeia (Ph.Eur.) defines oral films as melting sheets composed of one or more layers made from authorized components that dissolve immediately upon placement in the mouth. A major advantage of oral dissolving films (ODFs) is their ability to bypass hepatic first-pass metabolism, contributing to more efficient systemic drug delivery.[EuropeanPharmacopeia]

Several businesses have created thin-film and strip intraoral dosage forms, including LTS (LohmannTherapie-System) AG, Zengen Inc., and Lavipharm Laboratories (Quick-Dis™ and Slow-Dis™ technologies), as well as Pfizer's Warner-Lambert consumer healthcare division (Listerine® Pocket Packs™).[El-Enin,2015]

Figure No.1: Buccal film

Advantages of Buccal film:[Jain,2023;Kshirsagar,2021]

a) Swallowing doesn't require water.
b) Bitter medications have the potential to be taste-masked.
c) More affordable.
d) The dosing procedure is simple and precise.
e) Reasonable transportation.

Disadvantages of Buccal films:[More,2019;Ketul,2013]

a) Dose uniformity is a technical challenge.
b) Hygroscopic in nature.It takes moisture from atmosphere.
c) High doses cannot be incorporated.
d) It requires special packaging for product's stability and safety.

Advantages of thin film over conventional dosage form: [Karki,2016]

a) Faster dissolution than standard dosage forms.
b) Easier to transport and less friable than orally dissolving tablets, which require
c) specialised packaging.

Major limitations:[Jadhav,2013;Sharma,2015]

There are various limitations of BFs that can hamper the manufacturing process,

a) Combining multiple drugs in an film is challenging due to varying adsorption rates and disintegration times.
b) Drying film takes more than a day, reducing production time.

Classification of Fast Dissolving Technology for ease of description,[Mandeep,2013]

1. Lyophilized systems
2. Compressed tablet-based systems
3. Thin film strips

Packaging of films:[Ketul,2013]

1. Single pouch and Aluminum pouch
2. Foil, paper or plastic pouches
3. Blister card with multiple units

Table No.1: List of Marketed Films [Kshirsagar,2021]

Sr.no	Product	Manufactured by
1.	Donepezil rapid dissolving films,	Labtec Pharma
2.	Altoid cinnamon strips	Dow chemical company
3.	Listerine Pocket Paks	Pfizer's
4.	Klono pin Wafers	Solvay Pharmaceuticals
5.	Listerine Cool Mint Pocket Paks	Pfizer, Inc
6.	Triaminic Novartis	Novartis

Manufacturing methods for producing of films:

1. **Solvent casting method:** The most preferred way for preparing Films because it requires no additional equipment and is straightforward. A mixture of API and excipient is cast onto a surface, dried, and then cut to the required size. To achieve a homogeneous film and thickness, the suspension of API, polymer, and plasticizer must be degassed. The suspension is then vacuumed to eliminate any trapped air bubbles before being transferred to a Petri dish or Teflon plate and dried.[Kshirsagar,2021]

Advantages: [Garsuch,2009]

I. Ideal uniformity of thickness and clarity compared to extrusion for an Film.
II. This approach can be used to make films of different thicknesses and can also be used to meet API loading and dissolving requirements.

Disadvantages: [Nagaraju,2013]

I. The polymer needs to dissolve in water or a volatile solvent.
II. It must be feasible to form a uniform film and release from casting support.

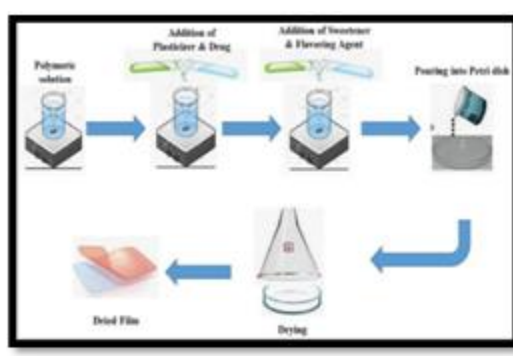


Figure No.2: Solvent casting method

2. Hot-melt extrusion (HEM): Hot Melt Extrusion (HME) is a continuous processing procedure used in pharmaceuticals to achieve the required drug release profile using an API-polymer mixture. The important process parameters of HME include speed, pressure, feeding rate, and temperature.[Fule,2015]

Advantages: [Flemings,2022]

I. Fewer operation units.
II. Minimum production wastage.

Disadvantages: [Flemings,2022]

I. Heat processing causes stability issues in drugs and polymers.
II. Limited quantity of polymer in stock.

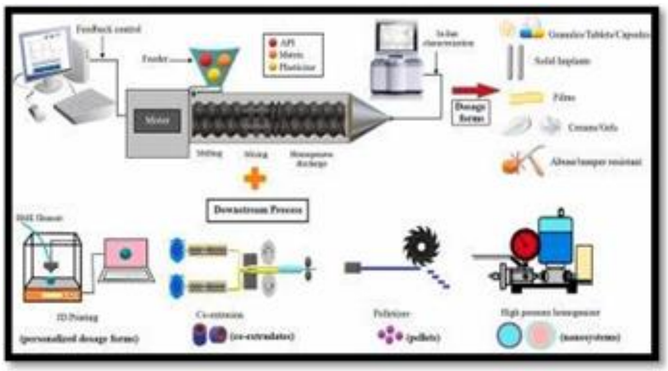


Figure No.3: Hot-melt extrusion

3. Semi solid casting method: Semi solid casting is a revolutionary technology that includes the benefits of casting and forging to make complex-shades components. It requires two types of polymers: hydrophilic and hydrophobic, however this approach is comparable to the solvent casting method described above. [Preis,2013]

4. Solid dispersion extrusion: Using this process, one or more APIs are dispersed in a suitable solvent and incorporated into polyols such as melted PEG.[Baunz,2015]

5. Rolling method: The rolling method begins with preparing a suspension of water, film forming polymer, a combination of water and alcohol, and additional excipients (except APIs) while processing rheological characteristics. [Nagaraju,2013]

6. Printing method:[Koo,2011] Printing method is subdivided in two methods are: Inkjet printing and Flexographic printing.

Mechanism of film formation: [Lade,2013;Quazi,2020]

The film-forming system is applied directly to the skin and, upon solvent evaporation, produces a thin, transparent film in situ. Super saturation reduces adverse effects and irritation by raising the formulation's thermodynamic activity without compromising the skin's barrier, which leads to an improved drug flow through the skin.

The concept of super saturation can be explained by the modified form of Fick's law of diffusion

Fick's law of diffusion given ,
Eq: $J= DKCv/h$
Where, J = rate of drug permeation per unit area of skin per unit time (flux)
D = diffusion coefficient of drug
Cv= concentration of drug
h = thickness of barrier to diffusion

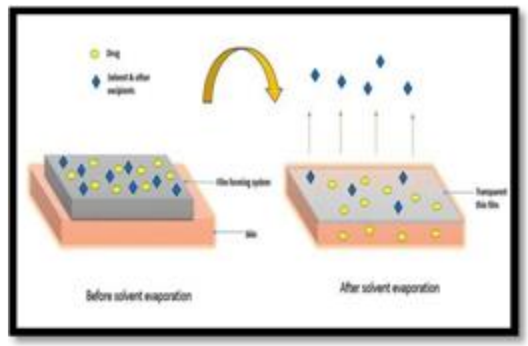


Figure No.4: Mechanism of film formation

Biology of Mucosa:

The initial part of the digestive system is the oral cavity, which is enclosed by the lips on the front and posterior surfaces of the face, respectively. The tongue occupies the area in the mouth that is accessible. There are two areas in the oral cavity:

I. The vestibule
II. The actual oral cavity [Elebi]

Function of tongue: [Tortora]

I. **Intrinsic muscles:** Responsible for altering its shape and size.
II. **Extrinsic muscles:** Moving of tongue

Routes of drug transport:**[Baunz,2015]**

The medication molecule diffuses passively across the membranous tissue in two primary way.

I. The intracellular route
II. The intercellular route

Three kinds can be distinguished in the oral cavity membrane:

I. **Buccal delivery:** This refers to the systemic circulation's distribution of the medication through the mucosal membranes lining the cheeks, the space between the gums, and the upper and lower lips.

II. **Sublingual delivery:** This method involves delivering a medication to the systemic circulation via the floor of the mouth via the mucosal membrane lining.

III. **Local delivery:** This type of medication delivery to the gingiva is mostly utilized for the local treatment of periodontal disease, bacterial and fungal infections, and ulcers.

Classification of oral mucosa: [Baunz,2015]

I. Three groups can be distinguished between the oral mucosa based on function and histology.

a. Living mucosa: (Stratified squamous epithelium, nonkeratinized) present in the oral cavity elsewhere, including the

i. **Alveolar mucosa:** This layer of tissue lies between the buccal and labial mucosae. It has numerous smooth, glossy, brightly red blood vessels that are not attached to the surrounding tissue.

ii. **Buccal mucosa:** This refers to the inside lining of the cheeks as well as the floor of the mouth.

iii. **Labial mucosa:** This is the inner lining of the lips and a portion of the mucosa.

iv. b. Masticatory mucosa: This layer of keratinized stratified squamous epithelium covers the dorsum of the tongue, the hard palate, and the gingiva that is connected.

v. **Specialized mucosa:** It has nerve terminals for taste perception as well as general sensory reception. located at the tongue's dorsal surface at the lingual papillae, which house the taste buds.

II. Based on Keratinization:

i. The keratinized state

a) **Orthokeratinized: -** The epithelium loses its nuclei.

b) **Parakeratinized: -** The nucleus is still present in the superficially dead cells.

ii. **Nonkeratinized:** The super facial layer's nonkeratinized epithelial cells lack keratin filaments
in their cytoplasm.

III. **Predicated on place:** Lingual mucosa, Buccal mucosa, The mucous palate, Alveolar mucosa, Labial mucosa.

Functions of oral mucosa: [Cate] Sensation, Protection, Secretion, Immune mucosal network, Thermal regulation, Absorption

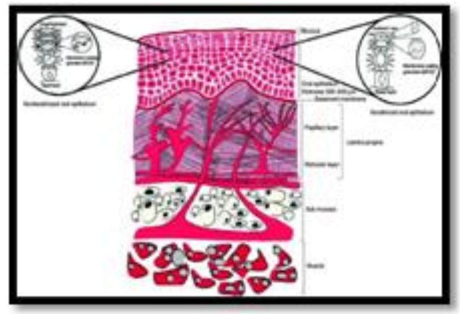


Figure No.5: Structure of mucosa

Formulation consideration:

1) **Drug:** Any class of medicinally active medications that are administered orally or through the buccal mucosa is regarded as an active pharmacological substance like expectorants, antipsychotics, antianginals, antitussives, antihistaminic, antiemetic, antihypertensive, antiepileptic and antiulcer medications.[Pandit,2021]
2) **Film forming agent:** Water-soluble polymers are used as film formers because they provide mechanical properties, a pleasant mouth feel, and a rapid disintegration to the films [Akarte,2021]
3) **Plasticizer:** Plasticizers that are commonly used include dimethyl, propylene glycol, polyethylene glycol, and glycerol. [Khan,2016]
4) **Saliva stimulating agent:** Citric acid is the most widely used.[Shrivastava,2018]
5) **Sweetening agent:** Types of sweeteners includes natural sweeteners such as glucose, sucrose and saccharin. [Jain,2023]

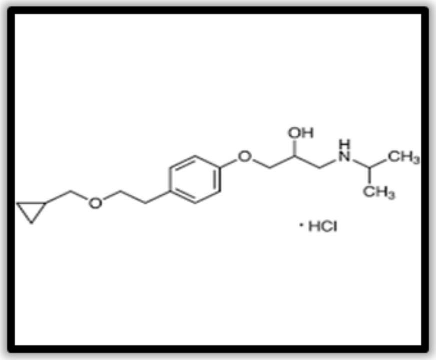
Antihypertensive Drug

BetaxololHCl is a cardio selective beta-1 adrenergic blocker used primarily to treat high blood pressure (hypertension). By selectively blocking beta-1 receptors in the heart, it reduces heart rate and cardiac output, leading to lower blood pressure. Its selectivity means it has fewer effects on the lungs compared to non-selective beta-blockers, making it safer (though not completely risk-free) for patients with respiratory conditions like asthma. Betaxolol is also available as eye drops for treating glaucoma due to its ability to reduce intraocular pressure.

This medication is typically taken once daily due to its long half-life and is well-absorbed orally. Common side effects include dizziness, fatigue, and slow heart rate, with more serious risks like heart block or worsening heart failure in certain individuals. It should be used cautiously in patients with diabetes, asthma, or kidney problems and should not be stopped abruptly to avoid rebound effects. Betaxolol may also interact with other heart or blood pressure medications, so close monitoring is advised.

1 Drug Profile:

Drug: Betaxolol HCL



FigureNo.6: Structure of Betaxolol HCL

Brand name: Kerlone
Colour: White to off-white crystalline powder
IUPAC name:1-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)propan-2-ol hydrochloride
Drug class: Beta-1 selective adrenergic receptor blocker (cardioselective beta-blocker)
Molecular formula: $C_{18}H_{29}NO_3$
Synonym: Betaxololum, Betoptic, Kerlone
Molecular weight: 343.89 g/mol
Melting point : 154–158°C
Water Solubility: 0.00417 mg/ml
Log p: 2.64
Pka: ~9.5 (secondary amine group)
Background:
BetaxololHCl is a cardioselective beta-1 adrenergic receptor blocker commonly used for managing hypertension, angina pectoris, chronic heart failure, post-myocardial infarction, and ocular hypertension (glaucoma). It reduces heart rate and blood pressure by inhibiting the effects of catecholamines.
Mechanism of Action:
It selectively blocks beta-1 receptors, decreasing heart rate (negative chronotropy), contractility (negative inotropy), and renin release from the kidneys. This results in reduced cardiac output and systemic vascular resistance, effectively lowering blood pressure.
Pharmacokinetics:

- Half-life: 14–22 hours, enabling once-daily dosing.
- Metabolism: Primarily hepatic (via cytochrome P450 system).
- Excretion: Renal; partially unchanged in urine.

Dosage Forms & Administration:

- Oral Tablets: 5–40 mg/day for cardiovascular uses.
- Ophthalmic Solution: 1–2 drops daily for ocular conditions.
- Dosage must be adjusted in hepatic impairment; caution in renal impairment and elderly patients.

Adverse Effects (Common and Serious):

- Common: Fatigue, dizziness, bradycardia, hypotension, cold extremities.
- Less common: GI disturbances, depression, mood changes, sexual dysfunction.
- Serious: Bronchospasm (esp. in asthma/COPD), heart block, arrhythmias, visual disturbances.

Contraindications:

- Severe bradycardia, second- or third-degree heart block, cardiogenic shock, decompensated heart failure, hypersensitivity to beta-blockers, and use in late pregnancy.

Monitoring Parameters:

- Blood pressure, heart rate, ECG (for arrhythmias), renal and hepatic function, especially in elderly or compromised patients.

Toxicity Signs:

- Bradycardia, hypotension, heart block, respiratory distress, hypoglycemia (especially in diabetics), confusion, or altered mental status.

2 Excipients :

I] Pullulan
II] PEG-400
III] Citric acid
IV] Sucralose

Evaluation parameters of films[Tonia,2024]

1. **Visual Inspection:** Consistency, quality, and hue of the produced ocular examinations of the film conducted.
2. **Thickness:** Digital Vernier Callipers that have been calibrated or a micrometer screw guage are used to measure the thickness of film. The thickness of the film needs to be measured at five separate points- four at the corners and one in the middle. This is because the uniformity of the film thickness directly affects how accurately the dose is distributed across the film.

3. **Weight Variation:** Every batch of Bucal film had three films measuring 2×2 cm^2, which were weighed on an electronic balance to determine the average weight and standard deviation.
4. **Drug Content:** A random sample of drug BF was used to determine the total amount of drug in each film. The medication analysis was done with a UV spectrophotometric approach. Drug content is limited to 85- 115%.
5. **Folding endurance:** This attribute contributes to a film's brittleness. The technique utilized to ascertain the endurance value involves repeatedly folding the film specimen, measuring 2 by 2 cm^2, at the same location until it breaks or a visible crack appears. The computed folding endurance value is the number of times the film can be folded without breaking or showing any visible cracks.
6. **Surface pH test:** The film was put in a petri dish to evaluate this test. It was then soaked for 30 seconds with 0.5 ml of phosphate buffer. After contacting the formulation's surface with the pH meter's electrode and letting it acclimate for a minute, the pH was measured. For every formulation, the mean of three determinations was calculated.
7. **In -vitro disintegration test:** The point at which an film begins to disintegrate when it comes into contact with water is known as the disintegration time or vomit. The disintegration time of a buccal film should be between five and thirty seconds. Ten milliliters of distilled water were poured in a glass petri dish along with the film size (2×2 cm^2) needed for dosage administration. Every ten seconds, the content of the petri dish were gently swirled until the film began to break. The duration needed for the film to shatter was identified as the in-vitro disintegration period.
8. **In-vitro dissolution studies:** A 2×2 cm^2 film was put in a container with 50 cc of Ph 6.8 phosphate buffer that was kept at 37± 0.5°c and 50 rpm stirring speed using a magnetic stirrer. At regular intervals of 0.5, 1, 1.5, 2, 2.5, 3, 4, 5 minutes, samples are removed. After being filtered via 0.45 Whatman filter paper, the samples were measured spectrophotometrically at 223 nm. It was determined what proportion of drug was released from each film. For every formulation, graphs showing the percentage of drug release versus time were drawn.

NEED OF THE STUDY.

Buccal films offer a convenient, fast-acting drug delivery system that adheres to the inner cheek, bypassing first-pass metabolism and improving bioavailability. They are ideal for delivering drugs like betaxolol hydrochloride, especially for conditions such as hypertension. These films can enhance solubility, mask unpleasant taste, and protect drugs from environmental degradation. This study focuses on formulating HPMC- and pullulan-based buccal films using the solvent casting method to improve the stability, efficacy, and patient compliance of betaxolol hydrochloride therapy.

FORMULATION AND EVALUATION STRATEGIES OF BETAXOLOL HCL BUCCAL FILMS

Preformulation and formulation studies of BetaxololHCl buccal films have been extensively reported in the literature. BetaxololHCl, a white to off-white crystalline powder belonging to BCS Class III (high solubility and low permeability), is typically characterized through organoleptic evaluation, solubility determination, and melting point analysis. The drug exhibits maximum absorption in the UV region at 226–228 nm, confirming its purity and suitability for spectrophotometric analysis (Nimase, 2022).

For compatibility studies, researchers have employed Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) to assess potential interactions between BetaxololHCl and excipients such as Pullulan and PEG-400. The absence of significant peak shifts or new peaks in FTIR spectra and the retention of characteristic endothermic peaks in DSC thermograms indicate chemical stability and compatibility (Jang, 2011; Latif, 2020; Bala, 2018).

The solvent casting technique is the most widely used approach for preparing BetaxololHCl buccal films. In this method, hydrophilic polymers such as Pullulan, HPMC, or PVA are dissolved in aqueous or hydroalcoholic systems, followed by the addition of plasticizers (PEG-400, glycerol) and sweeteners or saliva stimulants. The drug is incorporated into the polymeric solution and cast onto Petri plates or glass molds to obtain uniform films after drying (Hussain, 2017). This method offers simplicity, reproducibility, and good control over film thickness and drug uniformity.

To optimize formulation variables, several studies have utilized statistical design of experiments, particularly the 3^2 factorial design, to evaluate the combined effects of polymer concentration and plasticizer level on key film properties such as drug release, mechanical strength, and folding endurance

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