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Original Article

Anticoagulant and Pharmacokinetic Evaluation of Apixaban Sublingual Tablets in Wistar Rats

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ABSTRACT

Background: Apixaban is a novel oral anticoagulant widely used in the treatment and prevention of thromboembolic disorders. However, oral administration is associated with delayed onset of action and inaccurate gastrointestinal absorption paired with difficulties in swallowing among those people who have swallowing difficulties, which restricts its clinical applicability in some patients. Sublingual route has a fast systemic absorption and avoids first-pass metabolism in the liver. **Objectives:** The current research aimed for developing and evaluating Apixaban sublingual tablet and comparing its anticoagulant effects and *in vivo* pharmacokinetic properties within a marketed available oral formulation. **Materials and Methods:** Sublingual tablets have been formulated using direct compression method and assessed its physicochemical parameters such as hardness, thickness, friability, wetting time, disintegration time as well as *in vitro* drug release. The *in vivo* anticoagulant properties was investigated in Wistar rats using bleeding time and clotting time models, as well as, measuring mucoadhesion, retention period, and sublingual mucosal pH. Plasma sample analysis based on validated HPLC method for determine of pharmacokinetic parameters. **Results:** The sublingual tablets showed rapid disintegration within 10-12 sec, good mechanical properties, and drug release exceeding 94%. Bleeding and clotting times were significantly prolonged compared with placebo and marketed tablets. The sublingual formulation achieved higher C_{max} (0.40±0.005 µg/mL) and $AUC_{0-\infty}$ (2.146±0.010 µg/mL hr) than the marketed formulation, resulting in 11.54% higher bioavailability. **Conclusion:** The sublingual tablet demonstrated excellent anticoagulant activity and improved bioavailability compared to the conventional oral formulation, making it a promising alternative for emergency or swallowing-impaired patients.

Keywords Anticoagulant Activity, Apixaban, Bioavailability, Pharmacokinetics study, Sublingual Tablet.

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INTRODUCTION

Apixaban is a highly potent, reversible, and selective oral anticoagulant that works against Factor Xa, an essential part of the blood coagulation process. It belongs to the class of Novel Oral Anticoagulants (NOACs) and is commonly administered to prevent and treat thromboembolic conditions include strokes, Pulmonary Embolism (PE), and Deep Vein Thrombosis (DVT) in patients diagnosed with atrial fibrillation (Agrawal and Manna, 2024; DeHaas, 2017). Among other anticoagulants, such as warfarin, apixaban has various therapeutic advantages, including fewer dietary restrictions, fewer drug interactions, and the absence of the need for regular coagulation testing (Kustos and Fasinu, 2019). Thus, the fact that it directly inhibits Factor Xa early in the coagulation cycle helps to prevent the formation of clots without having a significant impact on haemostasis. Although apixaban has a favorable pharmacodynamic profile, it has certain pharmacokinetic limitations that influence its clinical application, particularly in emergencies where a swift onset of action and consistent systemic absorption are essential (Bauer, 2011; Risman *et al.*, 2024). Apixaban is taken orally, typically in the immediate-release tablets. Nevertheless, oral delivery mode has some problems, which include delay in the effects, first pass in the liver and differences in individuals because of Gastrointestinal (GI) factors. Apixaban has a bioavailability of approximately 50% after oral intake with a peak plasma concentration occurring in the range of 3 to 4 hr of dosage ingestion (Hindley *et al.*, 2023; Wong *et al.*, 2011a). Patients who require immediate anticoagulation effects or have difficulty swallowing tablets, such as the elderly, those with dysphagia, or those who are unconscious, face substantial therapeutic challenges due to the restrictions of oral administration. Moreover, a formulation that facilitates fast and efficient drug absorption into the system is urgently required in an emergency medical situation like stroke or thromboembolic

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crises (Hindley *et al*., 2023; Nutescu *et al*., 2016). Sublingual drug delivery is a viable option in comparison to the conventional oral therapies as it enables the drugs to enter into the systemic circulation directly through the highly vascularized mucosa in the mouth floor. This is a bypass of hepatic first-pass metabolism and the gastrointestinal tract which leads to faster action and better bioavailability (Zhang *et al*., 2002). Furthermore, sublingual tablets are convenient and non-invasive, making them suitable for both outpatient and emergency care. Sublingual delivery of drugs such as apixaban, which require rapid therapeutic plasma concentrations, especially in healthcare institutions, may provide significant pharmacokinetic and therapeutic benefits (Ahmad *et al*., 2025; Kraan *et al*., 2014). While sublingual formulations are well known for certain drugs, such as Nitroglycerin and fentanyl, their use to anticoagulants has received less attention. Apixaban's physicochemical characteristics, such as limited bioavailability and intermediate permeability, provide formulation challenges for sublingual delivery (Joshi and Raval, 2019). A sublingual apixaban tablet should improve rapid disintegration, effective drug release, and successful mucosal absorption in order to quickly achieve therapeutic plasma levels (Boddupalli *et al*., 2010; Prasanth *et al*., 2014). Furthermore, anticoagulant efficacy must be sustained and quantified after systemic absorption. Thus, preclinical *in vivo* studies are required to investigate the pharmacokinetics and pharmacodynamics of this type of formulation (Khutoryanskiy, 2011). The current study focuses on developing sublingual formulations of apixaban for its anticoagulant activity and pharmacokinetic profile, while addressing the challenges associated with conventional oral dosage forms.

MATERIALS AND METHODS

Materials

Apixaban (APX) was achieved as gift sample from Morepen Laboratory Ltd., Parwanoo Himachal Pradesh India. The Crospovidone INF-10 was bought from Scope Ingredients Pvt. Ltd., Mumbai, PVPK-30 was bought from PS Impex Panchkula Haryana, Microcrystalline Cellulose PH-112 was purchase from Biosmith Lifesciences Baddi Himachal Pradesh India, Pearlitol 200SD was purchase from Signet Excipients Pvt. Ltd., Others inactive ingredients also were acquired as a gift sample from Morepen Laboratory Ltd., in Parwanoo, Himachal Pradesh, India. The remaining solvents and reagents were all analytical grade.

Methods

Preparation of Apixaban Sublingual Tablets

Sublingual tablets were developed using the direct compression method, which is a simple and effective approach widely used in the pharmaceuticals industries. During this process, precisely measured amounts of apixaban, selected polymers, and excipients were passed separately through a # 40 sieve to ensure constant particle size and remove any clumping (Table 1). The sieved components were then thoroughly mixed in an appropriate blender to obtain a uniform blend. Once uniform mixing was confirmed, the powder mixture was compressed directly by utilizing the tablet punching machine with the suitable punches and dies. The formulated tablets were also tested on different physicochemical properties including hardness, disintegrating time, weight variation, friability and percent cumulative drug release to establish their suitability for sublingual use and enhanced bioavailability (Prajapati *et al*., 2014).

Physicochemical Characterization

Thickness

The thickness of prepared sublingual tablets were evaluated using a vernier caliper. Individual ten (n=10) tablets from each batch were analysed to establish the average thickness (Bansal *et al*., n.d.).

Hardness

A Pfizer hardness tester was used to evaluate the developed tablets' hardness. A tablet hardness of around 2-3 kg/cm^2 is measured appropriate for mechanical stability. Evaluation was done in triplicate (Li *et al*., 2025).

Friability

A Roche Friabilator was used to evaluate the developed tablet's friability. 6 g tablets were weighed for this test, then subjected to a mixture of shock and abrasion in the Friabilator plastic chamber rotating at 25 r.p.m. for 4 min. The tablets were then dusted and weighed again (Godbole *et al*., n.d.).

Weight variation

The weight variation test was carried out by weighing ten randomly selected tablets (n=10) on an analytical balance. Individual tablet weights were compared to determine average weights (Alali *et al*., 2021).

Wetting time

To determine the wetting time, the tablet was located in the midpoint of two layers of absorbent paper within a petridish. After completely saturating the paper with distilled water, the additional water was completely drained from the dish. A timer was used to record how long it took for the water to dispersed from the wetted absorbent paper during the complete tablet (Prajapati *et al*., 2012).

In vitro disintegration test

The disintegration test of prepared sublingual tablets was carried out in compliance with the US Pharmacopeia (USP) criteria. A tablet disintegration equipment was utilized without plastic discs. Officially, the allowable disintegration time for sublingual tablets is less than 2 min. The test was conducted using a tablet

disintegration instrument (Model ED-4L, Lab India) and distilled water at 37±0.2°C as the disintegration medium. The time mandatory for complete disintegration of each tablet was carefully recorded (Gupta *et al*., 2009).

In vitro Drug Release Study

The developed formulations were subjected to dissolution studies with individually selected six tablets (n=6) using a USP dissolution apparatus type II (paddle) (Model ED-4L, Lab India), operated at a rotational speed of 75 rpm. The dissolution medium contained of 900 mL of phosphate buffer (pH 6.8), maintained at 37±0.5°C. By predecided time periods, 5 mL samples were removed and exchanged with an equal quantity of fresh dissolution medium to maintain sink conditions. The amount of drug released into the dissolution medium was quantified using the previously described HPLC method for drug content analysis (Rachid *et al*., 2011).

In vivo Study Design

The rodent species utilized in this study are male albino wistar rats, each weighing 150-200 g. The rats were housed in polyacrylic cages and kept under typical laboratory conditions (temperature maintained at 25±2°C) and humidity levels (50±5%) with a light/dark cycle as per CCSEA. The animals underwent a period of fasting overnight. The experimental procedures received approval from the Institutional Animal Ethical Committee (IAEC) established under CCSEA (Reference No.: CCSEA/1205/2025/9). The rats were divided into four groups, each consisting of six individuals, with group I serving as control (disease-free). Group II served as a negative control (with disease and blank (placebo) tablet). The group III served as a standard control (with disease and marketed immediate release Apixaban tablet (2.5 mg)). The rats in group IV acted as a test control (with disease and prepared Apixaban sublingual tablet (2.5 mg)). Wistar rats were selected as the animal model for the *in vivo* pharmacokinetic and anticoagulant evaluation of the sublingual Apixaban formulation because of their well-defined physiology, manageable size, and compatibility for oral and sublingual drug administration investigations. Rats have long been employed in preclinical pharmacokinetic studies in order to predict human drug absorption and disposition characteristics, providing an acceptable balance between ethical feasibility and therapeutic relevance. While there are interspecies differences in mucosal thickness, enzymatic activity, and absorption kinetics between rats and humans, rats provide a consistent and reproducible model for evaluating relative bioavailability, systemic exposure, and anticoagulant efficacy in controlled conditions. Furthermore, while rats sublingual anatomy differs from that of humans, it is sufficiently vascularized to allow for significant assessment of mucosal drug absorption and systemic circulation. The pharmacokinetic data obtained from rats serves as a useful first step in evaluating the formulation's performance before going on to more advanced animal models or clinical studies (Prajapati *et al*., 2012).

Toxicity Study

In vivo assessment was performed using Acute oral toxicity test was performed under OECD guideline 423. Male albino wistar rats were randomly chosen, weighed and casually categorized into two groups of six animals each. One group was a test group and given one oral dose of Apixaban prepared sublingual tablets dissolved in normal saline at the following doses of 2.5 to 10 mg/kg of body weight. The other group was used as the normal control and was only given normal saline of 10 mL/kg body weight. The animals were closely observed at time interval (1, 2, 4 and 6 hr) after administration where systematic observations were made. Physical alterations such as those in the skin, fur, eyes, and mucous membranes were examined in the study. Moreover,

Table 1: Preparation of sublingual tablets of Apixaban.

Ingredients (% w/w)	Formulation Code		
	F1	F2	F3
Apixaban	2.5	2.5	2.5
Pearlitol SD 200	70.50	71.00	70.00
Anhydrous Lactose	10.20	10.20	10.20
MCC PH-112	3.30	3.30	3.30
Crospovidone INF-10	8.00	8.00	8.00
PVPK30	1	1.5	2
Flavour Lemon	1.00	1.00	1.00
Quinoline Yellow Lake	0.10	0.10	0.10
Aspartame	0.80	0.80	0.80
Colloidal Silicon Dioxide	1.20	1.20	1.20
Magnesium Stearate	0.90	0.90	0.90

*Average weight per Apixaban sublingual tablet=100 mg

the respiratory, cardiovascular, autonomic, and CNS signs, motor functions, and overall behavior were evaluated. Survival rates were recorded at 48 hr post-dosing and monitored daily for an additional 14-day period (Byon *et al*., 2019).

Anticoagulant Activity of Apixaban Tablets Using Cutaneous Bleeding Time Model

Wistar rats were divided into 3 groups, each comprising six animals (*n*=6). Group II was administered a blank (placebo) tablet dissolved in normal saline and administered orally (Wong *et al*., 2011b). Group III received a marketed immediate release tablet 2.5 mg, also in normal saline, at the dose of 2.5 mg/kg body weight via oral administration. Group-IV was treated with apixaban tablets (2.5 mg/kg body weight, sublingual), after 1 hr. all animals were anesthetized using ketamine/xylazine (30/3 mg/kg, intraperitoneally) (Yoo *et al*., 1999). Each rat was then placed in a plastic restrainer with multiple access points to expose the tail. The surface of the tail was cleaned with water-moistened cotton. A standardized incision measuring 5 mm in length and 1 mm in depth was made between 9-9.5 cm from the tail tip using a scalpel. Bleeding time was measured at 15-sec intervals (Chng *et al*., 2022).

Anticoagulant Activity of Apixaban Tablets Using Clotting Time Model

Wistar rats were divided into 3 groups, each comprising six animals (*n*=6). Group II received a blank (placebo) tablet dissolved in normal saline and administered orally. Group III was treated with a marketed immediate release tablet 2.5 mg, dissolved in normal saline and administered orally at a dose of 2.5 mg/kg body weight. Group IV received the prepared Apixaban tablets (2.5 mg/kg Body weight, sublingual). After 1 hr, all rats were anesthetized using ketamine/xylazine (30/3 mg/kg, intraperitoneally). Blood samples was collected using retro-orbital plexus using capillary tubes, which were filled to approximately three-fourths of their capacity. Every 30 sec, a portion of the capillary tube was broken off and the ends were gently pulled apart to observe the formation of clots. The clotting time was measured as soon as a fibrin-like structure formed between the two ends of the ruptured capillary tube (Gawade *et al*., 2022).

In vivo Mucoadhesion and Residence Time

To assess the *in vivo* mucoadhesive properties of the sublingual Apixaban tablets, a qualitative residence time study was conducted in healthy male Wistar rats (*n*=3). The rats were slightly anesthetized using isoflurane to minimize movements and make it easy to place pills. The tablet was wetted and placed sublingually beneath the tongue with the aid of sterile forceps and the animal monitored until it completely broke and had lost all contact with the mucosa (Szekalska *et al*., 2019).

Determination of Sublingual Mucosal pH

The pH of the sublingual mucosal surface was measured to assess the compatibility of the formulated sublingual Apixaban tablets with the local physiological environment. The research was carried out in healthy male Wistar rats (*n*=3) under light anaesthesia (isoflurane) to reduce mobility and facilitate accurate measurement. A pre-calibrated digital micro-pH meter (or narrow-range flat-surface glass electrode pH probe) was used to determine pH. The electrode was softly put beneath the tongue, making direct contact with the sublingual mucosa while avoiding damage. The pH reading was left to settle for about 30-45 sec before the final result was recorded. The electrode was rinsed with normal saline and gently dried with lint-free tissue before each new measurement (Baliga *et al*., 2013).

In vivo pharmacokinetic studies for apixaban tablet in albino Wistar rats

A total of 16 male albino wistar rats, each weighing between 150-200 g, were casually distributed into two groups for the pharmacokinetic evaluation. Group-A was administered a commercially available Apixaban tablet, while Group B were

Table 2: Thickness, Hardness, and Friability Parameters of formulated Apixaban Sublingual Tablets.

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)
F1	2.8±0.010	2±0.104	0.10±0.061
F2	2.9±0.021	2±0.076	0.30±0.047
F3	3.2±0.015	3±0.152	0.11±0.061

*Note: All values are expressed as Mean±SD

Table 3: Results for Wetting Time, Disintegration Time, and Percent Cumulative drug release.

Formulation Code	Wetting Time (Sec)	Disintegration Time (Sec) (*n*=6)	Percent Cumulative Drug release (*n*=6)
F1	42±1.52	12±1.527	95.71±0.423
F2	43±2.51	10±1.154	94.27±0.219
F3	49±1.73	10±1.527	94.01±0.145

*Note: All values are expressed as Mean±SD

administered with a sublingual formulation of Apixaban (2.5 mg/kg, orally). Prior to dosing, the animals were fasted overnight, with access to water maintained. Following drug administration, blood samples (approximately 0.5 mL) were collected from the retro-orbital venous plexus at specific time points, 0, 2, 4, 6, and 8 hr, using heparinized capillary tubes. Samples were placed in tubes containing a 1% ammonium oxalate solution as an anticoagulant. Plasma was then separated using chilled centrifugation at 10,000 rpm for 10 min. The plasma samples were examined using HPLC on a reversed-phase C18 column with an isocratic mobile phase over a 2-min run time. The calibration curve for the analysis was linear throughout concentration ranges of 0.02-0.20 µg/mL, with a Correlation Coefficient (R^2) of 0.998. Prior to HPLC examination, the substance was removed from plasma using trichloromethane (*In vivo* Bioavailability Studies of Sumatriptan Succinate Buccal Tablets - PubMed, n.d.) (Nandi *et al*., 2013).

Sample preparation from Apixaban plasma drug concentration

Approximately 0.5 mL of blood taken from the treated animal was centrifuged at 5000 RPM for 15 min. Out of this, 0.25 mL of plasma was carefully separated and transferred into Herfindahl tube. To this plasma, 150 uL of acetonitrile solution was added ensuring that the final acetonitrile content was greater than 75% to ease precipitation of the protein. The mixture was vortexed for 20 sec and then centrifuged a second time for 10 min at 20,000 RPM at 4ºC. The resultant supernatant, which contained the drug, was collected and analysed by using the HPLC to calculate the unknown plasma drug concentration by the observed peak area (Frost *et al*., 2013).

Quantification of Apixaban in plasma

Apixaban plasma levels were established by High-Performance Liquid Chromatography (HPLC) using Waters-2695 (Bangalore, India). The separation was done on a reversed-phase, C18 column (250 mm * 4.6 mm internal diameter, 5 um particle size). The mobile phase was composed of 80:20 (v/v) methanol and water with a flow rate of 1 mL/min. A sample volume of 5 µL was injected for each run. The detection of Apixaban was carried out at 279 nm by using UV-vis spectroscopy and the total run time between 10 to 20 min. A calibration curve was made with 8 standard solutions of Apixaban in phosphate buffer (pH 6.8) with different concentrations ranging from 0.02 to 0.20 g/mL (Hensler and Burghardt, 2025).

Statistical analysis

Pharmacokinetic parameters such as C_{max}, T_{max}, AUC_{0-24}, $AUC_{0-\infty}$ and MRT were evaluated to determine the enhanced bioavailability of the formulated dosage form. A pharmacokinetic comparison was conducted for each treatment group against the control group using the Analysis of Variance (ANOVA) based on the crossover study design. The data were log transformed and the 95% confidence intervals for the test/reference ratios were calculated using log transformed data. In order to find significant differences among treatment groups and control, one-way Dunnett's analysis of variance was used. A p-value of <0.05 was studied statistically significant. All statistical analyses were accomplished with trial version of GraphPad Prism software using windows operating system (Pasupuleti *et al*., 2021).

RESULTS

Physicochemical Characterization

Thickness, Hardness and Friability

The thickness of the sublingual tablets was established by use of a vernier caliper, by evaluating ten (n=10) tablets from each batch. The mean thickness was within the 2.8±0.010 to 3.2±0.015 mm which was in the range of ±2% of the standard value. All measurements were made in triplication. The tablet hardness was measured with the Pfizer hardness tester and a hardness value of 2±0.104 to 3±0.152 kg/cm^2 was acceptable in terms of mechanical stability. Friability was determined using a Roche friability tester and they ranged from 0.10±0.061 to 0.30±0.047% for all formulations well below 1% limit that is stipulated by IP standards and therefore indicated satisfactory mechanical strength of the tablets. The obtained results are presented in Table 2.

Wetting Time

The wetting time of the prepared tablets was evaluated and the results showed wetting times ranging from 42±1.52 to 49±1.73 sec, indicating rapid water uptake, which is favorable for prompt disintegration and effective sublingual drug release. The findings are presented in Table 3.

In vitro disintegration time

The disintegration time of the sublingual tablets was assessed using a disintegration testing apparatus (Model ED-4L; Lab India). The tablets exhibited rapid disintegration, with times ranging from 10±1.154 to 12±1.527 sec. The findings are summarized in Table 3.

In vitro drug release study

In vitro drug release studies of the formulated Apixaban sublingual tablets were evaluated using a USP dissolution test apparatus type II (paddle; Model ED-4L, Lab India). Three formulations (F1-F3), containing varying concentrations of the matrix polymer PVPK-30 and the superdisintegrant crospovidone-INF-10, were evaluated. All formulations showed rapid and high percent cumulative drug release, ranging from 94.01±0.145% to 95.71±0.423%. Formulation F1 had the maximum percent cumulative drug release rate (95.71±0.423%) between 180 Sec. The findings are presented in Table 3.

Table 4: Effect of Apixaban Sublingual tablet on Bleeding time using Cutaneous Bleeding Model in Rats (*n*=6).

Group	Treatment Description	Mean Bleeding Time (Sec)	*p*-value (vs. Normal)
Group I Normal Control	No disease / untreated rats	135.2±10.5	-
Group II Negative Control	Blank (placebo) tablet	138.6±9.8	0.64
Group III Standard Control	Marketed Immediate release Apixaban tablet (2.5 mg)	182.3±12.2	<0.01
Group IV Test Control	Prepared Apixaban sublingual tablet (2.5 mg)	215.4±18.7	<0.001

In vivo Study

Toxicity Study

The results showed that sublingual apixaban tablets were safe, with no cases of mortality or morbidity reported at doses up to 10 mg/kg.

Anticoagulant Activity of Apixaban tablet using Cutaneous Bleeding time Model

The *in vivo* anticoagulant activity of prepared Apixaban (sublingual) tablets dosage (2.5 mg) was tested in rats using the cutaneous bleeding time model and compared with several groups: group I normal control no disease normal saline, group II negative control, blank (placebo) tablet, group III standard control (marketed immediate release Apixaban tablets 2.5 mg), and group IV test control (prepared Apixaban sublingual tablet 2.5 mg. The normal control group showed the bleeding time to be 135.2±10.5 sec, within the physiological range for the normal rats. The negative control group having a blank (placebo) tablet had a bleeding time of 138.6±9.8 sec and it was statistically non-significant (p=0.64) from the normal group, thus proving that the excipients alone did not affect the bleeding profile. The standard control group that was administered the marketed immediate release Apixaban tablet 2.5 mg showed a significant effect on the bleeding time (182.3±12.2 sec, p<0.01), a 95% confidence interval, revealing the anticoagulant effect of the active drug. Notably, the test control group that received the prepared Apixaban sublingual tablet 2.5 mg showed significantly extended bleeding time which was 215.4±18.7 sec and found to be highly significant (p<0.001) than the normal control group. This shows that the sublingual route may provide higher bioavailability and a faster onset of action by avoiding first-pass metabolism as shown in Table 4 and Figure 1.

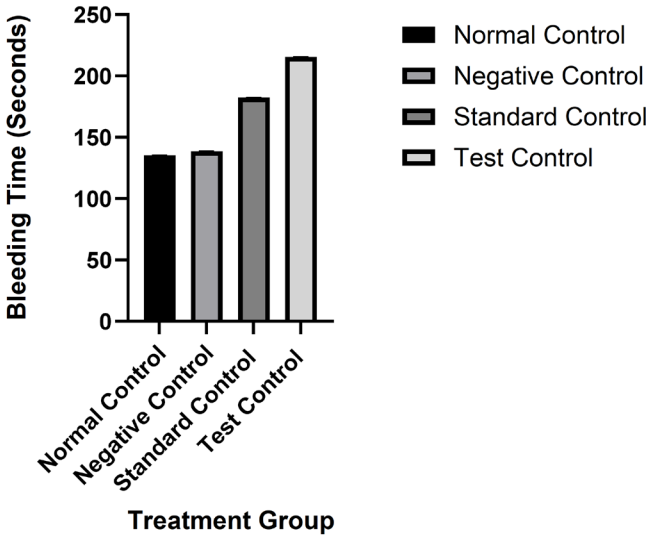

Figure 1: Comparative bleeding time in treatment groups: Normal Control, Negative Control, Standard Control, Test Control. Results are expressed as mean+SEM.

Anticoagulant Activity of Apixaban Tablets Using Clotting Time Model

The *in vivo* anticoagulant activity of Apixaban sublingual tablets (2.5 mg) was studied with the model of clotting time in rats and compared in four groups: normal control, negative control (blank/placebo tablet), standard control (marketed IR tablet), and test control (prepared sublingual tablet). The aim was to evaluate the effectiveness of the recently prepared sublingual formulation as compared to the standard marketed tablet. The group-I normal control had a clotting time of 150.6±11.2 sec which is within the normal physiologic range for no disease, untreated rats. The group-II negative control, which was given a blank (placebo) tablet that did not contain of Apixaban, had a clotting time of 152.8±9.6 sec. This was statistically non-significant (p=0.73) to the group-I normal control and the 95% confidence interval (-10.4 to +6.0 sec) indicated further that the placebo had no anticoagulant effect. This validates that the excipients in the formulation did not interfere with the blood coagulation parameters. The group-III standard control which was given the marketed IR Apixaban tablet showed a significant rise in clotting time to 192.5±13.4 sec. The difference between the group-I normal control was statistically significant (p<0.01), confirming the expected anticoagulant effect of Apixaban through the conventional oral route. Importantly, the group-IV test control, which was given the prepared Apixaban sublingual tablet, had the highest prolongation of the clotting time at 225.2 ±15.7 sec. This

increase was highly significant (p<0.001) compared to the group-I normal control implies a strong and reliable effect. The longer clotting time of the group-IV test control indicates increased bioavailability or improved absorption of the drug through the sublingual route leading to better anticoagulant activity than the marketed available IR oral tablets as shown in Table 5 and Figure 2.

In vivo Mucoadhesion and Residence Time

The *in vivo* mucoadhesive behavior of the prepared Apixaban sublingual tablets was evaluated in male Wistar rats (n=3) to assess the ability of the formulation to be in contact with the sublingual mucosa until complete disintegration. The average mucoadhesive residence time was seen to be 132±8.4 sec. All tablets were found to remain adherent under the tongue without displacement and premature swallowing during the observation period. The adhesion was obtained very quickly (in15-20 sec) gratitude to the presence of hydrophilic disintegrants, such as Crospovidone and PVPK 30, which contributed to the rapid swelling and intimate contact with the moist mucosal surface. The tablets retained their position up to complete disintegration, which was confirmed to be providing enough mucosal retention time for the drug to be dissolved and absorbed. No irritation, inflammation or behavioural discomfort was found in any of the animals during or after administration suggesting good mucosal compatibility and safety as shown in Figure 3.

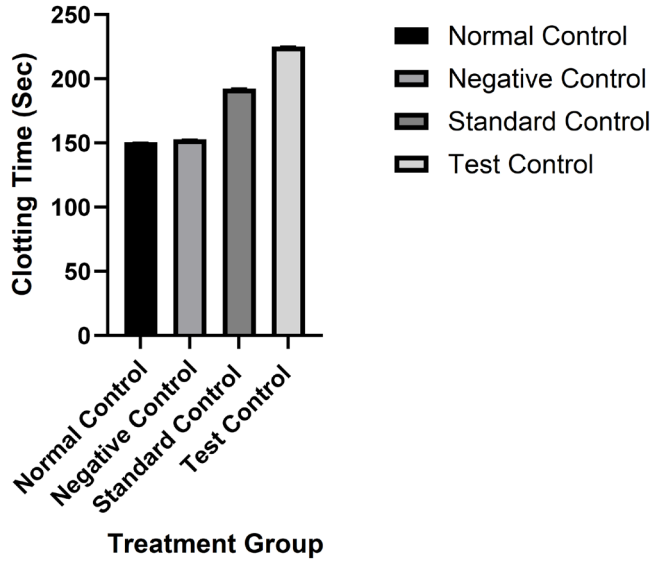

Figure 2: Comparative clotting time in treatment groups: Normal Control, Negative Control, Standard Control, Test Control. Results are expressed as mean+SEM.

Determination of Sublingual Mucosal pH

The pH of the sublingual mucosal surface was measured in healthy male Wistar rats (n=3) with a calibrated digital flat surface pH electrode. The measurements taken were in triplicate for each animal to ensure accuracy and reproducibility. Sublingual pH values observed ranged from 6.7 to 6.9 with a pH of 6.8±0.06 calculated as mean pH. These results confirm that the sublingual environment is mildly acidic to neutral as observed in reported physiological norms. The recorded pH is in the optimum range for mucosal drug absorption and is suitable for the usage of hydrophilic excipients in formulation. Importantly, no significant variability between animals was seen and the procedure caused no irritation and injury to the mucosa during or after the measurement.

Pharmacokinetic studies of various Apixaban formulations

The pharmacokinetic parameters of Apixaban Sublingual tablets was as shown in Table 6. *In vivo* pharmacokinetic plasma drug concentration profiles as shown in Figure 4. Concentration of the drug in blood was assessed at 8 hr using a USP authenticated HPLC method. The peak drug plasma concentration (C_{max}) was found to be 0.38±0.047 ug/mL for Group A and 0.40±0.005 ug/mL for Group B, there was a slight increase in C_{max}, 0.02 ug, for Group B. This slight elevation in Group B implies a slightly increased rate of absorption as a result of sublingual administration and may be because sublingual administration allows for more rapid systemic absorption by bypassing first pass metabolism. Despite this increase, time to reach maximum concentration (T_{max}) was unchanged at 4 hr for both formulations suggesting that while the rate of absorption is improved, the overall timing of peak

Table 5: Effect of Apixaban Formulations on Clotting Time in Rats (n=6).

Group	Treatment Description	Mean Clotting Time (sec)	p-value (vs. Normal)
Group I Normal Control	No disease / untreated rats	150.6±11.2	-
Group II Negative Control	Blank (placebo) tablet	152.8±9.6	0.73
Group III Standard Control	Marketed Immediate release Apixaban tablet (2.5 mg)	192.5±13.4	<0.01
Group IV Test Control	Prepared Apixaban sublingual tablet (2.5 mg)	225.2±15.7	<0.001

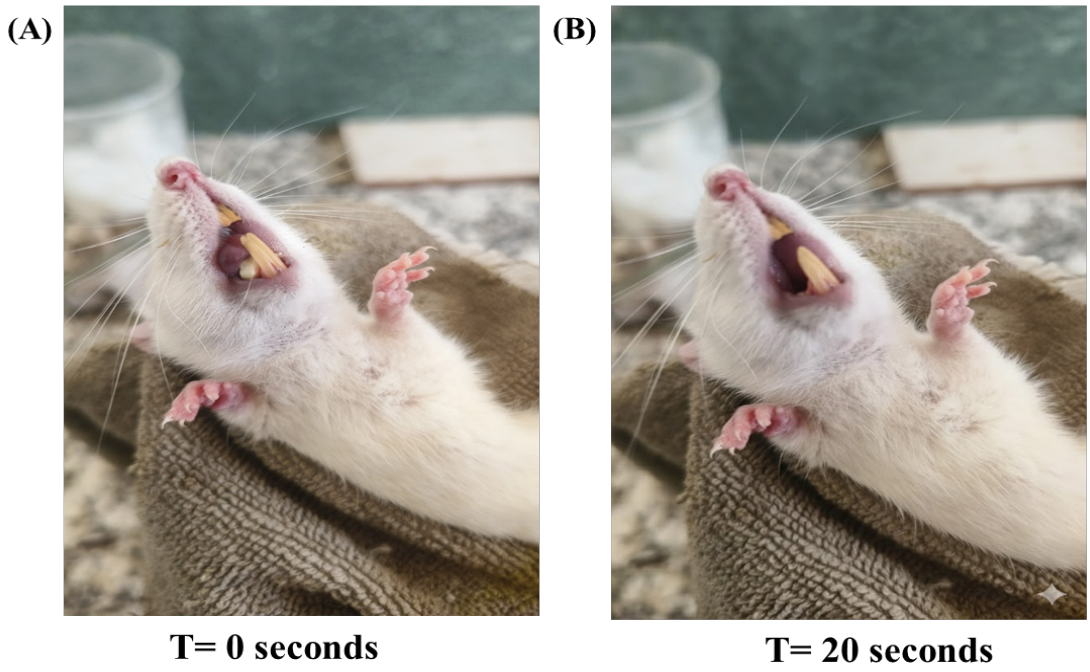

Figure 3: (A) showed the administration of a prepared sublingual tablet at time 0 sec. (B) shows the mucoadhesion and residence time of the prepared tablet at 20 sec.

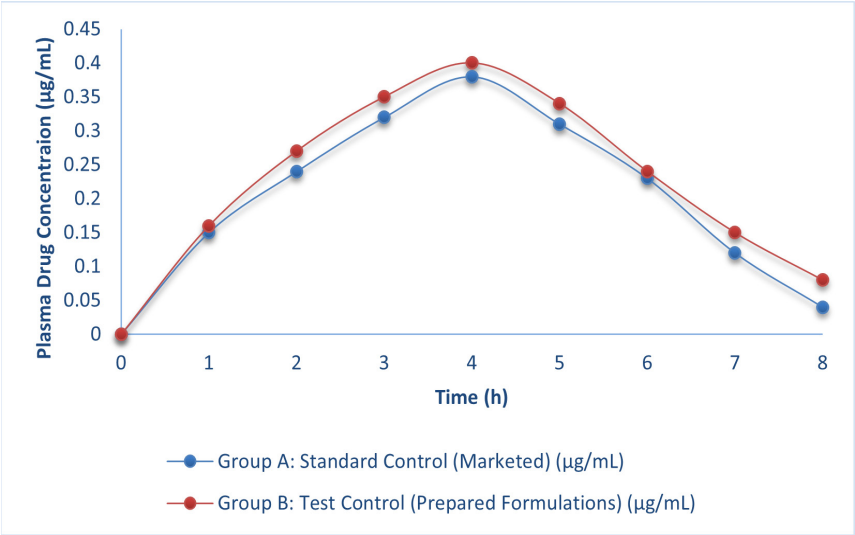

Figure 4: Comparative graph of *in vivo* pharmacokinetic study data between Apixaban treated groups.

concentration is not. A significant difference was observed in the area under the plasma Concentration-Time Curve (AUC), an important measure of the total drug exposure. The AUC_{0-24} of Group A was found to be 1.823±0.030 ug/mL/hr, and for Group B, the higher result of 1.990±0.020 ug/mL/hr was obtained. This shows that the test formulation achieved a greater sustained and complete absorption over the 8 hr sampling window, used here as a representative of the 24 hr period because of available data. More interest, $AUC_{0-\infty}$, encompassing extrapolated drug exposure beyond the last time point measured, amounted to 1.924±0.005 and 2.146±0.010 ug/mL/hr for and B, respectively. This shows that there is a definite improvement in the bioavailability of the test form. The Mean Residence Time (MRT) which is the mean time the drug stays in the body was little longer for Group A (3.51±0.037 hr) compared to Group B (3.09±0.024 hr). While this implies that the marketed formulation may stay out a bit longer in the circulation, the difference is not significant and could indicate more rapid absorption and subsequent elimination in the test formulation. The main thing that comes out of this comparison is the bioavailability enhancement in the test formulation. Calculated on the basis of the $AUC_{0-\infty}$, the test formulation showed an 11.54% increase in bioavailability over that of the marketed product. This improvement is likely because the sublingual route has an advantage in not being subject to

Table 6: Comparative *in vivo* pharmacokinetic study data between Apixaban treatment groups.

Parameter	Group A: Marketed Apixaban Tablets (2.5 mg)	Group B: Prepared Sublingual Apixaban Tablets (2.5 mg)
C_{max} (µg/mL)	0.38±0.047	0.40±0.005
T_{max} (hr)	4±0.014	4±0.012
AUC_{0-24} (µg/mL/hr)	1.823±0.030	1.990±0.020
$AUC_{0-\infty}$ (µg/mL/hr)	1.924±0.005	2.146±0.010
MRT (h)	3.51±0.037	3.09±0.024
Bioavailability Enhancement (%)	-	11.54%

Note: All values are expressed as Mean±SD

first pass hepatic metabolism, which in many cases reduces the effective dose delivered by the drug to systemic circulation in oral formulations.

DISCUSSION

The developed Apixaban sublingual tablets were analyzed using physicochemical properties and showed physicochemical characteristics that are favorable to the sublingual drug delivery system. The thickness, hardness and friability of the tablets were all within acceptable limit indicating that the mechanical strength was adequate to handling transportation and at the same time allow easy disintegration in the sublingual cavity. The acceptable range of 2-3 kg / cm^2 together with a friability of less than 1% is consistent with the pharmacopeial standards of fast disintegrating and sublingual tablets. Other sublingual formulations have also reported similar results, with moderate hardness and low friability was found to stimulate a rapid release of the drug without affecting the integrity of the tablet (Prajapati *et al*., 2012; Gupta *et al*., 2009).

The uniformity of thickness and weight variation also alternative indication of good powder flow and homogenous die filling during a direct compression, which points at the appropriateness of the selected excipients and manufacturing process. The rapid wetting time and *in vitro* disintegration tests were effective in providing a good therapeutic performance in the sublingual cavity. The ensuing wetting time of 42-49 sec suggests that water uptake was rapid, this implies that the drug dissolved in the limited amount of saliva contained in the sublingual area and was disintegration time. The rapid disintegration time (10-12 sec), especially, is beneficial in emergency administration of anticoagulants subsequently it reduces a chance of swallowing and assurances prompt mucosal contact. This outcome is explained by the inclusion of crospovidone Inf-10 and PVPK-30 that swell fast and cause capillary activity that causes rapid disintegration of the tablets. Previous research on sublingual and buccal tablets has pointed out that fast disintegration of a tablet is a precursor to effective transmucosal absorption and prompt action effect (Rachid *et al*., 2011; Boddupalli *et al*., 2010).

The *in vitro* drug release profile also provide strengthens assurance to the formulation technique, with all formulations exhibiting more than 94% cumulative drug release over the 180 sec, suggesting that Apixaban dissolves and absorbed quickly with sublingual mucosa. The higher dissolution rate can be attributed with the combination of rapid disintegration of the tablet with increased surface area exposure, and the hydrophilic properties of the excipients used. For drugs with lower oral bioavailability, such as Apixaban, which is metabolized in the liver, dissolution at the absorption site is critical for improving systemic exposure. Other cardiovascular and antimigraine medicines have demonstrated similar improvements in dissolving behavior, with rapid release having a direct positive association with *in vivo* performance (Prajapati *et al*., 2014; Alali *et al*., 2021).

The *in vivo* anticoagulant efficacies of the evaluated bleeding time and clotting time models showed the superiority of the sublingual formulation in comparison to the commercially available immediate-release oral tablet. Bleeding and clotting times in the test group were significantly prolonged, which is the indication of increased anticoagulant activity, which could be directly attributed to the increased systemic absorption of Apixaban through the sublingual route. The fact that the impact in the placebo group was non-significant demonstrates that the apparent pharmacological action was not caused by the excipients. These findings are consistent with Apixaban's recognized mechanism as a direct Factor Xa antagonist; thus, higher plasma concentrations result in more pronounced the coagulation process inhibition (Wong *et al*., 2011a; Bauer, 2011).

The improved anticoagulant effect with sublingual administration confirms the assumption that avoiding the first-pass effect in the liver leads to increased and quicker drug effect. Additional studies on mucoadhesion and residence time also confirmed the appropriateness of the formulation to be used when administered sublingually. The tablets were kept attached to the sublingual mucosa around 132 sec, which is long enough to ensure that the tablet disintegrates and the drug dissolves without being swallowed extremely fast. The fast formation of adhesion is due to the use of the hydrophilic polymers, which swell in the presence of hydration and close contact with the mucosal surface is formed. Particularly, there were no irritation or mucosal damage signs, which means that it is well-tolerated in the area. These findings correspond with previous studies that sufficient quality of residence time and mucosal compatibility are essential in effective transmucosal drug delivery (Khutoryanskiy, 2011; Szekalska *et al*., 2019).

The pharmacokinetic studies supported enhanced bioavailability of Apixaban when taken sublingually. The small increase in C_{max} and the significant improvement in AUC, despite the fact that T_{max} remained constant, indicate greater systemic exposure. This 11.54% increase in bioavailability in the sublingual formulation can be attributed to the avoidance of gastrointestinal degradation and hepatic first-pass metabolism, both of which have been shown to reduce Apixaban oral bioavailability. Other drugs administered through the sublingual route have showed similar pharmacokinetic benefits, with increased therapeutic effects attributed to high AUC values (Zhang *et al*., 2002; Yoo *et al*., 1999).

The shorter mean residence time seen with the sublingual tablet could be attributed to improved absorption and distribution, which is advantageous in the case of acute or emergency anticoagulation. In general, the extensive discussion reveals that the improved physicochemical features, rapid disintegration active anticoagulant action, and superior pharmacokinetic efficiency of Apixaban sublingual tablets are mechanistically correlated. The results are a strong indicator of the sublingual route's potential as an effective alternative to oral delivery in patients who require anticoagulation immediately or who have difficulties with swallowing, and they are strongly supported by the current literature.

CONCLUSION

The present study was aimed to formulation and evaluation of sublingual formulation of Apixaban to overcome the limitations associated with its conventional oral delivery. However, its oral administration is complicated by a delayed onset of action, reduced bioavailability due to hepatic first-pass metabolism, and limited efficacy in persons with swallowing difficulty or in emergency cases requiring urgent anticoagulation. This work successfully developed Apixaban sublingual tablets using direct compression method and evaluated their physicochemical properties, *in vivo* anticoagulant activity, and pharmacokinetic activity with comparison to the marketed oral formulation. The prepared sublingual tablets demonstrated excellent mechanical integrity, fast disintegration time (10-12 sec), and a wetting time ranging from 42-49 sec, all of which are perfect for sublingual administration. *In vitro* drug release assessments demonstrated over 94% cumulative drug release, indicating efficient drug dissolution from the formulation. Toxicological investigations using OECD 423 criteria established the tablets' safety, with no deaths or toxicity observed in Wistar rats up to a dose of 10 mg/kg/ body weight. The *in vivo* anticoagulant activity of the sublingual formulation was studied using bleeding and clotting time models. The test group receiving the sublingual tablets showed a significant increase in bleeding time (215.4±18.7 sec) and clotting time (225.2±15.7 sec) compared to the standard marketed IR tablet (182.3±12.2 sec and 192.5±13.4 sec, respectively). These findings suggest that the sublingual route not only improve the anticoagulant action of Apixaban but also ensures faster systemic drug availability due to avoidance of gastrointestinal degradation and hepatic metabolism. Pharmacokinetic studies further supported the superiority of the sublingual formulation. While both formulations had the same T_{max} of 4±0.014 hr, the sublingual tablets achieved a slightly higher peak plasma concentration (C_{max}) of 0.40±0.005 µg/mL versus 0.38±0.047 µg/mL in the marketed IR tablet. More importantly, the total drug exposure, as measured by $AUC_{0-\infty}$, was significantly higher for the sublingual formulation (2.146±0.010 µg/mL/hr) compared to the marketed formulation (1.924±0.005 µg/mL/hr), indicating an 11.54±0.025% enhancement in bioavailability. The shorter Mean Residence Time (MRT) of 3.09±0.024 hr for the sublingual formulation, as compared to 3.51±0.037 hr for the marketed product, may reflect more efficient systemic uptake and faster elimination following enhanced absorption. The results of the current study significantly indicate the potential benefits of sublingual Apixaban tablet as an alternative to oral tablets. The sublingual route considerably increases pharmacokinetic performance and anticoagulant activity, making it especially useful for patients who require a quick onset of action, have difficulty swallowing, or are in an emergency clinical circumstance. Future research should look into the stability, palatability, and long-term clinical safety of this formulation, as well as human pharmacokinetic trials, to help establish its therapeutic benefits and facilitate clinical translation.

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ABBREVIATIONS

APX: Apixaban, **NOACs:** Novel Oral Anticoagulants, **DVT:** Deep Vein Thrombosis, **PE:** Pulmonary Embolism, **GI:** Gastrointestinal **FXa:** Factor Xa, **pH:** Potential of Hydrogen, **HPLC:** High Performance Liquid Chromatography, **C_{max}:** Peak plasma concentration, **T_{max}:** Time to reach peak plasma concentration, **$AUC_{0-\infty}$:** Area under the plasma concentration versus time curve, **USP:** United States Pharmacopeia, **PVPK-30:** Polyvinylpyrrolidone K-30, **IAEC:** Institutional Animal Ethical Committee, **CCSEA:** Committee for Control and Supervision of Experiments on Animals, **ATC:** Acute Toxicity Class, **RPM:** Revolutions Per Minute, **MRT**: Mean Residence Time, **OECD:** Organization for Economic Cooperation and Development; **MCC:** Microcrystalline Cellulose; **SEM:** Standard Error of Mean; **SD:** Standard Deviation; **IR:** Immediate Release; **PVP:** Polyvinylpyrrolidone; **APX:** Apixaban.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTION

P.K.: Conceptualization and methodology V.R.: Supervision, Review.

SUMMARY

The study describes the formulation, evaluation, and in *in vivo* studies of Apixaban sublingual tablets as an alternative to the standard oral formulation of anticoagulants. Apixaban is a direct factor Xa inhibitor that commonly used in the prevention and treatment of thromboembolic disorders, including deep vein thrombosis, pulmonary embolism and stroke related to atrial fibrillation. Apixaban is efficacious and safe when taken orally, however its pharmacologic efficacy may be limited due to first-pass hepatic metabolism, delayed absorption, intermittent gastrointestinal absorption, and difficulties to administer in elderly, critically ill, or dysphagic patients. To address these shortcomings, the research focuses on sublingual drug administration as a non-invasive therapy that allows for rapid systemic absorption because it does not go through hepatic first-pass metabolism, which improves therapeutic efficacy and patient compliance, particularly in an emergency situation.

The primary goal of the research was to prepare Apixaban sublingual tablets and evaluate their physicochemical properties, *in vitro* drug release, *in vivo* anticoagulant effect, mucoadhesive properties, and pharmacokinetic profile in comparison to a commercially available oral drug formulation. The tablets were manufactured using the direct compression procedure, which is simple, inexpensive, and efficient when dealing with sublingual dosage forms. Excipients were also chosen with the purpose of improving tablet hardness, disintegration, wetting, and drug release. The manufactured tablets performed quality control checks to ensure that they met pharmacopeial criteria and were safe to swallow sublingually. These tests measured hardness, thickness, friability, weight change, wetting time, and disintegration time.

The physicochemical properties established that the sublingual tablets possessed adequate mechanical strength and low friability, which means that they would not be affected during handling and transportation. The rapid wetting and disintegration time was observed which is needed to facilitate the sublingual formulation to permit quick drug release and uptake via the highly vascularized sublingual mucosa. *In vitro* dissolution studies demonstrated that the improved formulation drug released more than 90% within a short period of time. This demonstrated that the drug could be absorbed systemically, which supported the notion that the drug would start working quickly. To investigate *in vivo* anticoagulant efficacy in Wistar rats, this research used previously described pharmacodynamic models, such as bleeding time and clotting time studies. These models will make accurate predictions about the effectiveness of anticoagulants. The Apixaban sublingual formulation significantly increased bleeding and clotting times when compared to the placebo group, indicating effective anticoagulant activity. The sublingual tablets showed a faster and more potent anticoagulant effect than the previously marketed oral formulation, demonstrating greater systemic availability when taken sublingually. Subsequent testing of mucoadhesive strength, retention time on the sublingual mucosa, and local mucosal pH demonstrated good adhesion and retention time without irritation or unfavourable pH changes, indicating that the formulation was acceptable and safe.

Pharmacokinetic studies were performed to quantify systemic drug exposure following sublingual and oral doses formulations. Apixaban Plasma levels in the blood were measured with a validated High-Performance Liquid Chromatography (HPLC) method at predetermined times. The important pharmacokinetic values include maximum plasma concentration (C_{max}), time required to reach maximum concentration (T_{max}), area under the plasma Concentration-Time Curve (AUC), elimination half-life, and mean residence time. The findings showed that the sublingual formulation was found to be having higher C_{max} and AUC levels than the current oral market tablet. This suggests that the drug was more readily absorbed by the sublingual mucosal. The T_{max} that was achieved with the earlier T_{max} showed that the drug was readily absorbed. This was happening because the drug did not undergo first-pass metabolism and therefore reached the bloodstream. Thus, the research demonstrates the clinical significance of sublingual Apixaban by attributing its high pharmacokinetic efficiency to an increasing anticoagulant activity. The rapid action and high bioavailability is a good sign that it can be used as a form of treatment in acute and emergency conditions. Furthermore, sublingual dose form may be an appropriate option if a patient has difficulty swallowing or requires anticoagulant medicine as soon as feasible. Finally, the outcomes presents a good evidence to favour that Apixaban sublingual tablets are feasible and beneficial in contrast to the regular oral tablets. The findings provide important information about sublingual drug delivery methods and suggest that additional clinical research are needed to transform preclinical findings into clinical therapeutic treatments.

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