Ind. J. Pharm. Edu. Res., 2027; XX(XX):1-20.
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Original Article

Design and Evaluation of Apixaban Tablets Using Quality By Design (Qbd) Approach for Enhanced Physicochemical Attributes

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ABSTRACT

Objectives: The present research aimed to formulation and evaluation sublingual tablets of apixaban to enhance its physicochemical properties. Apixaban, a selective Factor Xa inhibitor belonging to Biopharmaceutical Classification System (BCS) Class III, exhibits low permeability and variable oral bioavailability. Therefore, a sublingual delivery approach was adopted to bypass first-pass metabolism and has the potential to enhance oral bioavailability. **Materials and Methods:** The formulation was developed using the Quality by Design (QbD) approach and Design of Experiments (DoE) methodology in order to systematically identify and optimize Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs). A 3^2 Full Factorial Design was used based on independent variables of crospovidone INF-10 as superdisintegrant and Polyvinylpyrrolidone K-30 (PVPK-30) as matrix polymer. Their effect on Critical Quality Attributes (CQAs) i.e., tablet disintegration time, hardness, and percent cumulative drug release was analyzed using Response Surface Methodology (RSM). Optimization was done using Design expert software (Stat-Ease 360 Trial Version). **Results:** The optimized formulation showed the tablet hardness of 3.2 kg/cm^2±0.030, disintegration time of 12 sec±1.527 and a percent cumulative drug release of 95.71%±0.467. There was a good agreement between predicted and experimental values of the dependent variables with negligible percent bias, suggesting the validity of the model. The response surface plots were useful to illustrate the interactive effects of the chosen variables on the CQAs. **Conclusion:** The study concluded that the 3^2 Full Factorial Design effectively optimized the formulation of apixaban sublingual tablets, ensuring reproducibility and quality while minimizing resource utilization. The optimized sublingual formulation provides a promising alternative to conventional oral delivery and has the potential to enhance oral bioavailability and offering a rapid onset of action, contributing to improved patient compliance.

Keywords: Apixaban, Critical material attributes, Critical quality attributes, Factorial design, Polyvinylepyrrolidone K-30, Quality by design.

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Received: 11-05-2026;
Revised: 23-07-2026;
Accepted: 08-09-2026.

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INTRODUCTION

Solid dosage forms are the most often used pharmaceutical formulations because they are stable and easy to administer with accurate dosing, and patient compliance. These forms contain Active Pharmaceutical Ingredients (APIs) along with excipients, which aid in drug stability, absorption, and controlled release. Solid dosage forms are preferred in drug.[1] formulation and development because they offer longer shelf life, better dose uniformity Click or tap here to enter text.Sublingual solid dosage forms are pharmaceutical preparations planned to be administered under the tongue, where the medication dissolves and is absorbed immediately into the bloodstream throughout the sublingual mucosa. This route of administration does not require passage by the gastrointestinal tract and hepatic first pass metabolism, giving rapid onset of action and has the potential to enhance oral bioavailability for some drugs but not limitation sildenafil citrate (oral bioavailability about 40%),[2] zolmitriptan (oral bioavailability about 40 %),[3] which is absorbed directly into systemic circulation via a rich vascular sublingual mucosa. This route avoids the concern of enzymatic degradation in the gastrointestinal tract as well as liver first pass metabolism that can significantly decrease the bioavailability of orally administered drugs.[4] Moreover, the thinness and permeability of the sublingual mucosa assure rapid onset of action, and this route is very advantageous for the administration of drugs that need to have a rapid absorption and to be systemic.[5] Sublingual

DOI: 10.5530/ijper.20274651

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dosage forms present valuable advantages for the unconscious patients, because they present a non-invasive and efficient method of drug administration when oral intake is impossible.[6] This route bypasses the swallowing process and is therefore appropriate for patients who are unconscious, uncooperative or have difficulty swallowing due to medical conditions.[7] In addition, the promptness of action of the sublingual absorption is very relevant in emergency situations, such as administration of drugs for pain, cardiac disorders or seizures.[8] The sublingual route provides effective delivery of drugs even in cases where other routes are not possible. Apixaban is an oral anticoagulant that is a Direct Oral Anticoagulant (DOAC) that inhibits selectively factor Xa, which is a crucial enzyme in the coagulation cascade.[9] This inhibition prevents generation of thrombin from prothrombin, which in turn results in a reduction of blood clot generation.[10] It is used regularly in the prevention and management of thromboembolic diseases like DVT, PE as well as inhibition of stroke and systemic embolism in patients among non-valvular atrial fibrillation. Apixaban is mainly metabolized by the CYP3A4 enzyme and is excreted by both renal and fecal routes. It should also be used with attention in patients who have hepatic or renal impairment. That is directly supports the rationale for choosing the sublingual delivery route. Because CYP3A4-mediated metabolism contributes significantly to apixaban's first-pass effect and reduced oral bioavailability, bypassing hepatic metabolism becomes essential, as it has the potential to enhance oral bioavailability. Emphasizing this pharmacokinetic limitation reinforces the justification for developing a sublingual formulation to enhance absorption efficiency and therapeutic performance.[11] Moreover, it is contraindicated in people who have an ongoing bleeding or a high risk of haemorrhage.[12] Apart from its therapeutic benefits, apixaban showed pharmaceutical challenges in its low bioavailability properties. Apixaban bioavailability is approximately 50% and can be affected by various factors such as drug permeability, first pass metabolism, dissolution rate, and changes in pH in the gastrointestinal tract, and other medications.[13–15] This inconsistency in blood levels could affect its ability to prevent blood clots. The low bioavailability of drugs can hinder their effectiveness, because they may not be in adequate concentrations in systemic circulation.[16] The drug is subject to first pass metabolism in the gut and the liver which can cause incomplete absorption and decreased bioavailability.[17] Apixaban classified as a BCS Class III drug (high solubility, low permeability), suitable formulation strategies can enhance its mucosal permeation for sublingual delivery. With a molecular weight of 459.5 g/mol and log $P \approx 2.7$,[18] Apixaban possesses moderate lipophilicity ideal for transmucosal absorption (optimal log P: 1-3).[19] Being largely unionized at physiological pH (pKa≈13.2),[20] it can readily diffuse passively through the sublingual mucosa. The sublingual formulation of Apixaban was developed based on evidence from previous studies involving drugs with similar or higher molecular weights and low permeability (Natasha *et al*., 2021) formulated sublingual tablets of Desmopressin (1069.22 g/mol, BCS Class III),[21] (Changcheng *et al*., 2018) developed sublingual tablets of Oxytocin (1007.19 g/mol, BCS Class III).[22] Compared to these, Apixaban (459.5 g/mol, BCS Class III) exhibits a more favorable molecular profile. Additionally, successful sublingual formulations of Sildenafil Citrate (666.7 g/mol, BCS Class II). The study successfully demonstrated that a QbD-based 3^2 factorial design can be effectively applied to develop robust and reproducible apixaban sublingual tablets. The optimized formulation showed rapid disintegration, high drug release, and satisfactory stability, suggesting its potential as an alternative sublingual delivery system

The aimed of present study to develop sublingual tablet formulations to improve the physicochemical properties of apixaban, to solve the limitations associated with its conventional solid oral dosage forms. Generally, sublingual administration may be an effective strategy to increase the Potential to enhance bioavailability and therapeutics efficiency of anticoagulant drugs with inadequate oral bioavailability. The QbD-based technique ensured an extensive understanding of the formulation parameters, resulting in improved product quality and performance while reducing experimental effort and cost.[23]

MATERIALS AND METHODS

Materials

Chemical And Reagents

Apixaban (APX) had been provided as gift sample from Morepen Laboratory Ltd., Parwanoo, Himachal Pradesh, India. crospovidone INF-10 was bought from Scope ingredients Pvt. Ltd., Mumbai, India. polyvinylpyrrolidone K-30 (PVPK-30) was bought from PS Impex, Panchkula, Haryana, India. microcrystalline cellulose PH-112 was purchased from Biosmith Lifesciences Baddi, Himachal Pradesh, India. pearlitol SD 200 was purchased from Signet Excipients Pvt. Ltd., Other inactive ingredients were also collected as gift sample from Morepen Laboratory Ltd., Parwanoo Himachal Pradesh India. All of the other reagents were analytical grade.

Instruments

Fourier Transform Infrared Spectroscopy (FTIR PerkinElmer Spectrum IR model 10.7.2, United States), Differential Scanning Calorimetry (DSC) (model pyris 6 DSC perkin elmer, USA), X-ray diffraction (XRD) (X-ray diffractometer model UltimalV, Rigaku corporation Japan), High-Performance Liquid Chromatography (model ED-4L; Lab India). disintegration appratus (model ED-4L; LabIndia, India) 8Dissolution USP apparatus type II paddle (Model ED-4L, LabIndia, India), tablets compression machine (Cadmach model CPC20, India).

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Methods

Drug Polymer Interaction

The compatibility between the drug and excipients is an essential part of the preformulation process, as interactions between the drug and excipients can have a meaningful impact on the physical and chemical properties of final products. Such interactions may affect drug stability, bioavailability, safety and therapeutic efficacy. That is essential to confirm that the drug does not interact negatively with the polymers or excipients selected, under the experimental conditions. Unfavorable interactions can cause drugs and their active ingredients to degrade, lose potency or alter their pharmacokinetic behavior. To assurance compatibility and preservation of the formulation itself, sophisticated analytical methods, such as Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) and X-ray Diffraction (XRD) are frequently utilized. These methods are useful for screening for possible interactions and are a part of the development of a stable and effective formulations.[24,25]

Fourier transform infrared spectroscopy (FTIR)

The FTIR Spectrophotometer had been carried out to measure drug-polymer interaction. The analysis involved was conducted by the preparation of samples with enough placing of a required sample of powder with KBr at 1:100. Each cell was then scanned with an instrument (FTIR- PerkinElmer Spectrum IR version 10.7.2) in the range of 4000 to 450 cm^{-1} wave number, with transmittance spectra being recorded. The analysis focused on detection shift in the drugs spectra induced by the presence of polymer excipients, aiding in the evaluation of physical interactions among the drug and excipients.[26]

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry were carry out through model pyris 6 DSC perkin elmer, USA, which was indium calibrated. The DSC thermograms of pure apixaban, crospovidone INF-10, Polyvinylpyrrolidone K-30 (PVP K-30), and the optimized formulation were recorded and evaluated to investigate the thermal behavior and compatibility of the drug with the selected excipients. This was done using samples of approximately 3 mg placed in an aluminum pan, sealed and with a temperature of 40-300 °C at a ramp rate of 10 °C/min in an inert pure environment of nitrogen. The determination of the melting and transition points were carried out through software provided with the device.[27]

X-ray Diffraction (XRD)

X-ray diffraction were accomplished through X-ray diffractometer model UltimalV, Rigaku corporation Japan was employed to record X-ray diffraction design each of the powders when exposed to succeeding conditions. A single-spectral (CuK radiation source) had been conducted at 45 kV and 40 mA and scanned at a rate of $3^{o}(2\theta)$/min in 5^{o}-45^{o} (2θ) range. The amorphous or crystalline nature of following samples were concluded through occurrence of X-ray diffractogram of the respective products. In cases where discrete, sharp peaks of measureable intensity can be observed, we say that the material is crystalline or partly crystalline. In case of broad peaks, one can see a halo on the diffractogram which reveals the amorphous nature of the test material.[28]

Quality by design technique (QbD)

The Quality by design technique employed to formulation of drug product, a Quality Target Product Profile (QTPP) were establish for the preparation of sublingual tablets as shown in (Table 1). The apixaban sublingual tablets was formulated using matrix polymer polyvinylepyrrolidone K-30 (PVPK-30) and superdisintegrant crospovidone INF-10 to improved desired therapeutic response and patient compliance.To achieve QTPP criteria such as dosage form, drug delivery route, dose, and stability, Criteria Quality Attributes (CQAs) were identified. These CQAs included hardness, disintegration time, percent cumulative drug release as shown in (Table 1).[29]

Critical Materials Attributes (CMAs)

The critical material attribute are key of physical, chemical and biological characteristics of contributing ingredients, including both Active Pharmaceutical Ingredients (APIs) and excipients, that have a meaningful effect on efficiency, quality and safetyof final formulations. These attributes determine how raw materials behave during processing and how they influence the critical quality attributes of the formulation as shown in (Table 1).[30]

Fishbone/Ishikawa diagram

The Fishbone (Ishikawa) diagram, developed in 1943 by Kaoru Ishikawa, is a widely used quality improvement tool designed to identify root causes of problems and enhance process performance. It visually represents potential contributing factors in the form of a fish skeleton to help analyze quality issues systematically. In the present study, the fishbone diagram was applied to determine the factors affecting the Critical Quality Attributes (CQAs) of apixaban sublingual tablets. Key contributors were identified under categories including Materials (drug-excipient selection, purity, compatibility), Methods (formulation technique, compression parameters, QbD design), Machines (tablet compression, hardness and friability testers, weighing balance), Measurements (cGMP-compliant tests such

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Table 1: Quality By Design (QbD) Elements.

QTPP for development of apixaban sublingual tablets				
QTPP Components	Targets			Justification
Dosage form type	Tablets			Selection of highly water-soluble excipients, disintegrant and polymer to form bioavailable solid dosage form
Dose	2.5 mg			The target dose is 2.5 mg, equivalent to the lowest strength commercial oral tablet
Drug delivery type	Sublingual Delivery			To achieve the desired therapeutic effect
Route of Administration	Sublingual			Improved patient fulfilment in addition to most favored route of drug delivery
Stability	Accelerated Stability			Stability performs as per ICH guidelines to maintained therapeutic effect and bioavailability during storage conditions
CQAs for the preparation of Apixaban sublingual tablets with their rational				
CQAs	Targets			Justification
Hardness	2-3 kg/cm^2			as per Standard reference (IP/USP)
Disintegration Time	NMT-2 min			as per Standard reference (IP/USP)
The time necessary to release 80% of the drug (t80)	$Q_{80} \leq 15$ min			A drug release characteristic desired to release more than 80% as per Standard reference (IP/USP)
CMAs for development of Apixaban sublingual tablets				
CMAs (Independent Variable)	Concentration Range			CQAs (Dependent Variable)
Factors	Level			
	-1	0	+1	
A: Crospovidone INF-10 (mg)	4	6	8	hardness, disintegration time, t-80
B: Ppolyvinylpyrrolidone K-30 (PVPK-30) (mg)	1	1.5	2	

as hardness, friability, disintegration, dissolution, API assay), Environment (temperature, humidity), and Personnel (technical expertise and process handling). The analysis concludes that effective control and optimization of these interrelated factors are essential for achieving consistent quality, stability, and therapeutic performance of apixaban sublingual tablets as shown in (Figure 1).[31]

Design of experiment

A 3^2 Full Factorial Design was applied for development of sublingual dosage form of apixaban (APX). In the current investigation, concentration of crospovidone INF-10 and PVPK-30 was chosen as independent variables such as hardness, disintegration time and percent cumulative drug release were chosen as dependent variables. Every experiment runs, coded and actual levels of independent variables as shown in (Table 2).

The independent variables function were represented by the polynomial equations and effects of independent variables represented through the familiar polynomial equation (Equation 1)

The polynomial equation of the 3^2 factorial designs like this:

$$Y = \beta0 + \beta1A + \beta2B + \beta12\,AB + \beta11A^2 + \beta22B^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots..1$$

where Y is the dependent variable, β0 is the arithmetic mean response of prepared nine batches, and β1 is an projected coefficient for the factor A. The main effects (A and B) are the average of each effect by varying one factor at a time, from minimum to maximum levels. The interaction term "AB" indicates some variations in response after both the two factors are changing at one time. The interaction term "AB" demonstrates how the response alters as the two factors vary sequentially.

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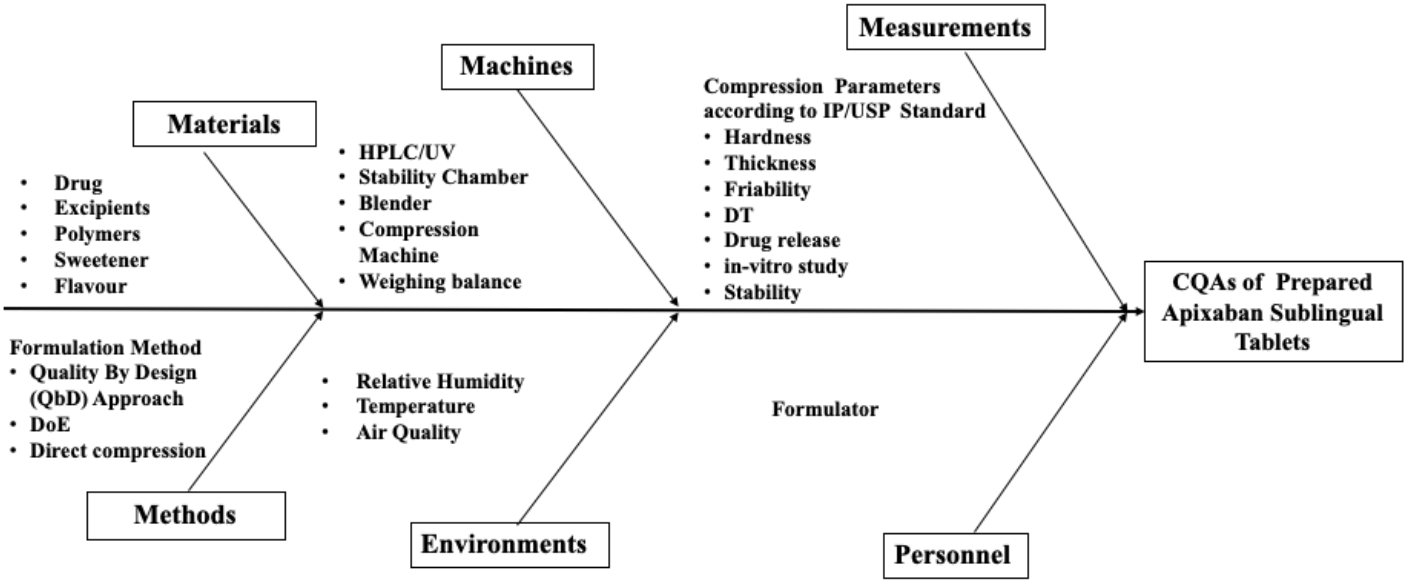


Figure 1: Fishbone/Ishikawa diagram depicting critical quality attributes for Apixaban sublingual tablet.

Table 2: 3^2 **Full Factorial Design with levels of independent variables.**

Formulation Code	Coded Value		Actual Value (mg)	
	Factor A	Factor B	Factor A	Factor B
F1	1	0	8	1.5
F2	1	-1	8	1
F3	-1	0	4	1.5
F4	-1	1	4	2
F5	0	0	6	1.5
F6	1	1	8	2
F7	-1	-1	4	1
F8	0	-1	6	1
F9	0	1	6	2

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Preparation of drug loaded formulation by using 3^2 Full Factorial design

Sublingual tablets were prepared by direct compression method, a straightforward and efficient technique widely used in pharmaceutical manufacturing. In this process, accurately weighed quantities of apixaban, selected polymers, and excipients were individually sifted through a ieve no #40 to ensure uniform particle size and remove any lumps. The sifted ingredients were then blended thoroughly in a suitable blender to achieve a homogeneous mixture. Once uniform mixing was confirmed, the powder mixture was compressed directly by utilizing the tablet punching machine with the suitable punches and dies. The tablets that were obtained and assessed on different physicochemical characteristics including hardness, thickness, disintegration time, weight variation, friability, and drug content to ensure their suitability for sublingual administration and optimal bioavailability as shown in (Table 3).

CHARACTERIZATION OF PREPARED FORMULATION

Thickness

A vernier calliper was used to identify the thicknesses of the sublingual tablets and the average thickness was recorded on individual ten (n=10) tablets of each batch.[32]

Hardness

The hardness of tablets were measured through Pfizer hardness tester. The ideal tablet hardness set around 2-3 kg/cm^2 is deemed appropriate for mechanical stability. The test were conducted in triplicate.[33]

Table 3: Preparation of drug loaded formulation by using 3^2 Full Factorial Design.

Ingredients (% w/w)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
apixaban	2.50	2.50	2.50	2.5	2.50	2.50	2.50	2.50	2.50
pearlitol SD 200	70.50	71.00	74.50	74.00	72.50	70.00	75.00	73.00	72.00
anhydrous lactose	10.20	10.20	10.20	10.20	10.20	10.20	10.20	10.20	10.20
MCC PH-112	3.30	3.30	3.30	3.30	3.30	3.30	3.30	3.30	3.30
crospovidone INF-10	8.00	8.00	4.00	4.00	6.00	8.00	4.00	6.00	6.00
PVPK30	1.5	1.00	1.5	2.00	1.5	2.00	1.00	1.00	2.00
flavour lemon	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
quinoline yellow lake	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
aspartame	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
colloidal silicon dioxide	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20
magnesium Stearate	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90

Friability

The friability test of prepared tablets were observed through Roche Friabilator. In this evaluation, 6 g tablets were weighed and placed in the combined abrasion and shock test, with the plastic chamber of Friabilator rotating at 25 r.p.m. for 4 min., after that the tablets were sifted as well as re-weighed.[34]

In vitro disintegration test

The disintegration test of sublingual tablets were performed by using the validated United States Pharmacopoeia (USP) guidelines. The disintegrating instrument for tablet is utilised without the covering of plastic discs. The appropriate time limit for tablet disintegration is less than 2 min, which meets official standards for the sublingual tablet (<2 min). A tablet disintegration instrument (model ED-4L; Lab India) was used in the test. At 37±0.2 °C, distilled water served as the disintegrating medium. The time required to totally disintegrate all of the tablets was recorded.[35]

Wetting time

The tablet was located in the middle of 2 layers of absorbent paper in a petri dish. After fully wetting the paper by purified water, and extra water was totally removed from the dish. The time that the water took to spread completely through the wetted absorbent paper in the entire tablet recorded using timer.[36]

Drug content uniformity

The uniformity of content is essential quality test of pharmaceutical production to test that every unit of a dosage (e.g., tablet, capsule) contains drug within a definite range relative with label claim. Each prepared formulation was randomly selected, and ten tablets were assayed. A pre-weighed tablet was crushed (powered) and then put into a 100 mL volumetric flask. Include approximately 70 mL of diluent and sonicate 30-45 min and bring the volume to a total of 100 mL with diluent. Analysed by HPLC equipment (Model ED-4L; Lab India). The chromatography was performed at room temperature with the Octadecylsilane (15 cm x 4.6 mm) Odiac C18 column with a mobile phase of buffer solution and acetonitrile (65:35) at a flow rate of 1.5 mL/min. A UV detector set at 225 nm detected the substance. This test had been performed on optimal formulation. In the uniformity test, 10 tablets have been crushed and extracted one at a time, and the quantity of the drug was measured. Drug content was stated as a percentage of label claim and should be 100±10%.[37]

In vitro drug release studies formulation F1 to F9

Prepared formulations were considered for dissolution study with randomly selected six tablets (n=6) using a USP apparatus type II paddle (Model ED-4L, Lab India) revolving at 75 rpm. The dissolution medium was a phosphate buffer solution with a pH of 6.8 (900 mL) at 37±0.5 °C Samples (5 mL) were taken by predefined periods also exchanged with an equal quantity of dissolution medium in order to maintain the sink condition. The quantity of drug dissolved in the dissolution medium had been evaluated by the above mentioned HPLC mthod for drug content.[38,39]

In vitro drug release kinetics

To identify the drug release kinetics for solid dosage form, the *in vitro* percent cumulative drug release data were incorporated into four models, such as zero order, first order, higuchi and korsmeyer peppas model.[40]

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Table 4: Criteria for numerical optimization and optimized formulation.

Sl. No.	Independent Variables (CMAs)	Dependent Variables (CQAs)	Target for dependent variables
1.	Crospovidone INF 10	Hardness (Y1)	3.2 kg/cm^2
2.	PVPK 30	Disintegration Time (Y2)	12 sec
3.	-	Percent cumulative drug release (Y3)	95.71%

Statistical analysis

Statistical analysis was perfomed with variance (ANOVA) to assess the significance and predictive ability of the fitted models for hardness (Y_1), disintegration time (Y_2), and percent cumulative drug release (Y_3). Data analysis and model optimization were performed using Design-Expert software (version 13). A p-value < 0.05 was considered statistically significant, ensuring control of the experiment-wise error rate.

Optimization using desirability

The three responses were optimized simultaneously in this work by a numerical optimization method (desirability function method) provided through George Derringer and Ronald Suich. Under this model, certain purpose is attributed to every response. A fractional desirability function is linked along with an indivisual response, in which the value 0 is allotted to unsuitable response, and, in the case of an suitable response, the value lies among 0 and 1. The value close to the range of 0 to 1 is used to show the nearness of the response to its target value (i.e., lowest to greatest desirable). Consequently, the desirability function can be used to determine the most desirable and proper design space point to achieve the targeted dependent variable response goals. In this study, design Expert 13 was applied to determine highest desirability value after allocating required targets for the responses as shown in (Table 4).[41]

Accelerated stability analysis

The optimized formulation was stored for six months under accelerated stability condition at 40 °C±2 °C and 75% RH ±5% away from light. At the end of the respective months, the formulations were exposed to several testing including as hardness, Disintegration time, drug content and percent cumulated drug release.[42]

RESULTS AND DISCUSSION

Results

Drug excipients and polymer interaction

Fourier Transform-Infrared Spectroscopy (FTIR) analyses

FTIR spectroscopy were carried out on the sample to determine the structure of the organic compound and to recognize the presense of definite fundamental groups within the sample. The IR spectral analysis of apixaban showed that the principal peak were observed at wave number 3464.99 cm^{-1}(N-H stretching), 3323.12 cm^{-1}(C=O stretching), 1774.29 cm^{-1}(C-H stretching), 1671.87 cm^{-1}(C=C stretching), 1464.96 cm^{-1}(NH_2 stretching) respectively as shown in (Figure 2). The IR Spectra of crospovidone INF-10 alone showed that the principal peak were observed at wave number at 2865.90 cm^{-1}(N-H stretching), 1613.69 cm^{-1}(C-H stretching),1418.69 cm^{-1}(C=O stretching), 1264.97 cm^{-1} (C-N stretching) and 1613.69 cm (C-C stretching) as shown in (Figure 2). The IR Spectra of PVPK-30 alone showed that the principal peak were observed at wave number at 3411.55 cm^{-1}, (N-H stretching). 2954.30 cm^{-1}, 1648.87 cm^{-1}, and 1277.86 cm^{-1}, resemble to C-H stretching, C=O stretching of the pyrrole group, and C-N stretching, individually as shown in (Figure 2). In the IR spectra of physical mixture of apixaban, crospovidone INF-10, PVPK-30 and other inactive ingredient of prepared formulation a boad peak of apixaban was observed 3262.28 cm^{-1} (N-H stretching),2921.42 cm^{-1} C=O stretching), 2287.39 cm^{-1} and (C-H stretching) respectively as shown in (Figure 2).

As a result, the principal peaks in the IR spectra of the apixaban and polymer blend remained unchanged when associated with the spectra of apixaban, showing that there was no substantial interaction among apixaban and polymer.

Different Scanning Calorimetry (DSC)

The thermogram of apixaban obtained through the DSC indicated a sharp endothermic peak in the case of pure apixaban around its melting point, typically observed near 245.77 °C, confirming its crystalline nature as shown in (Figure 2). In contrast, the DSC thermograms of crospovidone INF-10 exhibits a broad endothermic peak with a maximum at 61.87 °C, starting at 37.11 °C and ending at 84.26 °C. No melting peak is observed, indicating the amorphous nature of the material and its thermal stability up to higher temperatures, which is favorable for its application as a superdisintegrant in pharmaceutical formulations as shown in (Figure 2). On the other hand DSC thermogram of PVP K-30 primarily demonstrates an endothermic transition around 74 °C, likely attributed to moisture loss and/or glass transition. No melting peak is observed, indicating that PVPK-30 remains amorphous in the tested temperature range up to 300 °C, as shown in (Figure 2). The DSC thermogram of the prepared formulation blend containing apixaban, crospovidone INF-10, and PVPK-30 shows a sharp and intense endothermic peak at 167.90 °C, with a high enthalpy change (ΔH) of 231.8620 J/g, indicating the melting point of apixaban as shown in (Figure 2). No additional

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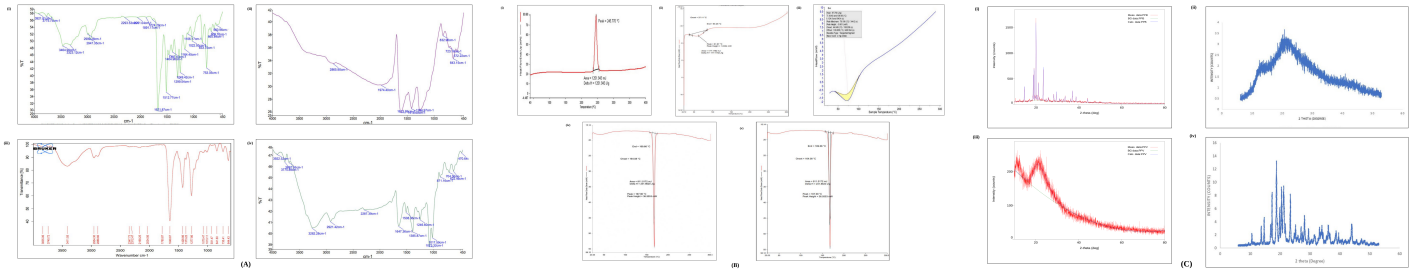


Figure 2: (A) FTIR (i) Apixaban, (ii) Crospovidone INF-10, (iii) PVPK-30 and (iv) Prepared sublingual tablets. (B) DSC (i) Apixaban, (ii) Crospovidone INF-10, (iii) PVPK-30 and (iv) Prepared sublingual tablets and (v) After six months of accelerated stability study. (C) XRD (i) Apixaban, (ii) Crospovidone INF-10, (iii) PVPK-30 and (iv) Prepared sublingual tablets.

peaks were detected in the DSC thermogram after six months of accelerated stability testing, indicating the absence of significant degradation, as shown in (Figure 2).

The DSC peak at 167.9 °C in the optimized formulation is attributed to the thermal behavior of excipients such as Pearlitol SD 200, which exhibits a melting range around 165-170 °C (Janga *et al.*, 2011). Since excipients are present in a much higher proportion than Apixaban, their endothermic signal overlaps and masks the drug peak.[43,44] The finding indicates no significant drug-excipient incompatibility, confirming good thermal stability and compatibility of the formulation.[45]

X-ray Diffraction (XRD)

The XRD pattern of pure apixaban displays a series of sharp, intense, and well-defined peaks in the 2θ at 12.82º,13.87º,16.9º,16.2º, and 18.4º, confirming its highly crystalline nature. The distinct and repeated diffraction signals indicate a well-ordered lattice structure characteristic of pure crystalline compounds. The intensity and clarity of the peaks suggest that apixaban exists in a thermodynamically stable crystalline polymorph, suitable for solid dosage form development where crystallinity is desired as shown in (Figure 2). On the other hands, crospovidone INF-10 displays a broad, diffuse halo centered around the 2θ range of 10º to 30º, specific of an amorphous material. These lack sharp and well-defined peaks, which is suggestive of the absence of long-range crystalline order as is characteristic of crospovidone INF-10 due to its cross-linked non-crystalline polymeric structure as shown in (Figure 2). The XRD pattern of Polyvinylpyrrolidone (PVPK-30) shows a broad diffuse peak in the center of the 2th range of 15º to 30º and no sharp diffraction peaks and this is typical of amorphous structure. This lack of crystallinity seems to indicate the lack of long-range molecular order in PVPK-30, which is a characteristic of synthetic polymers that are used as binders or solubilizers in pharmaceutical preparations as shown in (Figure 2). The XRD pattern of the prepared formulation blend of apixaban, crospovidone INF-10 and PVPK-30. The great diffraction peaks indicate that apixaban maintains its crystalline state in the formulation. The lack of substantial peak broadening or halo characteristics suggests a lack of total amorphization of the drug. Additionally, the lack of any new peaks suggests that no significant solid-state interaction or complex formation occurred between apixaban and the excipients as shown in (Figure 2). Generally, the XRD data confirms the crystalline stability and physical compatibility of the drug within the excipient matrix.

CHARACTERIZATION OF PREPARED FORMULATION USING THE 3² FULL FACTORIAL DESIGN

Data analysis

The data are statistically analyzed and indicate that the hardness, disintegration time and percent drug release are significantly influenced by the selected independent variables. Equation 2-4 present the relationship between dependent response such as hardness, disintegration time and percent cumulative drug release which were drive through ANOVA for various dependent variables. This study used a 3² Full Factorial Design (Montgomery *et al.*, 2017; Myers *et al.*, 2016).

$$\text{Hardness} = 3.10+0.2167A+ 0.3000B-0.3000AB \quad (2)$$

$$\text{Disintegration Time} = 13.11 -1.67A+ 1.17B-2.25AB \quad (3)$$

$$\text{Percent Cumulative Drug Release} = 92.67+1.49A-1.95B+ 1.78AB \quad (4)$$

Equation 2 represent the hardness of formulated sublingual tablets, as a function of the concentration of crospovidone INF-10 (A) and PVPK-30 (B). The equation indicates that tablet hardness is influenced by the main effects of crospovidone INF-10 and PVPK-30, as well as their interactions. An increase in the concentration of crospovidone INF-10 (A) lead to a slightly increase the tablet hardness indicated by the positive coefficient (0.2167). Crospovidone INF-10, which is a cross linked homopolymer of N-vinyl-2-pyrrolidone, has little binding characteristics and hence less influence on tablet hardness as compared with traditional binders. The cross-linked structure of crospovidone INF-10 does not dissolve and form cohesive films or

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strong interparticulate bonds when the tablet is compressed. On the other hand, increasing the concentration of PVPK-30 (B) leads to increase the tablet hardness indicating the positive coefficient (0.3000B). This shows that PVPK-30 (Polyvinylpyrrolidone K-30) is a linear polymer of N-vinyl-2-pyrrolidone and is used as a binder in tablet formulation. Its primary contribution to tablet hardness is said to be due to its excellent adhesive and cohesive characteristics. The carbonyl group in the pyrrolidone ring of PVP can hydrogen bond with hydroxyl or amino groups that are present in the drug or excipients to form stronger molecular interactions and binding. This leads to a dense and robust tablet matrix with the increased mechanical strength and hardness.[46,47] The integration term between crospovidone INF-10, PVPK-30 (AB) has a negative coefficient (-0.3000) indicting that the simultaneous decrease in the concentrations of both factor lead to a slightly reduced tablet hardness. Combination of crospovidone INF-10 and PVPK-30 produces a balance of acceptable mechanical strength and enhanced tablet hardness and structural integrity.[48]

Equation 3 describe disintegration time of tablet as a function of crospovidone INF-10 (A) and PVPK-30 (B) concentration highlighting the influence of their individual effect and interactions. A decrease in the concentration of crospovidone INF-10 (A) lead to slightly decrease the disintegration time as indicated by the negative coefficient (-1.67) The coefficient indicate that crospovidone INF-10 act as disintegrating agent. Its main effect on the disintegration time of tablets is the unique molecular structure and water-wicking function, and acts as mainly wicking mechanism. The cross linked structure of crospovidone INF-10 prevents it from dissolving but allows it to rapidly absorb water into its porous matrix with rapid water uptake through capillary action, facilitating quick disintegration.[49,50] On the other hand, increasing the concentration of PVPK-30 (B) lead to increase the disintegration time indicating the positive coefficient (1.17) PVPK-30 is a water-soluble, linear polymer which readily forms hydrogen bonds with drug particles and excipients, resulting in a cohesive and mechanically strong tablet structure. At higher concentrations, the polymer will form intermolecular hydrogen bonds to form a tightly packed matrix with a low porosity. Increasing polymer density prevents the interaction of water molecules with the inside components of tablets, which delays the breakdown of tablets. The interaction term between crospovidone INF-10 and PVPK-30 has been found to be negative coefficients (-2.25), indicating the complementary effect of decreasing the concentrations of both factor on tablet disintegration time balancing the structural integrity of tablets with rapid tablet disintegration. When combined, crospovidone INF-10 makes up for the potential disintegration delay induced by PVPK-30 by promoting the ingress of moisture and inducing rapid breakup of the tablet matrix.[51]

Equation 4 shows that the percent cumulative drug release is influenced by the major impacts of crospovidone INF-10 (A) and PVPK-30 (B) together with their interactions. An increase in the concentration of crospovidone INF-10 (A) contributes to an increase in the percent cumulative drug release, as indicated by the positive coefficient (1.49) This indicates that the cross-linked structure of crospovidone INF-10 allows it to rapidly absorb water into its porous matrix with rapid water uptake through capillary action, facilitating quick disintegration through its wicking and swelling mechanisms, ultimately producing smaller fragments with greater surface area for dissolution and thereby significantly improving the percent cumulative drug release.[52,53] In contrast an decrease in PVPK-30 concentration of factor (B) leads to an slightly decrease in the percent cumulative drug release indicated by negative coefficient (-1.95). PVPK-30 has a negative impact on the percent cumulative drug release since it diminishes its capacity of a solubilizing and binding agent. PVPK-30 increases the wettability and solubility of the drug through hydrogen bonding and hydrophilic interactions. Lowering its concentration diminishes these interactions, leading to reduced wetting and solubilization of drug particles. Therefore, drug particles may aggregate, slowing dissolution despite faster disintegration. The weaker polymeric network may also result in a decreased uniformity of water distribution within the tablet matrix and thus limit complete drug release. Thus, decrease the level of PVPK-30 can compromise dissolution efficiency and slightly decrease the percent cumulative drug release. However, the interaction term between crospovidone INF-10 and PVPK-30 (AB) has a positive coefficient (1.78), crospovidone INF-10, whose cross-linked, porous structure, quickly absorbs water and also favors the disintegration of tablets by capillary action. This rapid uptake of moisture disintegrates the tablet into smaller portions, which gives more surface area for the drug to dissolve into. At the same time, PVPK-30 is a binder which forms hydrogen bonds and adhesive interactions with the drug particles and excipients, imparting mechanical strength and ensuring uniform distribution of the drug in the matrix. Although the use of PVPK-30 may potentially slow the release of the drug because of the compaction and the reduced porosity, the hydrophilic nature of the polymer allows for water penetration into the system which also helps to solubilize the drug. The synergy between the crospovidone INF-10 rapid wicking and disintegrating capability PVPK-30's controlled binding ensures that the tablet will disintegrate in a timely manner while providing constant dispersion of the drug. This leads to an improved and more predictable percent cumulative drug release, with faster onset and sustained uniformity across the dosage form. The balance between mechanical strength and rapid disintegration thus enhances both the efficiency and reproducibility of drug release profiles.[54]

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Table 5: Uniformity of drug content, thickness, wetting time and friability of formulation F1 to F9.

Formulation Code	Uniformity of Drug Content (%)	Thickness (mm)	Wetting Time (Sec)	Friability (%)
F1	100.05±0.04	2.6±0.134	43±2.51	0.30±0.047
F2	100.50±0.05	2.8±0.152	42±1.52	0.10±0.061
F3	100.74±0.14	2.7±0.152	44±2.64	0.22±0.072
F4	99.99±0.06	2.9±0.173	46±1.52	0.14±0.035
F5	100.21±0.04	3.2±0.130	45±3.05	0.22±0.055
F6	100.25±0.07	3.1±0.062	49±1.73	0.11±0.061
F7	100.27±0.05	2.9±0.076	46±2.51	0.24±0.070
F8	101.16±0.08	2.7±0.120	48±2.08	0.31±0.015
F9	101.27±0.04	2.6±.137	52±2.64	0.15±0.035

***Note:** All values are conveyed as mean±SD (*n*=3).

Uniformity of drug content

The uniformity of the drugs in all the pepared formulations was assessed as per the method defined in the methodology above and the outcomes as shown in (Table 5). The range of percent drug content of formulations F1-F9 was between 99.99±0.06% w/w to 101.27±0.04% w/w, which was all within the acceptable limits of standards criteria NLT 85.0% and NMT 115.0% of the labelled claim.

In vitro drug release Study

In vitro drug release studies of all the prepared batches were accomplished and it was observed that dissolution data obtained for formulations F1 to F9 were lies in between 87.01±0.208% to 95.71±0.423% as shown in (Table 6) and (Figure 3). It was studied that formulation F2 indicated the maximum *in vitro* drug release. Whereas formulation F4 showed the lowest drug release because of PVPK-30 is a hydrophilic polymer commonly used in formulations as a matrix polymer. Due to its lactam groups, it has a strong affinity for water, forming hydrogen bonds with drug and excipient particles. Remarkably, an increase in the concentration of PVPK-30 leads to increased tablet hardness as well as slightly decrease the percent cumulative drug release in the formulation. Crospovidone INF-10 mainly acts as a superdisintegrant, allowing tablets to break down quickly into smaller particles when in contact with water. Its highly porous nature facilitates quick water uptake through capillary action. An increase in the concentration of crospovidone INF-10 enhances the percent cumulative drug release while slightly reducing the hardness of the formulation (Rowe *et al.*,). However it was found to be the best formulation F2 of all the prepared formulations.

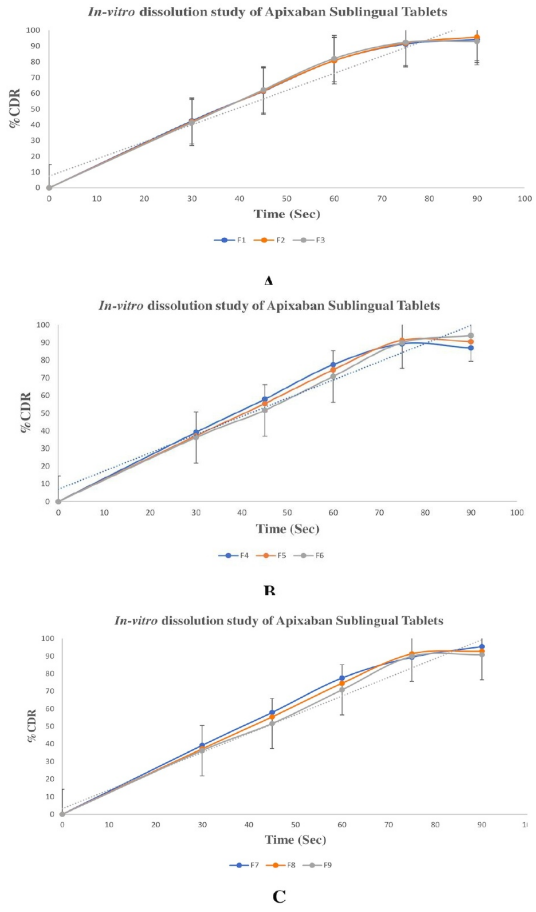


Figure 3: *In vitro* percent cumulative drug release for formulation F1 to F9.

Statistical analysis

The Analysis of Variance (ANOVA) results for sublingual tablets formulation provides insights into the significance and predictability of the fitted modelels for three key response variables, such as hardness (Y1), disintegration time (Y2) and percent cumulative drug release (Y3).

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Table 6: Results for hardness. disintegration time and percent cumulative drug release.

Formulation Code	Crospovidone INF-10 (mg)	PVPK-30 (mg)	Hardness (Kg/cm²) (*n*=3)	Disintegration Time (Sec) (*n*=3)	Percent Cumulative Drug Release (*n*=3)
F1	1	0	3.1±0.036	10±1.527	94.27±0.330
F2	1	-1	3.2±0.030	12±1.527	95.71±0.467
F3	-1	0	2.6±0.072	13±2.081	92.98±0.406
F4	-1	1	3.6±0.055	18±2.081	87.01±0.491
F5	0	0	3.2±0.052	14±1.527	90.55±0.939
F6	1	1	3.4±0.011	10±2.081	94.01±0.671
F7	-1	-1	2.2±0.050	11±1.527	95.45±0.939
F8	0	-1	3.2±0.050	14±1.527	92.78±0.694
F9	0	1	3.4±0.087	16±2.516	90.86±0.293

***Note:** All values are conveyed as mean±SD (*n*=3).

ANOVA analysis for each model selected for each response

The ANOVA for the hardness that the model is statistically significance with an F-value of 5.82 with corresponding *p*-value of 0.0437 (<0.05) confirms that the 2FI model for hardness is statistically significant. Among individual model terms, PVPK30 (B) was identified as the most significant factor (*p*=0.0369), indicating that the binder concentration exerts the greatest influence on tablet hardness. The non-significant Lack-of-Fit (*p*=0.2738>0.05) confirms that the model adequately represents the true relationship between the factors and the response, with no systematic deviation from the fitted model as shown in (Table 7). For disintegration time yielded an F-value of 5.44 (*p*=0.0494), confirming model significance. The AB interaction term was the most significant contributor (*p*=0.0424), emphasizing that the combined effect of Crospovidone and PVPK30 is the primary determinant of disintegration time. The non-significant Lack-of-Fit (*p*=0.3485) validates model adequacy as shown in (Table 7). For percent cumulative drug release model was significant with an F-value of 5.92 (*p*=0.0422). PVPK30 (B) emerged as a significant individual factor (*p*=0.0344), indicating that the binder level strongly governs drug dissolution. The lack-of-fit *p*-value of 0.2874 (non-significant) confirms the model's adequacy as shown in (Table 7).[55]

Fit Statistics: R^2, Adjusted R^2, Predicted R^2, and Adequate Precision

The R^2 values for Hardness, Disintegration Time (DT), and percent cumulative drug release (t80%) were 0.7774, 0.7649, and 0.7804, respectively, indicating that the models explained over 76% of the total variability in each response. The Adjusted R^2 values (0.6439, 0.6249, and 0.6487) and Predicted R^2 values (0.3397, 0.4731, and 0.2626) were in reasonable agreement, considering the limited number of experimental runs (*n*=9)

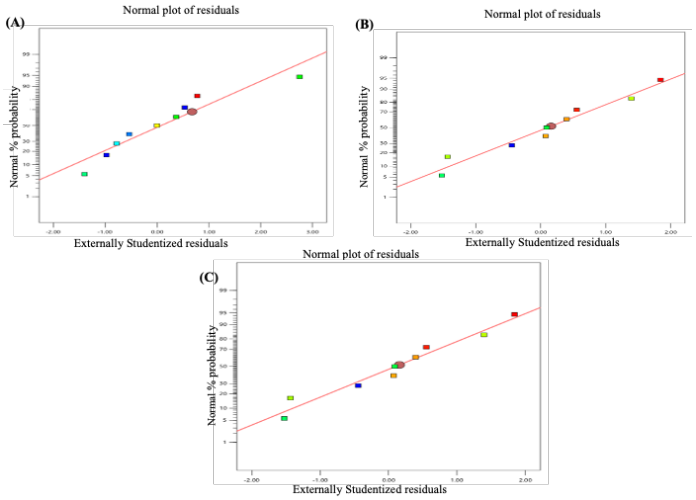


Figure 4: Residuals, plots A- Hardness, B- Disintegration Time and C- Percent Cumulative Drug Release.

inherent to the 3^2 factorial design. The Adequate Precision ratios of 6.92, 7.21, and 6.75 for Hardness, DT, and t80%, respectively, all exceeded the minimum desirable threshold of 4.0, confirming sufficient signal-to-noise ratios and the ability of all three models to reliably navigate the design space. as shown in (Table 7).[56]

Lack-of-Fit Analysis

Lack-of-Fit (LoF) was assessed for each response to determine whether the selected model adequately captured the underlying data structure, or whether there was evidence of systematic model error. For all three responses, the lack-of-fit p-values were non-significant (Hardness: *p*=0.2738; DT: *p*=0.3485; t80%: *p*=0.2874), all well above the threshold of 0.05. This confirms that there is no statistically significant lack of fit for any of the three models, meaning the 2FI polynomial adequately represents the true functional relationship between the factors and each response. The absence of significant lack-of-fit, together with

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Table 7: ANOVA for A- Hardness, B-Disintegration Time, C- Percent cumulative drug release and D- Fit statistics for all three 2FI models.

Source	Sum of Squares	d_f	Mean Square	F-value	*p*-value	
Model	1.18	3	0.3939	5.82	0.0437	significant
A-Crospovidone INF-10	0.2817	1	0.2817	4.16	0.0968	
B-PVPK 30	0.5400	1	0.5400	7.98	0.0369	
AB	0.3600	1	0.3600	5.32	0.0692	
Residual	0.3383	5	0.0677	-	-	
Lack of fit	-	-	-	-	0.2738 (NS)	
Cor Total	1.52	8	-	-	-	
(A)						
Source	**Sum of Squares**	**d_f**	**Mean Square**	**F-value**	***p*-value**	
Model	45.08	3	15.03	5.44	0.0494	significant
A-Crospovidone INF-10	16.67	1	16.67	6.04	0.0574	
B-PVPK 30	8.17	1	8.17	2.96	0.1461	
AB	20.25	1	20.25	7.33	0.0424	
Residual	13.81	5	2.76	-	-	
Lack of fit	-	-	-	-	0.3485 (NS)	
Cor Total	58.89	8	-	-	-	
(B)						
Source	**Sum of Squares**	**d_f**	**Mean Square**	**F-value**	***p*-value**	
Model	48.68	3	16.23	5.92	0.0422	significant
A-Crospovidone INF 10	13.26	1	13.26	4.84	0.0790	
B-PVPK 30	22.78	1	22.78	8.32	0.0344	
AB	12.64	1	12.64	4.61	0.0844	
Residual	13.69	5	2.74			
Lack of fit	-	-	-	-	0.2874 (NS)	
Cor Total	62.37	8				
(C)						

Statistical Parameter	Hardness (kg/cm²)	DT (sec)	t80% (%)	Statistical Parameter
R^2	0.7774	0.7649	0.7804	R^2
Adjusted R^2	0.6439	0.6249	0.6487	Adjusted R^2
Predicted R^2	0.3397	0.4731	0.2626	Predicted R^2
Adequate Precision	6.9197	7.2140	6.7543	Adequate Precision
Std. Dev.	0.2601	1.66	1.65	Std. Dev.
CV (%)	8.39	12.67	1.79	CV (%)
Mean	3.10	13.11	92.67	Mean
(D)				

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Table 8: Drug release kinetics of prepared formulation (F1 to F9).

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi Model (R^2)	Korsmeyer Pepas Model (n-value)	Drug Release Mechanism
F1	0.9574	0.9629	0.9706	0.8903	Super Case-II or Anomalous Transport
F2	0.9593	0.952	0.9701	0.8906	Super Case-II or Anomalous Transport
F3	0.9492	0.9732	0.9684	0.8889	Super Case-II or Anomalous Transport
F4	0.9436	0.9375	0.9605	0.8792	Super Case-II or Anomalous Transport
F5	0.9599	0.9262	0.9611	0.881	Super Case-II or Anomalous Transport
F6	0.9804	0.9169	0.9419	0.878	Super Case-II or Anomalous Transport
F7	0.9741	0.9194	0.9564	0.8833	Super Case-II or Anomalous Transport
F8	0.9683	0.9494	0.9634	0.8819	Super Case-II or Anomalous Transport
F9	0.9663	0.9427	0.9645	0.8765	Super Case-II or Anomalous Transport

the significant model F-values, provides strong evidence for the suitability of the 2FI models.[57]

Model Adequacy and Residual Analysis

Model adequacy was established through significant model F-values ($p<0.05$), non-significant Lack-of-Fit ($p>0.05$), adequate precision ratios exceeding 4.0 (6.92, 7.21, and 6.75 for Hardness, disintegration test, and percent cumulative drug release, respectively), VIF values of 1.0 confirming design orthogonality, and satisfactory R^2 values (>0.76) for all responses. Residual diagnostics further validated model assumptions: the normal probability plot confirmed approximate normality of residuals, plots of residuals versus predicted values showed random scatter confirming homoscedasticity, run-order plots confirmed independence of observations, and Cook's distance analysis confirmed the absence of influential outliers as shown in (Figure 4). Collectively, these criteria confirm that the fitted 2FI models are statistically valid and adequate for navigating the formulation design space.[58]

Response surface plots

The contour and 3D surface plots presented illustrate the influence of two formulation variables, crospovidone INF-10 (mg) and PVPK-30 (mg), on the tablet hardness, disintegration time and percent cumulative drug release. The contour plot provides a 2D representation of how the combination of these two factors affects the tablet hardness, disintegration time and percent cumulative drug release. The right 3D surface plot offers a three dimensional perspective, showing how both factors contributes to the response.

The analysis reveals that with an increase in the concentration of crospovidone INF-10, lead to slightly increase the tablet hardness, while the disintegration time decreases. As well the percent cumulative drug release is increase. On the other hand the analysis reveals that increasing the concentration of PVPK-30 lead to increase tablet hardness and disintegration time while the percent cumulative drug release was slightly decrease.The interaction term between crospovidone INF-10 and PVPK-30 produces a non-linear effect on tablet hardness. A high concentration of both components results in moderate tablet hardness while low crospovidone INF-10 with high PVPK-30 lead to the grater the tablet hardness.

The plots indicates that an increasing the concentration of PVPK-30 slightly increase the disintegration time, which is expected due to its binding properties. PVPK-30 is a water-soluble, linear polymer which readily forms hydrogen bonds with drug particles and excipients, resulting in a cohesive and mechanically strong tablet structure prevent it breakdown, leading to slightly increase the disintegration time. Similarly, a higher concentration of crospovidone INF-10 lead to reduces the disintegration time and enhances the percent cumulative drug release of the tablet. This indicates that due to it unique molecular structure and water-wicking capabilities, and acts as primarily by a wicking mechanism significantly improving

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Table 9: Assessment of predicted and observed experimental values of optimized batch.

Response	Predicted Value	Observed value	Percent bias (%) *
Hardness (Y1)	3.19	3.18±0.104	0.313
Disintegration Time (Y2)	12.39	12±1.527	3.147
Percent Cumulative Drug Release (Y3)	94.48	95.71±0.423	-1.409

***Note:** Percent bias (%) =(predicted value-observed value) / predicted value x 100. ***Note:** All values are conveyed as mean±SD (*n*=3).

Table 10: Accelerated stability analyses of optimized formulation.

Characteristics Parameters	Temperature: 40 °C±2 °C/75 %±5 % Relative Humidity (RH)			
	Initial	After 1 Month	After 3 Months	After 6 Months
Hardness	3.2±0.030	3.21±0.031	3.23±0.031	3.25±0.032
Disintegration Time	12±1.527	11±1.518	13±1.528	13±1.528
Percent Cumulative Drug Release	95.71±0.467	95.21±0.462	95.44±0.464	94.81±0.454
Drug Content	101.17±0.08	100.19±0.05	100.18±0.07	100.19±0.04

***Note:** All values are presented as mean SD (*n*=3).

the disintegration time. The interaction between these two components results in a non-linear effect of disintegration time, where high level of both crospovidone INF-10 and PVPK-30 slightly increase disintegration time whereas lower concentrations yield a moderate tablet disintegration time.

This analysis suggests that an increasing the concentration of PVPK-30 lead to slightly decrease the percent cumulative drug release. PVPK-30 forms a vast network of intermolecular hydrogen bonds, resulting in a densely packed matrix with low porosity. Increasing polymer density inhibits the interaction of water molecules with the tablet's interior components, delaying the breakdown of tablets. This is likely due to the creation of hydrogen bond among active and inactive ingredients hinders the dissolution of drug from the matrix. In contrast, higher concentration of crospovidone INF-10 appear enhance percent cumulative drug release. Since crospovidone INF-10 is a super disintegrant it facilitates drug dissolution by increasing porosity and hydrophilicity within rapid water uptake through capillary action, facilitating quick disintegration through its wicking and swelling mechanisms showing improve percent cumulative drug release. The interaction term between these two components results in-non-linear effect on percent cumulative drug release, whereas higher concentration of PVPK-30 combined with a low crospovidone INF-10 level results in slight decrease percent cumulative drug release, while a high concentration of crospovidone INF-10 with low PVPK-30 lead to increase percent cumulative drug release and the findings are as shown in (Figure 5).

In vitro drug release kinetics analyses

The drug release data were fixed in Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models using an in-house Excel-based analysis platform. The results showed variation in release patterns across the formulations. The release exponent (n) obtained from the Korsmeyer-Peppas model ranged between (0.878 and 0.8906) as shown in (Table 8), indicating that the apixaban sublingual tablets followed an anomalous or Super Case-II transport mechanism. This indicates that the drug release was influenced by a combination of polymer relaxation, swelling, and matrix erosion, rather than simple diffusion. The use of hydrophilic excipients and superdisintegrants likely enhanced rapid tablet hydration and swelling when exposed to saliva, leading to faster matrix breakdown and improved drug release. This release mechanism is extremely suitable for sublingual drug delivery, where rapid therapeutic action is required. The quick swelling and erosion allowed apixaban to dissolve rapidly and become available for absorption across the highly vascularized sublingual mucosa, while avoiding first-pass metabolism. This ultimately supports faster systemic absorption and improved bioavailability.[59,60]

Evaluation and identification of optimised formulation with the desirability function

The desirability function technique had been used in current analysis with Design expert 13.

The limitations were established for all responses. The independent variables (factors) were fixed within the limit specified. The best formulation (FF1) with the best desirability function, fulfilled the highest necessity of responses variables, were chosen. The preferred optimized formulation includes A= 7.548% w/w and B=1.0% w/w, the complete desirability was found

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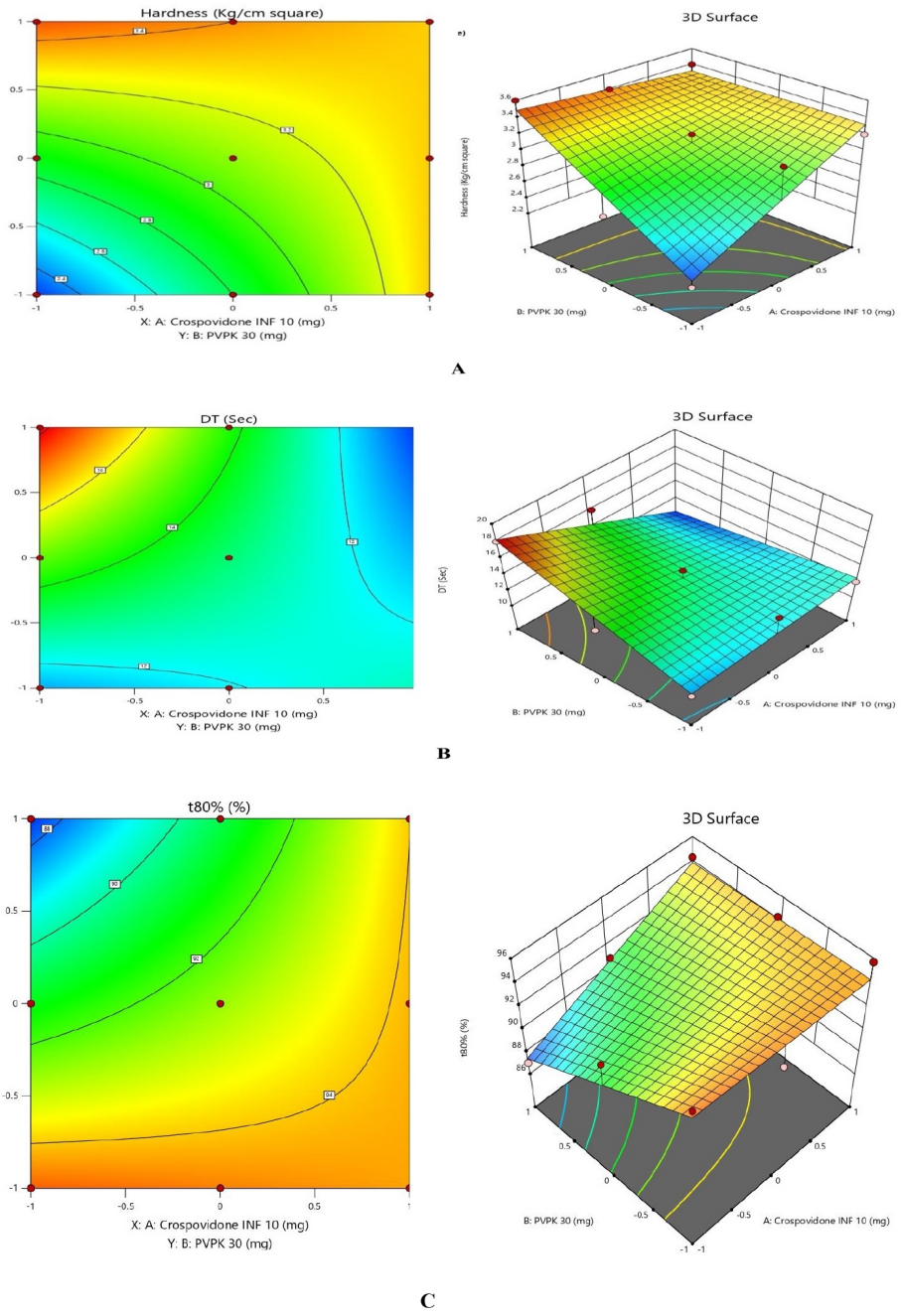


Figure 5: Response surface curve and contour plots. A- hardness, B- disintegration time, C- percent cumulative drug release.

to be 0.932. The predicted value of all optimized formulation (FF1) for the response Y1, Y2 and Y3 was 3.19 kg/cm^2,12.39 sec and 94.38%, separately. To check and validate the optimisation, the optimal formulation had been made in triplet. All of the responses for each formulation were analysed as observed values. The assessment of the observed and predicted values is shown in (Table 9 and Figures 6, 7) Shows the counterplot for the desirability function among A and B.[61]

Acelerated stability analyses

Acelerated stability analysis of the optimized formulation (FF1) had been performed for six months at 40 °C± 2 °C/75%±5%. as shown in Table 10, and suggested that there were no significant variations in the disintegration time, hardness, drug content and percent cumulative drug release of optimized formulation at the end of respective months of studies.

The accelerated stability data as shown in (Table 10) results showed that the optimized formulation retained its physical properties, hardness of 3.25 kg/cm^2±0.032, a disintegration time

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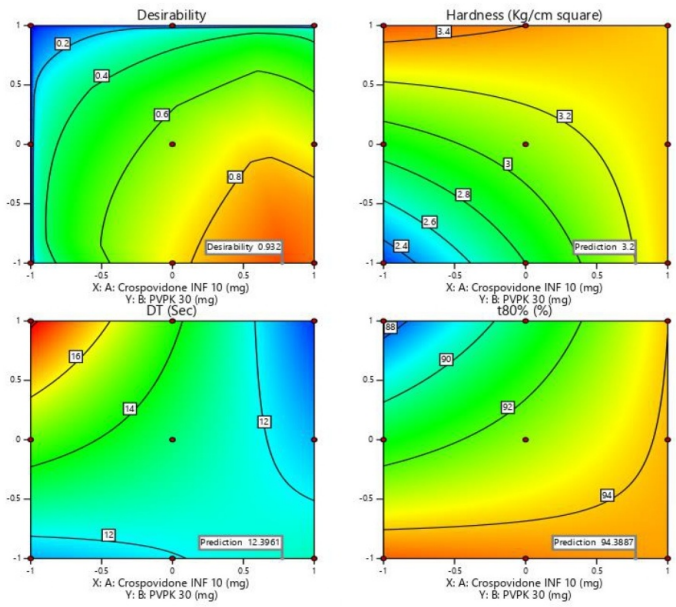


Figure 6: Contour plot of optimized formulation as a function of A and B (FF1) (a) for overall desirability (D); (b) for hardness (Y1); (c) for disintegration time (Y2); (d) for Percent cumulative drug release.

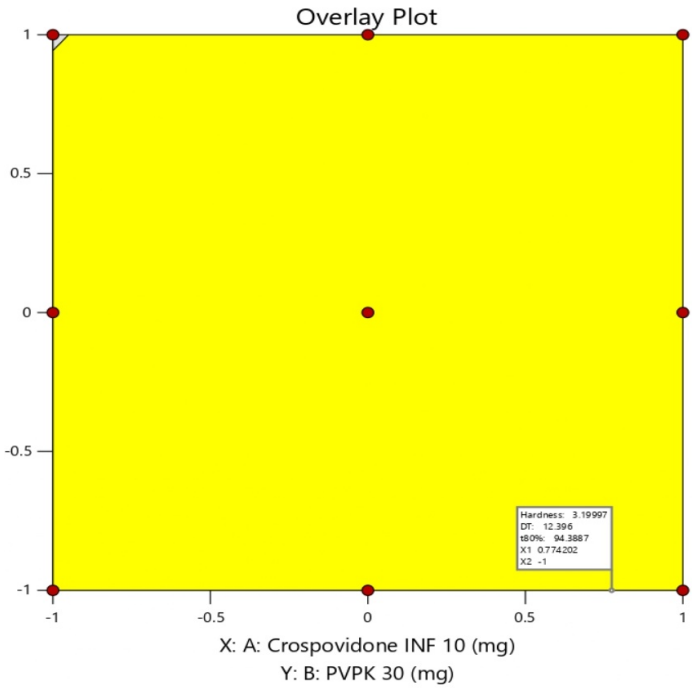


Figure 7: Overlay plot for optimized formulation.

of 13 s±1.528, percent cumulative drug release of 94.81%±0.454 and Drug content 100.19±0.04 within ICH limits, confirming accelerated stability. No new peaks were observed in DSC after storage, indicating no major degradation.

DISCUSSION

The present investigation aimed to formulation and development of sublingual tablets of apixaban using a 3^2 Full Factorial Design within the framework of Quality by Design (QbD). This formulation strategy was selected to overcome the limitations associated with apixaban conventional oral tablets, including low permeability, variable oral bioavailability (~50%), and extensive first-pass metabolism (Byon *et al*., 2019; Zaky *et al*., 2023). Sublingual administration offers the advantage of rapid systemic absorption through the highly vascularized mucosa while bypassing gastrointestinal degradation and hepatic metabolism, which has been successfully demonstrated in fast-acting drugs such as zolmitriptan, sildenafil citrate, and sumatriptan (Hosny *et al*., 2015; Prajapati *et al*., 2014; Abdelbary *et al*., 2005). Therefore, the formulation of sublingual apixaban tablets represents a clinically relevant approach for patients requiring rapid anticoagulant therapy, particularly in emergency thromboembolic events or in individuals with dysphagia.

The compatibility between apixaban and selected excipients (crospovidone INF-10 and PVP K-30) was confirmed using FTIR, DSC, and XRD analyses. FTIR showed retention of characteristic drug peaks without chemical shifts, indicating no incompatibility at functional group levels, in agreement with Chadha and Bhandari (2014), who reported that unchanged principal peaks signify absence of major interactions. DSC thermograms revealed that the sharp endothermic melting peak at 167.9 °C in the formulation, attributed to thermal overlap with excipients rather than degradation. Similar peak overlap with excipients has been reported in solid dispersion systems where excipients mask drug melting transitions (Janga *et al*., 2011). XRD diffractograms of the optimized formulation showed reduced intensity of characteristic crystalline peaks, suggesting partial conversion to amorphous form. Such a reduction in crystallinity is known to enhance aqueous solubility and dissolution velocity (Urvi *et al*., 2020), supporting the improved dissolution behavior observed.

The factorial design study demonstrated that crospovidone INF-10 and PVPK-30 significantly influenced hardness, disintegration time, and percent cumulative drug release. Crospovidone INF-10, a superdisintegrant operating primarily through capillary wicking, substantially reduced disintegration time and increased cumulative drug release by improving water penetration and particle breakage consistent with findings by Ajay and Saharan (2017), who reported enhanced wetting and dissolution using crospovidone in rapidly disintegrating tablets. In contrast, PVPK-30 increased hardness due to strong binder properties and hydrogen bonding capability (Meiyan *et al*., 2014), while slightly prolonging disintegration because of gel-layer formation upon hydration. However, synergistic interaction between both excipients resulted in a balanced formulation profile, in which rapid disintegration was achieved without compromising mechanical integrity.

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The *in vitro* dissolution results disclosed that formulation F2 exhibited the highest percent cumulative drug release (95.71%±0.47%) and fastest disintegration time (12 sec±1.52), meeting pharmacopeial requirements for sublingual tablets (NMT 2 min). Improved dissolution may be attributed to faster hydrating ability and increased exposure surface achieved through rapid disintegration. These findings correlate with (Omaima *et al*., 2006), who reported that superdisintegrant-based sublingual formulations significantly improve dissolution. Drug release kinetics analysis showed that the Korsmeyer-Peppas exponent values (n=0.878-0.8906) indicated Super Case-II transport, demonstrating that the mechanism was governed by polymer relaxation and matrix erosion rather than simple diffusion an expected behavior in hydrophilic polymer-based dispersing systems (Peppas and Sahlin, 1989). This release pattern is desirable for sublingual systems where rapid dissolution followed by uniform release is required for immediate therapeutic response.

The CQA target of "NMT 2 min" disintegration time was set to allow flexibility during formulation development. However, the optimized formulation (F2) demonstrated a significantly shorter disintegration time of 12 sec, which is advantageous for sublingual administration. Although this is faster than the predefined target, the rapid disintegration was achieved to facilitate immediate drug release and enhance sublingual absorption of apixaban because apixaban, being a BCS Class III drug with low permeability, requires maximum contact surface area and rapid wetting to facilitate diffusion across the mucosa. Apixaban undergoes extensive first-pass metabolism via CYP3A4, its oral bioavailability is limited. Therefore, delivering the drug rapidly within the sublingual cavity is essential to make it available at the absorption site before dilution and swallowing with saliva occur. Faster disintegration increases the probability of bypassing first-pass metabolism, supporting improved systemic availability and faster onset of action.[62]

The higher wetting time compared to the rapid disintegration time is attributed to the functional roles of the inactive excipients. PVP K-30, a hygroscopic matrix-forming polymer, initially forms a thin viscous gel layer upon contact with solvent (water), delaying surface wetting. In contrast, Crospovidone INF-10 acts through rapid capillary wicking rather than surface swelling, allowing water to penetrate the tablet core quickly and resulting in fast disintegration once internal hydration begins. Thus, the wetting time reflects delayed surface hydration caused by PVPK-30, while the disintegration time represents the efficient wicking-driven breakup provided by Crospovidone INF-10. Thus, the difference between wetting and disintegration times reflects the complementary mechanisms of these inactive excipients and does not indicate any formulation inconsistency.[63]

Optimization using desirability function indicated that crospovidone INF-10 at 7.55% and PVP K-30 at 1.0% yielded an optimal balance of hardness, disintegration, and dissolution (overall desirability value 0.932). Predicted and experimental responses showed minimal percent bias (<5%), confirming model predictability, which aligns with the principles of Design of Experiments for pharmaceutical optimization (Montgomery, 2017; Myers *et al*., 2016). Accelerated stability testing confirmed that optimized tablets retained quality attributes over six months without significant changes, demonstrating formulation robustness and compliance with ICH Q1A(R^2) guidelines.

CONCLUSION

This investigation applied a Quality by Design (QbD) based 3^2 full factorial design to systematically develop and optimize apixaban sublingual tablets with the objective of improving physicochemical performance and overcoming challenges related to low permeability and variable bioavailability. The QbD framework enabled a structured understanding of the formulation by defining the Quality Target Product Profile (QTPP) and identifying key Critical Material Attributes (CMAs) and Critical Quality Attributes (CQAs) that influence product quality and performance. Crospovidone INF-10 and polyvinylpyrrolidone K-30 (PVP K-30) were selected as independent variables based on their functional roles in tablet disintegration and mechanical strength. A total of nine experimental formulations were prepared according to the factorial design and evaluated for CQAs including tablet hardness, disintegration time, and percent cumulative drug release. Statistical modeling and response surface methodology using Design-Expert software demonstrated that variations in the concentrations of these excipients significantly affected all selected CQAs, confirming their criticality in sublingual tablet performance. Optimization studies identified a formulation exhibiting acceptable mechanical strength (3.2±0.03 kg/cm^2), rapid disintegration (12±1.53 s), and high drug release (95.71±0.47%), which are desirable characteristics for sublingual delivery. The experimentally observed responses were in close conformity with the predicted values, supporting the adequacy of the design model and indicating formulation reliability. Furthermore, the optimized batch showed no evidence of instability within the scope of the study, highlighting the effectiveness of the QbD-guided optimization strategy. Generally, the 3^2 full factorial design proved to be a resource-efficient and systematic approach for formulation development, reducing experimental problem while enhancing product understanding. Despite these strengths, the study has certain limitations. The statistical models exhibited p-values close to the 0.05 significance threshold, suggesting limited robustness and the need for validation through larger sample sizes or more complex experimental designs. Additionally, the dissolution testing was conducted using 900 mL of pH

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6.8 buffer, which does not accurately simulate sublingual physiological conditions. Future investigations will employ simulated salivary fluid in smaller volumes to improve *in vivo* relevance. Furthermorse, impurity profiling and related-substance analysis were not addressed in this preliminary work, and these assessments will be incorporated in extended stability studies in accordance with ICH Q1A(R^2) and Q3B(R^2) guidelines.

ACKNOWLEDGEMENT

The authors acknowledge the support from Teerthanker Mahaveer University Moradabad.

ABBREVIATIONS

APX: Apixaban; **API:** Active Pharmaceutical Ingredients; **BCS:** Biopharmaceutics Classification System; **CMA:** Critical Material Attributes; **CPP:** Critical Process Parameters; **CQA:** Critical Quality Attributes; **DoE:** Design of Experiments; **DOAC:** Direct oral anticoagulant; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transform Infrared Spectroscopy; **GI:** Gastrointestinal; **PVPK-30:** Polyvinylepyrrolidone; **QbD:** Quality by Design; **QTPP:** Quality Target Product Profile; **XRD:** X-Ray Diffraction; **HPLC:** High-Performance Liquid Chromatography; **UV:** Ultraviolet; **USP:** United States Pharmacopeia; **RH:** Relative Humidity; **DVT:** Deep Vein Thrombosis; **PE:** Pulmonary Embolism; **SD:** Standard Deviation; **w/w:** Weight by Weight; **NLT:** Not Less Than; **NMT:** Not More Than; **ICH:** International Council for Harmonisation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

The authors received no specific funding for this work.

SUMMARY

Apixaban is an selective and reversible Factor Xa inhibitor which is widely used in the treatment and prevention of thromboembolic disorders such as deep vein thrombosis as well as pulmonary embolism. Although its pharmacodynamic efficacy has been proven to be effective, classic of oral administration of apixaban is associated with several limitations, including a low oral bioavailability as well as a slow-acting quality and first-pass hepatic metabolism, which could weaken the therapeutic efficacy of apixaban under clinical conditions, especially those that require rapid anticoagulation. Sublingual drug delivery is another useful alternative since it allows quick absorption into the system affecting gastrointestinal degradation and first-pass metabolism. The current research aimed at developing and analyzing the apixaban sublingual tablets based on a systematic Quality by Design (QbD) strategy to improve the formulation performance and the release profile of drugs, it was necessary to define the Quality Target Product Profile (QTPP), which included rapid disintegration, enough mechanical strength, consistent drug content, and enhanced *in vitro* drug release. According to the QTPP, three Critical Quality Attributes (CQAs) in particular, tablet hardness, disintegration time, and percentage cumulative drug release appeared to be the product performance indicators. Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) that have the potential to affect these CQAs were identified by conducting a structured risk assessment. A Fishbone (Ishikawa) diagram helped to organize the review of the possible risks of the formulation and help to select excipients rationally. The Design of Experiments (DoE) strategy that included a 3^2 full factorial design was used to examine the whole effect of the formulation variables on the characteristics of the tablets. Independent variables were chosen as crospovidone INF-10, which was selected due to the efficiency of superdisintegrant and polyvinylpyrrolidone K-30, which was chosen as a binder and a forming substance. Response surface methodology and statistical modeling were used to determine their effects on the hardness of the tablets, their disintegration time, and percent cumulative drug release. Statistical analysis of variance allowed proving that these variables are statistically significant at the level of confidence $p<0.05$. Drugs-excipient compatibility studies were done before the formulation to assure stability and integrity of formulation. The FTIR spectroscopy, the use of differential scanning calorimetry, and X-ray diffraction revealed that the apixaban was not chemically interacting with another substance and remained in the crystalline form. Directly compressed sublingual tablets were tested for identified its physicochemical parameters, such as hardness, friability, weight variation, consistency of drug content, wetting time and disintegration time. Formulations were performed in accordance with pharmacopeial standards and demonstrated an excellent dissolution rate of the Apixaban, which is essential to effective sublingual delivery. *In vitro* dissolution tests in phosphate buffer pH 6.8 revealed the increased and accelerated drug release, especially on increasing the concentration of crospovidone INF-10. Statistical evaluation showed that the crospovidone had a significant decrease in disintegration time and enhance drug release profile, whereas PVP K-30 had a significant increase in tablet hardness, but has to be slighty slow the disintegration time. The optimized formulation was found that it had a hardness of 3.2±0.03 kg/cm^2, disintegration time of 12±1.52 sec and percent cumulative drug release of 95.71±0.47 which are close to the predicted and experimental results yielding the assumption that the model was adequate. The release kinetics of the drug showed an efficient release of the drug through the sublingual dosing form. Formulation stability was confirmed by accelerated stability testing performed under ICH conditions, which showed no substantial alterations in the physical characteristics, drug

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content, or dissolution properties. This paper demonstrates the efficacy of the QbD-based formulation approach and validates the possibility of the apixaban sublingual tablets as the potential alternative to the traditional oral therapy, characterized by faster onset of action, improved bioavailability.

AUTHORS CONTRIBUTION

Pradeep Kumar: Conceptualization, experimentation, manuscript preparation; Vaibhav Rastogi: Supervision, Review of the study.

ETHICAL STATEMENT

This study was an *in vitro* formulation development study and did not involve the use of human subjects or animal models, therefore, ethical clearance was not required.

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Cite this article: Kumar P, Rastogi V. Design and Evaluation of Apixaban Tablets Using Quality By Design (Qbd) Approach for Enhanced Physicochemical Attributes. Indian J of Pharmaceutical Education and Research. 2027;XX(XX):1-20.

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