

Formulation and Characterization of Metformin Buccal films for T2DM

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Abstract:

The drug delivery platform known as buccal films provides systemic medication access to precise target locations through the elimination of hepatic first-pass effect. The drug delivery format provides added convenience for patients during medication use. Metformin hydrochloride (Met) shows limited bioavailability as an antidiabetic drug because it has high solubility yet poor permeability. The present study aimed to develop metformin buccal films which would leverage the drug's therapeutic capabilities. The metformin buccal films were developed through solvent-casting methodology which incorporated polyvinyl alcohol (PVA) as polymer base material. Developing the formulation involved adding PEG 400 as plasticizer and sodium starch glycolate as disintegrant. Different ratios of PVA and SSG resulted in six distinct formulations (F1 to F6). Mannitol served as both a sweetening agent and a dissolution enhancer for the formulation. Buccal film evaluations included assessments of weight variation together with thickness measurements and folding endurance investigations as well as surface pH determinations and content uniformity testing and thermal stability measurements and tensile strength and percentage of elongation assessments. In vitro dissolution testing revealed that the disintegration time for all formulations remained beneath 60 minutes because of the disintegrant's influence. The drug release from Formulation F4 reached 99 % within a period of 60 minutes.

Keywords — sodium starch glycolate, solvent-casting method, drug-delivery system, controlled release.

I. INTRODUCTION

Drug delivery systems require current pharmaceutical research due to drawbacks found in traditional drug administration practices. Drug absorption requires understanding how drug characteristics combine with formulation elements alongside physiological interactions to determine absorption rates thus requiring the development of efficient drug carriers. Through this method drug availability would improve at the target location to deliver fast pharmacological effects. The systems improve patient adherence with treatment plans

particularly for elderly patients and young children (1).

Oral transmucosal drug delivery operates using three different types of oral mucosa known as sublingual, gingival, and buccal. sublingual, gingival, and buccal. Individuals receive direct systemic circulation access to therapeutic agents which absorbs through the oral cavity while bypassing hepatic first-pass metabolism and gastrointestinal breakdown (2,3). The buccal drug delivery route has gained the most research attention due to its distinct benefits against other oral transmucosal approaches. The perfect patch needs to exhibit elasticity while maintaining

strength sufficient to resist mouth stress throughout daily use. A successful buccal drug delivery system needs to demonstrate both adequate adhesive properties and enough strength to maintain position inside the oral cavity throughout the required drug release window. The patch should maintain moderate swelling to reduce any discomfort caused to the user. The field of mucoadhesive buccal delivery systems has introduced new formats including adhesive tablets together with films, patches, disks, strips, ointment, gel, and creams (4).

The disintegrating system of oral thin films (OTFs) functions through immediate absorption by saliva before adhering to the application site. These products rapidly disintegrate through oromucosal absorption to provide medication delivery. The application of this method has allowed numerous drugs previously susceptible to GI tract degradation to be successfully administered (5-7). The method enables patients with emesis and dysphagia and other swallowing difficulties to obtain medicine through small water amounts. Research groups emphasize that oral transmucosal drug delivery shows promising future potential over regular oral drug-delivery systems in this application context (8-10).

The researchers developed thin buccal films of metformin HCl using polyvinyl acetate (PVA) polymer for oral disintegrating systems as the study's main objective. Due to its pharmacological profile and physical properties metformin emerged as the drug selection standard for this study. Metformin shows limited therapeutic effectiveness due to its 50%–60% poor bioavailability and five-hour biological half-life and extensive first-pass metabolism associated with its primary absorption through the proximal small intestine (11). Buccal films offer an effective solution to overcome metformin's current therapeutic limitations through their ability to deliver drugs systemically. Researchers selected PVA polymer for its three key features including biocompatibility and biodegradability in addition to its strong mucoadhesive property. The addition of sodium starch glycolate (SSG) at various concentrations enhances both bioavailability and disintegration capabilities of OTFs designed for use in saliva.

New drug delivery systems represent a rapid and efficient method to achieve therapeutic applications according to research (12,13).

II. MATERIALS AND METHODS

The research utilized Atom Pharma's analytical grade metformin HCl derivatives from their Gujrat facility. Merck and S.D. Fine Chemicals provided Analytical Grade Polyvinyl alcohol, PEG-400 and SSG. All utilized chemicals and reagents during this study maintained analytical grade standards.

III. PRE-FORMULATION STUDIES

Different pre-formulation validation procedures including melting point analysis and solubility tests alongside partition coefficient assessment and UV-Vis spectrophotometric measurements along with an FT-IR drug interaction assessment were performed to validate the assay of metformin hydrochloride. IP 1996 provided the basis for preparing the dissolution medium at pH 6.8.

IV. PREPARATION OF ORAL BUCCAL FILMS

Six distinct metformin oral dissolving film formulations (F1 through F6) were developed by combining metformin HCl with polyvinyl alcohol (PVA) and sodium starch glycolate (SSG) and mannitol and PEG-400 through solvent-casting techniques (14).

A solution containing polyvinyl acetate (PVA) and PEG 400 with warm distilled water needed four hours of soaking to allow the polymer to swell. A mixture of Metformin HCl received addition to the stirring aqueous polymeric solution. After metformin HCl addition to the polymeric solution the formulation process includes mannitol for sweetening and solubilization followed by sodium starch glycolate for its disintegrating function. We spread the solution onto a plastic Petri dish before and dried it at room temperature for 24 hr. Positioned strips were inspected for flaws by obtaining two-by-two centimeter sections from the Petri dish. Research analysts then stored the film samples inside desiccators for forthcoming evaluation. The optimization process involved changing concentrations of film forming polymers alongside superdisintegrants (Table 1).

Table 1: Formulation composition

Ingredients	F1	F2	F3	F4	F5	F6
Metformin HCl (in mg)	45	45	45	45	45	45
Polyvinyl alcohol (in mg)	150	250	350	150	250	350
PEG 400 (in mg)	200	200	200	200	200	200
SSG (in mg)	30	35	40	40	30	35
D-Mannitol (in ml)	4	4	4	4	4	4
Distilled water (in mL)	qs	qs	qs	qs	qs	qs

V. CHARACTERIZATION OF BUCCAL FILMS

A. Mass uniformity and thickness

Three independent films from different batches (2X2 cm² in size) underwent individual weighing on an electronic balance. The researchers determined the films weight by averaging their measurements. We measured film thickness using Vernier caliper at three different points and calculated an average value from those measurements.

B. Uniform drug content of the buccal films

An 8-hour shaking process with 100 mL of phosphate buffer at pH 6.8 was used to determine the drug concentration in the films. Five milliliters of this solution received dilution up to 25 mL before being filtered through a 0.45 µm Whatman filter paper. UV spectrophotometer measured the drug content through wavelength absorption at 234 nm. Each experiment was performed three times with the research team taking the mean outcome.

C. Determination of surface pH

Surface pH measurements of films hold significant importance because extreme acid or base concentrations can lead to mucosal surface irritation. A 40 mL sample of phosphate buffer solution (pH 6.8) at 37°C±5°C enabled the films to soak for 2 hours. A pH meter was used to verify the pH

measurement on the surface of buccal films. for 2 hours.

VI. EVALUATION OF PHYSICAL STABILITY

D. Folding endurance

The number of times researchers folded a single buccal film (15) characterized its folding durability. Researchers cut the films into (2×2 cm²) dimensions before manually twisting them at one axis until achieving a 180° angle before breaking occurred. The test measured folding endurance by counting how many times a film could endure before tearing. For each film formulation, three repeats were performed and the average value was determined.

E. Tensile strength and percentage elongation studies of buccal films

A 2 X 2 cm² Metformin HCl formulation strip without bubbles or physical flaws was positioned 3 cm from two clamps. A cardboard applied to the clamp surface with double-sided tape protected the film from damage caused by clamp grooves. The researchers applied weights to the bottom clamp of the strips during measurement in order to break the film. The researchers measured force as the films broke. Three repeat of data collection yielded average results for analysis.

Tensile strength = Force at break/ Initial cross-sectional area of film (cm²)

F. Percentage elongation

We used a pulley system to pull the prepared Metformin HCl formulations. The pan received incremental weights to enhance pulling force until the film ruptured. The overall elongation measurement relied on tracking the pointer's movement until the film broke on the graph paper. Analysis of percent elongation relied on this specific mathematical formula. Percentage elongation functions as both an effective tool for measuring film elasticity and strength.

% elongation = (Increase in length/ Original length)*100

G. Percent hydration

A method was developed to measure film swelling through assessing percentage hydration. An

examination piece (1 x 1 cm) was placed on a stainless-steel mesh where laboratory workers determined its initial weight (W1). A stainless-steel mesh with the film was immersed in 10 mL of simulated saliva (pH 6.2) buffered solution at 37°C. Research carried out simulated saliva solution by mixing potassium di hydrogen phosphate (12mM) with sodium chloride (40 mM) and adding calcium chloride (1.5 mM) while sodium hydroxide adjusted the pH to 6.2. Researchers carefully collected film samples throughout specific duration periods before weighing them and then recording their weight (W2).

$$\text{Percentage hydration} = \frac{W2 - W1}{W1} \times 100$$

H. In vitro Drug release studies

Drug release tests of Metformin HCl buccal films was performed through Keshary-Chein diffusion cell analysis. The studies took place within phosphate buffer at 37°C under pH 6.8 conditions. Parchment paper underwent 1-hour soaking in phosphate buffer before experiencing air drying. The research apparatus positioned the film between donor and receptor sections with parchment paper covering it. The researcher combined both clamped compartments. The receptor compartment received phosphate buffer solution while a magnetic stirrer kept it in motion. The experiment collected buffer samples at times 0.5,1,2,3,4,5,6,7, and 8 h for replacement with equal amounts of buffer solution. The researchers used a UV spectrophotometer to analyze drug releases at 234 nm from their samples.

I. Stability Study

A stability assessment took place on the optimized formulation's film. The aluminum-wrapped patch underwent stability testing in 40°C/75% RH and 30°C/65% RH environments of stability chambers containing packed PVC containers for a month. The storage stability period included evaluations of physical properties as well as in vitro drug release testing and drug content measurements for the entire 30-day storage period.

VII. RESULTS AND DISCUSSION

The drug-polymer combinations displayed proper mixing behavior in addition to excellent surface

characteristics. Fourier transform infrared spectra was used to compare drug-polymer compatibility and disintegrant interactions. The stretching frequency positions for essential functional groups in each formulation (F1–F6) matched those observed for the pure drug-polymer when no disintegrant compounds were used. The study results demonstrated that drug-polymer chemical interactions with disintegrants were not detected (Figure 1).

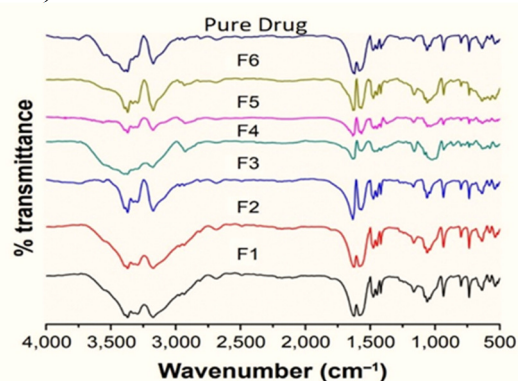


Figure 1: FTIR study outcomes

The measured melting point of Metformin hydrochloride averaged 225 ± 1.0 °C across all trials. Metformin hydrochloride demonstrated excellent water solubility and DMSO solubility and slight solubility in ethanol as well as petroleum ether and acetone were identified as its insoluble solvents. The UV scanner operated within the wavelength range of 200-400 nm, in UV-Vis spectrophotometer. The measured absorption maximum point occurred at 234 nm and agreed with the reference spectrum. using (figure 2).

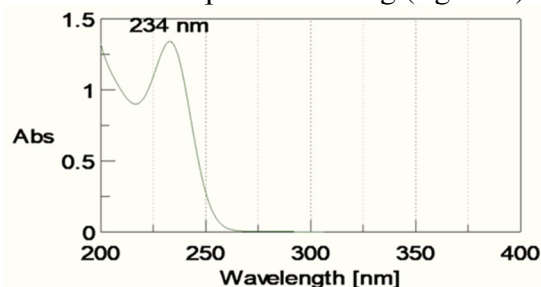


Figure 2: UV-Vis spectra of Metformin hydrochloride 0.38 ± 0.2 value was found for partition coefficient of Metformin hydrochloride.

J. Evaluation of Buccal Films

The laboratory evaluations of films showed similar results to standard limiting values that were

presented in table 2 for mass uniformity, thickness, folding endurance, surface pH, % elongation and TS measurements.

Table 2: Evaluation parameters of buccal films

Parameters	F1	F2	F3	F4	F5	F6
Thickness (mm)	0.96±0.01	0.95±0.01	0.93±0.01	0.88±0.02	0.92±0.02	0.94±0.02
Weight Variation(mg)	24±1.52	23±2.08	26±2.38	22±2.38	27±2.38	28±2.38
Surface pH	7.2	6.8	6.9	6.8	6.7	6.9
Folding Endurance	285±2.02	297±2.34	291±2.21	314±2.41	302±2.56	299±2.47
Tensile strength (N/cm ²)	2.89±0.25	3.20±0.24	2.32±0.27	3.57±0.25	2.67±0.19	2.78±0.23
% Elongation	8.33±0.25	16.88±0.25	22.43±0.25	33.33±0.25	25.46±0.25	28.21±0.25

Upon visual examination it was found that the films prepared had no surfaces cracks. These were cut into 2*2 cm² pieces. The weight measurements of films ranged between 22 to 28 mg with a thickness distribution between 0.88 to 0.96 mm. The thickness of the films remained unchanged regardless of the disintegrant amounts within the formulations. The folding endurance tests exhibited values ranging from 285 to 314 times with F4 demonstrating the highest flexibility. This range indicates optimal flexibility. All formulations maintained a neutral surface pH range between 6 and 7 which indicates they would not irritate the buccal cavity.

The buccal films gained flexibility and elasticity assessments through TS and % elongation measurements which revealed differences due to multiple disintegrant ratios as shown in Table 2. An ideal buccal film requires high values for percent elongation and tensile strength parameters (16). The TS measurement alongside % elongation results fell between 3.57 to 2.32 (N/cm²) and 33.33% to 8.33%.28.

The drug-content measurements showed each formulation maintained drug levels above 90% indicating these formulations could continue for

additional studies. Outcomes enlisted in table 3 under.

Table 3: Drug content study

Formulation	Observation
F1	93.24 ±0.94
F2	94.06 ±0.54
F3	92.69 ±1.03
F4	98.87 ±0.21
F5	95.69 ±1.03
F6	97.24 ±0.46

Swelling index was determined by using percent hydration. The relative moisture uptake behavior of polymers directly influences the formulation characteristics by showing how they maintain their structure during moisture absorption processes. The percentage of swelling measurements existed in a specified range between 33±0.79 to 46±0.53 (see table 4).

Table 4: % Hydration or Swelling Index

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	6.9±0.82	8.34±0.98	11.45±0.87	14.21±0.76	12.46±0.92	13.63±0.92
10	8.87±0.98	10.34±0.65	17.43±0.48	17.45±0.84	18.34±0.49	16.45±0.49
15	12.45±0.94	12.56±0.71	21.56±0.64	23.12±0.63	24.56±0.83	22.45±0.83
20	16.45±0.42	17.34±0.86	23.67±0.98	26.45±0.87	27.23±0.94	25.56±0.94
25	21.45±0.84	19.45±0.56	28.45±0.95	32.45±0.59	29.35±0.67	28.45±0.67
30	27.34±0.76	23.45±0.47	31.45±0.49	38.46±0.91	33.46±0.59	35.56±0.59
45	30.46±0.54	28.56±0.63	35.57±0.71	43.56±0.55	37.23±0.63	36.34±0.63
60	32.56±0.79	34.56±0.71	37.34±0.64	46.23±0.53	42.56±0.69	41.45±0.69

Findings using metformin from all formulations (F1–F6) revealed their drug release data shown in Table 5. The designed formulations exhibited immediate drug release properties to maintain a reduced contact duration in the oral cavity which minimized discomfort for patients.

Table 5: Percentage in-vitro release

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	6.9±0.82	8.34±0.98	11.45±0.87	14.21±0.76	12.46±0.92	13.63±0.92
10	8.87±0.98	10.34±0.65	17.43±0.48	17.45±0.84	18.34±0.49	16.45±0.49
15	12.45±0.94	12.56±0.71	21.56±0.64	23.12±0.63	24.56±0.83	22.45±0.83
20	16.45±0.42	17.34±0.86	23.67±0.98	26.45±0.87	27.23±0.94	25.56±0.94
25	21.45±0.84	19.45±0.56	28.45±0.95	32.45±0.59	29.35±0.67	28.45±0.67
30	27.34±0.76	23.45±0.47	31.45±0.49	38.46±0.91	33.46±0.59	35.56±0.59
45	30.46±0.54	28.56±0.63	35.57±0.71	43.56±0.55	37.23±0.63	36.34±0.63
60	32.56±0.79	34.56±0.71	37.34±0.64	46.23±0.53	42.56±0.69	41.45±0.69

0	0	0	0	0	0	0
10	25.67	20.06	22.42	28.17	18.72	18.72
20	38.82	30.21	33.58	41.53	27.60	28.60
30	52.84	42.41	46.48	55.59	39.13	40.13
40	67.23	56.31	61.05	70.32	51.77	52.77
50	82.94	71.95	77.29	85.43	68.29	67.29
60	98.35	91.07	96.99	99.98	90.22	92.22

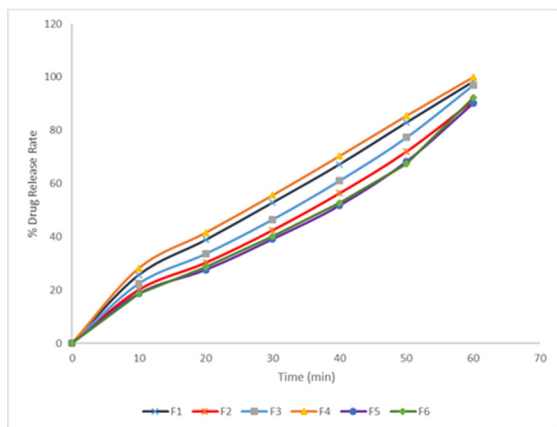


Figure 3: % Drug release profile of various formulations

The *in vitro* dissolution study results demonstrated that all tested formulations delivered their medication quickly as required. F4 achieved 99% drug release during a 60-minute time period. The other formulations surpassed a drug release threshold of 90% during a 60-minute period. Disintegrants used at multiple ratios caused variations in the release pattern of the formulations. Table 5 displays the cumulative % drug release data which also appears as Figure 3. The selected formulation for accelerated stability testing at 40°C/75% RH and 30°C/65% RH operated for one month was F4.

Table 6: Results of Stability study

Sampling time	Weight variation	Folding endurance	Thickness	Surface pH	Drug content
Initial	22±2.38	314±2.41	0.88±0.02	6.8	98.87±0.21
1month	20±1.45	301±1.34	0.85±0.11	7.1	98.70±0.32

After 1 month, the stability test on this particular patch design revealed minor alterations in drug content measurements and weight measurements and folding strength and *in-vitro* release dynamics which supported the stated requirements.

VIII. CONCLUSION

The presented research demonstrates that fast-dissolving metformin buccal films stand out as an effective systemic delivery method which bypasses hepatic first-pass metabolism. The different parameters evaluated demonstrate standard-conforming results while varying very minimally across formulations F1 to F6. The produced buccal films demonstrated suitable mechanical qualities through their measured TS and % elongation measurements. The immediate release of metformin occurred from these formulations without compromising the drug's therapeutic dosage as it was delivered by the buccal route. This test showed formulation F4 as the best immediate release formulation because of the combined disintegrant effect within this specific composition. The best method to predict drug *in vivo* bioavailability depends on *in vitro* dissolution testing results. These film types show promise for emergency use based on their future utility potential when stability is enhanced along with durability and efficacy improvements.

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