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Design and Characterization of Fast-Dissolving Oral Film of Apixaban

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Abstract

Background: Following the COVID-19 pandemic, microvascular and macrovascular thrombotic problems emerged that required anticoagulants. Apixaban (RN) is a factor X_a inhibitor that treats deep vein thrombosis and the two forms of artery diseases (coronary artery disease and peripheral artery disease).

Materials and Methods: The study objective was to create fast-disintegrating Apixaban Oral Thin Films (OTF) with the help of various super disintegrants to shorten disintegration time and enhance drug release in order to assist patients who have difficulty in swallowing conventional dosage forms and increase bioavailability. OTF was created using the solvent casting method. A 2^2 factorial design was employed in Design-Expert® software to develop an ideal formula.

Results: The optimized film formula pH, drug content, disintegration time, folding endurance, and dissolution rate were estimated, and the film was subjected to a short-term stability study. The optimized formula exhibited a cumulative drug release of 93.47% in 60 sec.

Conclusion: The drug's *in vitro* release pattern shows first-order kinetics and fickian diffusion was the mechanism of drug release. These findings supported that Apixaban OTFs offer a quick release of the medication from the administration site into the systemic circulation.

Keywords Statistical design, nanosponges, solubility, nano drug delivery

INTRODUCTION

Oral administration is the most effective method for achieving systemic effects. A solid dosage form constitutes around 60% of all formulations. The oral route of administration is widely used due to its ease, absence of pain, and versatility.[1] Dysphagia affects people of all ages, but it is more widespread in older persons. The fear of choking inhibits many pediatric and elderly patients from delivering this solid dosage forms.[2] Dysphagia is linked to clinical illnesses such as stroke, head and neck thyroid treatment, parkinson's

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disease, thyroidectomy, AIDS, and other neurological issues such as cerebral palsy. The most common concern was tablet size, followed by surface area and flavour.[3]Oral thin films have variety of approaches to solve the issues associated with the oral route of administration. Oral thin films are one example of a product in which we utilize super disintegrants to disperse the dosage form. These rapid-dissolving drug delivery systems will disperse on the patient's tongue without water or chewing in minutes or seconds.[4] Oral thin films is placed on the dorsum or the floor of the tongue. It confines to the application position, and the drug is absorbed by oral mucosa due to its highly permeable nature into systemic circulation. Due to its high vascularity and permeability, the active substance is delivered for local and systemic uptake. Hydrophilic polymers are chosen since they are easily dissolved when it comes in contact with saliva.This innovative drug delivery method can improve drug solubility/ stability, biological half-life, and bioavailability.[3,5] Hydroxypropyl methylcellulose (HPMC E 15 LV) was used as a film-forming agent. It contains 28-30% methoxyl, 7-12% hydroxypropyl. It encompasses thermal gelation with outstanding film characteristics (high tensile strength, strength, and elongation). DOACs (Direct Oral Anticoagulants) have been used for various indications- arterial diseases, heart failure, cancer, and the prevention of DVT in acute medical diseases. Post-COVID-19 pandemic, it was clear that the victims have been diagnosed with higher levels of thrombin, fibrin components, and other clotting factors that promote clot formation. This led to an increase in the administration of DOACs. One such anticoagulant is Apixaban - a factor X_a inhibitor capable of dissolving clots internally and externally with minimal drug-drug or drug-food interactions. Unlike indirect factor Xa inhibitors such as fondaparinux or heparin, Apixaban suppresses both free and clot-bound factor X_a and prothrombinase, which prolongs the clotting time.[6]

The aim of the study is to enhance the bioavailability of Apixaban at the receptor site by formulating oral thin films. The reason to enhance bioavailability of oral thin films is to over come the disadvanatges of conventional dosage forms.

MATERIALS AND METHODS

Materials

Apixaban was received as a gift sample from Alphamed Formulations Pvt. Ltd., Hyderabad. Propylene glycol was obtained from Thermo Fisher Scientific India Pvt. Ltd., Bengaluru, while HPMC was purchased from Loba Chemie Pvt. Ltd., Mumbai. Sodium starch glycolate and aspartame was supplied by Merck, Mumbai. All other chemicals and compounds utilized were of analytical grade.

Methods

Preformulation studies

The initial stage in the rational development of dosage forms is pre formulation study. It investigates drugs molecular and physical characteristics, both alone and when combined with excipients. Preformulation assessment aims to generate data to help the formulator construct safe, bioavailable, and mass-producible dosage forms.[7]

Excipient - Drug Compatibility Research

Fourier Transforms Infra-Red (FTIR) Spectroscopy: FT-IR spectra (Bruker alpha, Germany) was obtained to discover possible interactions between the drug and polymers. The ingredients were compressed with a hydraulic press to form a pellet (less than 5 k pas). The disc was put in the centre of the sample holding device and spectrum was recorded using an FT-IR spectrophotometer.[8]

Differential Scanning Calorimetry (DSC): DSC thermograms of API and physical mixture was recorded by enclosing them in heat-resistant aluminium pans. The surface of the pan lid was crimped by pushing them against a pellet mill. The pans were held in the heating chamber to temperatures ranging from 30 to 300°C at 10°C/min.[9]

Analytical Method Development

Determination of λ_{max} for Apixaban by using acetonitrile: The calibration curve for Apixaban was developed using acetonitrile.[9]

Thickness = (T1 + T2 + T3 + T4 + T5) / 5

Preparation of standard curve for Apixaban by using acetonitrile: From the 1000 µg/mL stock solution, 100µg/mL solution is prepared. Different concentrations of Apixaban at various concentrations 2, 4, 6, 8, 10 µg/mL were obtained, and its absorbance was determined.[9]

Preparation of oral Dissolving Film of Apixaban Using 2^2 Factorial Designs: A two-factor design has been used for optimization Table 1. The independent factors, as well as the dependent variables, were chosen. Three independent variables has been chosen. The highest and lowest factor values were marked as +1 and -1 Table 2. All samples were quantitatively assessed using ANOVA and Design Expert 11@software to determine the chosen variable significance and non-

Table 1: 2^2 Full Factorial design layouts.

Batch code	X_1	X_2
F1	+1	+1
F2	-1	-1
F3	+1	-1
F4	-1	+1

Table 2: Coded value for concentration of polymer (X_1) and concentration of super disintegrant (X_2).

Coded value	Concentration of Polymer(mg)	Concentration of super disintegrant (mg)
-1	350	40
+2	500	50

significance affect on responses such as disintegration time, folding endurance, and thickness. The factor impact was visually represented using 3D response surface plots and contour plots in design expert.[10]

Preparation of Apixaban mouth dissolving film

The solvent casting process involves adding HPMC E15 LV and propylene glycol to the water, keeping the temperature at 60°C and the stirrer rotating at 1000 rpm. Color, flavoring agent, sweetening agent, and disintegrant are dissolved in water with continuous stirring. The resultant solution is combined with the API dissolved in a solvent. To extract the trapped air, a vacuum is employed. The homogenous solution formed is cast as a film and allowed to dry before being cut into the appropriate size.[11]

Evaluation of mouth dissolving films of Apixaban

Physical appearance and surface texture of films: These criterias were confirmed easily by inspecting films visually and by feel or touch. The finding implies the films surface nature and visually appealing or not.[12]

Organoleptic analysis: Organoleptic assessment of prepared oral disintegrating films are performed with the previous agreement of a group of healthy participants with good organoleptic sensibilities. The flavor, tongue feel (grittiness or smoothness), and the oral disintegrating films outward look was evaluated.[13]

Thickness: The width of the film is proportionate to its dosage uniformity. The ultimate thickness of the film is checked by calculating the mean thickness at five distinct locations with micrometer screw gauge. It should be between 50 mm to 1000 mm.[14]

Average weight: About 10 films are individually weighed. The average weight was determined by adding the weight of all films and dividing by 10.[15]

Surface pH: The surface pH of the films was evaluated by exposing them to 1 mL of distilled water. The surface pH was determined by introducing pH paper close to the surface of the films.[16]

Average weight = weight of 10 strips / 10

Folding endurance: Film folding endurance is determined to check the film durability. Folding endurance was determined by repeatedly folding a tiny film strip until it breaks. The endurance value is determined by the number of times it can be folded without tearing.[17]

Content uniformity: Three films were individually assayed for their drug content. Film was dissolved and diluted with water to get a 1 µg/mL concentration. The film must contain API of 85-115% of the label claim to have content uniformity.[18]

Disintegration time (petri dish method): This technique was carried out on a petri plate. The oral thin film was placed in the centre of a petri dish filled with 10 mL of distilled water. The time taken for the thin layer to disintegrate is measured, and the procedure is done thrice.[19]

Moisture loss: The proportion of moisture loss defines a film's hygroscopicity. Typically, this parameter was found by first determining the original weight of the film, followed by placing it for three days in a desiccator. After three days, the films are removed and reweighed. The following algorithm is used to calculate moisture loss.[20-25]

Moisture absorption: The moisture absorption is measured by first dividing the film into 2 x 2 cm^2 squares. These strips are then subjected to a 75% relative humidity atmosphere at room temperature for a week. Moisture absorption is calculated as a percentage weight increase of the strip.[21-25]

In vitro dissolution studies

The dissolution study was carried out in a type II USP apparatus. 900 mL of dissolution medium was taken and maintained at 37°C ± 0.5°C. The film was attached to a rotating centre axis. Filtered samples were taken manually at 15, 30, 45, and 60 sec. At the same temperature, the samples were compensated with an equivalent volume of pure water. After appropriate dilution with the dissolving media, the concentration of the drug released in the medium was measured spectrophotometrically at 249 nm.[22]

Dissolution parameters

- Apparatus: Dissolution apparatus (Type II),

- Dissolution Medium: Purified water, 900 mL,
- RPM: 50,
- Temperature: 37°C ± 0.5°C,
- Withdrawal time: 15, 30, 45 and 60 sec,
- Volume withdrawal: 5 mL.

Release kinetics

The amount of drug released from the pharmaceutical dosage form and its processes is an essential but which is intricate process in matrix systems. Zero order or first order kinetics were used to characterize the sequence of drug release from matrix systems. The Higuchi diffusion model and the Hixon-Crowell erosion model were used to investigate the mechanism of drug release from matrix systems. The Korsmeyer- Peppas equation also categorized drug release mechanisms as Fickian/non- Fickian/anomalous. The release exponent 'n' value is utilized in the Korsmeyer-Peppas equation to characterize distinct release processes from the dosage form.[22]

Stability studies

To examine the stability of the drug formulation, stability experiments were conducted by ICH. The optimized formulation was sealed in a polyethylene-laminated aluminum container. Samples were stored at 40°C and 75% RH for a month. The formulation was examined for any changes in its characteristics.[23]

RESULTS

Determination of λ_{max} for Apixaban by using acetonitrile

The absorption maximum for Apixaban by using acetonitrile was noticed at 249 nm.

Percentage moisture loss = (Initial weight - Final weight) / Initial weight * 100

Percentage moisture uptake = (Final weight - Initial weight) / Initial weight * 100

Preparation of Standard Curve for Apixaban by using acetonitrile

The graph was plotted taking absorbance on x- axis and concentration on y-axis. The graph was linear at 2 – 10 µg/mL range and obeys Beer - Lambert's law Figure 1.

Drug-Excipient Compatibility Studies by FT-IR

Fourier transforms infrared (FT-IR) spectroscopy

Comparisons of the spectra of Apixaban Figure 2 with the physical combination reveal that there is no interaction and that the drug is in its unmodified form Figure 3.

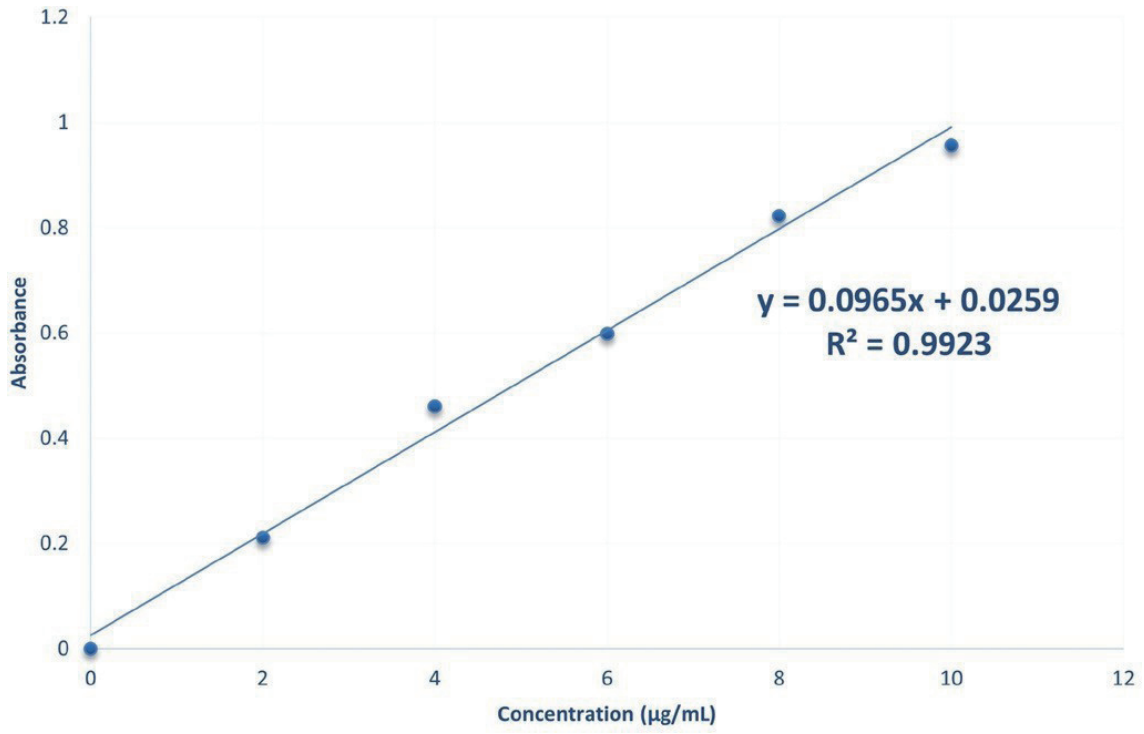

Figure 1: Standard Graph Of Apixaban in Acetonitrile.

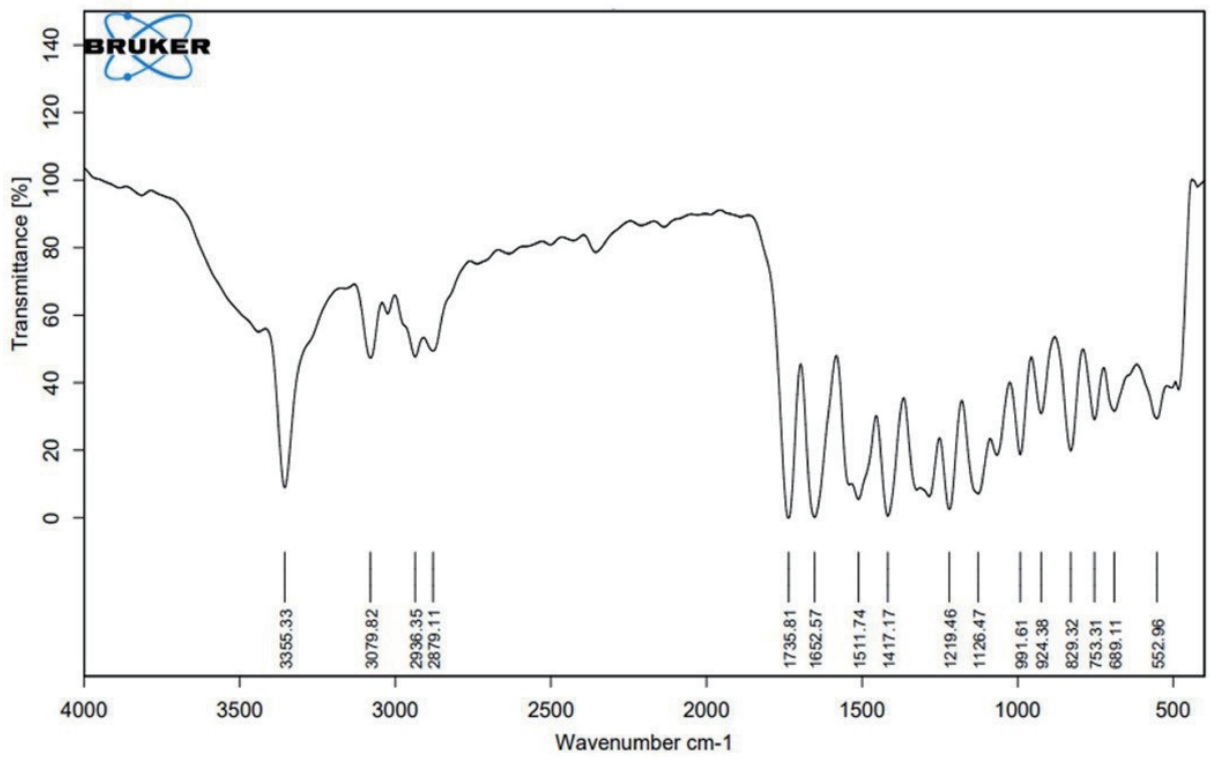

Figure 2: FT-IR Spectra of Apixaban.

Table 3: Formulation table of Oral thin films using DoE.

INGREDIENTS	Formulation			
Formulation code	**F1**	**F2**	**F3**	**F4**
Drug(mg)	10	10	10	10
HPMC (mg)	500	350	500	350
Sodium starch glycolate (mg)	50	40	40	50
Aspartame (mg)	15	15	15	15
Propylene glycol (ml)	1	1	1	1
Water(ml)	10	10	10	10

Differential Scanning Calorimetry (DSC)

In spectrum of Apixaban Figure 4, there was an endothermic peak at 231.88°C which may be because of oxidation or recrystallization Figure 4. The DSC curve of the physical combination demonstrates the existence of a melting peak at 227.70°C, Figure 5 which correlates to Apixaban melting. Comparisons of endothermic peaks of Apixaban and the physical mixture showed absence of interaction and presence of drug in unchanged form.

Experimental design

The prepared films were subjected to fundamental evaluation tests Table 4. Films are checked for thickness, folding endurance, and disintegration time and evaluated using Design Expert 11@ software for optimization Table 5.

Optimization of dependent variables

Response 1 (*in vitro* disintegration time): The formulations indicated a range of 35 to 62 sec. The equation from best suited model to coordinate the answer y and variables (HPMC and SSG) was R1 = +15.50000+0.140000HPMC-0.600000SSG. The equation of the model F value of 238.50 and *p* value is < 0.05, implying that the model is significant. The predicted r^2 0.9979 compared with adjusted r^2 0.9937

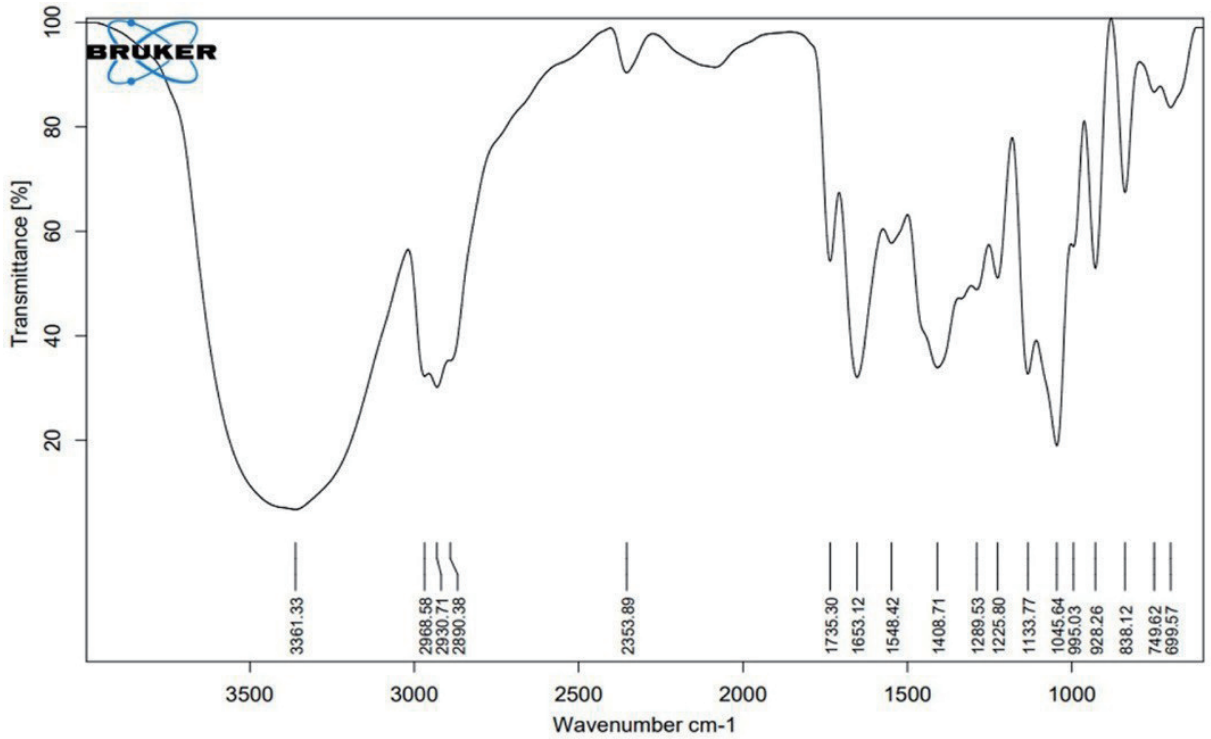

Figure 3: FT-IR spectra of physical mixture and Apixaban.

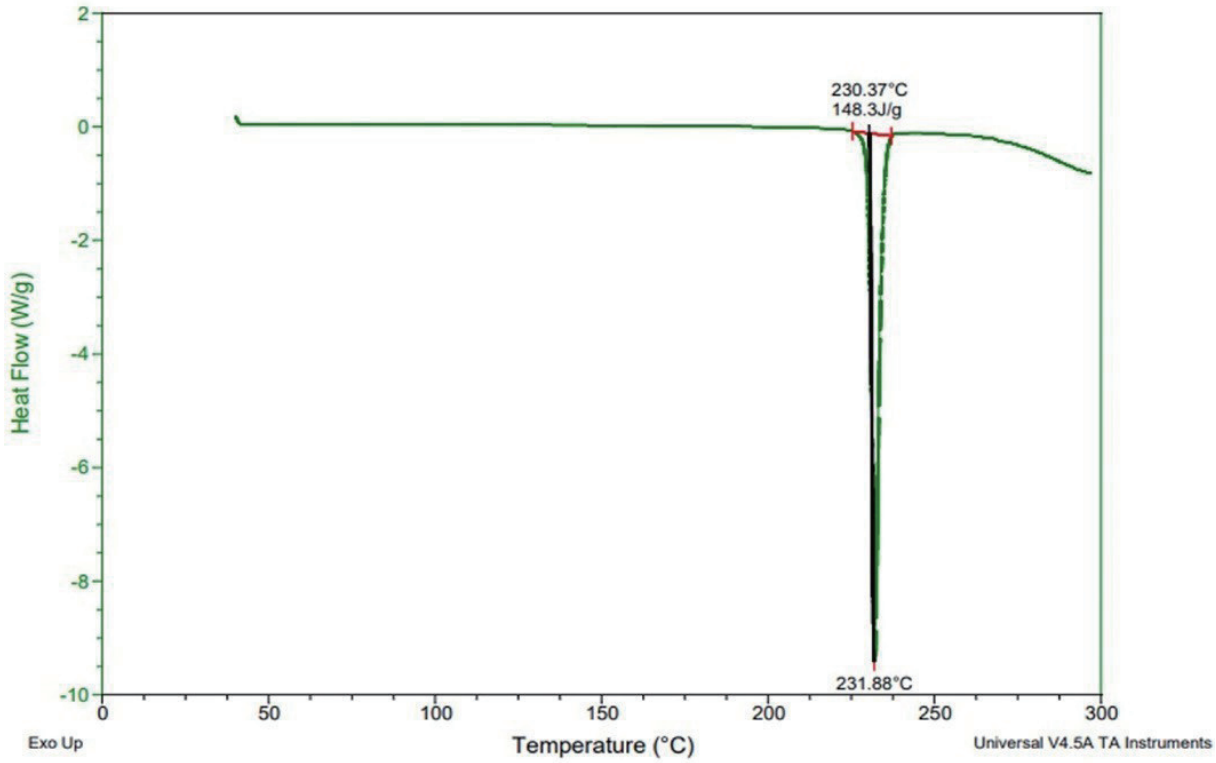

Figure 4: Thermogram of Apixaban.

demonstrated a nicely fit response of factors. R1 Three-Dimensional (3D) response surface plot showed with an increase in factors HPMC and Sodium starch glycolate. There is an increase in the disintegration time Figures 6 and 7.

Response 2 (Folding Endurance): In the range

Table 4: Reported and observed FT-IR frequencies of pure drug and physical mixture.

Functional Group	Reported Frequencies (in cm^{-1})	Observed Frequencies in the pure drug (in cm^{-1})	Observed Frequencies in the Physical mixture (in cm^{-1})
-NH	3400-3300	3355	3361
-CH(-ANE)	3000-2840	2936	2930
-CH(-ANE)	3000-2840	2879	2890
CH(AROMATIC)	2000-1650	1735	1735
C=C	1662-1626	1652	1653
-OH(COOH)	1440-1395	1417	1408

Table 5: DoE generated 2^2 factorial designs.

Run	Factor 1 a: HPMC	Factor 2 b: SSG	Response 1 (Disintegration Time)	Response 2 (Folding Endurance)	Response 3 (Thickness)
1	500	50	55 sec	350	0.47 mm
2	350	40	40 sec	290	0.4 mm
3	500	40	62 sec	324	0.51 mm
4	350	50	35 sec	312	0.37 mm

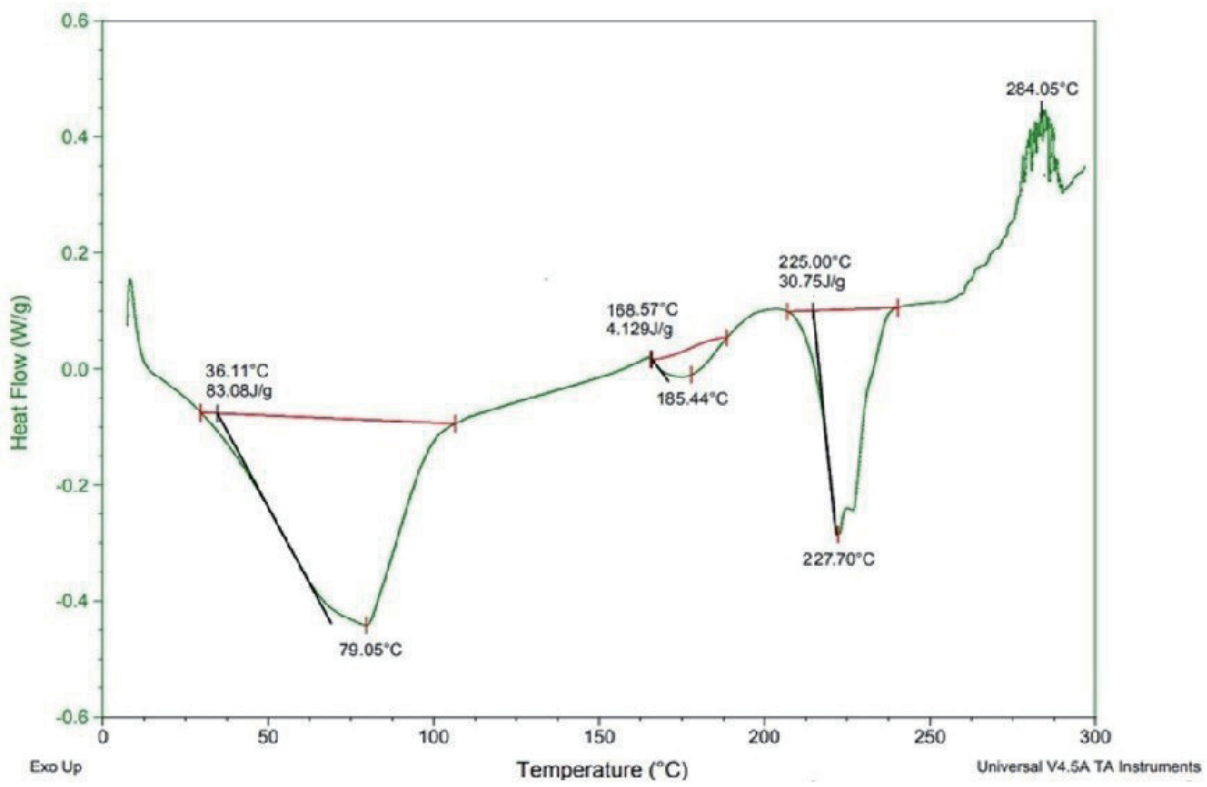

Figure 5: Thermogram of Physical mixture.

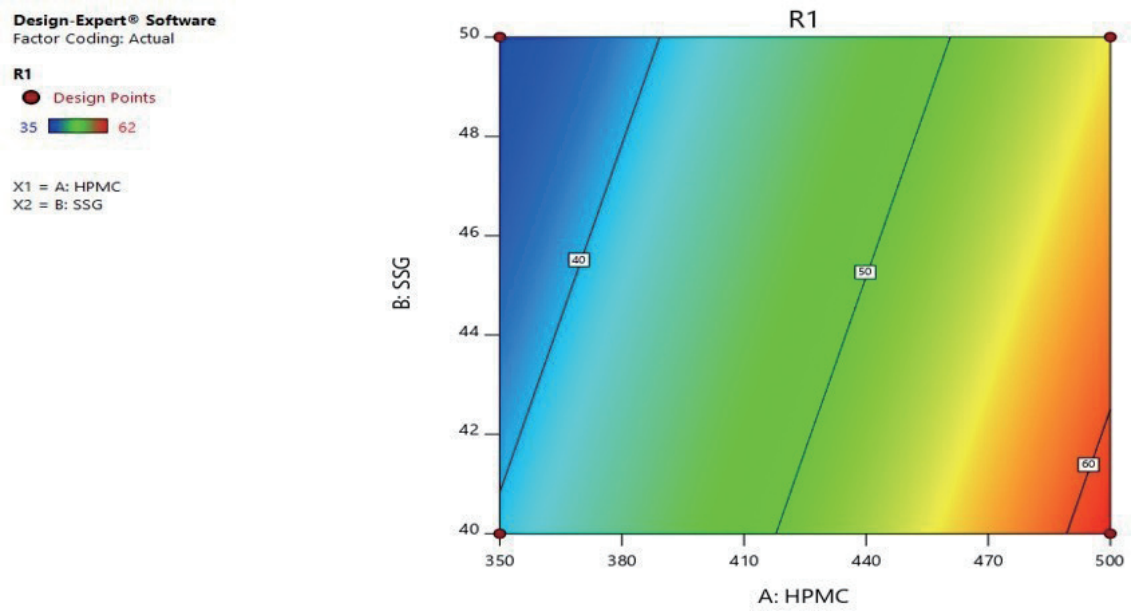

Figure 6: Contour plot of R1 (disintegration time).

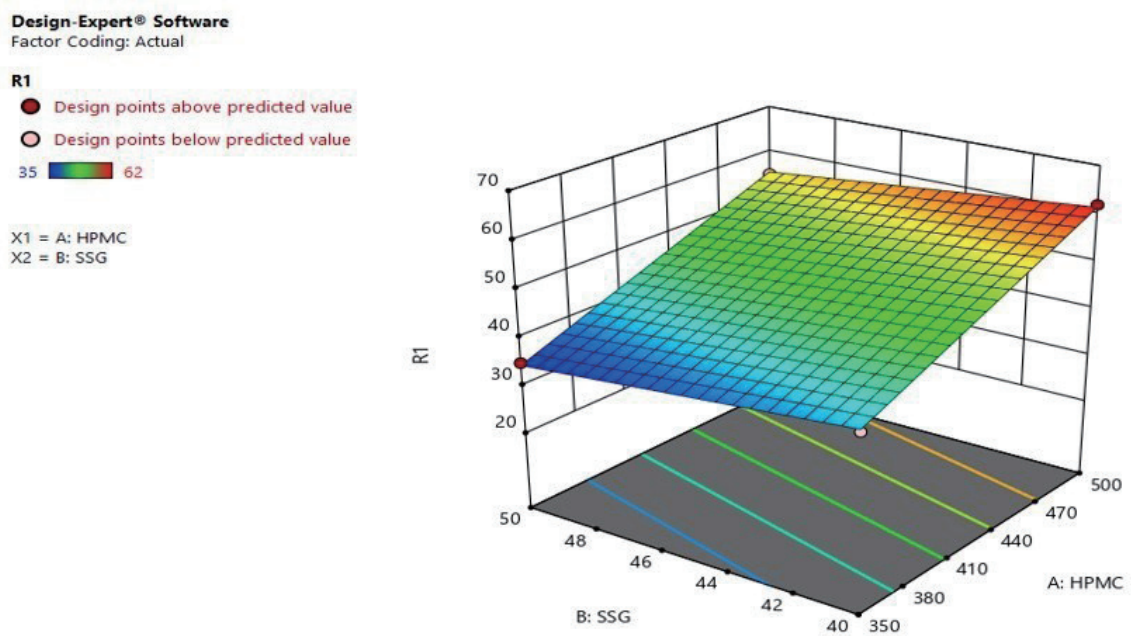

Figure 7: 3D response surface plot of R1 (disintegration time).

290 to 350, the folding endurance values of formulations(F1-F4) were found. R2 = -+109.00000 +0.240000HPMC+2.40000SSG was derived from the most appropriate mathematical model for R^2 and the independent variables. The model F value 234.00 and *P* value is < 0.05, implying that the model is significant. And, the r^2 0.9970 predicted is in fair competition with the r^2 0.9936 adjusted. Variables HPMC and SSG have significantly impacted the folding endurance. Enhanced HPMC and Sodium starch glycolate factors dramatically enhanced folding endurance, according to the R2 three-dimensional response plot Figures 8 and 9.

Response 3 (Thickness): Based on 2^2 factorial designs, Various combinations of parameters (HPMC and SSG) they influenced the thickness response (R3). R3= +0.297500+0.000700HPMC-0.003500SSG. The independent variables fit the equation derived from the best response R3. The F value 245.00, $p<0.05$ implying that the model is significant. And, the

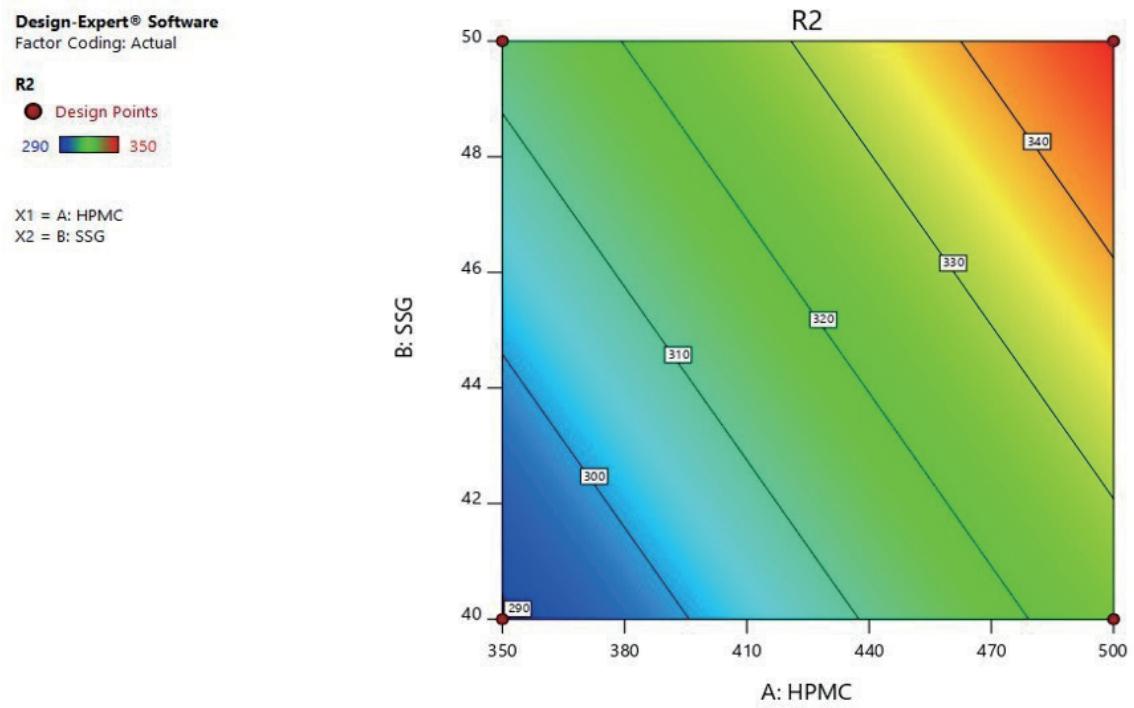

Figure 8: Contour plot of R2 (Folding Endurance).

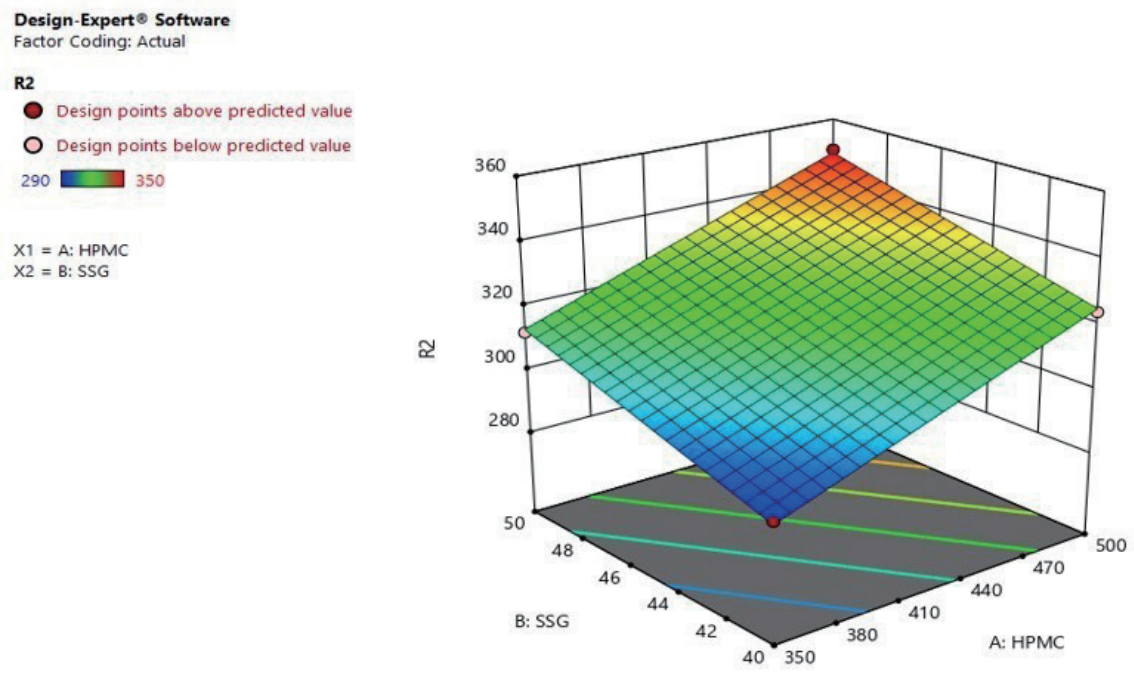

Figure 9: 3D response surface plot of R2 (Folding Endurance).

0.9980 r^2 predicted was comparable to the 0.9939 r^2 adjusted. It was discovered that the factors sodium starch glycolate and HPMC had a significant impact on thickness. R3's 3D response surface plot showed a significant rise in the thickness with increased levels of variables HPMC and Sodium starch glycolate Figure 11.

Checkpoint study and design optimization

By imposing restrictions on the response, such as R1 = 48.5 sec, R2 = 319.9, and R3 = 0.43 mm, the optimized formulation (F5) was discovered using an overlay

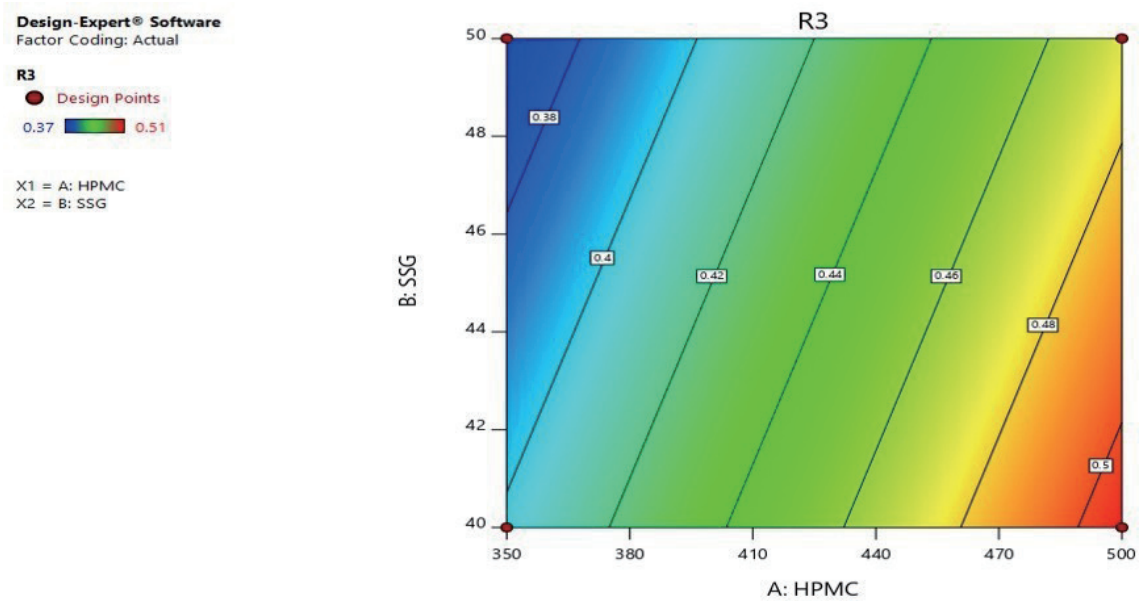

Figure 10: Contour plot of R3 (Thickness).

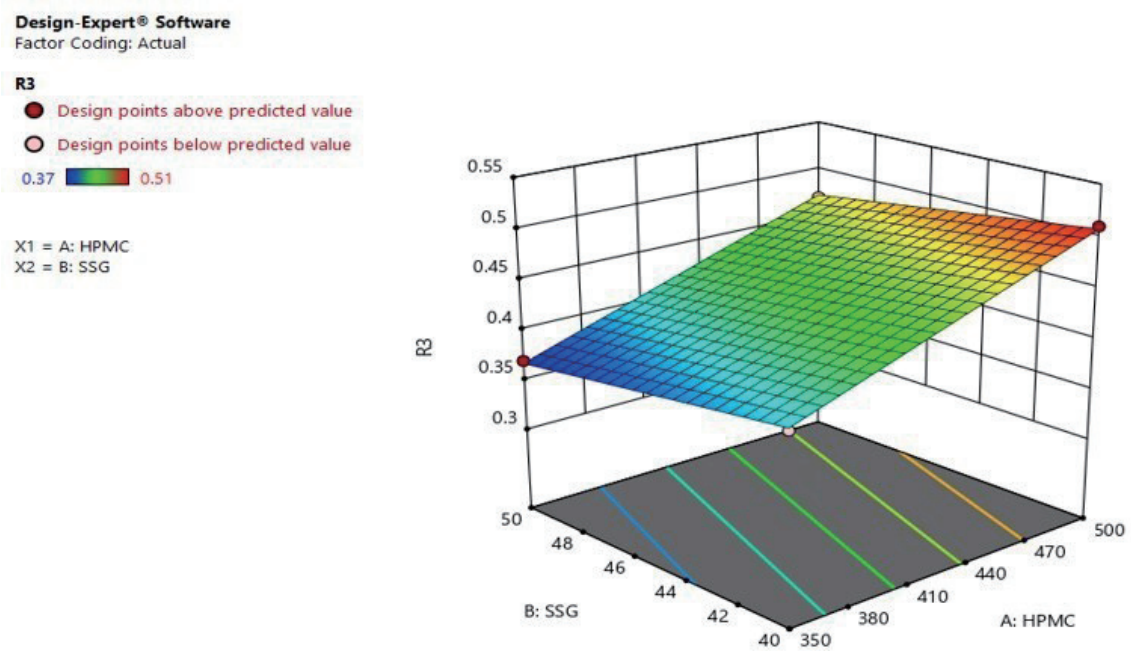

Figure 11: 3D response surface plot of R3 (Thickness).

plot Figure 12. DoE was used to indicate the levels of components from plots which showed a desirability of 0.9428 and the best values of the selected variables, estimated at 0.61 percent for HPMC and 0.67 percent for SSG.

The checkpoints were analyzed for the optimized formulation (F5) using thickness (mm), folding endurance, and disintegration time (sec).

Evaluation of Apixaban Oral Thin Film

Thickness, Average weight, and Uniformity of weight: These factors were tested visually and physically through touch or feel. According to the observation, the films have a smooth surface and are visually appealing. Utilizing an electronic balance, the weight of the prepared film was calculated; the average weight was 0.38±0.63 g, respectively. The film had a thickness of 0.45±0.50 mm, respectively.

Surface pH: According to the study, the normal physiological pH of the oral mucosa is 6.2-7.6. pH

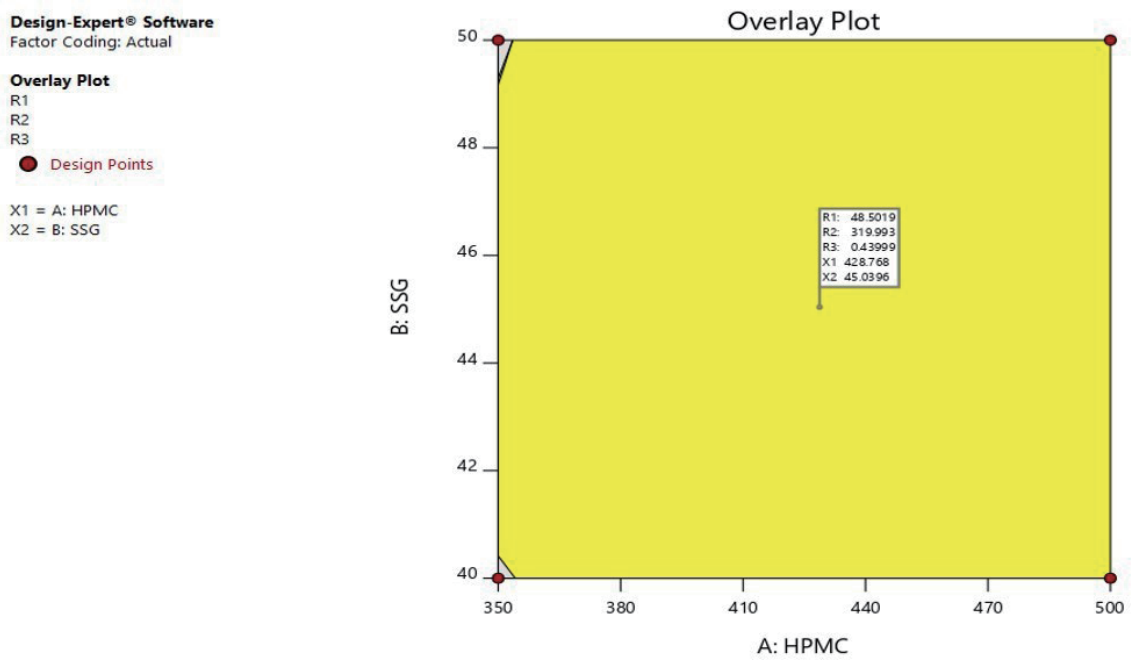

Figure 12: Overlay plot.

of the film was found to be around 7, which is an acceptable pH when measured with pH paper, while with that of the pH electrode, it was found to be 7.28.

Folding endurance: Flexibility of the film was due to the presence of propylene glycol, and the mechanical properties of film were due to HPMC. Optimized formulation showed a good quality film with folding endurance of 325.

Percentage Moisture loss: Percent moisture loss evaluation can be used to determine the durability and quality of oral films. It was evident from the outcomes that the optimized formulations percentage moisture loss was 1.087±0.264%, clearly showing a correlation between moisture loss and polymer content.

Percentage moisture uptake; Percentage moisture absorption indicates the sustainability of the film. The percentage moisture absorption of the optimized f5 formulation was 1.219± 0.512%. The formulation has been found to absorb less than 2% moisture. Since the films take up moisture, they have to be protected from such an environment.

Drug content and content uniformity: The drug content and homogeneity of the film made with polymer were assessed. The drug concentration was 96.8%. The drug content and homogeneity were judged to be within the pharmacopeial limit. Both results indicate that the API was evenly distributed throughout the film.

Disintegration time: Because there was no formal disintegration test for oral thin films, hence most widely used method was performed. The concentration of super disintegrant influences disintegration time. The time needed for disintegration decreased as the concentration of super disintegrants increased. The disintegration time of the film was found to be 33 ± 1.5 sec.

In vitro dissolution studies

A dissolution study was used to compare the release pattern of drug in dissolution media. The USP type II apparatus was used to estimate the dissolution of oral thin film. The drug release from the film began as soon as it came into contact with the medium, and the drug release was larger than that of the traditional dosage form available. At 60 sec, drug release rapid dissolving films obtained 93.47% (Figure 13 and Table 6).

Kinetic analysis of release data

The optimized formulation in vitro drug release pattern was best described by first order, as the plots exhibited the maximum linearity with R^2 =0.9664 Table 7. Higuchi has studied the rate laws anticipated by the various dissolving processes, both alone and in combination. The equation predicts a first order dependency on the concentration gradient between the static liquid layer near to the solid surface and the bulk liquid, similar to the other rate law equations. Noyes and Whitney employed a notion close to the diffusion model to explain their dissolution findings.

Table 6: *In vitro* dissolution studies.

	Absorbance	DF	Conc µg/mL	Amt in mg/ mL	Amn in mg/5 mL	Amt mg/900 mL	Cum. DR	%DR
15	0.061	10	0.6321	0.0063	0.0316	5.6891	5.7176	57.17
30	0.092	10	0.9533	0.0095	0.0476	8.5803	8.6404	86.40
45	0.094	10	0.9740	0.0097	0.0487	8.7668	8.8746	88.74
60	0.098	10	1.0155	0.0101	0.0507	9.1398	9.3471	93.47

Table 7: Release Kinetics of Apixaban OTF.

Formulation Code	Zero Order R^2	First Order R^2	Higuchi Matrix R^2	Korsmeyer- Peppas		Hixson-Crowell	Best Fit Model
				R^2	n	R^2	
F5	0.7891	0.9664	0.9512	0.8734	0.3161	0.9236	First order

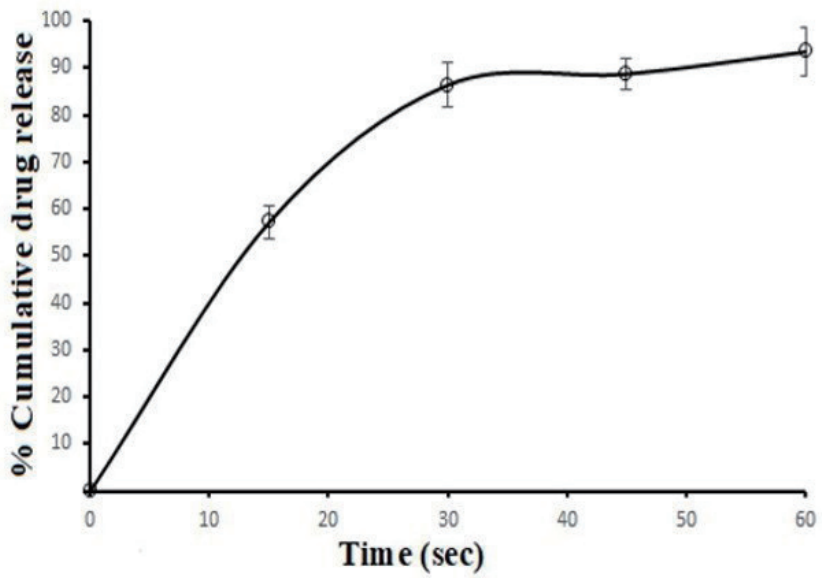

Figure 13: *In vitro* dissolution studies.

The data produced by the formulation did not correspond well to zero order kinetics, and this model was not appropriate for explaining the rate kinetics of oral rapid dissolving film formulation. The data was fitted with the peppas equation, which produced n = 0.31 for formulation, showing that fickian diffusion (case I diffusional) was the mechanism of drug release.

Stability studies

According to the findings, there is no substantial change in the surface pH, thickness, folding endurance, drug content, or percentage of drug release Table 8.

DISCUSSION

Apixaban Oral Thin Films (OTF) were developed utilizing the solvent casting method. A full factorial design with 2^2 experimental factors was employed using Design Expert 11 software. Both independent factors and dependent variables were carefully selected. Quantitative assessment of all samples was performed using Design Expert 11 software to determine the significant and non-significant effects of the chosen components on reactions such as Disintegration Time, Folding Endurance, and Thickness. Through the use of an overlay plot and response surface plot, the optimized formulation (F5) was successfully determined.[10]

Table 8: Optimized formulation F5 stability studies data for 1 month

Storage condition	Surface pH	Thickness	Folding endurance	%Drug content	%Drug release
25 ± 2°C/60 ± 5% RH	7.26	0.45±0.13 mm	325±0.02	96.8±0.12%	93.47±1.05%
40 ± 2°C/75 ± 5% RH.	7.25	0.45±0.04 mm	324±0.03	96.68±1.25%	91.15±1.03%

The FT-IR spectra analysis indicated the absence of any detectable chemical interactions between the medication and the polymer. The distinctive bands of the pure drug remained unaffected by the presence of the polymer.[8] Additionally, the comparison of melting peaks in the DSC curve between Apixaban and the physical combination demonstrated the absence of any interaction, confirming the presence of the drug in its original, unmodified form.[9]

The observations indicate that the optimized formulation F5 exhibited a visually seamless and attractive surface. The weight of F5 was determined using a digital balance, along with the average weight of the film. The film thickness was measured by calculating the mean value from five different locations using a micrometer screw gauge. The pH of the film was found to be approximately neutral, which is considered acceptable when measured using pH paper. A similar result was obtained when the pH was measured using a pH electrode, indicating a nearly neutral pH.[25] The presence of propylene glycol contributed to the flexibility of the film, while the mechanical properties were attributed to HPMC. As the concentration of the polymer increased, the percentage of moisture loss in the film also increased. However, the film was found to absorb less than 2% moisture. Therefore, it is necessary to protect the film from environmental moisture due to its tendency to absorb moisture.[26]

The drug content and content uniformity of the film were found to be within the acceptable range defined by the pharmacopeia. These results indicate that the medication was uniformly distributed throughout the film. The disintegration time of the film was found to be influenced by the concentration of the super disintegrant. Specifically, as the concentration of the super disintegrant increased, the disintegration time decreased.[27] The drug release from the film commenced immediately upon contact with the medium, and the extent of drug release was greater compared to traditional dosage forms currently available. The *in vitro* release pattern of the drug followed first-order kinetics, and the mechanism of drug release was identified as fickian diffusion.[28]

CONCLUSION

Solvent casting approach was effectively used to prepare oral thin films that were stocked with Apixaban. According to FT-IR spectrum, the polymer and formulation did not change the functional bands of Apixaban. A neutral surface pH of optimized formulation of F5 with smooth surface that was sufficiently elegant to be seen. The dose uniformity test's acceptance value requirement had been met by the optimized F5 formulation, which also showed excellent stability and a dissolution profile. Based on the findings, it can be said that the optimised formulation F5 offers a quick release of the drug from the site of administration into the systemic circulation, thereby enhancing the bioavailability of Apixaban.

Conflict of interest

The authors declare that there is no conflict of interest.

Abbreviations

RN: Apixaban; OTF: Oral thin films; DOACs: Direct oral anticoagulants; HPMC: Hydroxypropyl methylcellulose; SSG: Sodium starch glycolate.

References

[1] G. Erdem, M. Esme, B.B. Dogu, Systematic review and meta-analysis of randomized controlled trials on safety and effectiveness of oral anticoagulants for atrial fibrillation in older people, Ir, J. Med. Sci. 191 (6) (2022) 2517–2523, https://doi.org/10.1007/s11845-021-02891-x.

[2] Y. Miyasaka, M.E. Barnes, B.J. Gersh, S.S. Cha, K.R. Bailey, W.P. Abhayaratna, et al., Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence, Circulation 114 (2006) 119–125, https://doi.org/10.1161/ CIRCULATIONAHA.105.595140.

[3] Y. Zhan, J. Joza, M. Al Rawahi, R.S. Barbosa, M. Samuel, M. Bernier, et al., Assessment and management of the left atrial appendage thrombus in patients with nonvalvular atrial fibrillation, Can. J. Cardiol. 34 (2018) 252–261, https://doi.org/10.1016/j.cjca.2017.12.008.

[4] P. Merella, G. Lorenzoni, N. Marziliano, P. Berne, G. Viola, P. Pischedda, et al., Nonvalvular atrial fibrillation in high-hemorrhagic-risk patients: state of the art of percutaneous left atrial appendage occlusion, J. Cardiovasc. Med. 20 (2019) 1–9, https://doi.org/10.2459/JCM.0000000000000735.

[5] S.V. Garkina, T.V. Vavilova, D.S. Lebedev, E.N. Mikhaylov, Compliance and adherence to oral anticoagulation therapy in elderly patients with atrial fibrillation in the era of direct oral anticoagulants, J. Geriatr. Cardiol. 13 (2016) 807–810, https://doi.org/10.11909/j.issn.1671-5411.2016.09.010.

[6] C.B. Granger, J.H. Alexander, M.H. S, J.J.V. McMurray, R.D. Lopes, E.M. Hylek, et al., Apixaban versus warfarin in patients with Atrial fibrillation, N. Engl. J. Med. 365 (11) (2011) 981–992, https://doi.org/10.1056/NEJMoa1107039.

[7] P. Dodrill, M.M. Gosa, Pediatric dysphagia: physiology, assessment, and management, Ann. Nutr. Metab. 66 (S5) (2015) 24–31, https://doi.org/10.1159/000381372.

[8] D.J. Wright, D.G. Smithard, R. Griffith, Optimising medicines administration for patients with dysphagia in hospital: medical or nursing responsibility? Geriatrics 5 (2020) 9, https://doi.org/10.3390/geriatrics5010009.

[9] M.P. Ghourichay, S.H. Kiaie, A. Nokhodchi, Y. Javadzadeh, Formulation and quality control of orally disintegrating tablets (ODTs): recent advances and perspectives, BioMed Res. Int. 2021 (2021), 6618934, https://doi.org/10.1155/2021/6618934.

[10] N. Namiki, Clinical functionality required for orally disintegrating tablets selected as the next generation type, Yakugaku Zasshi 135 (2015) 237–243, https://doi.org/10.1248/yakushi.14-00228-3.

[11] A.F. Borges, C. Silva, J.F. Coelho, S. Simoes, Oral films: current status and future perspectives II - intellectual property, technologies and market needs, J. Contr. Release 206 (2015) 108–121, https://doi.org/10.1016/j.jconrel.2015.03.012.

[12] E.M. Hoffmann, A. Breitenbach, J. Breitkreutz, Advances in orodispersible films for drug delivery, Expet Opin. Drug Deliv. 8 (2011) 299–316, https://doi.org/ 10.1517/17425247.2011.553217.

[13] M.S. Pacheco, D. Barbieri, C.F. da Silva, M.A. de Moraes, A review on orally disintegrating films (ODFs) made from natural polymers such as pullulan, maltodextrin, starch, and others, Int. J. Biol. Macromol. 178 (2021) 504–513, https://doi.org/10.1016/j.ijbiomac.2021.02.180.

[14] S. Jacob, A.B. Nair, S.H.S. Boddu, B. Gorain, N. Sreeharsha, J. Shah, An updated overview of the emerging role of patch and film-based buccal delivery systems, Pharmaceutics 13 (8) (2021) 1206, https://doi.org/10.3390/pharmaceutics13081206.

[15] L. Shipp, F. Liu, L. Kerai-Varsani, T.C. Okwuosa, Buccal films: a review of therapeutic opportunities, formulations & relevant evaluation approaches, J. Contr. Release 352 (2022) 1071–1092, https://doi.org/10.1016/j.jconrel.2022.10.058.

[16] M. Irfan, S. Rabel, Q. Bukhtar, M.I. Qadir, F. Jabeen, A. Khan, Orally disintegrating films: a modern expansion in drug delivery system, Saudi Pharmaceut. J. 24 (5) (2016) 537–546, https://doi.org/10.1016/j.jsps.2015.02.024.

[17] A. Salawi, An insight into preparatory methods and characterization of orodispersible film-A review, Pharmaceuticals 15 (7) (2022) 844, https://doi.org/10.3390/ph15070844.

[18] R.P. Shah, A.K. Patel, V.M. Patel, Characterization and optimization of mouth dissolving film of an anticoagulant drug: apixaban, IJPRA 7 (3) (2022) 190–210, https://doi.org/10.35629/7781-0703190210.

[19] [Online available] Eliquis Tablets, 2021. https://packageinserts.bms.com/pi/pi_eliquis.pdf.

[20] R. Bala, P. Pawar, S. Khanna, S. Arora, Orally dissolving strips: a new approach to oral drug delivery system, Int. J. Pharm. Investig. 3 (2013) 67–76, https://doi.org/10.4103/2230-973X.114897.

[21] K. Olechno, A. Basa, K. Winnicka, Success depends on your backbone-about the use of polymers as essential materials forming orodispersible films, Materials 14 (17) (2021) 4872, https://doi.org/10.3390/ma14174872.