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DEVELOPMENT AND EVALUATION OF APIXABAN BUCCAL TABLETS FOR ENHANCED BIOAVAILABILITY

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Abstract:

The present study was aimed at the formulation and evaluation of buccal tablets of Apixaban using different concentrations of polymers to achieve controlled drug release. A total of eight formulations (F1–F8) were prepared and evaluated for preformulation, physicochemical, and in vitro performance characteristics. FTIR studies indicated no significant interaction between the drug and excipients, demonstrating compatibility. Pre-compression parameters revealed good flow properties of the powder blends. Post-compression evaluation of tablets showed that all formulations complied with pharmacopoeial limits for weight variation, hardness, friability, thickness, drug content, and swelling index. In vitro dissolution studies demonstrated sustained drug release for all formulations, with formulation F5 showing the highest release of 98.69% at 8 hours. Drug release kinetics revealed that the optimized formulation followed zero-order and Higuchi models, indicating a controlled and diffusion-based release mechanism. Stability studies conducted for 90 days under accelerated conditions showed no significant changes in drug release or physical characteristics. In conclusion, the optimized formulation (F5) of Apixaban buccal tablets exhibited satisfactory physicochemical properties, controlled drug release, and good stability, suggesting its potential as an effective alternative drug delivery system for improved therapeutic efficacy and patient compliance.

Keywords: *Apixaban, Buccal tablets, FTIR Studies, Polymers, Sustained release, Drug release kinetics, Stability studies*

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INTRODUCTION:

Buccal drug delivery has emerged as an attractive alternative to conventional oral administration due to its ability to bypass hepatic first-pass metabolism and gastrointestinal degradation. The buccal mucosa is highly vascularized and provides a relatively permeable route for systemic drug delivery, resulting in rapid absorption and improved bioavailability. Furthermore, buccal tablets offer several advantages, including ease of administration, improved patient compliance, reduced dosing frequency, and the possibility of terminating therapy by removing the dosage form when necessary.[1,2] Buccal tablets are solid dosage forms formulated to adhere to the buccal mucosa and release the drug in a controlled manner over an extended period.[3] The development of mucoadhesive buccal tablets has gained significant attention in recent years for the delivery of drugs with poor oral bioavailability.[4] Apixaban is a direct oral anticoagulant (DOAC) that selectively inhibits Factor Xa, thereby preventing thrombin generation and blood clot formation. It is widely prescribed for the prevention and treatment of thromboembolic disorders, including deep vein thrombosis, pulmonary embolism, and stroke prevention in patients with non-valvular atrial fibrillation.[5] The present study aims to develop and evaluate mucoadhesive buccal tablets of apixaban for enhanced bioavailability.[6] The formulated tablets are evaluated for various physicochemical parameters, including weight variation, hardness, friability, drug content, swelling index and in vitro drug release studies. The successful development of apixaban buccal tablets may provide an effective alternative dosage form capable of improving systemic drug availability and therapeutic effectiveness while enhancing patient compliance.

MATERIALS AND METHODS:

MATERIALS

Apixaban was procured from Hetero Labs, HYD. Span 80, Tween 80 were obtained from Synpharma Research Lab, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METODOLOGY

Drug excipient compatibility studies

Accurately weigh 1–2 mg of drug or drug–excipient mixture. Mix with 100 mg of dry KBr powder using a mortar and pestle to make a homogeneous mixture. Compress the mixture under ~10 tons pressure to form a transparent pellet using a hydraulic press. Place the pellet or powder sample in the FTIR sample holder. Scan the sample over a wavenumber range of 4000–400 cm^{-1}. Record the IR spectrum. Repeat scanning 3 times for consistency. Identify characteristic peaks of functional groups ($–NH_2$, $–CH_3$, –OH, etc.).[7]

Formulations Table:

Table-1: Formulation of buccal tablets of Apixabán

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Apixabán	25	5	5	5	5	5	5	5
Sodium alginate	10	20	30	40	-	-	-	-
HPMC E15	-	-	-		10	20	30	40
Lactose	84	74	64	54	84	74	64	54
Talc	2	2	2	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3	3	3	3
Aspartame	1	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100	100

Preparation method

Accurately weigh the API and all excipients according to the formulation. Blend Apixabán with polymers, diluents, and other excipients using a mortar and pestle or mechanical blender. Add magnesium stearate and talc at the end of mixing. Mix gently to avoid over-lubrication, which can reduce tablet hardness. Compress the final powder blend into tablets using a single punch tablet press. Choose flat or convex punches suitable for buccal tablets. [8]

Evaluation parameters

Weight Variation

Twenty buccal tablets were selected randomly and individually weighed using a calibrated digital analytical balance. The average weight of the tablets was calculated, and the individual tablet weights were compared with the average weight to determine the percentage deviation. The tablets were evaluated according to pharmacopeial specifications for weight variation.[9]

Thickness and Diameter

The thickness and diameter of ten tablets were measured using a digital Vernier caliper. The measurements were recorded in millimeters (mm), and the mean values along with standard deviations

were calculated to assess the uniformity of tablet dimensions.[10]

Hardness
The hardness of the buccal tablets was determined using a Monsanto or Pfizer hardness tester. Ten tablets were tested individually, and the force required to break each tablet was recorded in kg/cm². The average hardness value was calculated.[11]

Friability
Friability was evaluated using a Roche friabilator. Ten tablets were accurately weighed (W_0) and placed in the friabilator, which was operated at 25 rpm for 4 minutes (100 revolutions). The tablets were then dedusted and reweighed (W_t).[12] The percentage friability was calculated using the following formula:

$$\text{Friability (\%)} = [(W_0 - W_t) / W_0] \times 100$$

A friability value of less than 1% was considered acceptable.

Swelling Index
The swelling behavior of buccal tablets was determined by placing pre-weighed tablets (W_0) on the surface of phosphate buffer pH 6.8 maintained at 37 ± 0.5°C. At predetermined intervals, the tablets were removed, excess surface moisture was carefully blotted with filter paper, and the swollen tablets were weighed (W_t).[13] The swelling index was calculated using the following equation:

$$\text{Swelling Index (\%)} = [(W_t - W_0) / W_0] \times 100$$

where W_0 is the initial weight of the tablet and W_t is the weight of the swollen tablet at time t.

Content Uniformity
Ten tablets were individually powdered, and an amount equivalent to the required dose of Apixaban was transferred into a volumetric flask containing phosphate buffer pH 6.8. The solution was sonicated, filtered, and suitably diluted. The absorbance was measured using a UV-Visible spectrophotometer at the predetermined λmax of Apixaban. The drug content was calculated and expressed as a percentage of the labeled claim.[14]

In-Vitro Drug Release Study
The in-vitro drug release study was carried out using USP Dissolution Apparatus II (Paddle Method). The dissolution medium consisted of 900 mL phosphate buffer pH 6.8 maintained at 37 ± 0.5°C with a paddle speed of 50 rpm. Buccal tablets were attached to a glass slide using a suitable adhesive with the drug-releasing surface exposed to the dissolution medium. At predetermined time intervals, 5 mL samples were withdrawn and replaced with an equal volume of fresh dissolution medium. The samples were filtered, appropriately diluted, and analyzed spectrophotometrically at the λmax of Apixaban. The cumulative percentage drug release was calculated and plotted against time.[15]

Drug release kinetics[16]
The obtained dissolution data was fitted into various kinetic models to understand the pattern of the drug release from floating tablets. The models used were zero order (equation 1) First order (equation 2) and Higuchi model (equation 3) and Korsmeyer Peppas model (equation 4).

Stability studies[17]
Stability studies of the optimized Apixaban buccal tablet formulation were carried out according to the guidelines of the International Council for Harmonisation (ICH) to evaluate the effect of storage conditions on the physical and chemical stability of the formulation. The tablets were packed in aluminum foil or suitable airtight containers and stored under accelerated stability conditions of 40 ± 2°C temperature and 75 ± 5% relative humidity (RH) for a period of 3 months in a stability chamber.

RESULTS AND DISCUSSION:

FT-IR Spectrum of Apixaban
FT-IR Spectra of Apixaban and excipients were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Apixaban and Excipients. It also confirmed that the stability of drug during formulation process.

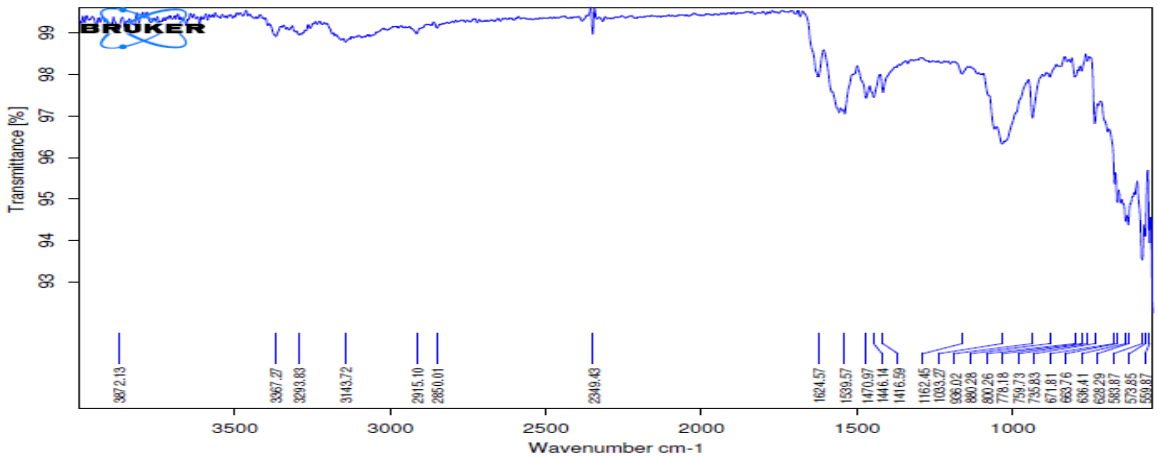

Fig-1: FTIR Spectra of Apixabán

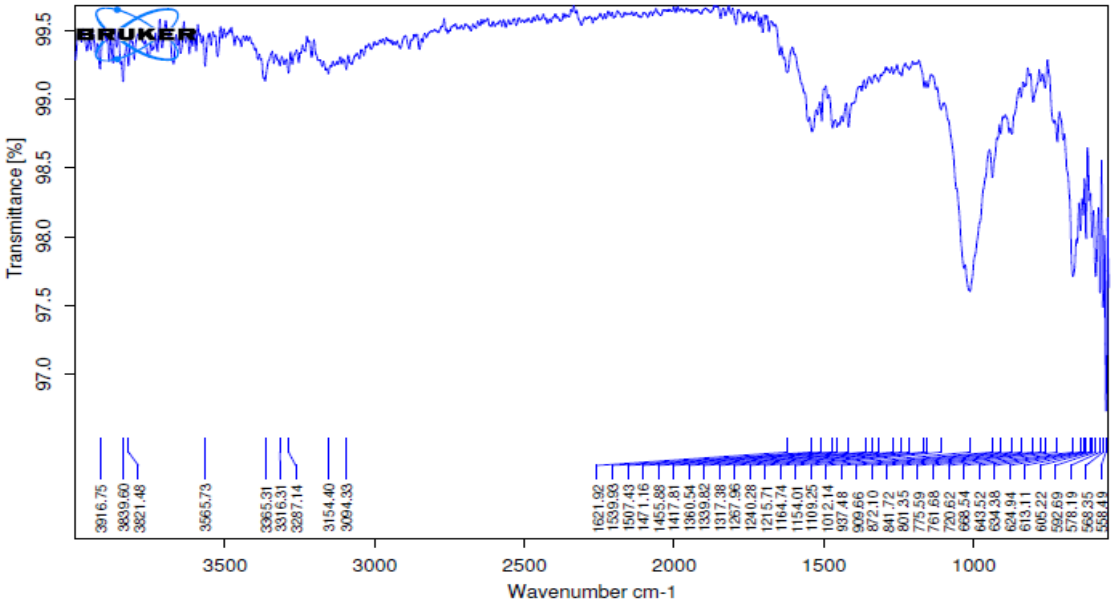

Fig-2: FTIR Spectra of physical mixture of drug and excipients

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Evaluation parameters

Weight variation: All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness: Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 3.1 to 3.7 mm.

Hardness: The measured hardness of tablets of each batch ranged between 4.01 to 4.32 kg/cm^2. This ensures good handling characteristics of all batches.

Friability: The % Friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity: The percentage of drug content for F1 to F8 was found to be between 79.56 % to 83.26% of Apixabán , it complies with official specifications.

Swelling index: The swelling index for F1 to F8was found to be between 92 to 101 % of Apixabán, it complies with official specifications.

Table-2: Evaluation parameters of Apixabán buccal tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)	Swelling index
F1	100	3.1	4.02	0.26	79.68	99
F2	100	3.6	4.12	0.28	80.12	101
F3	99	3.2	4.19	0.30	76.89	98
F4	100	3.3	4.32	0.25	81.52	100
F5	100	3.7	4.01	0.26	83.26	97
F6	99	3.5	3.36	0.29	80.15	95
F7	100	3.6	4.20	0.30	79.56	93
F8	99	3.1	4.25	0.32	81.25	92

Dissolution studies

All the 8 formulation of Apixabán buccal tablets were subjected to in vitro drug release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-3: Drug release studies of all formulations

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	16.39	17.10	18.12	19.26	20.97	18.97	16.39	17.89
2	25.67	26.39	28.16	27.48	28.15	26.46	25.48	26.58
3	35.91	34.57	36.97	38.10	37.48	35.23	36.74	35.67
4	44.50	45.95	49.86	46.89	45.82	44.79	45.10	44.20
5	56.79	55.89	57.82	58.46	54.82	55.28	58.25	59.86
6	64.59	65.93	66.91	67.81	68.97	67.82	69.85	65.35
7	75.10	79.39	80.25	81.36	82.35	79.68	76.85	78.85
8	93.26	94.56	95.69	96.98	98.69	95.37	93.25	92.35

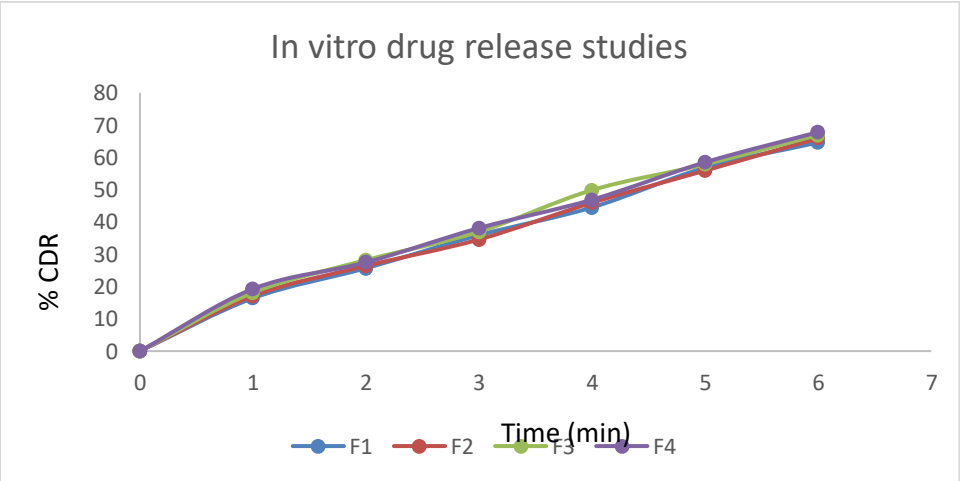

Fig-3: Dissolution Profile of F1to F4 formulations

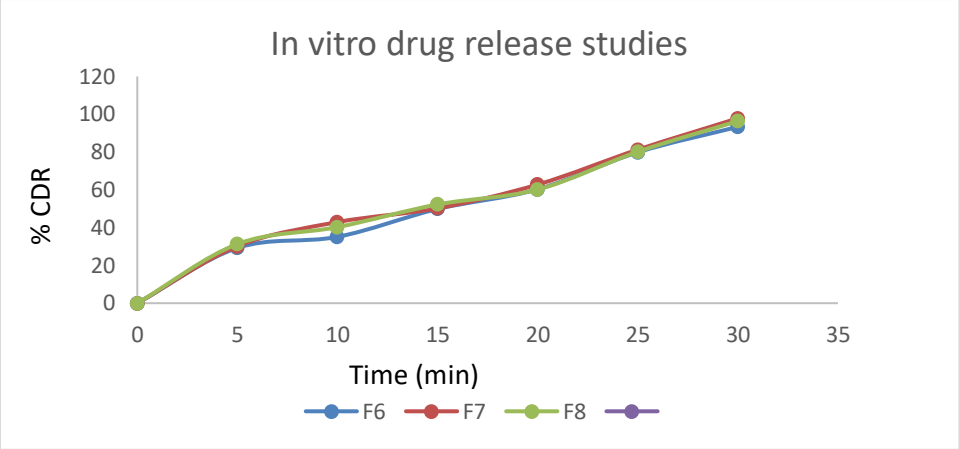

Fig-4: Dissolution Profile of F5to F8 formulations

Kinetic modeling of drug release

All the 8 formulation of prepared Apixabán buccal tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

Zero order kinetics

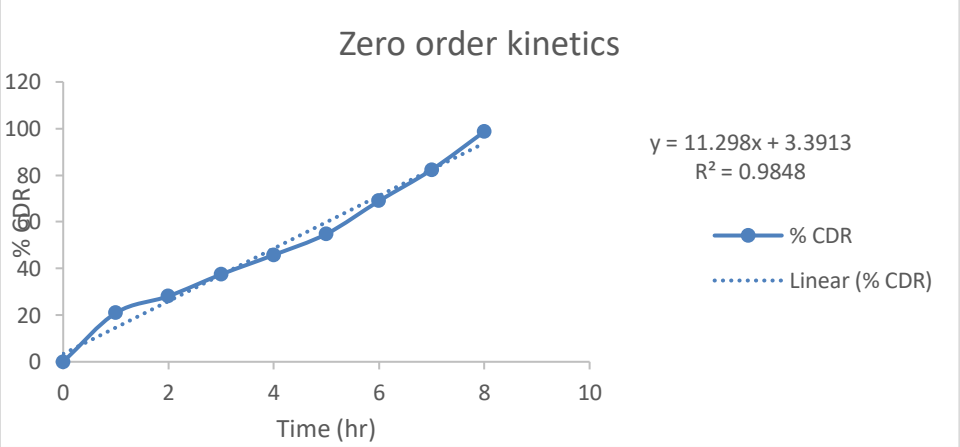

Fig-5: Zero order kinetics of optimized formulation

First order kinetics

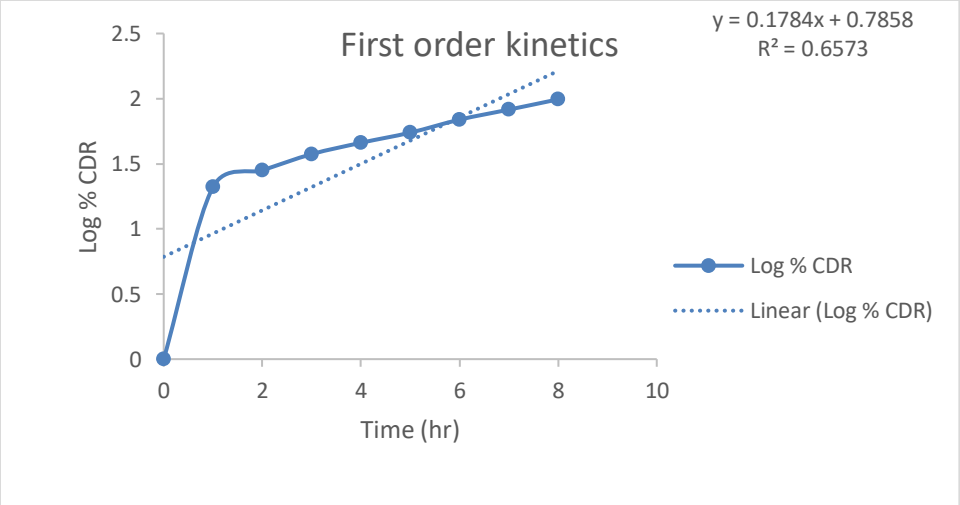

Fig-6: First order kinetics of optimized formulation

Higuchi model

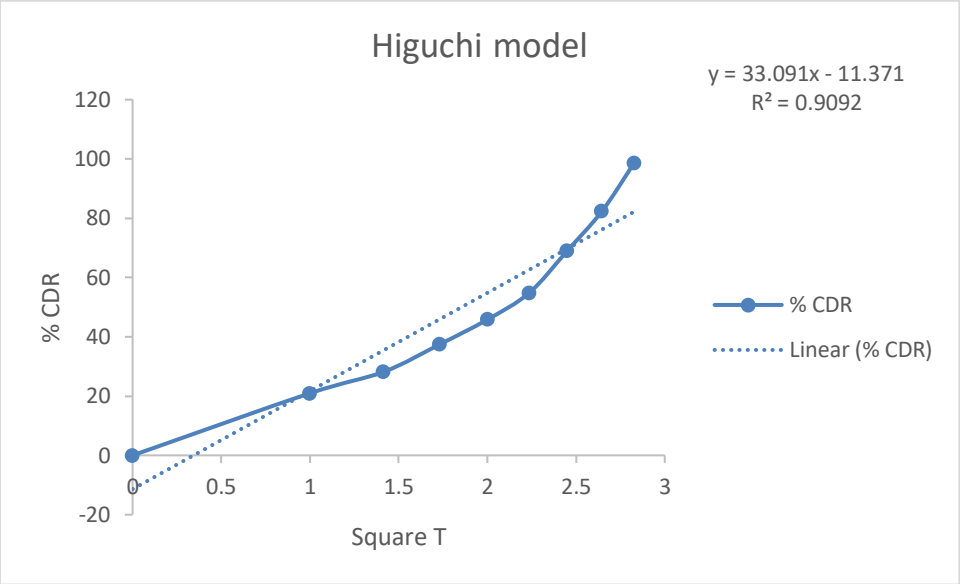

Fig-7: Higuchi model of optimized formulation

Korsmeyer peppas

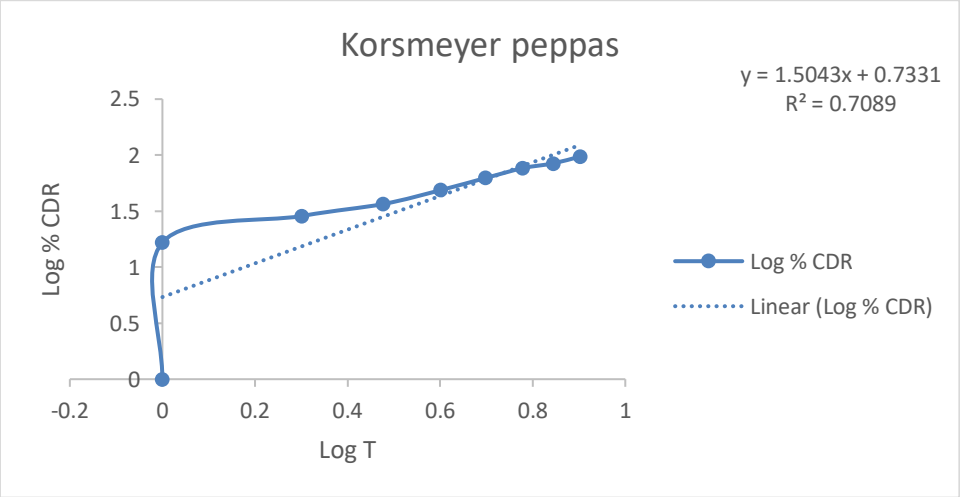

Fig-8: Korsmeyer peppas of optimized formulation

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix and Peppas. Regression values are higher with Zero order release kinetics. Therefore, all the Apixabán buccal tablets follows Zero order release kinetics. Apixabán release from all the dosage form followed dissolution rate controlled mechanism.

Stability Study

There was no significant change in physical and chemical properties of the buccal tablets of formulation F-5 after 90 days. Parameters quantified at various time intervals were shown.

Table-4: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-5	**25^{0}C/60%RH % Release**	98.69	97.58	96.35	95.84	**Not less than 85 %**
F-5	**30^{0}C/75% RH % Release**	98.69	97.52	96.20	95.26	**Not less than 85 %**
F-5	**40^{0}C/75% RH % Release**	98.69	97.16	96.15	95.20	**Not less than 85 %**

CONCLUSION:

The study successfully developed buccal tablets of Apixaban with desirable physicochemical and release characteristics. Among all formulations, F5 was identified as the optimized formulation due to its superior drug release profile, acceptable mechanical strength, and stability. The drug-excipient compatibility, good flow properties, and consistent tablet evaluation parameters indicate that the formulation approach is reliable. The optimized formulation followed controlled release kinetics, primarily governed by diffusion mechanisms, making it suitable for sustained drug delivery. Overall, Apixaban buccal tablets prepared in this study demonstrate promising potential as an alternative drug delivery system, which may improve patient compliance and provide effective therapeutic outcomes through controlled drug release.

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