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FORMULATION AND ESTIMATION OF ATOMOXETINE HCL BUCCAL DRUG DELIVERY SYSTEM

Ms. Geeta M. Khonde[1*], Dr. Kamble H. V[2], Mr. Deshpande M.J.[3], Mr. Sugriv R. Ghodake[4]

[1*]Research student, Loknete Shri Dadapatil Pharate College of Pharmacy Mandavgan Pharata, Ta - Shirur Dist-Pune 412211

[2]Principal, Loknete Shri Dadapatil Pharate College of Pharmacy Mandavgan Pharata, Ta - Shirur Dist-Pune 412211

[3]Research Guide, Loknete Shri Dadapatil Pharate College of Pharmacy Mandavgan Pharata, Ta - Shirur Dist-Pune 412211

[4]Research Co-Guide, Loknete Shri Dadapatil Pharate College of Pharmacy Mandavgan Pharata, Ta - Shirur Dist-Pune 412211

Abstract:

The study focused on developing and evaluating mucoadhesive buccal films for enhanced drug delivery using a solvent casting method. Among the formulations (F1-F9), F2 emerged as the optimized batch, demonstrating superior quality attributes. F2 exhibited excellent transparency, minimal weight variation (43.56%), low moisture content (3.2%), optimal thickness (0.02 mm), high folding endurance (110), and a pH of 6.8. It also achieved the highest drug content (98.14%) and tensile strength (25.63 gm/mm²), ensuring stability, robustness, and effective drug delivery. The ex-vivo diffusion study confirmed that F2 achieved 95.56% drug permeation at 10 minutes, surpassing other formulations. Stability studies over three months revealed no significant changes in thickness, drug content, or drug release. The results demonstrate that formulation F2 is a promising candidate for mucoadhesive buccal drug delivery, offering consistent quality, efficient drug release, and stability over time.

Keywords: *Mucoadhesive buccal films, drug delivery, solvent casting, folding endurance, drug content, ex-vivo diffusion, stability studies.*

Corresponding author:

Ms. Geeta M. Khonde,

Research student,

Loknete Shri Dadapatil Pharate College of Pharmacy,

Mandavgan Pharata, Ta - Shirur Dist-Pune 412211

geetakhonde7@gmail.com

QR code

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INTRODUCTION:

Atomoxetine hydrochloride (Atomoxetine HCl) is a selective norepinephrine reuptake inhibitor primarily used in the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adults.[1-4] Unlike other stimulants, Atomoxetine is not associated with abuse potential, making it an attractive therapeutic option for patients with a history of substance misuse. However, its clinical efficacy and patient compliance can be influenced by its pharmacokinetics, which are significantly impacted by the route of administration.[5-7]

The conventional oral delivery of Atomoxetine suffers from several drawbacks, including first-pass metabolism in the liver, which reduces its bioavailability and therapeutic effectiveness. To overcome these limitations, the development of an alternative, more efficient drug delivery system is essential. Buccal drug delivery systems (BDDS) represent an emerging approach that offers significant advantages in drug delivery, particularly for medications like Atomoxetine HCl. The buccal route, involving the absorption of drugs through the mucous membranes of the mouth, bypasses the first-pass effect and allows for rapid absorption directly into the bloodstream. This can lead to improved bioavailability, quicker onset of action, and better patient compliance, especially in individuals with difficulties swallowing conventional tablets or capsules.[8-12]

The purpose of this research is to formulate and estimate the effectiveness of a buccal drug delivery system for Atomoxetine HCl. This study focuses on designing a formulation that optimizes the stability, release, and absorption of the drug via the buccal mucosa. The development of an effective buccal system for Atomoxetine HCl could potentially offer a more efficient and patient-friendly therapeutic alternative.

The research includes the selection of appropriate excipients, the preparation of the formulation, and the evaluation of its physicochemical properties, such as drug release, mucoadhesive strength, and stability. Furthermore, the study aims to quantify the drug in the formulation using advanced estimation techniques, ensuring accurate dosing and the desired therapeutic effect.[13-18]

By advancing the development of buccal drug delivery systems for Atomoxetine HCl, this research hopes to provide a viable alternative to traditional oral dosage forms, enhancing the therapeutic outcomes and quality of life for patients managing ADHD.[19-20]

MATERIALS AND METHODS:

MATERIALS:

The formulation of the Atomoxetine HCl buccal drug delivery system includes several key excipients. Atomoxetine HCl, sourced from Cipla Pvt. Ltd., is the active ingredient for treating ADHD. Sodium Carboxymethyl Cellulose (film-forming polymer) from Ashland Pvt. Ltd. provides structure, while Sodium Starch Glycolate (super disintegrant) from Cosmo Chem Pvt. Ltd. ensures rapid drug release. Propylene Glycol (plasticizer), Mannitol (sweetener), and Menthol (flavoring agent), all from Cosmo Chem Pvt. Ltd., improve flexibility, taste, and patient acceptability. Distilled Water and Ethanol serve as solvents, aiding in drug dissolution and formulation preparation.

Pre-Formulation Study:

The preformulation study of Atomoxetine HCl involved several key tests to determine its physical and chemical properties. The drug's appearance, including its texture, color, and odor, was observed visually. The melting point of Atomoxetine HCl was determined using the capillary tube method, where the drug was heated in a Thiele tube, and the temperature at which the drug melted was recorded.

For solubility**,** Atomoxetine HCl was tested in different solvents, including methanol, ethanol, distilled water, phosphate buffer (pH 7.4, pH 6.8), and acidic buffer (pH 1.2). A 50 mg sample of the drug was dissolved in 100 ml of each solvent, stirred for 24 hours, and then filtered. The absorbance of the resulting solutions was measured at 269 nm using a UV spectrophotometer. Each solvent's ability to dissolve the drug was assessed, ensuring its suitability for formulation development.[21-22]

Spectrophotometric characterization of Lisinopril in UV Spectroscopy

Detection of Absorption Maxima (λ max)

The sample of the standard solution were scanned between 200-400 nm regions on Shimadazu 1800UV spectrophotometer. Atomoxetine HCL sample was prepared by dissolving 25 mg of drug in 25 ml of methanol respectively. The absorption maximum for distilled water was found to be 269 nm.[23]

Standard calibration curve of Atomoxetine HCL in Ethanol

Preparation of stock solution in Ethanol

Standard stock solution was prepared by taking 25

mg in 25 ml of ethanol (1000µg/ml). The stock solution scanned in the range 400-200 nm by UV spectrophotometer. The solution showed maximum absorbance at 218nm.

Preparation of dilutions for the standard curve:
From 1000µg/ml, diluted 10 ml to 100ml (100 µg/ml), from this solution 2-12 µg/ml dilutions prepared. Absorbance was taken at 269 nm using water as a blank. The absorbance v/s concentration graph is plotted.[24]

METHODS:
Mucoadhesive buccal films were prepared using the solvent casting method. The process involved soaking the polymer in water for 30 minutes, followed by the addition of ethanol. The drug solution was incorporated into the polymer mixture, and sweetener (mannitol) and plasticizer (propylene glycol) were added. The mixture was stirred continuously, and any air bubbles were allowed to dissipate by resting the solution for 30 minutes. Glass petri dishes were used as the base for film formation, selected for ease of film removal, uniform thickness, and cost-effectiveness.[25-2]

EXPERIMENTAL DESIGN:
A central composite design was used to evaluate the effects of independent variables on the drug content (%), thickness (mm), and drug release (%) of Atomoxetine HCL films. The films were prepared by the solvent casting method, and the design involved two independent variables: Hydroxypropyl methyl cellulose (X1) and Propylene glycol (X2) at two levels. Nine formulations were tested, and the optimized formulation was selected for further characterization based on the drug content, thickness, and drug release.[27-30]

Table 1: DOE suggested and experimental batches

Formulation code	Atomoxetine HCL (mg)	HPMC K4M (mg)	Propylene glycol (ml)	Mannitol (mg)	Menthol	Distilled water
F1	158.96	200	0.15	10	Q.s	Q.s
F2	158.96	500	0.15	10	Q.s	Q.s
F3	158.96	350	0.125	10	Q.s	Q.s
F4	158.96	562.132	0.125	10	Q.s	Q.s
F5	158.96	500	0.1	10	Q.s	Q.s
F6	158.96	350	0.160355	10	Q.s	Q.s
F7	158.96	200	0.1	10	Q.s	Q.s
F8	158.96	350	0.0896447	10	Q.s	Q.s
F9	158.96	137.868	0.125	10	Q.s	Q.s

Post formulation study:
Several tests were conducted to evaluate the quality and performance of the formulated buccal films. Transparency was assessed by observing the film against an illuminated background to check for opacity. Weight variation was determined by weighing five films individually and calculating the average weight. Moisture content was measured by weighing the film before and after exposure to a desiccator for 24 hours, and the percentage moisture was calculated. Thickness was measured using a digital Vernier Caliper, with an average thickness determined from five randomly selected films. Folding endurance was tested by repeatedly folding the film until it broke, with the number of folds recorded. Surface pH was measured by placing a water droplet on the film and using a pH meter to check the surface pH. Drug content was determined by estimating the active pharmaceutical ingredient (API) in individual films to assess content uniformity. Tensile strength and percentage elongation were calculated to evaluate the mechanical properties of the film, with tensile strength measured by the applied load at rupture and percentage elongation determined by the increase in film length.[31-33]

***In-Vitro* Disintegration Time**
Each OFDF was placed in a glass Petri dish, then, 10 mL phosphate buffer of phosphate buffer(pH 6.8) was added to the petri dish at 25 °C. The time required to

disintegrate or break each OFDF was recorded. For each OFDF, measurements were performed three times, and the meanvalue was calculated.[34]

***Ex-Vivo* Diffusion Study:**

Ex-vivo permeation studies were conducted using goat oral mucosa and a modified Franz diffusion cell, consisting of donor and receptor chambers. The system was maintained at 37°C, with the receptor compartment containing phosphate buffer pH 6.8 and stirred by a magnetic bead at 50 rpm. Goat oral mucosa served as the model membrane, and the optimized film (2x2 cm) loaded with 5 mg of drug was placed in contact with the mucosa. Samples were withdrawn at intervals (2, 4, 6, 8, 10 min) and replaced with fresh medium to assess drug diffusion.[35,36]

Stability studies:

Stability study as per ICH guideline the accelerated stability was checked by keeping the film at room temperature up to 30 and 90 days. Samples were evaluated for Drug content, disintegration time and drug release.[37]

RESULT AND DISUSSION:

Pre-formulation study:

Identification of drug:

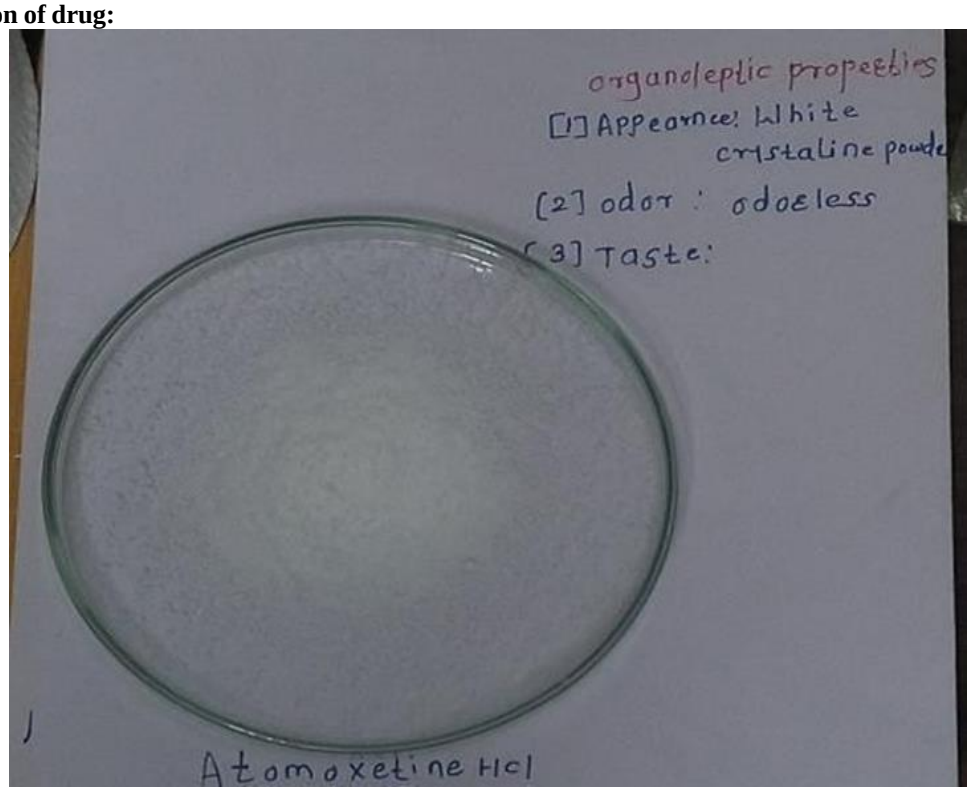

Figure 1: Atomoxetine HCL

Melting point

The observation of the melting points for Atomoxetine HCl shows an observed value of 162°C,which falls within the reported range of 161-165°C. This consistency between the observed and reported values confirms the purity and identity of the Atomoxetine HCl sample.

Solubility study of Atomoxetine HCL

The solubility study of Atomoxetine HCl in various media reveals that it has the highest solubility in distilled water (38.46 mg/mL), followed by methanol (34.89 mg/mL) and ethanol (29.14 mg/mL). Its solubility decreases in phosphate buffers at pH 6.8 (26.54 mg/mL) and Ph 7.4 (24.79 mg/mL), and is lowest in an acidic buffer at pH 1.2 (19.78 mg/mL). This indicates that Atomoxetine HCl is most soluble in distilled water and organic solvents, while its solubility is significantly reduced in more acidic environments and at higher pH levels. These findings are crucial for pharmaceutical formulation and experimental applications, suggesting that distilled water and methanol are preferable solvents to achieve higher solubility ofAtomoxetine HCl.

Table 2: Solubility in different Medium

Medium	Solubility(mg/ml)
Distilled water	38.46
Methanol	34.89
Ethanol	29.14
Phosphate buffer ph 6.8	26.54
Phosphate buffer ph 7.4	24.79
Acidic buffer ph 1.2	19.78

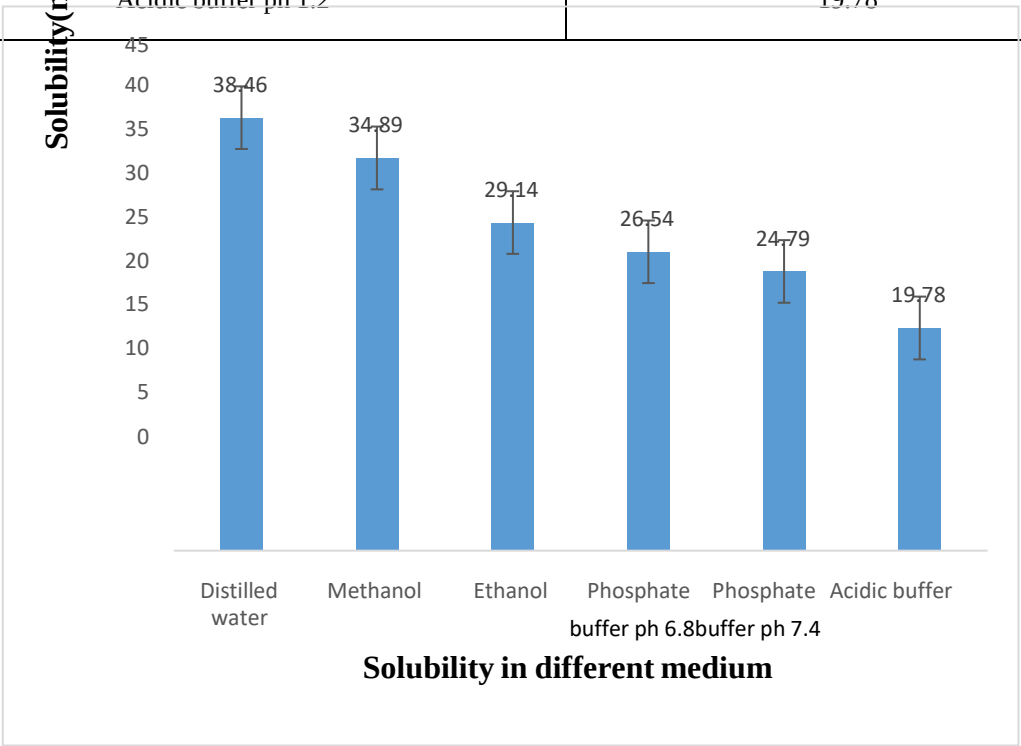

Figure 2: Solubility in different Medium

Calibration curve in Ethanol

The calibration curve developed in ethanol provides a reliable means of quantifying the concentration of a substance based on its absorbance within this solvent. With a high correlation coefficient (R^2) of 0.9817, the curve demonstrates a strong linear relationship between the concentration (µg/ml) and absorbance values. Utilizing the equation y = 0.0505x + 0.0425, where y represents absorbance and x represents concentration, accuratedetermination of unknown sample concentrations within the tested range can be achieved. Thiscalibration curve serves as a dependable analytical tool, offering precise concentration measurements in ethanol solutions, and underscores the effectiveness and reliability of the analytical method employed.

Table 3: Calibration curve in Ethanol

Concentration (µg/ml)	Absorbance
0	0
2	0.165
4	0.293
6	0.325
8	0.456
10	0.541
12	0.637

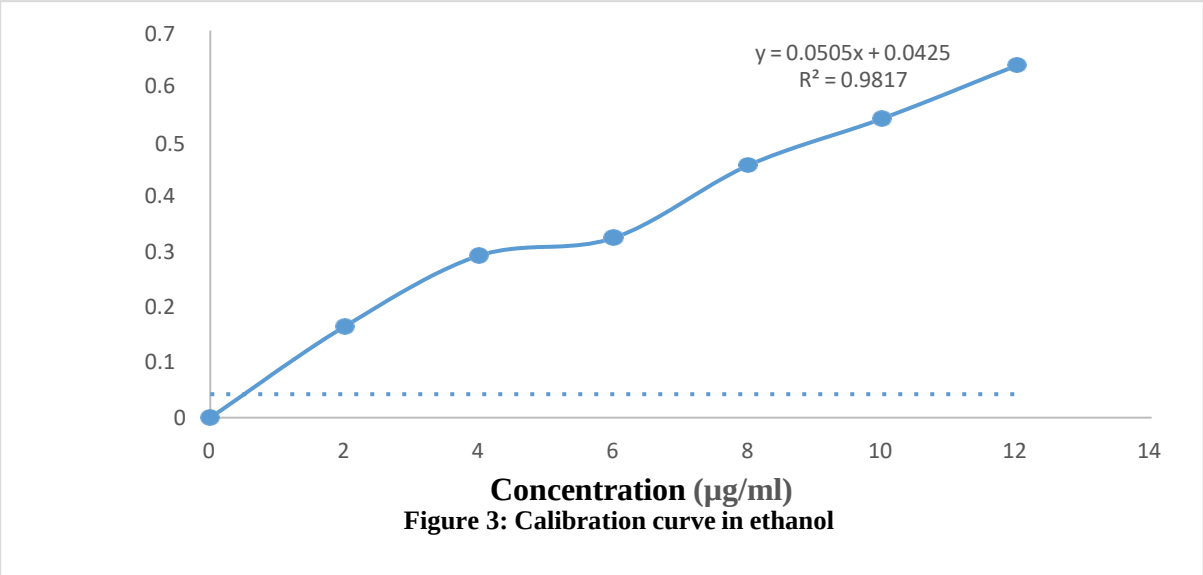

Figure 3: Calibration curve in ethanol

POST FORMULATION STUDY

Formulation F2, the optimized batch, demonstrates a remarkable balance of key quality attributes, making it the most suitable formulation for its intended application. One of its standout features is its excellent transparency, which not only reflects the high quality of the formulation but also suggests that it is free from any particulate matter or turbidity. This transparency is indicative of the formulation's stability, ensuring that no impurities are present to compromise its performance or safety.

Additionally, F2 shows the lowest weight variation (43.56%) among all the formulations tested. This low variation is crucial for ensuring consistent and uniform drug delivery, which is essential for achieving the desired therapeutic effect. A consistent weight across all units of the batch guarantees that each dose will deliver the intended amount of active ingredient, contributing to the overall reliability of the formulation.

The moisture content of F2 is another important aspect, with a value of 3.2%. This low moisture content not only helps to maintain the formulation's stability over time but also minimizes the risk of microbial growth, which can be a concern in formulations with higher moisture levels. By reducing the potential for contamination and degradation, the optimized formulation offers improved shelf life and safety.

The formulation's thinness (0.02 mm) is another advantage, as it enhances material efficiency and provides flexibility, which can be beneficial for the application and performance of the buccal film. A

thinner film is often easier to handle and more comfortable for the patient, while still delivering the drug effectively. The reduced thickness also allows for better control over the release of the drug, contributing to a more precise and controlled therapeutic effect.

F2's high folding endurance of 110 cycles is indicative of its excellent mechanical properties, including flexibility and resilience. This makes the formulation highly durable under stress, ensuring that the film will not crack or break easily when manipulated, such as during the process of buccal adhesion or while in use. This durability is crucial for ensuring that the film remains intact and functional during its application.

The pH of 6.8 places F2 within the optimal range for mucoadhesive buccal films, ensuring compatibility with the oral mucosa and facilitating effective drug absorption. This pH level is ideal for maintaining the integrity of the film while also promoting the adhesive properties that ensure the film stays in place during use.

In terms of drug delivery, F2 demonstrates the highest drug content (98.14%), making it highly efficient in delivering the intended therapeutic dose. The high drug content indicates that a significant amount of the active ingredient is incorporated into each unit, ensuring that the desired pharmacological effect is achieved. The tensile strength of 25.63 gm/mm² further supports the robustness of the formulation, contributing to its mechanical integrity and resilience under stress. A high tensile strength ensures that the film will not easily tear or lose its shape, making it a reliable delivery system.

While the formulation exhibits a percentage elongation of 10.53%, which is lower compared to some other formulations, this characteristic is not necessarily a drawback. The overall optimization of F2 takes into account a comprehensive set of parameters, and the slightly lower elongation may be balanced by the formulation's superior tensile strength, drug content, and other key properties. This balance ensures that F2 is optimized for both performance and efficiency, making it the most reliable and effective formulation for its intended application.

Table 4: Post formulation study of Formulations F1-F9

Formulation Code	Transparency	Weight Variation (%)	Moisture Content (%)	Thickness (mm)	Folding Endurance	Surface pH	Drug Content (%)	Tensile Strength (gm/mm²)	Percentage Elongation (%)
F1	Clear	53.65	5.6	0.3	45	6.2	95.46	11.5	18.79
F2	Clear	43.56	3.2	0.02	110	6.8	98.14	25.63	10.53
F3	Clear	84.56	8.3	0.6	64	7.2	87.36	17.6	15.43
F4	Clear	65.23	5.3	0.05	43	6.7	92.3	18.32	21.36
F5	Clear	56.89	6.8	0.8	52	7.5	89.64	12.46	16.44
F6	Clear	72.56	8.1	0.07	68	6.9	95.0	14.63	12.55
F7	Clear	48.63	5.6	0.8	73	6.3	89.46	9.5	14.89
F8	Clear	52.36	8.6	0.4	86	6.5	79.44	19.34	19.63
F9	Clear	65.89	7.4	0.9	93	7.3	82.16	10.56	11.23

***Ex- vivo* diffusion study**

The *ex-vivo* drug permeation study highlights that formulation F2 demonstrates the highest and most consistent drug permeation among all tested formulations. At 10 minutes, F2 achieves 95.56% drug permeation, outperforming the other formulations, indicating its superior efficiency in drug delivery. Other formulations, such as F6 and F9, also show good permeation profiles but fall short of F2's performance. This data underscores F2's optimization in terms of permeability and effective drug release, making it the most suitable candidate for achieving the desired therapeutic outcomes.

Table 5: Drug permeation of F1-F9

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	
1	9.22±	11.42±	8.55±	9.22±	10.55	13.51	11.32	7.44	10.44
2	23.55±	27.43±	14.54±	19.05±	21.56	25.04	20.44	20.15	19.12
3	32.51±	36.75±	27.45±	29.06±	32.53	39.77	34.04	26.55	30.08
4	45.75±	44.30±	33.62±	38.42±	39.24	47.76	45.86	35.14	42.65
5	57.64±	54.47±	46.4±	49.45±	51.03	52.65	52.44	41.52	49.14
6	62.40±	64.75±	51.14±	53.47±	60.36	69.78	61.42	48.65	50.42
7	72.51±	74.60±	63.35±	69.44±	69.04	76.42	75.55	54.45	69.89
8	80.44±	86.23±	70.66±	72.55±	72.45	83.09	78.08	68.87	78.87
9	87.62±	90.56±	85.56±	78.82±	84.75	87.44	82.14	73.01	84.45
10	90.02±	95.56±	89.06±	84.42±	87.23	93.22	86.05	77.35	87.65

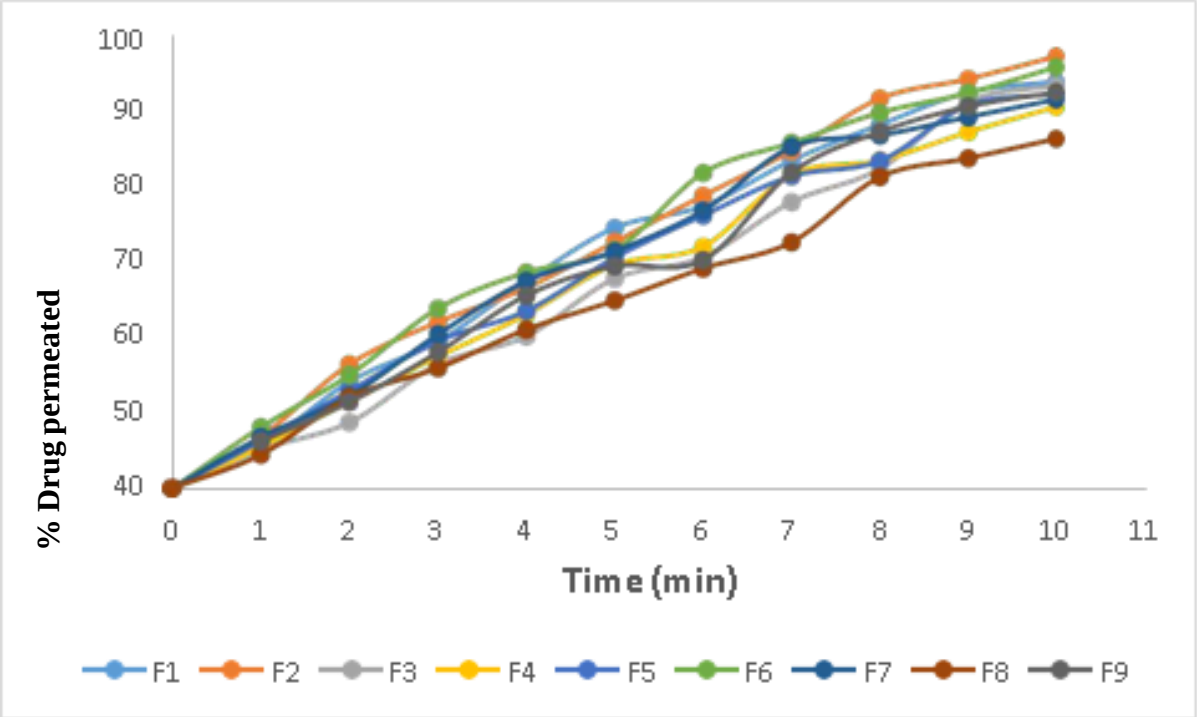

Figure 4: % Drug permeation of F1-F9

Stability studies

The stability study data for the F2 optimized batch over a period of three months indicates excellent stability. The formulation maintained a consistent thickness of 0.02 mm throughout the study period. Drug content remained virtually unchanged, starting at 98.14% on day 0 and showing a negligible change to 98.13% after 90 days. Similarly, drug release efficiency remained consistent, with only a minor variation from 96.56% initially to 96.55% at three months. These results demonstrate that F2 retains its physical and chemical integrity over time, making it a stable and reliable formulation.

Table 6: Stability studies data of F2 optimized batch

Sr.no	Time in days	Thickness(mm)	Drug Content(%)	Drug release(%)
1.	Initial (0 days)	0.02	98.14	96.56
2.	1 month(30days)	0.02	98.14	96.56
3.	3 months(90days)	0.02	98.13	96.55

CONCLUSION:

The comprehensive study on the formulation and evaluation of mucoadhesive buccal films highlights the successful development of an optimized formulation (F2) with superior physicochemical, mechanical, and drug release characteristics. The transparency of all formulations ensured stability, while F2 exhibited the lowest weight variation (43.56%), ensuring uniformity and reliability. Its thinness (0.02 mm), high folding endurance (110), and tensile strength (25.63 gm/mm²) indicate robust mechanical properties and flexibility, ideal for buccal application. The pH value of 6.8 aligns with buccal tissue compatibility, minimizing irritation risks. Additionally, the drug content of 98.14% and drug release of 95.56% demonstrated F2's efficacy in delivering the therapeutic agent efficiently.

Ex-vivo diffusion studies further corroborated F2's superior drug permeation performance, achieving 95.56% release at 10 minutes, surpassing all other formulations. Stability studies over 90 days affirmed the robustness of F2, maintaining its physical and chemical integrity without significant variations.

In conclusion, the optimized formulation (F2) proves to be a promising candidate for buccal drug delivery, combining stability, biocompatibility, mechanical strength, and efficient drug delivery. This study underscores the potential of mucoadhesive films as a patient-friendly and effective alternative for drug administration. Future work can focus on clinical evaluation and exploring other therapeutic agents for similar delivery systems.

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AUTHORS CONTRIBUTIONS:
All authors have contributed equally.

CONFLICTS OF INTERESTS:
All authors have declared no conflict of interest.

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