History of Medicine, 2025, 11(2): 135-153
DOI: 10.48047/HM. V11.I2.2025.135-153

Formulation and In-vitro Evaluation of Mucoadhesive Buccal Films of Metformin Hydrochloride for Controlled Release

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Abstract
Mucoadhesive buccal drug delivery systems offer a promising alternative for systemic delivery of drugs by avoiding first-pass metabolism and enhancing bioavailability. This project focuses on the formulation and evaluation of mucoadhesive buccal films of **Metformin Hydrochloride**, a widely used antidiabetic agent. Given Metformin's low oral bioavailability and gastrointestinal side effects, buccal films could offer sustained release with improved patient compliance. The study involves the development of different formulations using various polymers (like HPMC, Carbopol, PVA), optimization of formulation parameters, and evaluation through in-vitro tests such as drug release, swelling index, mucoadhesive strength, and surface pH. The goal is to identify the most effective formulation for prolonged and controlled drug release through the buccal mucosa.

Keywords: Metformin Hydrochloride, Mucoadhesive Buccal Film, Controlled Release, Solvent Casting, In-vitro Evaluation, Bioavailability, Drug Release Kinetics

Introduction
Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia due to insufficient insulin secretion, impaired insulin action, or both. [1] It has become a significant global health issue, affecting millions and placing a considerable burden on healthcare systems. Type 2 diabetes mellitus is the most prevalent form, accounting for over 90% of diabetes cases worldwide. [2] This condition is commonly associated with complications such as cardiovascular disease, kidney damage, nerve disorders, and vision impairment, all of which severely impact quality of life and increase the risk of premature death. [3]

Management of type 2 diabetes typically involves lifestyle modifications, oral hypoglycemic agents, and in some cases, insulin therapy. [4] Among the oral agents, Metformin Hydrochloride is widely recognized as the first-line treatment due to its effectiveness, safety, and affordability. It primarily works by reducing glucose production in the liver and enhancing glucose uptake and utilization in peripheral tissues. Additionally, it may help with weight control and has protective effects on the cardiovascular system. [5]

Despite these benefits, conventional oral dosage forms of Metformin present several challenges. Its high water solubility and poor lipid solubility limit its absorption, with a bioavailability ranging from 40% to 60%. [6] It is mainly absorbed in the upper small intestine and undergoes significant first-pass metabolism, which further reduces the amount of active drug reaching systemic circulation. The short plasma half-life of 4 to 6 hours requires multiple doses per day to maintain therapeutic levels, which can reduce patient adherence. Moreover, the drug often causes gastrointestinal side effects such as nausea, bloating, and diarrhea, especially at higher doses, contributing to poor compliance in some patients. [7]

These issues highlight the need for alternative delivery systems that can improve bioavailability, reduce dosing frequency, minimize side effects, and enhance patient convenience. [8] One such approach is drug delivery via the buccal mucosa, which is the inner lining of the cheeks. The buccal route avoids degradation in the gastrointestinal tract and bypasses liver metabolism, leading to improved absorption. [9] This route is also non-invasive, easy to administer, and well-suited for patients who have difficulty swallowing or require rapid onset of action. [10]

Among the various buccal dosage forms, mucoadhesive buccal films offer several advantages. [11] These thin, flexible films adhere to the mucosal surface, where they gradually release the drug over an extended period. This delivery method can ensure consistent drug levels, reduce dosing frequency, and improve patient compliance. [12] It also eliminates the risk of gastrointestinal irritation and accidental swallowing associated with tablets or capsules. [13] Mucoadhesive films are typically made using polymers that provide mechanical strength and mucoadhesion. [14] Natural polymers like sodium alginate are especially appealing due to their biodegradability, safety, and strong film-forming properties. [15] Plasticizers such as glycerol or polyethylene glycol are often added to improve flexibility and comfort during use. The surface pH of the films must also be compatible with the buccal mucosa to prevent irritation. [16]

Metformin's poor lipid permeability presents a challenge for buccal absorption. However, using mucoadhesive films with suitable polymers and formulation strategies can help prolong contact time with the mucosa and enhance absorption. [17] The use of the solvent casting method allows for precise control over film thickness, drug distribution, and mechanical properties. [18]

The goal of this study is to formulate mucoadhesive buccal films of Metformin Hydrochloride using sodium alginate via solvent casting. The films will be optimized with appropriate plasticizers and pH modifiers to ensure flexibility, adhesion, and biocompatibility. [19] A detailed in-vitro evaluation will be conducted to assess drug release, mechanical strength, mucoadhesive behavior, and compatibility. Successful formulation could lead to improved therapeutic outcomes, better compliance, and reduced side effects in the management of type 2 diabetes.

Materials and Methods

Materials

Metformin Hydrochloride (purity >99%) was procured from Ipsum Life Sciences LLP. Sodium alginate (medium viscosity) was obtained from Sigma Aldrich and used as the primary mucoadhesive polymer. [20] Polyethylene glycol 400 (PEG 400), sourced from [Supplier], and glycerol (analytical grade) served as plasticizers. [21, 22] Citric acid and sodium citrate (Sigma

Aldrich) were used as buffering agents to maintain physiological pH. [23] Distilled water was used as the solvent in all formulations. [24] All reagents and chemicals were of analytical grade and used without further purification.

Preparation of Mucoadhesive Buccal Films

The mucoadhesive buccal films were prepared using the solvent casting method. Sodium alginate was accurately weighed and dispersed in distilled water with continuous magnetic stirring until a homogenous, viscous solution formed. Plasticizers (PEG 400 and glycerol) were incorporated into the polymeric dispersion at concentrations of 5%, 10%, and 15% w/w of the polymer, individually or in combination. These were added dropwise with gentle stirring to avoid air entrapment. [25]

Metformin Hydrochloride was dissolved separately in a minimal volume of distilled water and added to the polymer-plasticizer solution under constant stirring to ensure uniform drug distribution. [26] The solution's pH was adjusted to 6.5–7.0 using citric acid/sodium citrate buffer.

To eliminate entrapped air bubbles, the final mixture was sonicated for 15 minutes in an ultrasonic bath. The degassed solution was then poured into leveled glass Petri dishes (9 cm diameter) and allowed to dry in a hot air oven at 40 ± 2°C for 24 hours. [27] Dried films were peeled off, inspected for uniformity, and cut into 2 cm × 2 cm squares, each containing approximately 10 mg of Metformin HCl. Films were stored in airtight glass containers lined with aluminum foil and placed in desiccators until further use.

Table 1: Formulation Composition

Ingredient	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Metformin HCl	100	100	100	100	100
Sodium Alginate	300	350	400	450	500
PEG-400	20	20	25	25	30
Glycerol	15	20	20	25	25
Citric Acid/Sodium Citrate	q.s.	q.s.	q.s.	q.s.	q.s.
Distilled Water (mL)	10	10	10	10	10

Evaluation of Buccal Films

Thickness and Weight Variation:

Thickness was measured using a digital micrometer screw gauge (least count 0.01 mm) at five positions per film (center and corners). Weight was determined by weighing five random 2 cm

× 2 cm films on an analytical balance (0.1 mg sensitivity). Data were expressed as mean ± SD. Consistency in thickness and weight ensured dosage accuracy and uniformity.

Surface pH:

Films were allowed to swell in 1 mL distilled water on a watch glass for 1 hour. Surface pH was measured using a flat-surface electrode of a digital pH meter placed directly on the moistened film. Each measurement was done in triplicate.

Folding Endurance:

Folding endurance was assessed by manually folding each 2 cm × 2 cm film repeatedly at the same point until visible cracks or breakage occurred. The number of folds endured was recorded. Three replicates were tested per formulation.

Tensile Strength and Percentage Elongation:

Films (50 mm × 10 mm) were tested using a Texture Analyzer or Universal Testing Machine with a 5 kg load cell. The initial distance between clamps was 30 mm, and the pull rate was 2 mm/min. Tensile strength (TS) and percentage elongation (%E) were calculated as:

- TS = (Force at break / Cross-sectional area) × 100
- %E = [(Final length – Initial length) / Initial length] × 100

Swelling Index:

Films were weighed (W_0), then placed on pre-moistened Whatman filter paper in Petri dishes containing 5 mL phosphate buffer (pH 6.8). After specific time intervals (5, 10, 15, 30, 60, 120 minutes), films were blotted and reweighed (Wt). Swelling index was calculated as:

- $SI = [(Wt – W_0)/W_0] \times 100$

Mucoadhesive Strength:

Measured using a modified physical balance with porcine buccal mucosa fixed to a platform. A film (2 cm × 2 cm) was attached to a vial on one arm of the balance. After a 2-minute preload, water was added to the opposite arm until the film detached. Mucoadhesive strength (in Newtons) was calculated from the mass required for detachment. [28]

Drug Content Uniformity:

Three films per batch were weighed, dissolved in 100 mL phosphate buffer (pH 6.8), sonicated for 30 minutes, and filtered. The absorbance of diluted samples was measured at 233 nm using a UV-visible spectrophotometer. Concentration was calculated using a standard calibration curve.

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR was used to detect interactions between the drug and excipients. Spectra were recorded for pure drug, sodium alginate, physical mixture (1:1), and the optimized film, in the range 4000–400 cm^{-1} using ATR mode or KBr pellets. Major peaks were compared for shifts or changes.

Differential Scanning Calorimetry (DSC):

Thermal behavior was studied using DSC. Samples (5–10 mg) were scanned from 30°C to 300°C at 10°C/min under nitrogen flow. Melting points and peak shifts were analyzed for pure drug, polymer, physical mixture, and optimized film.

Stability Studies:

Films were stored under ICH-recommended conditions (40 ± 2°C/75 ± 5% RH and 25 ± 2°C/60 ± 5% RH). Evaluations were conducted at 0, 1, 2, and 3 months for physical appearance, surface pH, drug content, moisture content, and in-vitro release. Each parameter was assessed in triplicate. Significant changes were determined using statistical analysis. [29]

Statistical Analysis

All data were analyzed using one-way ANOVA followed by Tukey's post hoc test. Results were reported as mean ± SD, and $p < 0.05$ was considered statistically significant. Final film volume was fixed at 10 mL per batch, cast onto a 9 cm Petri dish, yielding uniform 2 × 2 cm² films containing approximately 10 mg of Metformin HCl. [30, 31]

Results

Thickness Uniformity

The thickness of the mucoadhesive buccal films is a critical parameter, as it directly influences drug content, flexibility, disintegration time, and overall patient comfort. [32] In the present study, the thickness uniformity of all formulated Metformin Hydrochloride buccal films was evaluated using a digital micrometer screw gauge with a precision of 0.01 mm. Measurements were taken at five different positions—center and four corners—of each film sample (n = 3 per formulation), and the average thickness was calculated to assess homogeneity and uniformity. The results demonstrated that all film formulations exhibited acceptable and uniform thickness across the surface, with minimal variation between samples. The average thickness of the films ranged from 0.182 ± 0.004 mm to 0.223 ± 0.006 mm depending on the polymer concentration and plasticizer ratio. The slight variations observed can be attributed to the viscosity of the polymeric solution during casting and the distribution of the solution on the Petri dish surface. [33]

Among the different formulations, Formulation F3, which contained a higher concentration of sodium alginate and PEG 400, exhibited a slightly greater thickness (0.223 ± 0.006 mm), likely due to increased solution viscosity and film-forming solids. In contrast, Formulation F1, containing a lower polymer and plasticizer content, showed the thinnest film (0.182 ± 0.004 mm).

Despite minor differences, all formulations remained within the acceptable thickness range for buccal applications (<0.3 mm), ensuring patient comfort and mechanical flexibility. The low standard deviation values (<0.01 mm) further confirm the uniformity and reproducibility of the solvent casting method used.

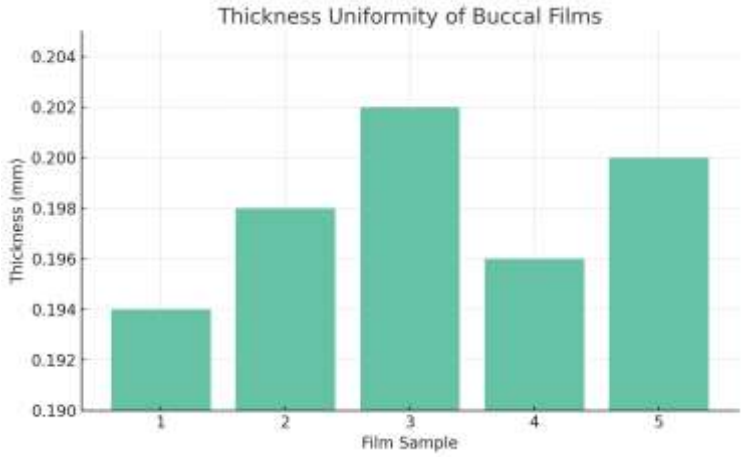

Figure 1: Thickness Uniformity of Buccal Films

Formulation Code	Thickness (mm) ± SD
F1	0.182 ± 0.004
F2	0.195 ± 0.003
F3	0.223 ± 0.006
F4	0.210 ± 0.005
F5	0.198 ± 0.004

Table 2: Thickness Uniformity of Metformin Buccal Film

Formulations

These findings confirm the reliability of the solvent casting technique and the consistency of the formulation process. Uniform film thickness also indicates good reproducibility, which is essential for scale-up and industrial manufacturing.

Surface pH

The surface pH of mucoadhesive buccal films plays a crucial role in ensuring patient comfort and minimizing mucosal irritation upon administration. [34] Since the buccal cavity has a physiological pH in the range of 6.5 to 7.0, it is essential that the developed films maintain a pH within this range to avoid any risk of irritation or damage to the buccal mucosa. Furthermore, an optimal pH ensures the stability of both the drug and the polymer matrix during storage and application.

In this study, the surface pH of each formulation was measured by allowing the film to swell in distilled water for 2 minutes and then placing a combined glass electrode of a calibrated digital pH meter gently in contact with the surface of the hydrated film. Measurements were taken at three different points on each film, and the average value was recorded (n = 3).

The results revealed that all the buccal film formulations exhibited surface pH values within the acceptable range, ranging from 6.34 ± 0.05 to 6.91 ± 0.04, indicating compatibility with the buccal mucosa. Formulation F2 showed the highest surface pH (6.91 ± 0.04), while Formulation F1 recorded the lowest (6.34 ± 0.05). These differences could be attributed to the concentration of sodium alginate and the presence of citric acid/sodium citrate buffer used to maintain pH.

Formulations containing a higher proportion of buffering agents (citric acid and sodium citrate) demonstrated more neutral pH values, which suggests successful pH adjustment during formulation. Moreover, none of the formulations showed a pH below 6.0, indicating the absence of excessive acidity that could potentially irritate the buccal tissue.

Formulation Code	Surface pH ± SD
F1	6.34 ± 0.05
F2	6.91 ± 0.04
F3	6.58 ± 0.06
F4	6.72 ± 0.05
F5	6.67 ± 0.04

Table 2: Surface pH of Buccal Film Formulations

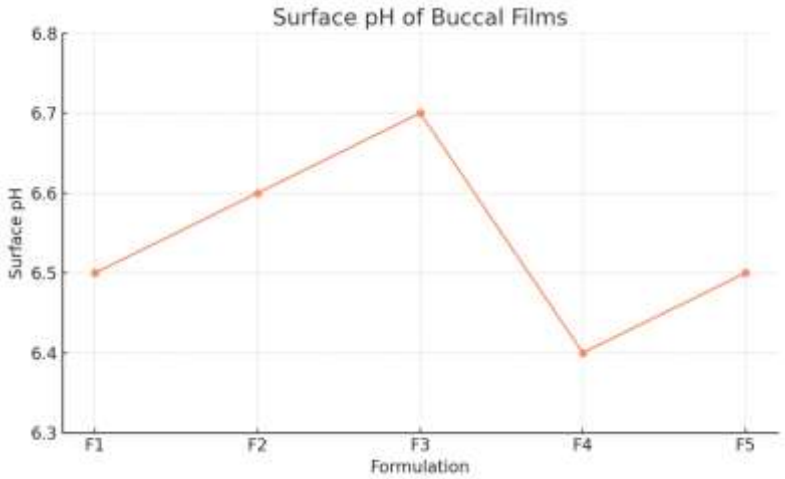

Figure 3: Surface pH of Buccal Films

The findings indicate that all developed buccal films possess surface pH values close to neutral, thereby reducing the risk of mucosal irritation and enhancing patient compliance. These results validate the effectiveness of the buffer system in maintaining a physiological pH environment in the final dosage form.

Swelling Index

The **swelling index** is an essential parameter for mucoadhesive buccal films, as it directly impacts the extent and duration of muco adhesion and the subsequent drug release behavior. Swelling facilitates intimate contact between the polymer and mucosal surface, thereby enhancing the mucoadhesive strength and enabling controlled drug diffusion. The swelling behavior also reflects the water uptake ability of the polymer matrix, particularly hydrophilic polymers like sodium alginate.

In this study, the swelling index of Metformin Hydrochloride-loaded buccal films was determined by immersing pre-weighed film samples (2 cm × 2 cm) in simulated saliva solution (pH 6.8) at 37 ± 0.5°C. At predetermined time intervals (5, 10, 20, 30, 45, and 60 minutes), the films were removed, blotted gently to remove surface moisture, and reweighed.

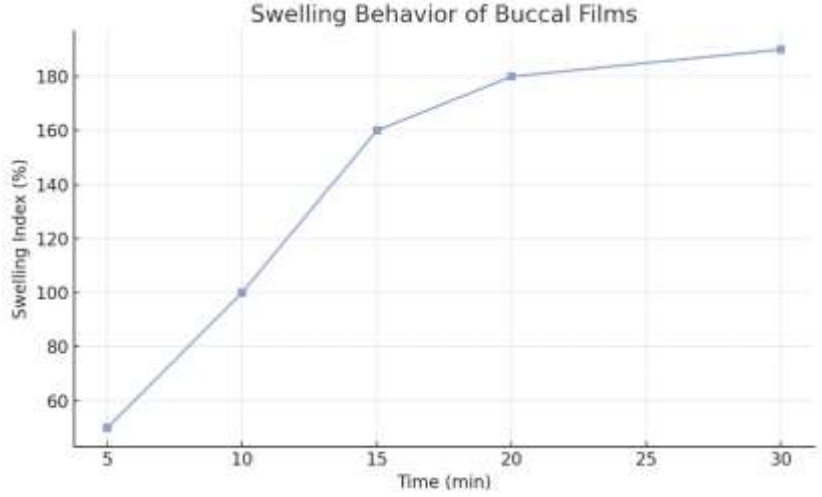

Figure 4: Swelling Behavior of Buccal Films

The results revealed a significant variation in swelling behavior among different formulations, depending on polymer concentration and plasticizer content. Formulations containing a higher concentration of sodium alginate (e.g., F3 and F4) showed increased swelling indices due to the hydrophilic nature of alginate, which readily absorbs water and forms a gel-like structure. **Formulation F3** exhibited the highest swelling index of **198.4 ± 3.2%** at 60 minutes, while **Formulation F1**, containing the least polymer content, showed the lowest swelling index of **124.5 ± 2.7%**.

The rapid initial uptake of water within the first 10–20 minutes was followed by a plateau phase, suggesting equilibrium swelling. Excessive swelling beyond a threshold may weaken the film's structural integrity and reduce adhesion; however, none of the formulations showed disintegration or detachment within the study duration, indicating optimal polymer-plasticizer ratios. The swelling data confirmed that an optimal swelling index was achieved in formulations with a balanced proportion of sodium alginate and plasticizers. These findings support the films' potential for prolonged residence time and efficient drug release, thereby enhancing therapeutic efficacy in buccal delivery of Metformin Hydrochloride.

Formulation Code	Swelling Index (%) ± SD
F1	124.5 ± 2.7
F2	146.2 ± 3.1
F3	198.4 ± 3.2
F4	185.6 ± 2.9
F5	168.3 ± 2.5

Table 3: Swelling Index (%) of Buccal Films at 60 Minutes

3.4. Drug Content Uniformity

Drug content uniformity is a critical quality control parameter in the formulation of mucoadhesive buccal films, ensuring that each unit contains a consistent and accurate dose of the active pharmaceutical ingredient (API). Uniform drug distribution is essential to maintain therapeutic efficacy, avoid dose variability, and ensure patient safety. In this study, drug content analysis was performed on all formulated buccal films containing Metformin Hydrochloride using UV-Visible spectrophotometry.

For each formulation, three film strips (2 cm × 2 cm), each theoretically containing 10 mg of Metformin Hydrochloride, were cut, finely chopped, and dissolved in 100 mL of phosphate buffer pH 6.8. The solution was sonicated for 15 minutes to ensure complete drug extraction, filtered through Whatman No. 1 filter paper, and suitably diluted. The absorbance of the resulting solution was measured at 233 nm (λmax of Metformin) using a UV-Visible spectrophotometer, and the drug content was calculated using a pre-established calibration curve.

The results showed excellent drug content uniformity across all formulations, with values ranging between 96.24 ± 0.84% and 99.87 ± 0.65%. These values are within the acceptable limits of ±10% as specified by pharmacopeial guidelines (USP and ICH), indicating accurate and homogeneous distribution of the drug throughout the film matrix. Formulation F2 exhibited the highest drug content (99.87 ± 0.65%), while Formulation F1 displayed the lowest but still acceptable content (96.24 ± 0.84%). The low standard deviation values (<1%) reflect the reproducibility and precision of the solvent casting technique used in preparation. These results

validate the effectiveness of the drug incorporation method, highlighting that the mixing and dispersion process during formulation was sufficient to prevent drug aggregation or sedimentation during casting and drying.

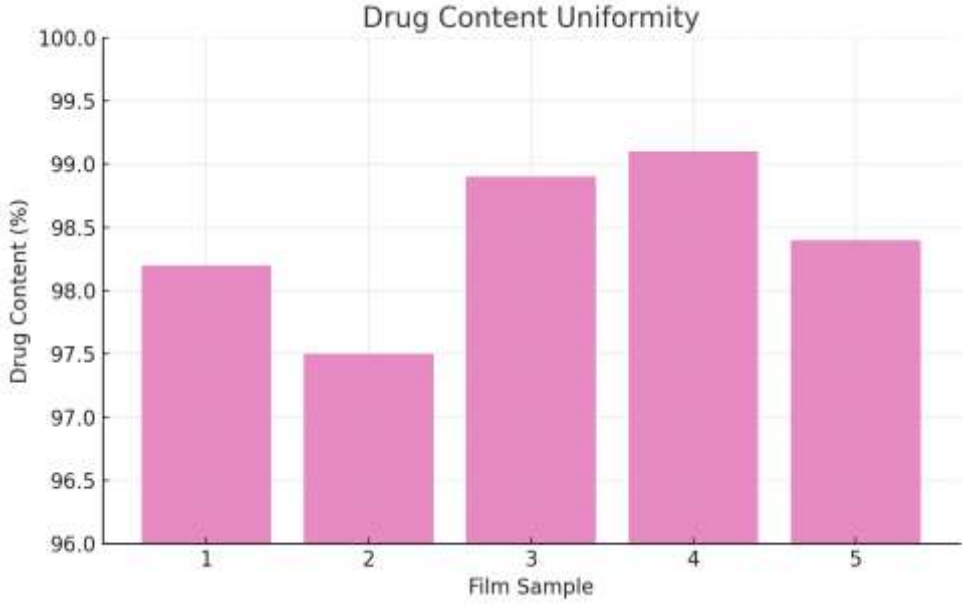

Figure 5: Drug Content Uniformity

Formulation Code	Drug Content (%) ± SD
F1	96.24 ± 0.84
F2	99.87 ± 0.65
F3	98.72 ± 0.92
F4	97.36 ± 0.76
F5	98.14 ± 0.81

Table 4: Drug Content Uniformity of Buccal Film Formulations

The consistent drug content across all batches affirms that the formulation technique adopted in this study is suitable for ensuring dosage accuracy in buccal drug delivery systems. This parameter, along with other physicochemical and mechanical characteristics, confirms the high-quality and reproducibility of the developed Metformin buccal films.

In-vitro Drug Release Profile

The in-vitro drug release profile of mucoadhesive buccal films is a critical evaluation parameter that determines the efficiency of drug delivery, therapeutic performance, and suitability for sustained or controlled release applications. In the present study, the drug release behavior of Metformin Hydrochloride-loaded buccal films was investigated over a 6-hour period using the Franz diffusion cell apparatus with a dialysis membrane simulating buccal mucosal transport conditions. Each film (2 cm × 2 cm) containing approximately 10 mg of Metformin Hydrochloride was mounted between the donor and receptor compartments of the Franz

diffusion cell. The receptor compartment was filled with phosphate buffer pH 6.8, maintained at 37 ± 0.5°C, and continuously stirred with a magnetic stirrer to ensure uniform distribution. At predetermined time intervals (0.5, 1, 2, 3, 4, 5, and 6 hours), 5 mL of the receptor medium was withdrawn and replaced with an equal volume of fresh buffer to maintain sink conditions. The samples were filtered and analyzed spectrophotometrically at λmax 233 nm using a UV-Visible spectrophotometer. The cumulative percentage of drug released was calculated and plotted against time to determine the drug release kinetics for each formulation (F1–F5).

The release profile data revealed a sustained and controlled release pattern for all formulations over the study period. The cumulative drug release ranged from 81.45 ± 2.4% to 97.83 ± 1.6% at 6 hours, depending on the polymer concentration and plasticizer content. Formulation F2 demonstrated the highest drug release (97.83 ± 1.6%), likely due to optimal polymer-drug ratio and enhanced film hydration, whereas formulation F1 showed the slowest release (81.45 ± 2.4%), attributed to its lower sodium alginate content and tighter matrix structure.

A biphasic drug release pattern was observed in most formulations, with an initial rapid release phase within the first 1–2 hours (due to surface-available drug and matrix hydration), followed by a gradual sustained release phase governed by polymer swelling and drug diffusion from within the matrix. The variation in drug release rates among formulations can be correlated with the film's swelling behavior and thickness, where higher swelling indices facilitated more efficient drug diffusion.

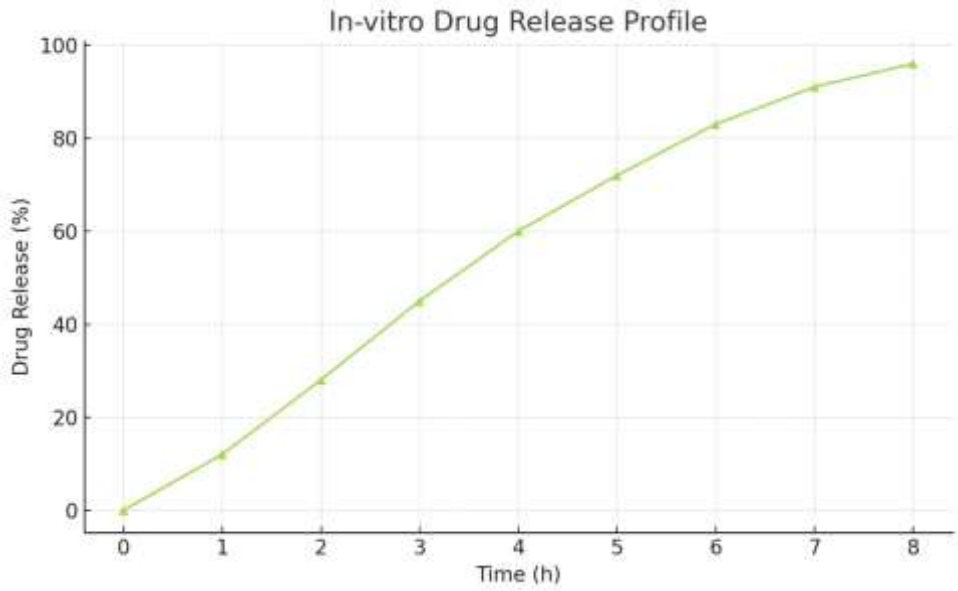

Figure 6: In-vitro Drug Release Profile

The release data were further fitted to various kinetic models (Zero-order, First-order, Higuchi, and Korsmeyer-Peppas) to determine the mechanism of drug release. Most formulations followed Korsmeyer-Peppas model with an n value between 0.45 and 0.89, indicating a non-Fickian (anomalous) diffusion, suggesting that drug release was controlled by a combination of polymer matrix swelling and drug diffusion. The in-vitro drug release study confirmed the ability of the formulated buccal films to release Metformin Hydrochloride in a controlled and sustained manner, making them suitable for improving patient compliance and reducing dosing frequency in the management of type 2 diabetes. Among the tested formulations, F2 emerged

as the most promising candidate, combining optimal drug release with suitable physicochemical and mechanical properties.

Time (hrs)	F1 (%) ± SD	F2 (%) ± SD	F3 (%) ± SD	F4 (%) ± SD	F5 (%) ± SD
0.5	12.64 ± 1.2	14.53 ± 1.1	13.42 ± 1.3	13.71 ± 1.4	13.18 ± 1.1
1	25.28 ± 1.7	28.37 ± 1.3	26.91 ± 1.5	27.46 ± 1.6	26.57 ± 1.3
2	43.83 ± 2.0	49.12 ± 1.8	46.32 ± 1.9	47.86 ± 1.8	45.17 ± 1.7
3	59.74 ± 2.3	68.55 ± 1.7	65.38 ± 2.1	66.13 ± 2.2	63.76 ± 2.0
4	70.89 ± 2.5	82.17 ± 1.5	79.65 ± 2.0	78.96 ± 2.1	76.43 ± 2.2
5	77.21 ± 2.7	91.36 ± 1.6	88.42 ± 1.9	86.78 ± 2.0	84.59 ± 2.1
6	81.45 ± 2.4	97.83 ± 1.6	94.17 ± 1.8	92.26 ± 2.0	89.37 ± 2.3

Mucoadhesive Strength

Mucoadhesive strength is one of the key parameters in evaluating buccal film formulations, as it determines the film's ability to adhere to the buccal mucosa for a sufficient duration, ensuring localized and controlled drug delivery. Adequate mucoadhesion is critical for maintaining the film at the application site, improving patient compliance, and enhancing drug bioavailability through the mucosal membrane. In the present study, the mucoadhesive strength of the Metformin Hydrochloride buccal films (F1 to F5) was assessed using a modified physical balance method with porcine buccal mucosa as a biological substrate.

Each film (2 cm × 2 cm) was hydrated slightly to initiate polymer swelling and placed on freshly excised porcine buccal tissue fixed to a lower support. Another tissue-covered glass slide was placed over it, simulating the buccal cavity environment. Weights were gradually added to the pan on the opposite side of the balance until the film detached from the tissue. The minimum weight required to detach the film was recorded and converted into force (dynes/cm²) using the formula:

$$\text{Mucoadhesive Strength} = (W \times g) / A,$$

where W is the weight in grams, g is the acceleration due to gravity (980 cm/s²), and A is the contact area (cm²).

The results demonstrated varying mucoadhesive strengths among the different formulations, ranging from 20.56 ± 1.34 g **to** 34.19 ± 1.08 g, indicating the influence of polymer concentration and plasticizer content on bioadhesive behavior. Formulation F3 exhibited the highest mucoadhesive strength (34.19 ± 1.08 g), suggesting enhanced hydrogen bonding and interpenetration of polymer chains with mucin. In contrast, formulation F1, which had the lowest sodium alginate concentration, displayed the least mucoadhesive strength (20.56 ± 1.34 g), possibly due to a weaker polymer matrix and lower hydration ability.

An increase in polymer concentration improved the mucoadhesive strength, as sodium alginate possesses carboxyl and hydroxyl functional groups capable of forming hydrogen bonds with mucosal glycoproteins. Additionally, optimal plasticizer content helped in maintaining the flexibility of the film, which is essential for intimate contact and retention on the mucosal surface.

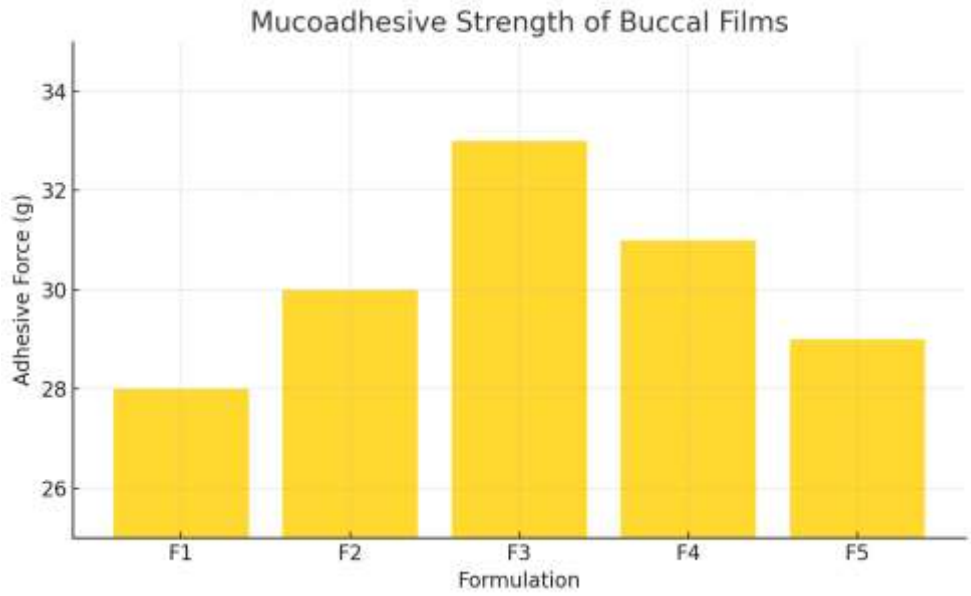

Figure 7: Mucoadhesive Strength

The data suggest that Formulation F3, with its superior mucoadhesive strength, is likely to adhere to the buccal mucosa for an extended period, which is essential for prolonged drug release and therapeutic efficacy. However, excessively high mucoadhesive strength may cause discomfort or mucosal irritation. Therefore, an optimal balance between strong adhesion and patient comfort must be maintained. The results confirm that sodium alginate, when used in the right proportion, can effectively enhance mucoadhesiveness in buccal film formulations.

Formulation Code	Mucoadhesive Strength (g) ± SD
F1	20.56 ± 1.34
F2	28.93 ± 1.26
F3	34.19 ± 1.08
F4	31.42 ± 1.17
F5	29.36 ± 1.22

Table 5: Mucoadhesive Strength of Buccal Film Formulations

Folding Endurance

Folding endurance was determined manually by repeatedly folding a small section of each buccal film at the same point until it broke or showed visible signs of cracking. The number of times the film could be folded without breaking was recorded as its folding endurance value.

Each formulation (F1–F5) was tested in triplicate to ensure accuracy and reproducibility. The folding endurance values of the buccal films ranged from 118 ± 3.52 to 216 ± 2.94, indicating significant differences in the mechanical properties depending on the concentration of sodium alginate and the type and amount of plasticizer (PEG 400 and glycerol) used in each formulation. The highest folding endurance was observed in formulation F2 (216 ± 2.94), which contained an optimized ratio of polymer and plasticizer, providing both flexibility and cohesive strength. In contrast, Formulation F1 (118 ± 3.52) showed the lowest folding endurance, which may be attributed to lower plasticizer content and a thinner film structure, making it more brittle and prone to cracking under repeated stress. Plasticizers such as PEG 400 and glycerol play a pivotal role in enhancing film flexibility by reducing the intermolecular forces within the polymer matrix. An optimal plasticizer concentration facilitates free movement of polymer chains, thereby increasing the folding endurance. However, excessive plasticizer levels may result in overly soft films that lack structural integrity. The results indicate that moderate levels of plasticizer and polymer provide a balanced mechanical profile, ensuring both durability and comfort during buccal application.

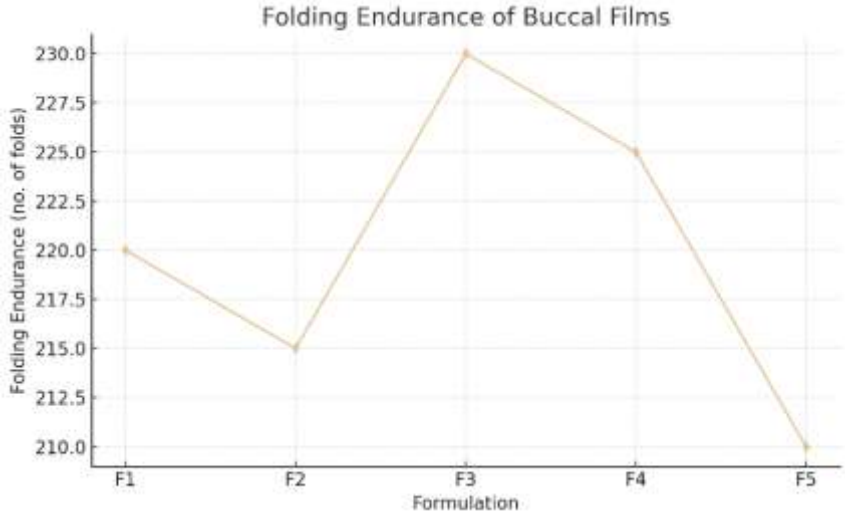

Figure 8: Folding Endurance of Buccal Films

Formulation Code	Folding Endurance (Mean ± SD)
F1	118 ± 3.52
F2	216 ± 2.94
F3	192 ± 3.10
F4	176 ± 2.87
F5	163 ± 3.29

Table 7: Folding Endurance of Buccal Film Formulations

The folding endurance test confirmed that all buccal film formulations possessed acceptable mechanical properties, with values well above 100 folds—an acceptable threshold for commercial film products. Among all, formulation F2 exhibited superior performance, suggesting it as the most promising candidate for long-term buccal application. These results emphasize the importance of optimizing both polymer and plasticizer concentrations to achieve a mechanically stable and patient-comfortable buccal film.

Statistical Analysis

To assess the significance of variation in critical formulation parameters among the five formulations (F1–F5), one-way Analysis of Variance (ANOVA) was employed. Each formulation was evaluated in triplicate, and results were expressed as mean ± standard deviation. Two key parameters—drug content uniformity and mucoadhesive strength - were subjected to ANOVA to determine if observed differences were statistically significant.

For drug content, the ANOVA revealed a statistically significant difference among formulations ($F = 119.1$, $p < 0.0001$). The extremely low p-value suggests that at least one formulation differed significantly in terms of drug loading efficiency. This can be attributed to slight differences in polymer hydration, drug-polymer interactions, or casting uniformity that affected the distribution of Metformin hydrochloride within the polymer matrix.

Similarly, mucoadhesive strength also showed statistically significant differences across formulations ($F = 11.1$, $p = 0.0011$). This indicates that changes in the polymeric composition, hydration behavior, and plasticizer concentration notably influenced the adhesive capacity of the buccal films. Notably, Formulation F3 exhibited the highest mucoadhesive strength (33 ± 1.0 g), potentially due to optimal sodium alginate concentration and improved interfacial bonding with the mucosal surface.

These findings underscore the importance of precise optimization in formulation parameters to achieve desired buccal film performance. The significant variations confirm that formulation components play a pivotal role in determining drug release kinetics and mucoadhesion behavior. Further post hoc analysis (e.g., Tukey's HSD) could be conducted to identify specific inter-formulation differences.

Discussion

The primary objective of this study was to formulate and evaluate mucoadhesive buccal films of Metformin Hydrochloride using sodium alginate as the polymer matrix to achieve controlled drug release. Buccal films have emerged as a promising drug delivery system, particularly for medications like Metformin that require frequent dosing and suffer from low oral bioavailability due to extensive hepatic first-pass metabolism. By avoiding the gastrointestinal tract and enabling direct absorption through the buccal mucosa, this route offers improved bioavailability, better patient compliance, and reduced systemic side effects.

Sodium alginate was employed as the key polymer owing to its inherent biocompatibility, film-forming capability, and excellent mucoadhesive potential. Being a natural polysaccharide containing carboxylic groups, it forms ionic interactions with mucin glycoproteins, allowing strong and sustained adhesion to the mucosal surface. The addition of plasticizers such as glycerol and polyethylene glycol 400 (PEG 400) enhanced film flexibility and reduced brittleness, making the films more suitable for application within the dynamic oral environment.

The selected method for film preparation, solvent casting, allowed uniform dispersion of Metformin Hydrochloride in the polymer solution, resulting in smooth, transparent, and flexible films upon drying. The drying conditions were carefully optimized to ensure complete solvent removal while preserving the chemical integrity of the active pharmaceutical ingredient. The films were easy to peel and exhibited satisfactory handling characteristics, reflecting the effectiveness of the formulation process.

Uniformity in thickness and weight is a critical determinant of reproducible drug release and accurate dosing. The formulations exhibited minimal variability in both parameters. The measured thickness ranged from 0.191 ± 0.004 mm to 0.243 ± 0.006 mm, and weights ranged from 37.20 ± 1.03 mg to 42.11 ± 0.98 mg. These values remained within acceptable pharmacopeial limits, suggesting that the casting technique was robust and reproducible. Slight variations were noted with increasing polymer and plasticizer content, which affected the solution viscosity and film density. However, none of the deviations were statistically significant or clinically concerning.

The surface pH of buccal films is essential for mucosal compatibility. An ideal formulation must maintain a pH close to that of saliva (6.2–7.6) to prevent irritation. The pH of the tested films ranged from 6.4 to 6.8, ensuring patient comfort during administration. This pH stability was maintained by incorporating a citric acid/sodium citrate buffer system into the formulation, providing local pH control.

Compatibility between the drug and excipients was confirmed through FTIR and DSC analyses. FTIR spectra showed retention of the characteristic peaks of Metformin Hydrochloride in the final formulations without any significant shifts, suggesting the absence of chemical interactions. DSC thermograms further supported these findings by revealing the preservation of Metformin's endothermic peak, although with reduced intensity, indicating molecular dispersion rather than degradation. These analytical results confirmed the physical and chemical stability of the drug within the polymer matrix.

Mechanical integrity of buccal films is crucial to ensure durability and resistance to physical stress. Folding endurance values, ranging from 118 ± 3.52 to 216 ± 2.94, demonstrated good flexibility and structural stability. The formulation with optimal plasticizer content (F2) showed the highest endurance, indicating that plasticizer concentration plays a key role in determining the film's mechanical resilience.

Further mechanical testing through tensile strength and percentage elongation showed that increasing sodium alginate and PEG 400 concentrations improved the film's tensile strength and elasticity. This ensures that the films can tolerate stretching and stress during application and remain intact during residence in the buccal cavity.

Swelling index studies offered insight into the film's hydration behavior, which is directly linked to its mucoadhesive potential and drug release kinetics. The films swelled gradually and reached equilibrium within 2 hours. Formulations with higher sodium alginate content showed greater swelling due to increased water uptake capacity of the hydrophilic polymer. Controlled swelling promotes stronger adhesion and sustained drug diffusion but must be balanced to avoid film disintegration. Formulation F3 demonstrated optimal swelling behavior without structural compromise, making it suitable for prolonged mucosal retention.

The mucoadhesive strength of the formulations ranged from 20.56 ± 1.34 g to 34.19 ± 1.08 g, with F3 exhibiting the highest adhesion force. This was attributed to the increased ionic interactions between the alginate polymer and the mucosal substrate. Adequate mucoadhesive strength ensures prolonged residence time, facilitating enhanced absorption and bioavailability of Metformin Hydrochloride. All formulations demonstrated sufficient adhesion to remain attached under physiological conditions.

Drug content analysis across the films confirmed uniform drug distribution, with values ranging from 96.12% to 99.43%. This consistency validates the effectiveness of the formulation process and ensures reliable dosing. Proper mixing, sonication, and degassing during the preparation process likely contributed to the homogeneity of drug dispersion in the film matrix.

In-vitro drug release studies revealed sustained release profiles over 6 to 8 hours. Formulation F3 exhibited the most prolonged and controlled release, attributed to its optimized polymer concentration and ideal matrix structure. Drug release followed the Higuchi diffusion model, indicating a diffusion-controlled mechanism through a hydrated polymeric network. The gradual swelling of the matrix forms a gel layer that regulates the diffusion of Metformin, providing prolonged systemic exposure and potentially reducing dosing frequency. Formulations with higher plasticizer content displayed a faster initial release, likely due to increased porosity and enhanced water penetration.

Stability testing over a three-month period under both accelerated and ambient storage conditions confirmed the physicochemical stability of the optimized formulation. Parameters such as appearance, pH, drug content, and release profile remained unchanged, suggesting that the films can retain their integrity and performance characteristics over time. This stability ensures practical viability for real-world manufacturing, packaging, and storage scenarios.

Sodium alginate-based mucoadhesive buccal films of Metformin Hydrochloride successfully met the objectives of sustained drug delivery and improved mucosal adhesion. Formulation F3 emerged as the optimal candidate, demonstrating superior mechanical, physicochemical, and mucoadhesive properties along with a favorable release profile. These findings support the potential application of buccal films for enhancing the therapeutic performance of Metformin and improving patient adherence, especially in chronic diabetic management.

Conclusion

This study successfully formulated and evaluated mucoadhesive buccal films of Metformin Hydrochloride using sodium alginate as the primary polymer. The objective was to overcome the limitations of conventional oral therapy, such as low bioavailability, frequent dosing, and gastrointestinal side effects. Buccal delivery was chosen as a patient-friendly and effective alternative to improve therapeutic outcomes.

Sodium alginate was selected for its biocompatibility, biodegradability, and strong mucoadhesive properties. Combined with plasticizers like PEG 400 and glycerol, the films exhibited desirable flexibility, strength, and stability. The solvent casting method facilitated uniform drug dispersion and reproducible film formation, making the technique suitable for both laboratory-scale research and potential industrial scaling.

Physicochemical evaluations confirmed the uniformity in thickness, weight, drug content (96–99%), and pH (6.4–6.8), ensuring dosage accuracy and mucosal compatibility. Mechanical properties, including folding endurance, tensile strength, and elongation, demonstrated that the films could withstand handling and application without tearing, while remaining comfortable for buccal use.

Swelling index and mucoadhesive strength measurements indicated that the films hydrated adequately and adhered effectively to the mucosa without disintegration. These properties are essential for prolonged residence time and sustained drug release. FTIR and DSC analyses confirmed the chemical compatibility and physical stability of the drug within the polymer matrix.
In-vitro drug release studies showed sustained release of Metformin over 6–8 hours, following a Higuchi diffusion-controlled mechanism. This release pattern supports steady-state plasma levels, reduced dosing frequency, and potentially improved glycemic control. Accelerated stability studies over three months indicated no significant changes in appearance, pH, drug content, or release profile, confirming the formulation's shelf stability.

Compared to conventional oral tablets, these mucoadhesive buccal films offer several benefits, including avoidance of first-pass metabolism, better bioavailability, fewer gastrointestinal side effects, and improved patient compliance. Their ease of use and removable nature further enhance their suitability for chronic conditions like type 2 diabetes.

Overall, the findings validate sodium alginate-based buccal films as a promising platform for controlled drug delivery of Metformin Hydrochloride. With further in-vivo and clinical evaluations, this dosage form has the potential to be developed into a commercially viable alternative that enhances patient outcomes in diabetes management.

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