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Research Article

Formulation and Evaluation of Buccal Mucoadhesive Bilayer Tablets of Apixaban

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Abstract

Background: Apixaban is a factor Xa inhibitor, an anticoagulant; that exhibits low oral bioavailability (around 50%) as a result of its extensive first-pass metabolism, which highlights the need for improved delivery methods.

Aim: This research is carried out to formulate and evaluate a bilayered buccal tablet formulation of Apixaban that adheres to mucosal surfaces.

Materials and Methods: Apixaban was obtained from (NATCO Pharma Limited-Chemical Division, Hyderabad); The specified qualities were achieved in formulations (F1 to F9) by varying the amounts of polymers such as sodium alginate, hydroxypropyl methylcellulose (HPMC K4M), and Carbopol (934p). To make mucoadhesive bilayered buccal tablets, the direct compression method was employed. Tablets were evaluated for physicochemical properties (thickness, weight, hardness, drug content), mucoadhesive strength, in vitro drug release, and stability. Fourier-Transform Infrared (FTIR) spectroscopy assessed drug-excipient compatibility.

Results: The optimized formulation (F7), with its 20 mg of Carbopol, was emerged from a series of testing. Excellent drug uniformity (approximately 99%), and strong adhesive properties. Drug release testing showed nearly 88% release within 180 minutes, following the first-order and Higuchi diffusion model (R^2 = 0.9904). FTIR confirmed no drug-excipient interactions, and stability studies at 40 °C / 75 % RH demonstrated physical and chemical integrity over three months.

Conclusion: The formulated buccal mucoadhesive bilayer tablets provide a potentially effective, non-invasive route for apixaban administration that circumvents hepatic metabolism and enhance bioavailability.

Keywords: Apixaban, Bilayered Buccal Tablet, Mucoadhesion, Direct compression method, Carbopol.

1) INTRODUCTION

A buccal mucoadhesive bilayer tablet is a drug delivery system designed to adhere to the inner lining of the cheek (buccal mucosa) through a special adhesive polymer, consisting of two distinct layers where one layer contains the active drug meant for absorption.[1]

While the second layer acts as a barrier (backing layer) to prevent premature release and ensures the drug is delivered directly into the bloodstream, bypassing the digestive system, potentially leading to improved bioavailability and faster onset of action compared to traditional oral tablets.[2]

The bio-adhesive polymer in the tablet layer directly interacts with the mucous membrane of the cheek, allowing the tablet to firmly adhere and release the drug gradually over a prolonged period.[3]

When the tablet comes into contact with the buccal mucosa, the bio-adhesive layer rapidly hydrates, forming a gel-like structure that adheres to the mucosa. As the tablet dissolves, the API is released and absorbed through the buccal mucosa, providing a systemic or local therapeutic effect.[4]

Thrombosis is a serious condition where one or more blood clots (thrombus) in the blood vessels or chamber of the heart. When this happens, the clot can block blood flow where it formed, or it can break loose and travel elsewhere in the body. If a moving clot gets stuck in a critical area, it can cause life-threatening conditions like stroke and heart attack.[5]

The two main types of thrombosis are: Arterial thrombosis: This is when a blood clot forms in an artery. Arterial thrombosis is the most common cause of heart attacks and strokes. Venous thrombosis: This is when a blood clot forms in a vein. Venous thrombosis is the most common cause of a pulmonary embolism (blood clot in the lung).[6]

Apixaban is a factor Xa inhibitor, an anticoagulant. It works by decreasing the clotting ability of the blood and

helps preventing harmful clots from forming in the blood vessels. It is used to treat or prevent deep venous thrombosis, a condition in which harmful blood clots (thrombus) form in the blood vessels of the heart and legs.[7] The literature review highlights the significant benefits of APIXABAN in the management of Prevention of venous thromboembolic events (VTE) and Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF).[8]

The present study aims to perform pre-formulation studies, to develop an analytical method of UV determination and standard calibration curve for the drug, to study the drug-excipient compatibility, to design and formulate buccal bioadhesive bilayer tablets of Apixaban, selection of optimized bilayer tablets by direct compression method, to perform the different post-compression in-vitro tests of the tablets, including its mucoadhesive properties, swelling behavior, and drug release kinetics. And to perform the stability studies of the optimized dosage form.

2) MATERIALS AND METHODS:

2.1 COLLECTION OF DRUG AND EXCIPIENTS: Apixaban (NATCO Pharma Limited-Chemical Division, Hyderabad); Sodium Alginate, Carbopol 934P, Ethyl Cellulose, Mannitol (SDFCL, s.d. fine-chem limited); HPMC K4M, PVP K30, Magnesium stearate (Otto kemi); Sucralose (Kanbo Biochemical Tech, Co., Ltd).

2.2 PREFORMULATION STUDIES:

ORGANOLEPTIC PROPERTIES:

Using descriptive vocabulary, the drug's color, smell, taste, and texture are assessed.

SOLUBILITY ANALYSIS:

In order to find the saturated solubility, the drug is added to an overabundance of methanol or ethanol in a 50 ml volumetric flask. After that, for a specific amount of time—say, 24 hours—the flask is shaken on a rotatory shaker that is set to 50 rpm and 25ºC.

We collect, filter, and dilute the samples at regular intervals. Next, we measure the absorbance at 280 nm to find the concentration. [9]

MELTING POINT DETERMINATION:

We utilize the Melting/Boiling point instrument to find out how hot the drug becomes.

It is possible to transport the medicine via a capillary tube to a device that measures melting points, and then heat the combination until it melts.

The melting point of a medicine can be determined, in part, by monitoring the temperature range in which its physical state changes.[10]

SPECTROSCOPIC STUDIES:

DETERMINATION OF λ MAX OF APIXABAN: Apixaban standard stock solution was prepared by dissolving 10 mg of Apixaban in 10 ml of 6.8 pH phosphate buffer to obtain a concentration of 1,000 µg/mL. The solution was analyzed in a Shimadzu UV spectrophotometer in the wavelength of range of 200-400 nm. The wavelength maxima (λmax) for the pure drug was determined as the wavelength at which maximum absorbance were obtained.[11]

CALIBRATION CURVE OF APIXABAN:

Preparation of Standard Stock solution, working standard and dilutions:

- Solubilizing 100 mg of Apixaban in 100 ml of 6.8 pH phosphate buffer produces stock solution-I with a concentration of 1000 µg/ml.
- The second stock solution (working standard) has a concentration of 100 µg/ml, which was reached by taking 1 ml of the first stock solution and adding 10 ml of 6.8 pH phosphate buffer to the volume.
- The stock solution-II that was previously indicated is used to make concentrations of 5, 10, 15, 20, 25, and 30 µg/ml. [12]
- **Scanning:** The UV scan is taken between 280nm.

DRUG-EXCIPIENTS COMPATIBILITY STUDY: FTIR studies

The drug's stability and effectiveness are greatly affected by the excipients used. FTIR (Fourier-transform infrared spectrophotometer) techniques is used to study the physical and chemical interactions between the medication and the excipients.[13,14] The samples are scanned between the range of 4000 to 400 cm^{-1}

2.3 FORMULATION DESIGN OF MUCOADHESIVE BUCCAL BILAYERED TABLET OF APIXABAN:

Before adding the excipients, polymer, and medication, measured everything out precisely according to the batch formula. With the exception of ethyl cellulose, all ingredients must be sieved and mixed in ascending weight order. A tablet punching machine is used to pre-compress each 200 mg mixture of the manufactured formulation into a single-layered, flat-faced 9 mm tablet. Ethyl cellulose powder, with a dosage of 100 mg, is then added to the second layer. It follows the compression of the bilayer buccal tablet.[15,16]

TABLE 1: FORMULATION DESIGN OF BILAYERED BUCCAL TABLETS OF APIXABAN

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid dispersion (1:2)	40	40	40	40	40	40	40	40	40
Sodium Alginate	20	30	40	-	-	-	-	-	-
HPMC K4M	-	-	-	20	30	40	-	-	-
Carbopol 934p	-	-	-	-	-	-	20	30	40
PVP K30	10	10	10	10	10	10	10	10	10
Mannitol	124	114	104	124	114	104	124	114	104
Sucralose	2	2	2	2	2	2	2	2	2
Magnesium stearate	3	3	3	3	3	3	3	3	3
Titanium dioxide	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Vanilla flavour	1	1	1	1	1	1	1	1	1
Ethyl cellulose (mg)	100	100	100	100	100	100	100	100	100
Total (mg)	300	300	300	300	300	300	300	300	300

Figure 1: Prepared formulations of bilayered buccal tablets (F1 to F9)

CHARACTERISTICS OF BILAYER TABLET

POST-COMPRESSION PHYSICOCHEMICAL EVALUATION

1) APPEARANCE: A bilayer tablet can be visually distinguished by its size, colour, shape, surface texture, odour, and presence or lack of taste.

2) WEIGHT VARIATION TEST: Get the exact weight of twenty pills. Find out how many tablets weigh around. We compared the average tablet weight to the weight of each individual tablet.[17]

TABLE 2: IP LIMITS FOR AVERAGE WEIGHT OF TABLETS.

S. No.	Average weight of tablet	Percentage
1.	80 mg or less	± 10%
2.	More than 80mg and less than 250mg	± 7.5%
3.	250 mg or more	± 5%

3) THICKNESS: Thickness of tablet is important for uniformity of tablet size. Thickness is measured using vernier calipers. It is determined by checking ten tablets from each batch. It is expressed in mm.[18,19,20]

4) HARDNESS TEST: How sturdy a tablet is while kept, transported, or handled before usage is dependent on its hardness. The tablet's hardness can be determined using the Monsanto hardness tester. Use ten tablets per batch for hardness testing; report results in Kg/cm2.[21,22,23]

5) FRIABILITY TEST: This test determines how well the tablets will withstand abrasion while they are packed, handled, and transported. Twenty tablets are placed in the Roche friabilator and spun at 25 rpm for four minutes after they have been weighed. The disparity in mass is shown as a percentage. Ideally, it should be between 0.5 and 1 percent. [24,25,26]

$$\%friability = (W_1-W_2)/W_1 \times 100$$

Where, W_1= weight of tablets before test

W_2 = weight of tablets after test

6) DRUG CONTENT: To determine the amount of medication contained in each tablet, six tablets were extracted from each formulation that was developed. Mix 100 millilitres of pH 6.8 phosphate buffer solution with the powdered drug, which is equivalent to one tablet's weight, and agitate the mixture for 10 minutes. After the solution was diluted to the correct concentration, it was filtered through a 0.45µ membrane filter. A UV-Visible spectrophotometer was used to measure its absorbance, with a pH 6.8 phosphate buffer serving as a blank.[27]

7) SURFACE pH STUDY: Measuring the buccal pills' surface pH levels allowed to test them for possible in vivo harmful effects. The goal of the treatment was to keep the surface pH close to neutral, since acidic or alkaline pH levels might irritate the buccal mucosa. The tablet was allowed to expand for two hours at room temperature after being mixed with 15 ml of phosphate buffer (pH 6.8) in a petri plate. It was possible to determine the surface pH after the electrodes had been equilibrated with the tablet surface for one minute. [28]

8) MUCOADHESION TEST: The following is the setup for determining the mucoadhesive strength utilizing modified physical balancing with buccal mucosa and the provided apparatus.[29,30]

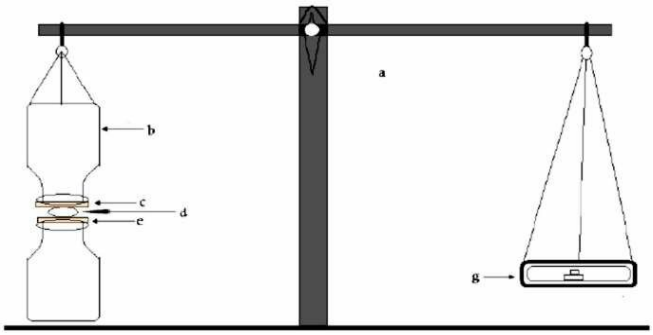

Figure 2: Modified physical balance

9) SWELLING INDEX: The formed tablets were added to a petri dish along with 15 mL of phosphate buffer solution (pH 6.8). At 1,2,3,4,5, and 6 hour intervals, the formed buccal tablets were weighed separately. After removing the tablets from the petri dishes, any residual water was filtered out using filter paper. Then, the tablets were weighed again (W2) and the results were computed.[31]

$$S.W = (W_2- W_1) / W_1 \times 100$$

10) *In vitro* DRUG RELEASE STUDIES: The USP XXIV dissolution apparatus type II is used to conduct in vitro drug release experiments. In this apparatus, 900 ml of dissolution media is kept at 37±0.5 ºC for 1 hour while being spun at 75 rpm in an appropriate dissolving medium. At regular intervals, remove 5 ml of the sample and replace it with an equivalent volume of drug-free dissolving fluid. Following which the samples were filtered through a 0.45µ membrane filter. The drug release in each sample were examined using a UV Spectrophotometer at 280 nm after appropriate dilution.[32]

Dissolution test apparatus	USP II (Paddle)
Speed	50 rpm
Time interval	0.5, 1, 2, 4, 6, 8, 10,12h
Medium used	Phosphate buffer pH 6.8
Temperature	37 ± 0.5 ^{O}C.

11) KINETIC STUDIES: In order to determine the release mechanism of the optimized formulation, the data obtained was fitted into the zero, first, higuchi and peppas model and its release mechanism was studied. The regression coefficient R2 value nearer to 1 indicates the model best fits the release mechanism.[33,34]

Zero order release rate kinetics: plot of drug release vs time and is linear.

$$F = K_0t$$

First order release rate kinetics: plot of log cum percent of drug vs time.

$$Log (100-F) = kt$$

Higuchi release model: plot of cum percent drug release vs SQRT

$$F = k_2 t^{1/2}$$

Korsmeyer and Peppas release model: plot of log percent of drug release vs log time.

$$Mt / M\infty = K tn$$

12) STABILITY STUDIES: Typically, the long, intermediate, and accelerated conditions are the ones that undergo these kinds of investigations. In order to ascertain the quality of an active pharmaceutical ingredient and to gather data in support of it, this study

is evaluated under a number of environmental conditions, including temperature, humidity, and light relative to time. Additionally, it is useful for determining the appropriate storage conditions, retest period, and shelf life of pharmaceutical ingredients and compounded medicinal products.[35]

As previously mentioned for accelerated stability conditions, the final formulation is typically placed in an environmental stability chamber at a temperature of 40°C ± 2°C and a relative humidity of 75± 5% for a week. After that, samples are taken at 30, 60, and 90 day intervals and analyzed for their physical properties.[36,37]

3) RESULTS AND DISCUSSION:

3.1 Preformulation Studies:

a. Organoleptic properties

TABLE 3: IDENTIFICATION TEST DATA OF APIXABAN

S. No	Properties	APIXABAN
1.	State	Solid
2.	Color	White to pale yellow
3.	Odor	Odorless
4.	Taste	Bitter
5.	Appearance	Crystalline powder

b. Melting point:

TABLE 4: MELTING POINT DATA

Drug	Reference Range	Observed Range
APIXABAN	238-240°C	238°C

c. Solubility analysis:

TABLE 5: SOLUBILITY ANALYSIS DATA OF APIXABAN

Ratios	Solubility in mg/ml
Pure drug (APIXABAN)	0.029 mg/ml
SD- 1:1	0.295 mg/ml
SD- 1:2	**0.398 mg/ml**
SD- 1:3	0.373mg/ml

d. Calibration curve:

TABLE 6: UV-SPECTROSCOPIC METHOD OF ANALYSIS OF APIXABAN

Drug	λ max
APIXABAN	280nm

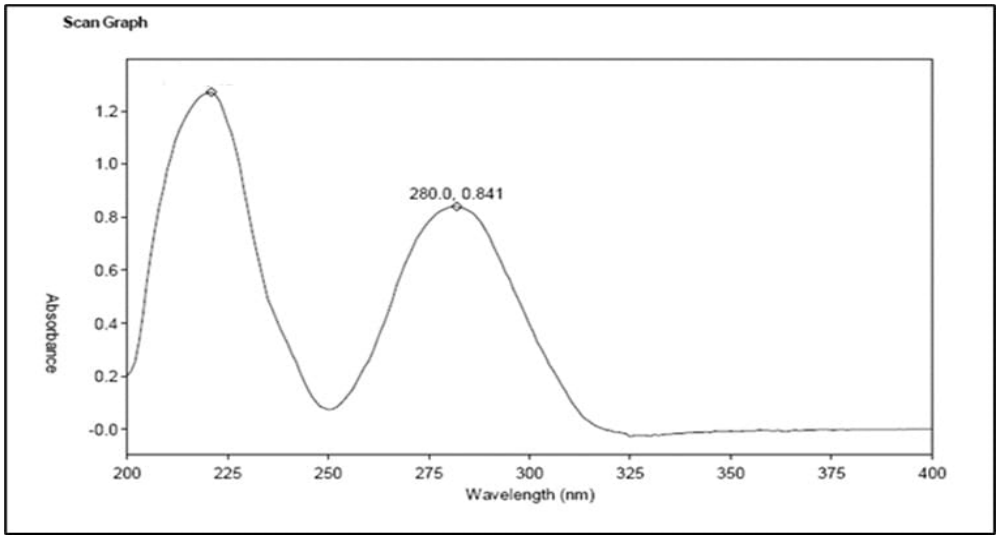

Figure 3: Lambda max of APIXABAN (280nm)

Table 7: CALIBRATION CURVE OF APIXABAN

Concentration (µg/ml)	Absorbance ±SD
0	0
5	0.151±0.010
10	0.295±0.011
15	0.422±0.014
20	0.545±0.015
25	0.684±0.019
30	0.810±0.071

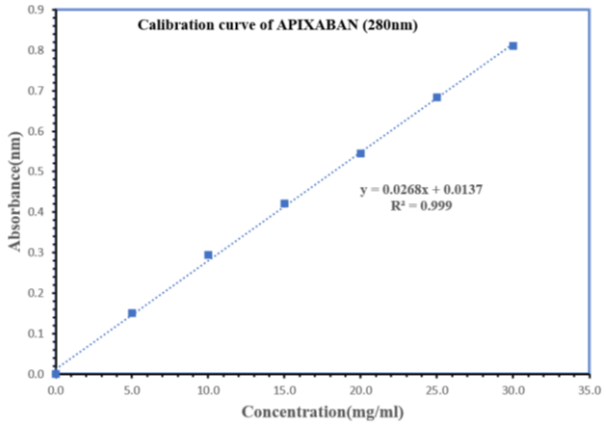

Figure 4: CALIBRATION CURVE of APIXABAN (280nm)

Observation: The physicochemical parameters of the medicine were examined, including its solubility and melting point, which were shown to be within acceptable limits. Additionally, the standard calibration graph demonstrated strong linearity, with a R^2 of 0.999, suggesting that the drug complies with ''Beers lambert's'' law.

DRUG- EXCIPIENT COMPATIBILITY STUDIES:

FTIR ANALYSIS:

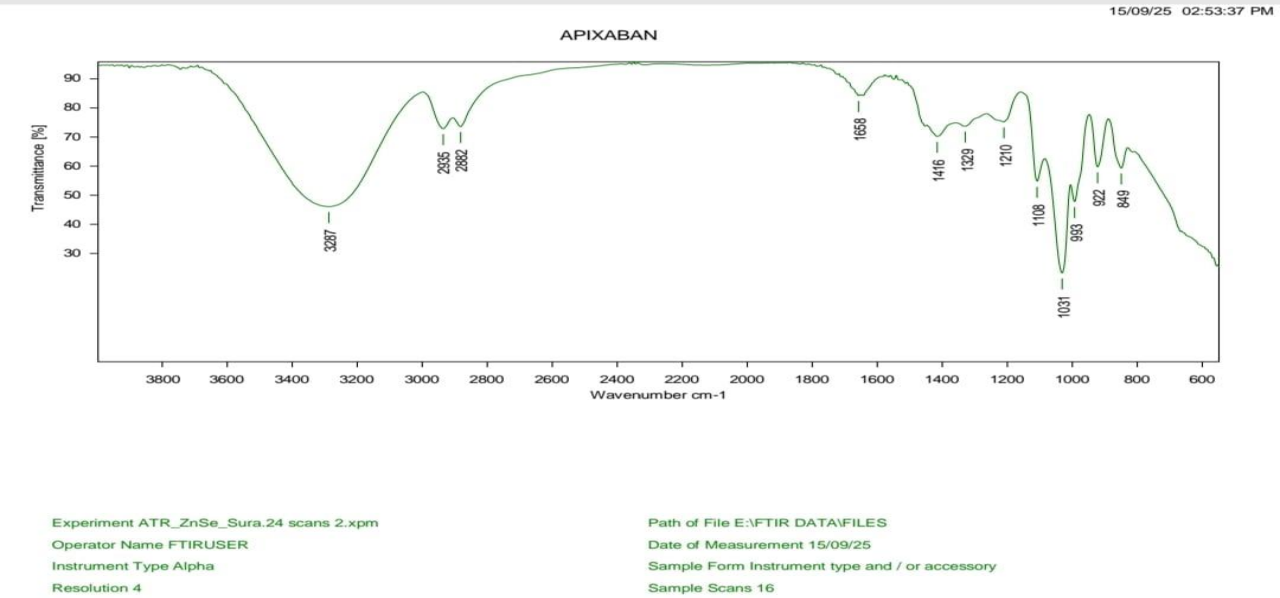

Figure 5: FTIR analysis of APIXABAN (Pure drug)

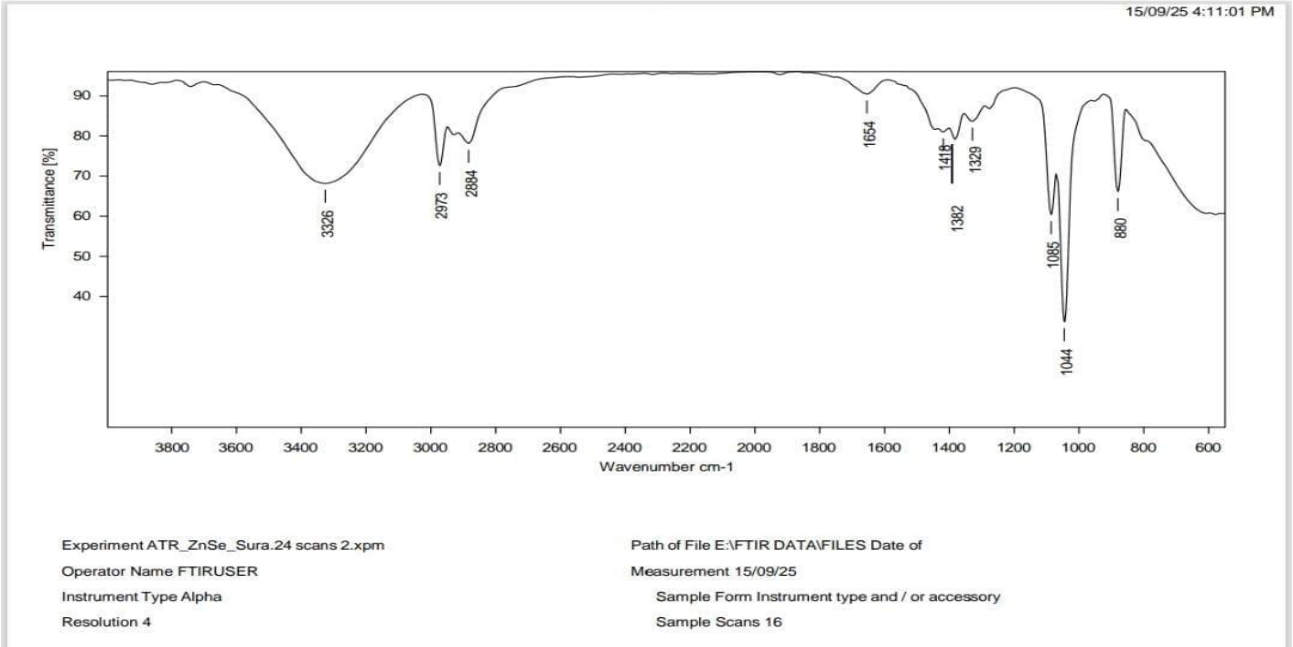

Figure 6: FTIR of Drug APIXABAN + Excipients (Optimized formula – F7)

TABLE 8: CHARACTERISTIC PEAKS AND FREQUENCIES OF APIXABAN

S. No.	Characteristic Peaks	Standard Drug Peaks cm $^{-1}$	Drug + Excipients Peaks cm $^{-1}$
1.	O-H/N-H (ALCOHOL/AMINE)	3400-3200	3326
2.	C-H (ALKANE)	3000-2850	2973, 2884
3.	C=O/C=C (CARBONYL/ALKENE)	1800-1700	1654
4.	C-H bending (ALKANE/PHENOLIC O-H)	1450-1400	1418
5.	C-N stretching (AMINE)/C-H bend	1350-1300	1329
6.	C-O (ETHER/ALCOHOL/ESTER)	1100-1000	1085, 1044
7.	C-H (AROMATIC out-of-plane)	900-700	880

A wide peak at around 3283 cm^{-1} is seen in the FTIR spectrum, which verifies the existence of O-H or N-H groups. The existence of a carbonyl (C=O) or C=C group is indicated by a significant absorption at ~1654 cm^{-1}, while aliphatic C-H stretching is correlated with peaks at ~2973 and 2884 cm^{-1}. Extra bands at approximately 1415 and 1329 cm^{-1} indicate vibrations of C-H bending and C-N stretching, respectively. Aromatic C-H bending is shown by the band at ~860 cm^{-1}, whereas strong absorptions at ~1092 and 1044 cm^{-1} validate C-O stretching. Taken together, these findings suggest that the material is functionalized with aromatic, hydroxyl/amine, aliphatic, carbonyl, and ether/alcohol groups. The absence of noticeable changes or removal of identifiable peaks in the FTIR spectra of the drug in combination with excipients suggests that the drug remains intact in the formulations and that the drug and excipients do not interact.

4.2 POST COMPRESSION EVALUATIONS

Physicochemical Evaluation Parameters

The results are outlined in the following: The data regarding the drug content was within the permissible range, the hardness values were within the recommended range of 5 to 6 kg/cm2, the friability values were below 1%, the weight variation values were within the acceptable range, and the tablet thickness were consistent.

TABLE 9 POST-COMPRESSION EVALUATIONS OF BILAYER TABLETS

Formulation Code	Average weight (mg)±SD	Thickness (mm) ±SD	Hardness (kg/cm²) ±SD	Friability (%) ±SD	Drug content (%) ±SD	Mucoadhesion strength (g)±SD
F1	300±0.43	3.8±0.24	4.5±0.58	0.1±0.21	99.7±0.52	20.0±0.32
F2	297±0.54	3.5±0.12	4.5±0.32	0.8±0.10	99.9±0.37	19.0±0.21
F3	299±0.31	3.7±0.43	4.0±0.26	0.6±0.34	100.2±0.41	20.0±0.56
F4	299±0.61	3.7±0.40	4.5±0.21	0.9 ±0.31	99.9±0.34	20.4±0.61
F5	297±0.32	3.44±0.64	4.0±0.42	0.4±0.32	99.6±0.22	17.5±0.45
F6	301±0.41	3.5±0.39	4.5±0.13	0.06±0.22	99.8±0.36	15.0±0.40
F7	**300±0.26**	**3.8±0.30**	**5.0±0.20**	**0.1±0.16**	**99.9±0.31**	**20.0±0.23**
F8	299±0.26	3.4±0.31	4.0±0.27	0.6±0.23	101±0.23	20.0±0.33
F9	300±0.53	3.7±0.41	4.5±0.31	0.7±0.21	99.9±0.21	20.0±0.31

SURFACE pH: The table shows that the surface pH values for the produced tablets comprising Sodium alginate, HPMC, and Carbopol ranged from 6.8 to 7.1. It may be concluded that the produced tablets do not cause irritation in the oral cavity because the results were close to the buccal pH (6.8).

TABLE 10: DATA FOR SURFACE PH STUDIES.

S.No.	Formulation code	Value
1.	F1	6.59 ± 0.45
2.	F2	7.18 ± 1.05
3.	F3	7.03 ± 1.09
4.	F4	7.12 ± 0.35
5.	F5	6.50 ± 0.49
6.	F6	6.45 ± 0.43
7.	F7	7.10 ± 0.19
8.	F8	6.90 ± 0.45
9.	F9	6.89 ± 0.41

MUCOADHESIVE STRENGTH: The optimized formulation was selected and mucoadhesive test was carried out and the result indicates that 20.0 gm of strength was required for its detachment from the surface".

TABLE 11: DATA FOR MUCOADHESIVE STRENGTH

Formulation code	Mucoadhesive strength (gm)
F7	20.0

Figure 7: Mucoadhesive test by modified physical balance

SWELLING INDEX: Swelling studies showed that the tablets containing Carbopol showed faster swelling behavior when compared to tablets containing Sodium alginate and HPMC.

TABLE 12: DATA FOR SWELLING INDEX

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	4.3	4.0	6.5	9.3	6.0	13.0	20.2	15.2	19.3
2	9.3	6.0	15.0	16.5	18.3	20.0	26.3	22.0	23.0
3	13.0	10.3	25.1	20.0	25.0	24.3	32.1	25.1	36.6
4	21.4	22.1	36.3	27.3	33.0	29.5	45.2	33.1	47.4
5	33.1	31.3	47.4	35.1	41.1	48.3	59.4	45.4	51.3
6	40.6	43.0	50.5	38.6	45.0	50.3	65.0	48.6	62.6

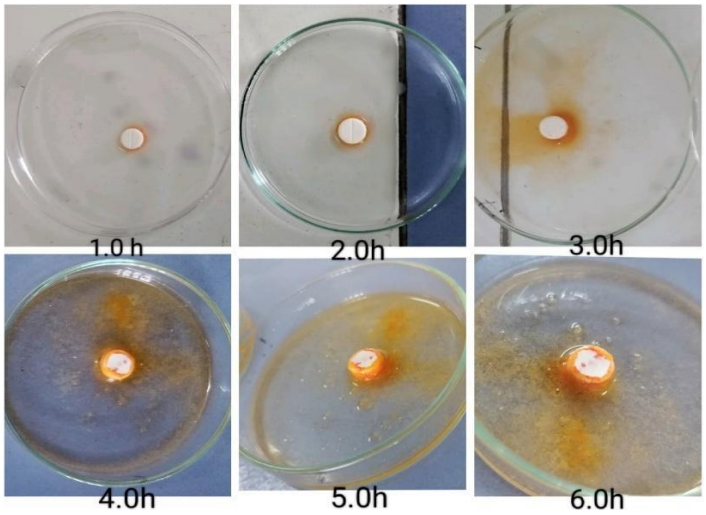

Figure 8: Swelling behaviour of optimised formulation (F7)

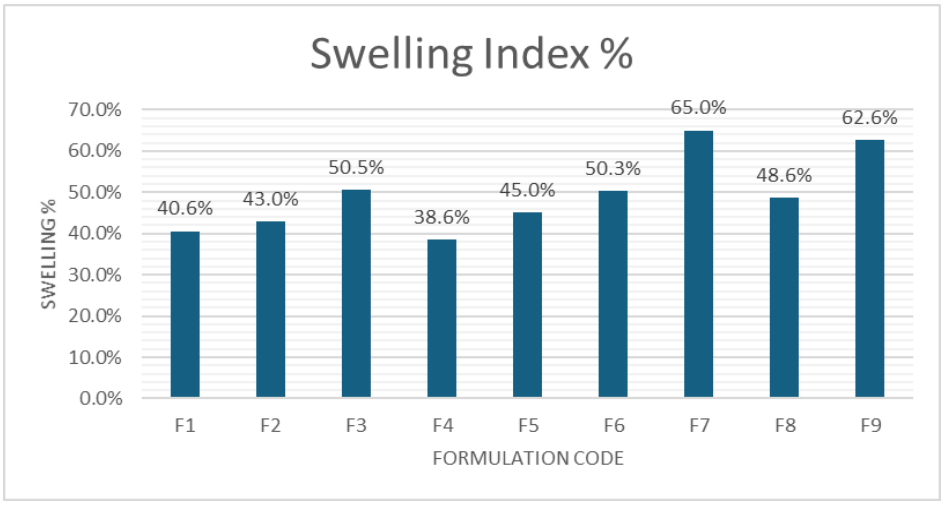

Figure 9: COMPARATIVE SWELLING BEHAVIOUR OF FORMULATIONS (F1 to F9)

TABLE 13: *IN-VITRO* DRUG RELEASE PROFILES OF BUCCAL MUCOADHESIVE BILAYER TABLETS

Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
15	18.10±0.59	17.64±0.22	12.20±0.32	18.45±0.19	14.60±0.32	10.01±0.15	**19.52±0.41**	12.10±0.22	10.26±0.67
30	22.09±0.62	19.05±0.51	14.66±0.28	24.25±0.53	18.25±0.24	16.14±0.35	**28.96±0.20**	20.25±0.50	14.96±0.27
45	33.81±0.14	25.65±0.42	18.05±0.12	30.63±0.64	26.52±0.18	18.43±0.46	**39.96±0.18**	28.05±0.62	25.09±0.23
60	42.53±0.46	33.92±0.11	24.25±0.56	40.23±0.25	34.90±0.27	25.23±0.28	**48.85±0.36**	36.96±0.31	34.92±0.40
90	58.10±0.58	45.94±0.56	32.50±0.44	56.39±0.17	44.30±0.50	39.71±0.51	**62.98±0.20**	48.93±0.44	42.10±0.31
120	70.24±0.30	55.69±0.49	46.10±0.21	66.76±0.33	58.56±0.16	48.56±0.41	**75.99±0.33**	59.64±0.52	49.35±0.57
150	78.92±0.32	62.34±0.62	52.10±0.43	73.24±0.56	62.79±0.27	54.69±0.30	**80.55±0.45**	66.87±0.29	58.24±0.52
180	86.05±0.21	75.20±0.22	68.60±0.42	81.56±0.31	71.83±0.52	63.78±0.27	**88.84±0.42**	74.98±0.18	60.85±0.43

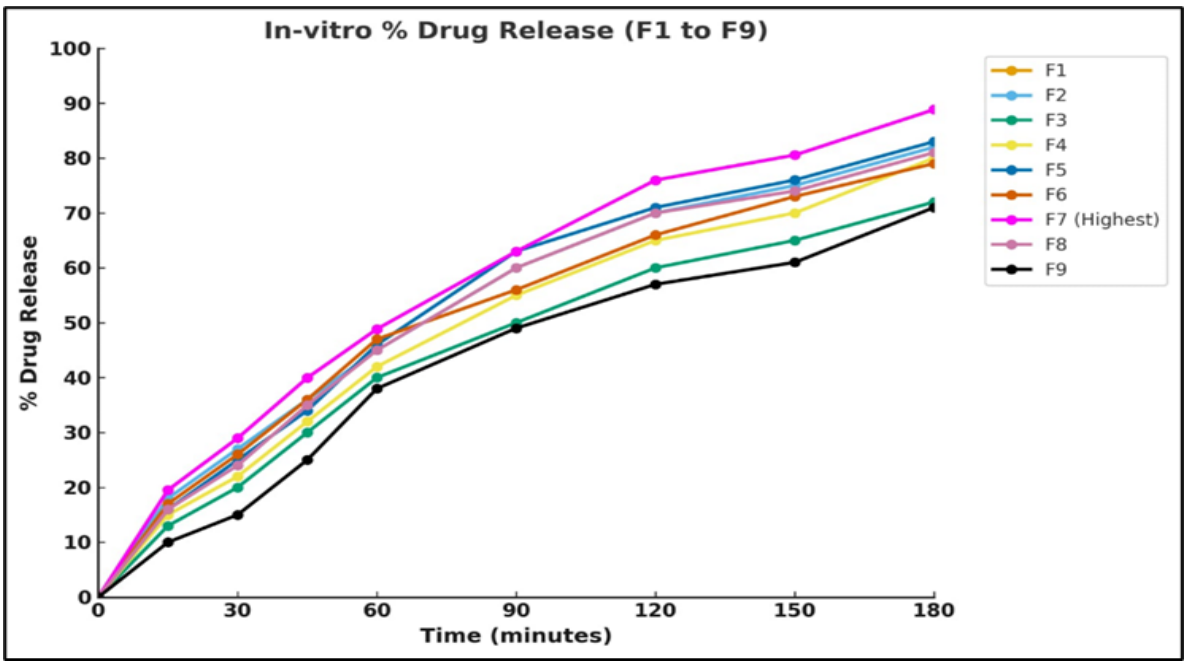

Figure 10: *In-Vitro* DRUG RELEASE PROFILES OF F1 to F9

TABLE 14: *IN-VITRO* DRUG RELEASE PROFILE OF OPTIMIZED BILAYER TABLET

Time (mins)	F7
15	19.52
30	28.96
45	39.96
60	48.85
90	62.98
120	75.99
150	80.55
180	88.84

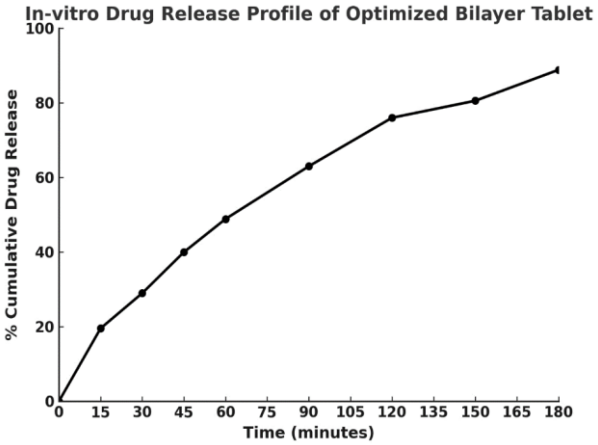

Figure 11: *In-Vitro* DRUG RELEASE PROFILE OF OPTIMIZED BILAYER TABLET

4.3 KINETIC RELEASE MODELS:

DRUG-RELEASE KINETICS OF OPTIMISED FORMULATION

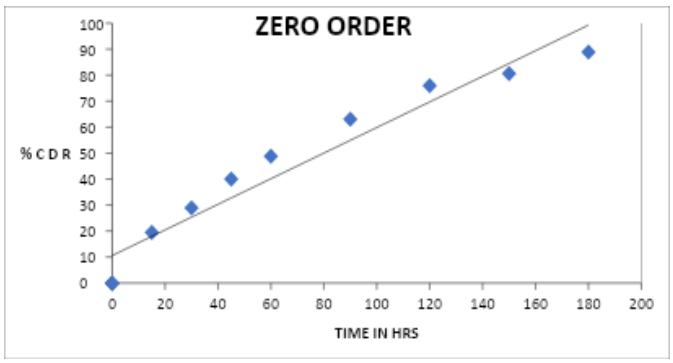

Figure 12: Zero Order Model graph for F7 (Optimized) formulation

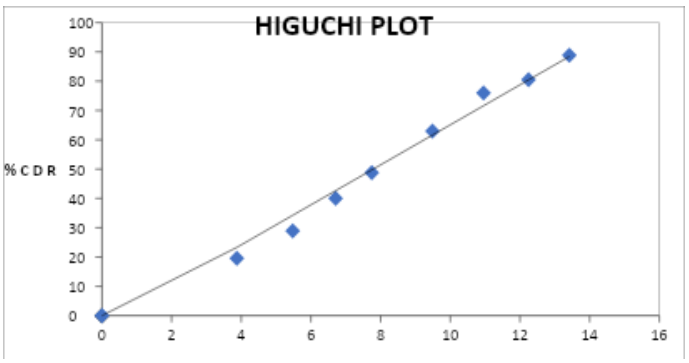

Figure 14: Higuchi's Model graph for F7 (Optimized) formulation

Figure 13: First Order Model graph for F7 (Optimized) formulation

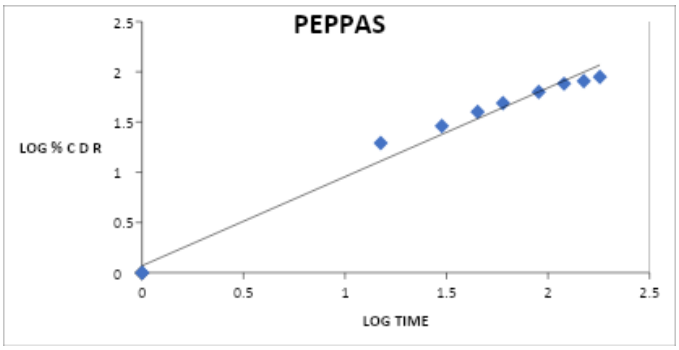

Figure 15: Peppas Model graph for F7 (Optimized) formulation

TABLE 15: KINETIC STUDIES OF F7 (OPTIMIZED) FORMULATION

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	0.46672	-0.005073389	6.990510279	0.8861
Intercept	13.7348	2.003391974	-4.783691105	0.0316
Correlation	0.968471038	-0.996764587	0.99475649	0.9941
R 2	0.937936151	0.993539642	0.9904	0.9842

Based on Fick's law of diffusion and first-order release kinetics, the regression analysis shows that formulation F7 with 20 mg of Carbopol 934p releases the drug through a diffusion mechanism. —Higuchi layout.

4.4 STABILITY STUDIES:

No notable changes were observed in the optimized formulation during the storage conditions period at 40 °C / 75 % RH, demonstrated physical and chemical integrity over three months; according to stability experiments conducted on it. These changes were assessed using the drug content, drug release (%), and its physical appearance.

TABLE 16: DATA FOR STABILITY STUDIES

Formulation (F7)	Physical appearance	Thickness	Hardness	Drug content	Cumulative % drug release
1st day	No change	3.8±0.30	5.0±0.20	99.9±0.31	88.84±0.42
30th day	No change	3.8±0.30	5.0±0.20	99.9±0.31	88.84±0.42
60th day	No change	3.8±0.30	5.0±0.20	99.9±0.31	88.84±0.41
90th day	No change	3.8±0.29	5.0±0.10	99.9±0.30	88.84±0.40

SUMMARY OF FINDINGS:

FTIR analysis confirmed that the medicine and excipients did not interact, and the results of the pre-formulation experiments were within permissible limits. The final composition was found to meet all criteria after compression. The formulation demonstrated an adequate swelling index, a mucoadhesive strength of 20.0 gm, and a surface pH that was near to the buccal cavity. Results from in vitro drug release tests showed that the optimized formulation followed first-order and Higuchi release kinetics, releasing 88.84% of the medication over 180 minutes. Over the course of the research, the formulations also showed no signs of change.

CONCLUSION

The purpose of this research was to design and test a mucoadhesive bilayered buccal tablet containing the anticoagulant Apixaban, a factor Xa inhibitor, for the treatment or prevention of deep vein thrombosis. The buccal route acts as a potential alternative to improve therapeutic efficacy because APX's oral bioavailability is poor (~50%) due to first-pass metabolism and unpredictable absorption. Polymers like sodium alginate, hydroxypropyl methylcellulose (HPMC K4M), and Carbopol (934p) were used in different concentrations to create the formulations (F1 to F9) that had the needed properties. The direct compression technique was used to produce mucoadhesive bilayered buccal tablets. The formulations that were created were then tested for physicochemical characteristics and assessment tests. The optimized formulation, F7, which contains 20 mg of Carbopol, was determined by evaluation tests. The results indicated that the mucoadhesive strength of the formulation was 20.0 gm, that the drug release at 180 mins was 88%, and that the formulation remained stable throughout the stability studies. The values of the post compression parameters were also within the limits. So, it is possible to make Apixaban mucoadhesive bilayered buccal tablets. All things considered; the results show that mucoadhesive bilayered buccal tablets are feasible to create. The formulation specifies that the chosen polymer or excipient, as well as the concentration of polymers, determine the tablet's character.

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Author Contributions:

Ayesha Juveria*[1] : Conceptualization, methodology, investigation, writing – original draft.

Abdul Mannan[2] : Supervision, validation, formal analysis, writing – review.

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Ethical Statement: Not applicable. No human or animal subjects were involved in this study. All experiments were conducted using in vitro models.

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