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FORMULATION AND EVALUATION OF FILMS FOR BUCCAL DRUG DELIVERY SYSTEM

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Abstract : The buccal drug delivery system (BDDS) is a novel and effective route for systemic drug administration through the buccal mucosa, offering advantages such as improved bioavailability, rapid onset of action, and avoidance of first-pass metabolism. Buccal dosage forms like films, tablets, and patches are thin, mucoadhesive, and easy to administer—making them especially suitable for paediatric, geriatric, and dysphagic patients.This system overcomes limitations of conventional oral delivery for drugs with poor gastrointestinal stability or low solubility. The formulation involves key components such as bioadhesive polymers, plasticizers, permeation enhancers, and flavoring agents. Common manufacturing methods include solvent casting and hot-melt extrusion.Evaluation parameters like mucoadhesive strength, film thickness, disintegration time, drug content, and in vitro drug release help assess product performance. Overall, BDDS represents a patient-friendly, non-invasive, and efficient alternative for systemic drug delivery with strong potential for future pharmaceutical applications.

Index Terms **- Buccal films, Betaxolol HCl, Buccal 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 (Lohmann Therapie-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.

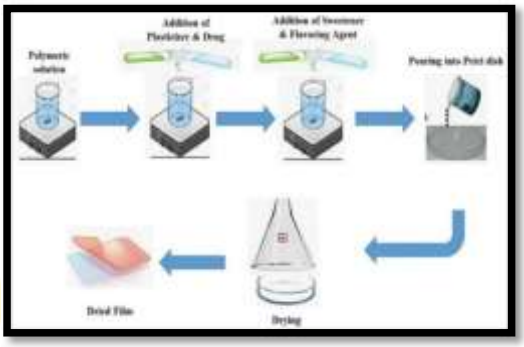


Figure No.2: Solvent casting method

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.

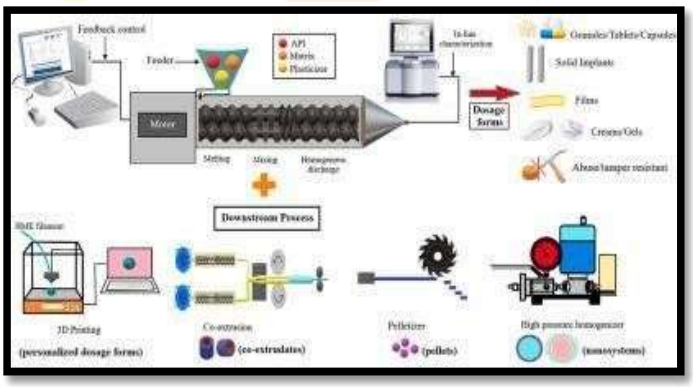


Figure No.3: Hot-melt extrusion

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

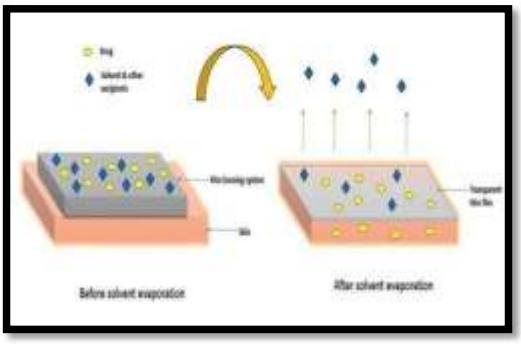


Figure No.4: Mechanism of film formation **Biology**

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

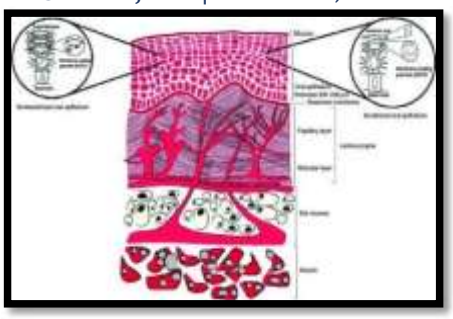


Figure No.5: Structure of mucosa **Formulation consideration:**

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]

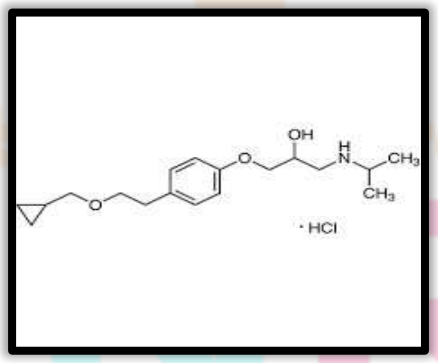
Antihypertensive Drug

Betaxolol HCl 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:**

Betaxolol HCl 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.

RESEARCH METHODOLOGY

3.1Population and Sample

Betaxolol HCl was procured from Aster Analytics Research Institute., Palghar, Maharashtra, India. Pullulan, PEG-400, citric acid, and sucralose were obtained from SD Lab Chemicals, Mumbai, India. All chemicals used were of analytical grade.

3.2 Data and Sources of Data

The following instruments were used: Shimadzu electronic balance (Japan), Jasco V-630 UV-Visible spectrophotometer, LABLINE ultrasonicator, Remi magnetic stirrer (Mumbai), ELECTROLAB TDT-08L dissolution apparatus (USP), Contech PH102 pH meter, Shimadzu DSC 60 differential scanning calorimeter, FT-IR 4600 spectrophotometer, Eltek microspin centrifuge, and WENSAR weighing balance.

3.3 Theoretical framework

Preformulation studies

Identification and characterization of betaxolol hcl

Identification of pure Betaxolol HCL: A)

Description:

The sample of Betaxolol HCL was analysed for its nature, color and physical properties. Betaxolol HCL is a White to off-white crystalline powder. It belongs to class III drug of BCS scale.

B) Solubility study:

Solubility of the drug was determined using distilled water.

C) Melting point:

The melting point was measured by introducing small amount of substance in the capillary attached to graduated thermometer and continuous heat was applied with assembly suspended in the Thiele's tube containing paraffin bath. The temperature at which the drug melted was noted as melting point.

D) UV/Visible spectra: [Nimase,2022]

Determination of λmax

1% w/v Betaxolol HCL was prepared in water and the maximum absorbance was scanned on the double beam UV spectrophotometer (Shimandzu-1800) in the range of 200 to 400 nm, using 0.1 N as a blank. The drug's λmax was found to be 226 nm.

E) Standard curve for Betaxolol HCL:

To make the initial stock solution, 100 mg of Betaxolol hydrochloride was properly weighed and diluted in 100 ml of water. 10 ml of the above solution were taken and diluted to 100 ml with the same solvent to prepare the stock solution II. The aliquot of stock solution II was further diluted with water to obtain 10 µg, 20 µg, 30 µg, 40 µg, 50 µg and 60 µg of drug per ml of the final solution. The absorbance was then measured on a UV spectrophotometer at 223 nm against water as a blank. The graph was plotted for absorbance versus concentration.

F) Drug and excipient's compatibility studies:

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method and Differential Scanning Colorimetry (DSC) method.

1) Fourier transform infrared spectroscopy (FTIR): [Jang,2011;Latif,2020]

A Fourier transform Infrared spectrophotometer was used to record FTIR spectra of pure drugs, polymers, and physical mixtures. The examination was carried out on a Thermo Fisher Scientific Spectrophotometer. The device was operated under dry air purge, and the scan was acquired at a scanning speed of 2mm/sec with a resolution of 4 cm-1 over a range of 4000-400 cm-1. The scan was assessed for the presence of drug principle peaks, their shifting and disappearance, and the emergence of new peaks as a result of solid dispersion agent interactions.

2) Differential Scanning Colorimetry (DSC): [Bala,2018;H.Chaudary,2013,Latif,2020]

Differential Scanning Colorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The DSC thermograms were recorded for pure drug, Pullulan, Drug and polymer mixture. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC /min, over a temperature range of 0 to 250ºC.

FORMULATION OF BUCCAL FILMS:

Formulation of buccal films was done by solvent casting method. Using the solvent casting procedure, which involves dissolving the polymer in a suitable amount of distilled water on a hot plate magnetic stirrer, the films of various formulations were created. Subsequently, the polymer solution was mixed with the other chemicals (plasticizer, saliva stimulant, and sweetener). A different solution was made with the drug dissolved in the least amount of distilled water possible. Next, the drug solution and the polymer solution were thoroughly combined while being constantly stirred. The last solution was then set aside to eliminate the bubbles for a short while. The solution was cast onto 50.24 cm2 plastic petri plates after the bubbles were eliminated. For drying, the plates were left overnight at room temperature. Subsequently, the dehydrated films were meticulously removed and sliced into the appropriate dimensions to administer the corresponding dosage, before being preserved within the aluminum foil. [Hussian,2017]

Formulation of Buccal Film by using 3^2 factorial design: [Panchal,2012]

Since the combined effects of independent variables are not taken into account, it could be challenging to create the perfect formulation using this traditional method. Therefore, it is crucial to use well-established statistical approaches, such factorial design, to comprehend the complexity of pharmaceutical formulations. The factorial design technique, in addition to the art of formulation, is a useful way to show the relative importance of several factors and their interactions.

The number of independent variables chosen will determine how many experiments are needed for these investigations. For every trial, the response (Yi) is assessed.

$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_{12}+b_{22}X_{22}$

The dependent variable is denoted by Y, the estimated coefficient for the factor Xi is bi, and the arithmetic mean response of the nine runs is represented by b_0. The average outcome of gradually raising a factor's value from a low one to a high one is represented by the primary effects (X_1 and X_2). When two factors are adjusted simultaneously, the response varies, as indicated by the interaction terms (X_1X_2).

In this investigation, a 3^2 randomized complete factorial design was used. Two parameters were assessed in this design, each at three levels, and experimental trials were conducted at each of the nine potential configurations. Preliminary research was used to select the criteria. The concentrations of the polymer (X_2) and plasticizer PEG 400 (X_1) were chosen as the independent variables.

Table No.2: Coding of factor

Factor	**Plasticizer (X_1) ml**			**Pullulan (X_2) mg**		
Conc.	0.2	0.5	0.8	200	250	300
Levels	-1	0	1	-1	0	1

Table No.3: Factorial design 3^2 = 9 Runs

Formulation	**(X1)ml**	**(X2)mg**
F1	-1(0.2)	-1(200)
F2	-1(0.2)	0(250)
F3	-1(0.2)	+1(300)
F4	0(0.5)	-1(200)
F5	0(0.5)	0(250)
F6	0(0.5)	+1(300)
F7	+1(0.8)	-1(200)
F8	+1(0.8)	0(250)
F9	+1(0.8)	+1(300)

*Coded value -1, 0, +1 with their actual value in bracket.

Table No.4: Formulation of buccal films of betaxolol HCL

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Betaxolol HCL (mg)	251	251	251	251	251	251	251	251	251
Pullulan (mg)	200	250	300	200	250	300	200	250	300
PEG 400 (ml)	0.2	0.2	0.2	0.5	0.5	0.5	0.8	0.8	0.8
Citric acid (mg)	30	30	30	30	30	30	30	30	30
Sucralose (mg)	30	30	30	30	30	30	30	30	30
Distilled water (ml)	8	8	8	8	8	8	8	8	8

Calculation of dose:

Diameter of petri dish = 8cm

radius = 4 area of circle = π

r^2 π r^2=3.14(4)2=50.24cm^2

Area of petri dish = 50.24 cm^2

Area of single film = L x W

= 2x2

so

50.25/4 = 12.55 total number

of films =12.55

total amount of drug require is = 20mg

= 20x12.55

= 251 mg drug for per petri dish

Characterization and evaluation parameters of buccal films Characterization of buccal films:

1. **FTIR study:**

The method of matching FT-IR spectra of the FT-IR data was used to find the chemical interaction between the medication and particular polymers. Changes in the peak (characteristic wave numbers) can be used to identify the chemical interaction between the medication and polymer.

2. **DSC study:**

Studies involving Differential Scanning Calorimetry (DSC) were conducted with Shimadzu, Japan's DSC 60, which was equipped with TA60 software. Recorded were the DSC thermograms for the optimized formulation. Precisely weighed specimens were positioned onto aluminum plates, sealed with aluminum covers, and subjected to a steady heating rate of 5ºC / min, spanning from 0 to 250ºC.

Evaluation parameters of buccal films:

1. **Morphological properties:** Visual inspection was used to assess the oral film's characteristics, including homogeneity, color, transparency, and surface.[More,2019]
2. **Weight variation:** Each prepared buccal film was divided into three pieces, each measuring 2 by 2 cm^2, and each piece was weighed separately using a digital balance. The average weight was calculated.[Kunte,2010]
3. **Film thickness:** A micrometer screw gauge should be used to determine the film's thickness. Five points on the film should be measured: the center, four corners, and the mean thickness and standard deviation were calculated. [More,2019]
4. **Folding endurance:** For the prepared buccal film, it is measured by hand. A film was folded in the same spot repeatedly until it broke. The value of folding endurance was determined by counting how many times the film could be folded in the same direction without breaking. Calculations were done for mean folding endurance and standard deviations. [More,2019]
5. **Surface pH:** 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.[Yehia,2009]
6. **Disintegration time:** The film strip (2 × 2 cm^2) was placed in a 6 cm diameter Petri dish with 6 ml of pH 6.8 phosphate buffer to determine the disintegration time. The amount of time needed for the film to completely dissolve was noted. Every measurement was performed three times, and the average results were reported.[R.C.Mashru,2005]
7. **Drug content uniformity test of prepared fast dissolving films:** The ideal range for content uniformity is 85–115%. The test for content uniformity involved taking a 2x2 cm2 sample film and placing it in a beaker with 50 ml of pH 6.8 phosphate buffer. The film was dissolved by stirring the fluid, and it was subsequently filtered. Using a standard assay method specified for the specific active pharmaceutical ingredient (API) listed in any standard pharmacopoeia, the absorbance of the solution was measured at a given wavelength against the corresponding blank solution. After substituting these absorbance values into the drug's standard curve equation (y = mx + c), the concentration of the drug (x) was found for each absorbance value. Since the concentration was measured in µg/ml, it was translated to mg/50 ml and the formula % drug content = {practical yield (x in 50 ml) / theoretical yield (drug incorporated)} × 100 was used to get the percentage drug content.[Akhtar,2017]
8. **Dissolution test and percentage drug release of prepared fast dissolving films:** The percentage of drug release from prepared fast-dissolving films and the in vitro dissolution test. The point at which the film totally dissolves is known as the dissolution time. A USP-I rotating basket dissolution equipment was used to conduct the in vitro dissolution test. Films containing drugs were cut into 2 cm diameter pieces and inserted into the disso-apparatus basket. The phosphate buffer pH 6.8, which serves as the dissolution media, had a volume of 900 ml and was kept at a temperature of 37±4°C. The basket was spun at a rate of 25 revolutions per minute (rpm). At prearranged intervals, 10 ml samples were removed and replaced with 10 ml of fresh media. Using Whatmann filter paper, the extracted solution was filtered. The absorbance was measured with a UV-visible spectrophotometer against a blank at a wavelength of 223 nm. In order to calculate the percentage of drug release, the absorbance values from the dissolution test were inserted into the drug's standard curve equation (y = mx + c), and the concentration of the drug (x) was calculated for each absorbance value. Since the obtained concentration was in µg/ml, it was converted to mg/900 ml. The formula used to compute the percentage drug release was [% Drug release = (x in 900 ml buffer / drug incorporated) × 100].[Narang,2011]

Figure No.11: Dissolution test apparatus

IV. RESULTS AND DISCUSSION

7.1 Preformulation study

A. Description:The sample of Betaxolol HCL was found to be odorless White to off-white crystalline powder.
B. Melting point:The melting point of Betaxolol HCL was found to be 117^0C was in range in1113- 117°C. The results of melting points of Betaxolol HCL were in the range of reported melting point of Betaxolol HCL by drug bank. It also inferred the purity of drugs.
C. Construction of standard curve of Betaxolol HCL -Standard calibration curve of Betaxolol in 6.8 phosphate buffer was plotted by using the observation recorded in table.

Table No.5: Observation for calibration curve of Betaxolol HCL

Sr.no	Concentration (µg/ml)	Absorbance (nm)
1	10	0.0461
2	20	0.0678
3	30	0.0891
4	40	0.1091
5	50	0.1285
6	60	0.1478

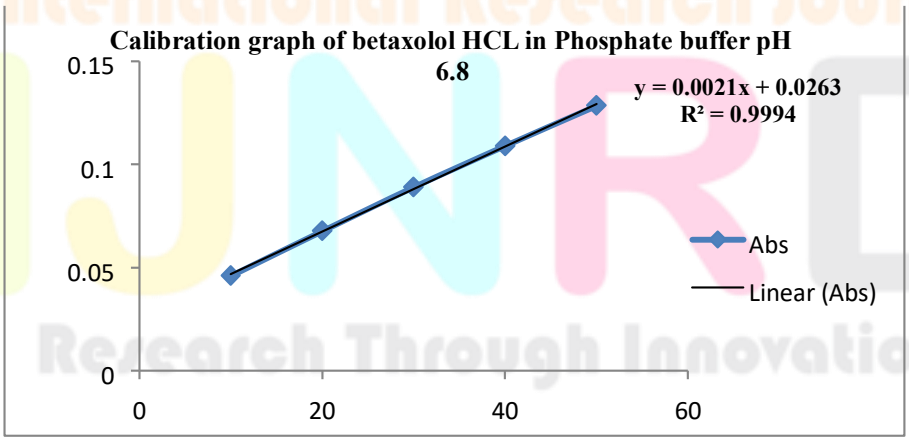


Figure No.12: Standard calibration curve of Betaxolol HCL

Table No.6: Standard curve statistics

Sr.no	Parameter	Observations
1	Absorbance maximum	203nm
2	Coefficient of correlation (r^2)	0.9994

Compatibility study:

1) Infrared Spectrum Analysis

The infrared spectrum of pure drug betaxolol HCL, pullulan and physical mixture was studied, and it was discovered that all of the important peaks that correspond to various functional groups were present. Thus, the purity of the all compounds were determined using infrared spectroscopy. The details of the observed peaks and the corresponding functional groups are shown in the tables below.

A) FTIR of drug:

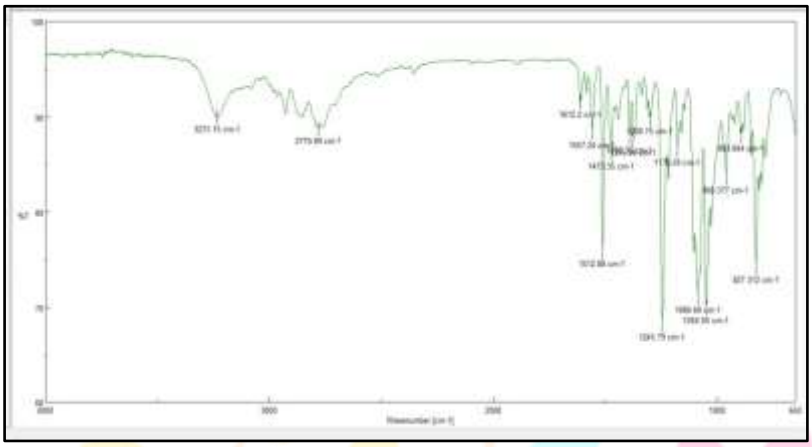


Figure No.13: IR spectrum of Betaxolol HCL

Table No.7: Data of IR spectrum of Betaxolol HCL

Sr.no	Wave Numbers	Interpretation	Peak observed
1	3400–3300	O–H and N–H stretch	3231.15
2	2950–2850	C–H stretch	2779.89
3	1600–1580	C=C Stretch	1557.24
4	1500–1450	C–H Stretch	1473.35
5	1250–1050	C–O–C Stretch	1245.88

B) FTIR drug and excipients:

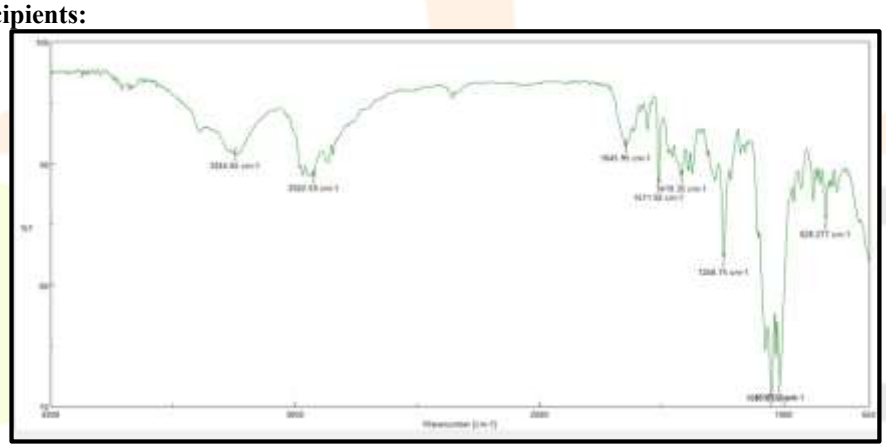


Figure No.14: IR spectrum of drug and excipient's

Table No.8: Data of IR spectrum of drug and excipient's

Sr.no	Wave Numbers	Interpretation	Peak observed
1	3400–3300	O–H and N–H stretch	3231.15
2	2950–2850	C–H stretch	2779.89
3	1600–1580	C=C Stretch	1557.24
4	1500–1450	C–H Stretch	1473.35
5	1250–1050	C–O–C Stretch	1245.88

2) Thermal Analysis:

A) Differential Scanning Colorimetry of Betaxolol HCL:

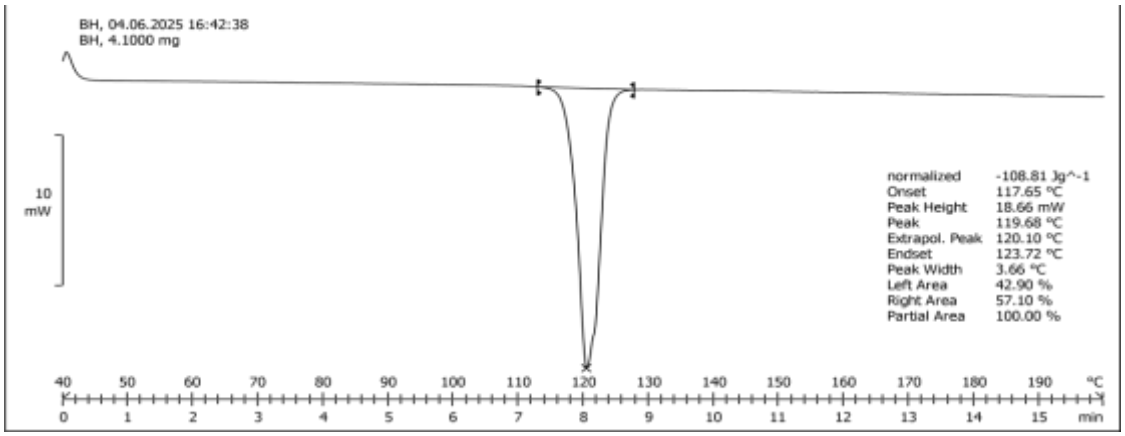


Figure No.15: Differential Scanning Colorimetry of Betaxolol HCL

B) Differential Scanning Colorimetry of drug and excipient's:

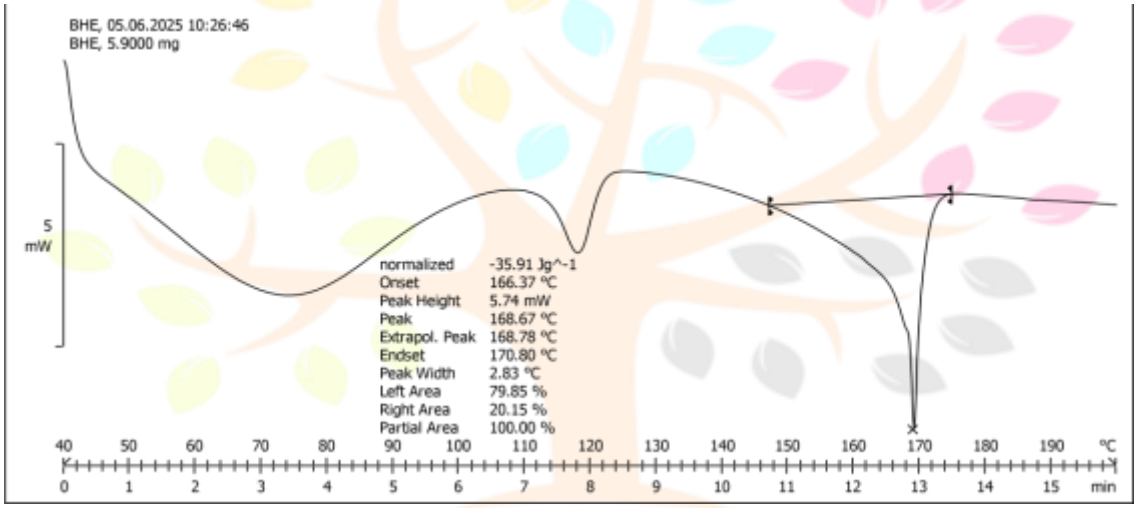


Figure No.15: Differential Scanning Colorimetry of drug and excipient's:

Formulation of Buccal Film's by using 3^2 factorial design:

F1

F2

F3

F4

F5

F6

F7

F8

F9

Evaluation of buccal Film's:

1. Morphology of Buccal Film's:

The morphology of all film formulation was found to be smooth, Semi-transparent and white in colour.

Table No.11: Morphology of Buccal Film's

Sr.no	Smoothness	Transparency	Color
F1	Smooth	Semi-transparent	White
F2	Smooth	Semi-transparent	White
F3	Smooth	Semi-transparent	White
F4	Smooth	Semi-transparent	White
F5	Smooth	Semi-transparent	White
F6	Smooth	Semi-transparent	White
F8	Smooth	Semi-transparent	White
F8	Smooth	Semi-transparent	White
F9	Smooth	Semi-transparent	White

2. Weight variation:

Table no 12 displays the average weights of the various formulated film pieces. Based on the findings, it was noted that the weight of each batch was generally consistent, with virtually no difference in the weight of any particular formulation. The weight increased when more polymer was added, according to the results.

Table No.12: Weight variation of Buccal Film's

Batch Code	Weight (mg)
F1	52.06±0.20
F2	49.63±0.55
F3	45.43±1.26
F4	54.93±0.40
F5	50.86±0.45
F6	55.63±0.32
F8	60.26±0.87
F8	45.53±2.40
F9	57.23±0.40

3. Thickness:

The thickness of all formulations F1-F9 was found by using micrometer screw gauze and the results were shown in the table no.13.

Table No.13:Thickness of Buccal Film's

Batch Code	Thickness (mm)
F1	0.06±0.01
F2	0.10±0.01
F3	0.08±0.02
F4	0.06±0.02
F5	0.04±0.02
F6	0.08±0.03
F7	0.08±0.02
F8	0.06±0.10
F9	0.07±0.005

4. Folding Endurance:

The film's ability to fold repeatedly was assessed by hand. Folding a film repeatedly until it broke was used to measure folding endurance. The concentration of plasticizer and polymer affects folding endurance. The average of three readings was calculated and the result was given in Table No. 14.

Table No.14: Folding Endurance of Buccal Film's

Batch Code	Folding Endurance (no. of folds)
F1	74.3±0.5
F2	71±1
F3	78.6±0.5
F4	88±1
F5	81.3±1.5
F6	70.3±1.5
F8	80±1
F8	67.3±1.15
F9	75.3±1.15

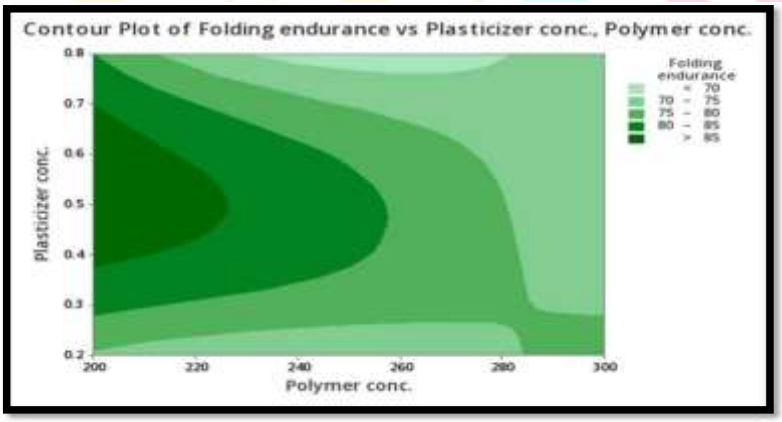


Figure No.17: Contour plot for folding endurance

Above graphical representation of contour plot for folding endurance is a graphical interpretation of interactions between different factors in an experiment which represent the combination of levels from the factors being studied. The response variables is typically represented by green colour. The colour changes from green to dark green which indicate whether the significant interaction between factors.

This visual representation aids in understanding how different factors influence the outcome of the experiment in relation to each other.

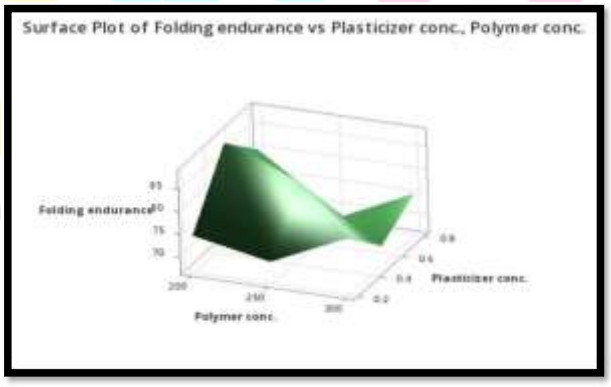


Figure No.18: Three-dimensional surface plot for folding endurance

The above representation of surface plot for folding endurance is a three-dimensional surface plot which indicates the concentration of polymer and plasticizer which represents the combination of levels from the factors. The visual interpretation of response variable is typically seen in the coloured format from dark green colour to light green. That indicates significant interaction between concentration of polymer of plasticizer on folding endurance of BF's of Betaxolol HCL.

Regression Equation:

Folding endurance = 76.23 + 4.533 Polymer conc._200 - 3.033 Polymer conc._250
- 1.500 Polymer conc._300 - 1.600 Plasticizer conc._0.2
+ 3.633 Plasticizer conc._0.5 - 2.033 Plasticizer conc._0.8
- 4.867 Polymer conc.*Plasticizer conc._200 0.2
+ 3.600 Polymer conc.*Plasticizer conc._200 0.5
+ 1.267 Polymer conc.*Plasticizer conc._200 0.8
- 0.6000 Polymer conc.*Plasticizer conc._250 0.2
+ 4.467 Polymer conc.*Plasticizer conc._250 0.5
- 3.867 Polymer conc.*Plasticizer conc._250 0.8
+ 5.467 Polymer conc.*Plasticizer conc._300 0.2
- 8.067 Polymer conc.*Plasticizer conc._300 0.5
+ 2.600 Polymer conc.*Plasticizer conc._300 0.8

Analysis of Variance:

Table No.15: Analysis of variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	8	330.92	41.36	*	*
Linear	4	155.69	38.92	*	*
Polymer conc.	2	96.01	48.00	*	*
Plasticizer conc.	2	59.69	29.84	*	*
2-Way Interactions	4	175.23	43.81	*	*
Polymer conc. *Plasticizer conc.	4	175.23	43.81	*	*
Error	0	*	*		
Total	8	330.92			

[* - it indicates that it is significant]

5. Surface pH:

The surface pH of every oral dissolving film made with pullulan as the polymer was found to be between 6.3 and 6.8 pH (Table no. 16), which is close to neutral pH. This suggests that the films may be less likely to irritate the sublingual mucosa and, as a result, more patient-accepted.

Table No.16: Surface pH

Batch code	Surface pH
F1	6.69±0.16
F2	6.32±0.12
F3	6.86±0.05
F4	6.72±0.02
F5	6.50±0.05
F6	6.42±0.03
F8	6.53±0.02
F8	6.63±0.01
F9	6.70±0.01

6. Disintegration time:

The majority of the films in the disintegration test disintegrated in less than 30 seconds. Table no. 17 showed that the F4 batch had the minimum disintegration time while the F2 batch had the largest disintegration time. The disintegration time of all formulations tested was less than 24 seconds.

Table No.17: Disintegration time

Batch Code	Disintegration time (sec)
F1	22±1
F2	24±1
F3	22.3±0.57

F4	17.3±1.15
F5	21.3±0.57
F6	20±1
F8	23.6±0.57
F8	20±1
F9	22±3

7. % Drug content:

As indicated by Table no. 18, the results demonstrated good consistency of drug content across the films with no apparent variance. Films were determined to contain between 83 and 94% mg of drug. It was discovered that Formulation F4, containing 200 mg of pullulan, had the highest proportion of drug content.

Table No.18: % Drug content

Batch Code	% Drug content
F1	84.37±0.89
F2	91.62±0.59
F3	85.55±0.69
F4	94.60±0.52
F5	90.86±0.30
F6	83.94±0.69
F8	91.44±0.76
F8	87.92±0.91
F9	87.38±0.94

8. In-Vitro Drug release:

The in vitro dissolution profile of drug loaded Buccal films of Betaxolol HCL with pullulan and percentage drug release at different time interval were recorded up to 5 min in Table 23. It showed that the drug Betaxolol HCL get rapidly released from all formulations. Maximum in vitro release was found to be 99.1% over a period of 3 min in batch F4 while minimum in vitro release was found to be 20.9 % in batch F9 in 0.5 min.

Table No.19: In-Vitro Drug release (F1-F9)

Batch Code	Time(min)									
	0.5	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**
F1	31.7± 0.35	60.46 ±0.76	65.68 ±1.03	71.85 ±1.62	81.89 ±1.12	97.40 ±0.52				
F2	23.02 ±0.63	55.81 ±0.84	61.48 ±1.50	72.07 ±0.27	80.85 ±0.88	82.59 ±1.70	91.24 ±0.96	97.33 ±0.92		
F3	30.64 ±0.77	42.68 ±1.29	50.67 ±0.78	59.82 ±0.15	67.42 ±1.49	74.23 ±1.10	79.82 ±1.10	79.88 ±1.02	85.69 ±0.56	98.35 ±0.54
F4	33.34 ±0.66	55.71 ±1.24	61.69 ±0.80	79.74 ±1.07	86.65 ±1.36	99.16 ±0.21				
F5	31.84 ±0.17	50.38 ±1.09	59.22 ±1.02	67.55 ±1.44	80±0. 48	81.33 ±1.05	88.04 ±1.06	96.90 ±0.78		
F6	32.17 ±0.95	40.20 ±1.13	44.22 ±1.09	50.38 ±0.94	54.42 ±0.78	60.72 ±1.09	68.64 ±0.69	77.62 ±0.75	90.27 ±0.82	97.18 ±0.17
F7	39.11 ±0.17	50.67 ±1.57	70.36 ±1.00	82.33 ±1.05	91.11 ±0.94	97.77 ±0.68				

F8	34.18 ±1.05	42.73 ±1.66	53.24 ±1.20	61.48 ±0.63	63.10 ±1.33	79.76 ±0.98	80.08 ±0.97	94.42 ±0.94		
F9	20.99 ±0.99	38.61 ±0.59	44.98 ±0.43	48.54 ±0.78	53.90 ±0.53	60.78 ±0.51	64.45 ±1.39	76.36 ±0.62	81.00 ±1.12	98.24 ±0.22

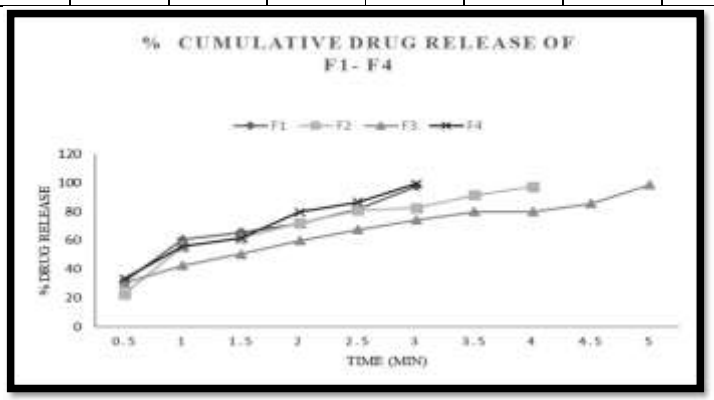


Figure No.19: % Cumulative drug release(F1-F4)

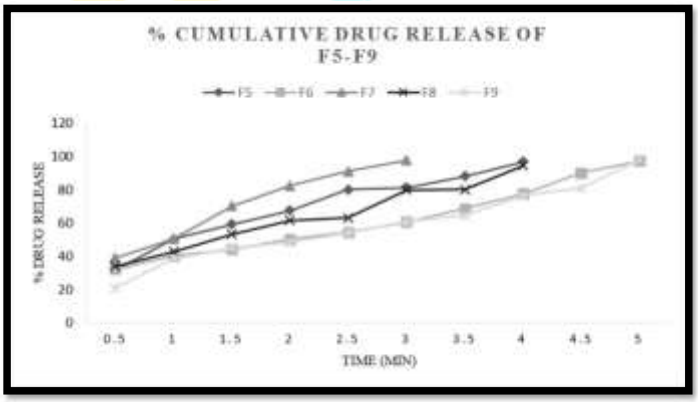


Figure No.20: % Cumulative drug release (F5-F9)

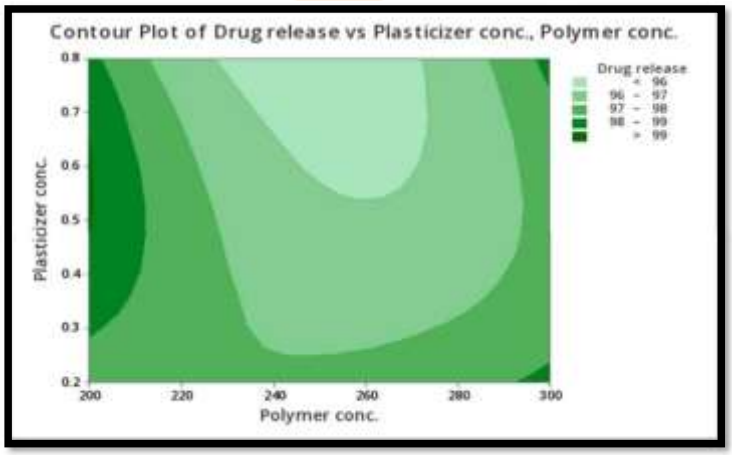


Figure No.21: Contour plot for dissolution rate

Above graphical representation of contour plot for dissolution rate is a graphical interpretation of interactions between different factors in an experiment which represent the combination of levels from the factors being studied. The response variables is typically represented by green colour. The colour changes from green to dark green which indicate whether the significant interaction between factors.

This visual representation aids in understanding how different factors influence the outcome of the experiment in relation to each other.

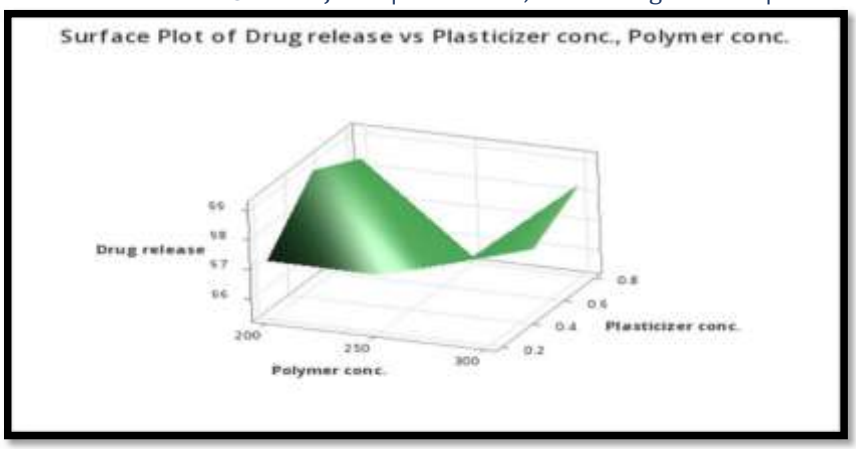


Figure No.22: Three dimensional surface plot for dissolution rate

The above representation of surface plot for dissolution rate is a three dimensional surface plot which indicates the concentratton of polymer and plasticizer which represents the combination of levels from the factors. The visual interpretation of response variable is typically seen in the coloured format from dark green colour to light green. That indicates significant interaction between concentration of polymer of plasticizer on folding endurance of MDF's of Chlorpromazine HCL.

Regression Equation

Drug release = 97.48 + 0.7311 Polymer conc._200 - 1.209 Polymer conc._250
+ 0.4778 Polymer conc._300 + 0.05778 Plasticizer conc._0.2
+ 0.06778 Plasticizer conc._0.5 - 0.1256 Plasticizer conc._0.8
- 1.058 Polymer conc.*Plasticizer conc._200 0.2
+ 0.8222 Polymer conc.*Plasticizer conc._200 0.5
+ 0.2356 Polymer conc.*Plasticizer conc._200 0.8
+ 0.8522 Polymer conc.*Plasticizer conc._250 0.2
- 0.1278 Polymer conc.*Plasticizer conc._250 0.5
- 0.7244 Polymer conc.*Plasticizer conc._250 0.8 + 0.2056 Polymer conc.*Plasticizer conc._300 0.2
- 0.6944 Polymer conc.*Plasticizer conc._300 0.5
+ 0.4889 Polymer conc.*Plasticizer conc._300 0.8

Analysis of Variance

Table No.20: Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	8	10.6251	1.32814	*	*
Linear	4	6.7437	1.68593	*	*
Polymer conc.	2	6.6726	3.33631	*	*
Plasticizer conc.	2	0.0711	0.03554	*	*
2-Way Interactions	4	3.8814	0.97034	*	*
Polymer conc. *Plasticizer conc.	4	3.8814	0.97034	*	*
Error	0	*	*		
Total	8	10.6251			

[* - it indicates that it is significant]

Conclusion:

The present study successfully formulated and optimized buccal films of Betaxolol HCl using pullulan as a natural, film-forming polymer and PEG 400 as a plasticizer. Utilizing a 3^2 factorial design, the impact of polymer and plasticizer concentrations was systematically evaluated on key in vitro parameters including surface pH, disintegration time, folding endurance, drug content, and drug release. Among the tested formulations, batch F4 demonstrated optimal performance with a surface pH of 6.72, rapid disintegration time of 17 seconds, high drug content of 94.60%, and excellent in vitro drug release of 99.16% within 3 minutes.

The buccal films also exhibited satisfactory mechanical strength and flexibility, as evidenced by high folding endurance, and maintained uniform drug distribution across the film. These in vitro findings highlight the potential of pullulan-based buccal films as a stable, fast-dissolving, and effective formulation for delivering Betaxolol HCl via the buccal route.

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