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Original Article

Formulation Development and Evaluation of Fast Dissolving Sublingual Film of Apixaban: Design of Experiment-Based Approach

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ABSTRACT

Objectives: The benefits of the active ingredients are circumvented due to poor bioavailability or presystemic metabolism. Apixaban is an oral anticoagulant possessing high lipophilicity and bioavailability of less than 50%. This drawback can easily be overcome with the help of a sublingual route of administration in the form of the oral thin film. The present research was carried out to improve Apixaban solubility, bioavailability, and therapeutic efficacy. **Materials and Methods:** The compatibility of Apixaban with the HPMC E15 (film former) was assessed with FTIR, DSC, and crystallinity with XRD. The quality-by-design approach was implemented with 3 independent factors such as concentration of HMPC E15, PEG 400, and cross-povidone. The disintegration time and cumulative percentage of drug release were recognized as critical quality attributes. **Results:** The ANOVA model predicted 0.0017 and 0.03111 *p*-values for disintegration and dissolution, respectively, indicating a significant model. The optimized batch F11 disintegrated within 15 sec, and 99.11% of the drug was released. The surface morphology was estimated with a scanning electron microscope. Compared with the marketed tablet formulation (70 min), the developed sublingual film was released completely within 10 min. Hence, the sublingual film of Apixaban is highly preferred in the prevention and treatment of deep vein thrombosis and pulmonary embolism. **Conclusion:** The sublingual film of Apixaban reflected an enormous rise in solubility, thereby attaining bioavailability.

Keywords: Oral thin film, Apixaban, HPMC E15, Box-Behnken Design, Deep vein thrombosis, Pulmonary embolism.

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INTRODUCTION

Deep Vein Thrombosis (DVT) is an unobservable serious condition mostly noticed in the legs of the deep veins due to the formation of blood clots (thrombus). The advancement in the DVT resulted in painful conditions and swelling at the site. These clots circulate through the blood and enter the lungs, which causes Pulmonary Embolism (PE).[1] The Venous Thromboembolism (VTE) developed after the formation of DVT and PE. Whenever any injury or trauma occurs, a blood clot forms to minimize the bleeding process. These clots are removed naturally by the body after the healing process, but due to the lack of factors sometimes remain in the bloodstream. Upon reaching the brain, the condition of Central Venous Sinus Thrombosis (CVST) arises, which leads to the development of hemorrhagic strokes. Moreover, heart attack, renal failure, and cardiovascular complications are the most observable life-threatening problems that occur due to blood clots. Recent studies revealed that obesity is another prime cause of blood clots.[2]

The oral anticoagulant agents are the prime treatment for the prevention and cure of blood clots, DVT, VTE, etc. Warfarin is a well-known anticoagulant agent useful in all the above conditions, but at the same time shows several other complications and limitations. Hence, currently, direct and factor Xa suppressors are in huge demand for better therapeutic efficacy than warfarin.[3] Apixaban is a direct and orally active anticoagulant that works by suppressing the factor Xa, prothrombinase, and thrombin. It is a versatile agent utilized in the prevention and therapy of stroke, PE, DVT, and CVST. Apixaban is routinely recommended by the physician after knee and hip replacement surgery. The beneficial usefulness of Apixaban is constrained because of the limited bioavailability of approximately. 50%. Hence, the current research mainly focused on the enhancement of solubility, bioavailability, and prompt therapeutic efficacy of Apixaban via oral thin film technology.[4]

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Currently, the oromucosal drug delivery is becoming popular for the prevention and treatment of several diseases. The conventional dosage forms, such as tablets and capsules, showed less absorption and ultimately resulted in poor bioavailability. Moreover, several patients (pediatric and geriatric), as well as surgery conditions, have problems with dysphagia where these dosage forms can't be administered. These limitations are easily overcome with the help of oral thin film, which is considered as best alternative option for the conventional dosage forms.[5]

Oral Thin Film (OTF) is a patient-friendly dosage form intended to be placed inside the oral cavity, which disintegrates quickly without the need for water. The OTF is gaining tremendous attention for patient comfort, and convenience to carry during traveling, and is typically recommended in the conditions of psychiatric disorders, mental illness, emesis, and oral surgeries.[6] The mechanism involved in the absorption of active ingredients from the oromucosal cavity via permeation into the bloodstream. Hence, the degradation of the active medicament is prevented by the gastric juice. The highest bioavailability of active ingredients is achieved through sublingual OTF.[7]

The OTF comprises active therapeutic ingredients as well as several proteins, peptides, nutraceuticals, antioxidants, vitamins, immunomodulatory, prebiotics, and probiotics that are available in the market. The OFT is developed by solvent casting, hot-melt extrusion, electrospinning, freeze-drying, and 3-D printing technology. The formulation of OTF requires the therapeutic active agent, film former, plasticizer, disintegrant, sweetener, saliva-stimulating agent, and coloring and flavoring agent. The tensile strength of the OTF mainly depends on the type of film former and plasticizer.[8]

The product with minimal investment of material and providing the best-optimized formulation by randomization is attained with a Quality-by-Design (QbD) approach. The possibility of any errors is not associated with the QbD design. Moreover, the safety and toxicity indications can be checked before formulation by the QbD.[9]

MATERIALS AND METHODS

Apixaban was provided by the Natco Pharma, Kothur, Telangana, India. Nitika Pharmaceuticals, Nagpur, gifted HPMC E15. Aspartame and citric acid were purchased from Loba Chemicals, Mumbai. All other ingredients utilized in the research work were of analytical grade only.

Preformulation studies

The powder sample of Apixaban was evaluated for the preliminary characteristics such as melting point (digital melting point apparatus) and loss on drying (hot air oven method).[10]

Solubility studies of Apixaban

The therapeutic dose of Apixaban was carefully transferred into the various test tubes mounted on the test tube stand containing distilled water, methanol, Tween 20, Tween 80, Span 80, PEG 200, propylene glycol, etc. Further, these test tubes were subjected to the vortex mixer for about 5-10 min. These test tubes were observed visually for the dissolution of the powder sample of the drug and investigated spectrophotometrically by UV-visible spectrophotometer at 264 nm.[11]

FTIR interaction study

The recognition of the powder sample of Apixaban and its compatibility with the ingredients were investigated with the FTIR (Affinity-1s, Shimadzu, Japan). The powder samples were scanned in a series of 400-5000 $cm^{-1,}$ and interpretations were recorded.[12]

Differential Scanning Calorimetry (DSC)

The DSC analysis was assessed (DSC, Mettler, Star SW13, UK) by heating the sample in the range of 50-300° C under inert nitrogen gas at a flow speed of 40 mL/min. The thermogram of the samples was collected.[13]

X-ray Diffraction

The diffractometer was utilized the check the crystalline nature of the samples. The samples were scanned at 2 Θ at the range of 5-90° along with the current supply of 45 kV and 40 mA, respectively.

Formulation of the artificial saliva

The saliva that existed in the oral cavity contributed significantly to the disintegration and dissolution of the OTF. Hence, the prepared film needs to be checked *in vitro* by formulating the artificial saliva at the same pH. An accurately weighed amount of 2.382 g of disodium hydrogen phosphate was transferred to 500 mL of distilled water. Further, potassium dihydrogen phosphate of 0.190 g and 8 g of sodium chloride were weighed accurately and added to the beaker containing distilled water. The volume made up to 1 L was made with DW. Finally, the pH was attuned to the phosphoric acid.[14]

Development of OTF of Apixaban

The process employed for the formulation of OTF was a modified solvent casting method. The appropriate size of a petri dish was selected and sterilized by hot air oven at 160°C for about 2 hr. Thereafter, the surface area of the entire plate was measured from the point of view of 3 x 2 size dimension. According to the surface area, the required dose of Apixaban was calculated. In the first beaker, 10 mL of double-distilled water was taken and boiled further. The desired extent of HPMC E15 was transferred carefully and permitted to swell for about 3-4 hr. In another beaker, along with 10 mL of solvent, the required concentration

of plasticizer (PEG 200) was added and stirred on the magnetic stirrer. Thereafter, the calculated dose of Apixaban was added to it.

Thereafter, both solutions were mixed gradually under uninterrupted stirring at 2000 rpm until a homogenous solution was achieved. Finally, the remaining components were incorporated and agitated. The plate is set aside in an oven at 40-45°C for about 12 hr. The film was cautiously unwrapped and amended into portions (3×2 size). The formulation components are depicted in the Table 1.[15,16]

Optimization of OTF of Apixaban

The successful development of OTF primarily depends on the three formulation components, such as concentration of film former HPMC E15 (X1), plasticizer PEG 200 (X2), and superdisintegrants cross-povidone (X3), considered as independent parameters. The Critical Quality Attributes (CQA) for the OTF were disintegration time (Y1) and dissolution release (Y2), which were recognized as dependable parameters. According to these factors, Box-Behnken Design (BBD) (Design of Expert, Statease, and Version 13) along with a quadratic model, was implemented. The DoE software predicted 12 trial runs by using BBD. Further, response surface methodology was implemented, and quadratic equations were elaborated. [17]

Evaluation of OTF

Superiority of film

The prepared OTF was confirmed for transparency, smoothness, and ease of detaching.

Thickness of OTF

The thickness of the prepared films was assessed with the digitally calibrated Vernier caliper.[18]

Folding endurance

The capacity of folding endurance confirms about strength and breakability of the film. It was determined by uninterrupted folding of film at the same point until it broke.[19]

Measurement of pH of OTF

The ready film was transformed into a solution and exposed to digital pH estimation by the electrode (Lab India, Pico model).

Determination of moisture content

Approximately 1 g of film was mounted on the digital moisture analyzer, which was set at a temperature of 105°C. After onset, the moisture available in the films was noted.[20]

Disintegration time

The film size (3x2) was positioned in the 10 mL of artificial saliva solution. The time requisite to entirely disintegrate was recorded.[21]

In vitro dissolution study

The films were located in a USP type II dissolution apparatus (Electolab India, 8 stations, Inspire-08) using the simulated saliva fluid at 37±0.5°C. The 5 mL of fluids were quiet at 1 min and switched with 5 mL of salivary fluids to uphold equilibrium.[22]

Content uniformity

An arbitrary OTF film was picked and characterized with a UV-visible spectrophotometer at 264 nm.[23]

Evaluation of surface morphology

The improved batch was subjected to Scanning Electron Microscopy (SEM).[24]

Table 1: Components of OTF of Apixaban.

Batch	Apixaban (mg)	HPMC E15 (mg)	PEG 200 (mL)	Cross povidone (mg)	Citric acid (mg)	Distilled water (mL)
A1	2.5	500	0.8	15	4	20
A2	2.5	550	0.6	13.5	4	20
A3	2.5	450	0.8	13.5	4	20
A4	2.5	450	0.7	15	4	20
A5	2.5	550	0.7	15	4	20
A6	2.5	550	0.8	13.5	4	20
A7	2.5	450	0.7	12	4	20
A8	2.5	450	0.6	13.5	4	20
A9	2.5	500	0.8	12	4	20
A10	2.5	550	0.7	12	4	20
A11	2.5	500	0.6	15	4	20
A12	2.5	500	0.6	12	4	20

Stability study

The optimized OTF was packed in the aluminum pouch at 40°C and 75% RH for 90 days (Remi India, SC-12 plus). The material was quiet after 30 days and verified for its efficacy parameters.[25]

RESULTS AND DISCUSSION

Preformulation study

The powder of Apixaban is observed as white to colorless and odorless. The melting point of the powder initiated at 236°C and melted entirely at 239°C.

Solubility studies of Apixaban

The solubility of the powder sample of Apixaban was tested in aqueous, organic, and non-volatile solvents. The Apixaban was slightly soluble in distilled water and soluble in methanol, ethanol, and chloroform. The solubility of Apixaban was found maximum in the PEG 200 (52±0.48 mg/mL) comparatively with PEG 400 (50±0.29 mg/mL), propylene glycol (41±0.39 mg/mL), Tween 20 (29±0.24 mg/mL), Tween 80 (27±0.65 mg/mL), and Span 20 (4±0.12 mg/mL). Hence, PEG 200 was selected as a solubilizing agent and plasticizer in the development of OTF.

FTIR interaction study

The powder material received was analyzed for the purity and identity of Apixaban by FTIR. The spectrum achieved was construed for the bands and the stretching. The high-pitched peak was noted at 3743.83 cm^{-1}, and 3309.85 N-H cm^{-1} for N-H stretching, 2166.06 cm^{-1} observed for C-H stretching, 1625.99 cm^{-1}, and 1595.13 cm^{-1} for C=C stretching, and 1186.22 cm^{-1}, 1510.26 cm^{-1}, 1251.80 cm^{-1} for C=O stretching. The compatibility of Apixaban with their formulation ingredients, such as HPMC E15 and cross-povidone, was analyzed and found to be compatible. The FTIR spectra are showed in Figure 1.

DSC

The thermal analysis was carried out by differential scanning calorimetry (Mettler, Star SW 13). The DSC thermogram of Apixaban is shown in Figure 2, which shows the sharp peak of onset at 237.03°C and decomposes completely at a peak of 239.11°C. Furthermore, the Apixaban combined with the HPMC E15 was also tested by the DSC, as shown in Figure 2. The existence of a peak in the combined form revealed that Apixaban was found to be compatible with the HPMC E15.

XRD

The XRD graph showed a sharp peak at 18.64, 22.29, 21.75, and 17.18. Moreover, additional peaks were also obtained at 30.068, 27.109, and 24.930. These results indicated the crystalline nature of Apixaban. After combining with HPMC E15, the peaks were sharply minimized.[16] The XRD images are shown in Figure 3.

Optimization of OTF of Apixaban

The optimization analysis incorporates the selection of formulation ingredients such as film former (HPMC E15: X1), Plasticizer (PEG 200: X2), and superdisintegrant (cross-povidone: X3). The therapeutic efficacy of the OTF was fully dependent on the disintegration time and the percentage of drug dissolved; hence, these were recognized as dependent factors. The utilization of the Box-Behnken design model predicted 12 trial batches for the progress of OTF, illustrated in Table 2. Furthermore, the results obtained from the evaluation of OTF batches were fitted

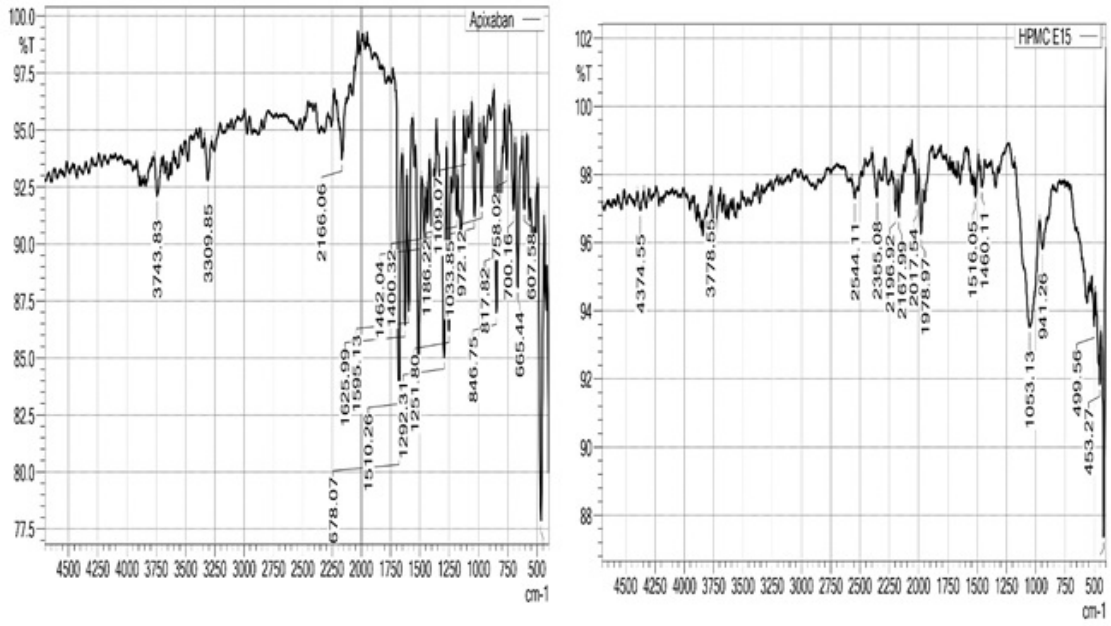

Figure 1: The FTIR spectra of Pure Apixaban and HPMC E15.

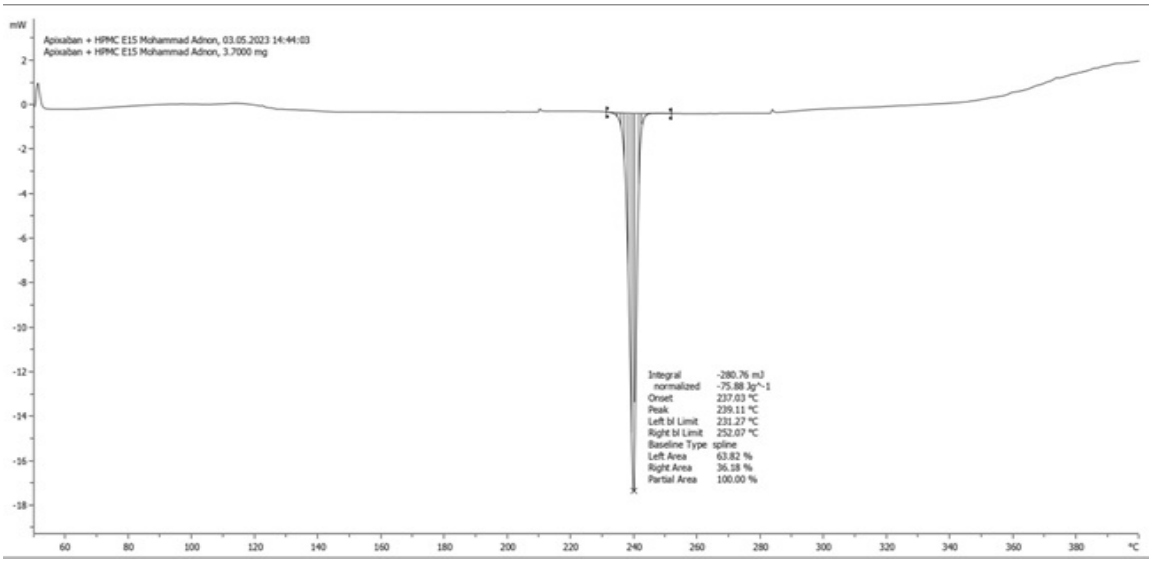

Figure 2: DSC Thermogram of Apixaban and HPMC.

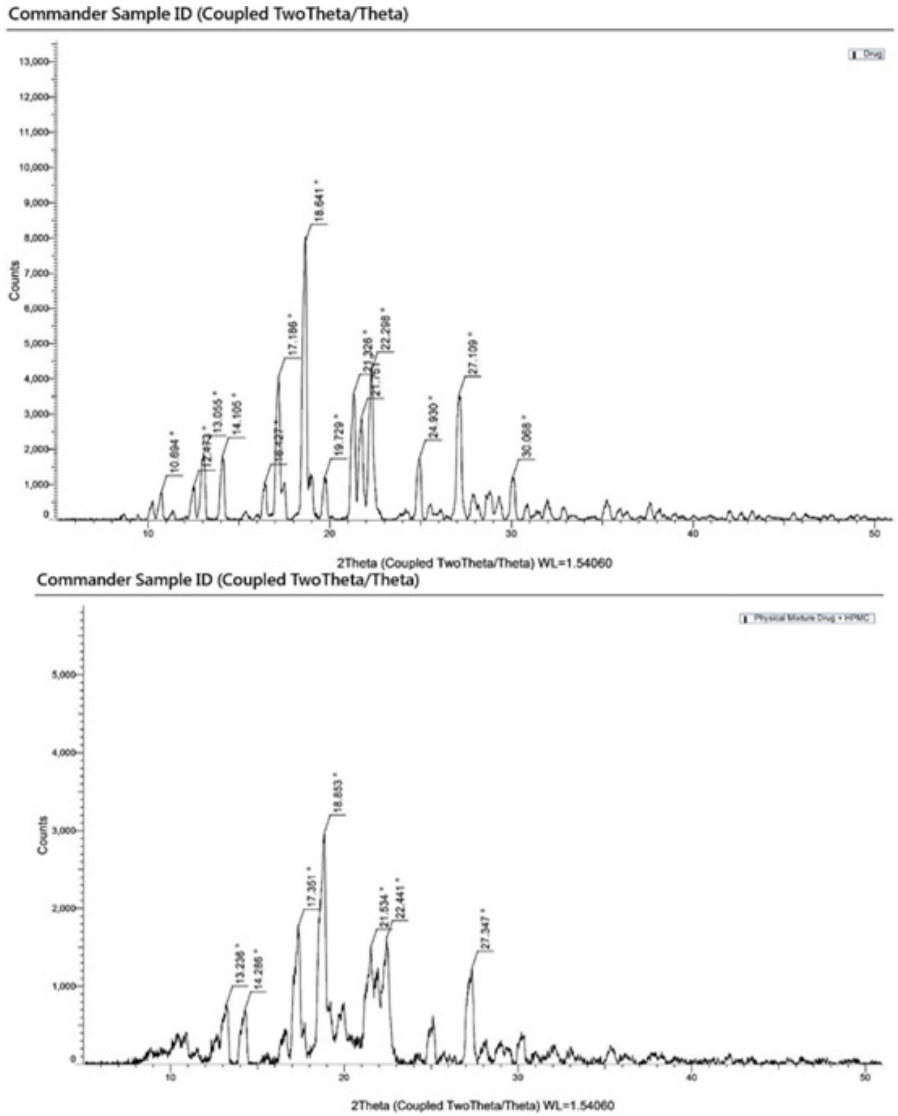

Figure 3: XRD of pure Apixaban and HPMC E15.

into the ANOVA model. These results indicated the quadratic model was significantly retrieved with a *p*-value less than 0.05. The *p*-values for the disintegration time and dissolution release were found to be 0.0017 and 0.0311, respectively. The ANOVA results for the dependent parameters are depicted in Tables 3 and 4, respectively.

The quadratic polynomial equation was predicted by the Design Expert software (Version 13, Stat-Ease) for both dependent factors, illustrated in equations 1 and 2, respectively. The mean disintegration time was 20.50 min, and dissolution was 98.95%. The terms utilized in the equations below signify the effects of film former, plasticizer, and superdisintegrant by A, B, and C, respectively. The combined terms (AB, AC, and BC) illustrated the combined effects of the formulation ingredients on the DT and dissolution. The individual and combined parameter effects on the dependable factors were showed with the help of 2-D Contour plots and 3-D Response surface plots in Figures 4 and 5.

DT = +20.50 +0.3750 A +1.00 B -4.62 C +0.2500 AB -0.5000 AC -0.2500 BC +0.0000 A^2 +0.2500 B^2 +0.0000 C^2.

Dissolution = +98.95 +0.1462 A -0.0650 B +0.2288 C +0.3125 AB +0.1300 AC -0.1625 BC -0.4050 -0.3025 +0.0000 C^2.

The film former HPMC E15 showed altered effects on the disintegration time and drug release from the film. The lower concentration of HPMC E15 showed excellent transparency and a disintegration time of 16 sec to 24 sec. The dissolution of film at the lower concentration was reported from 97.79% to 98.50%. The optimum concentration (500 mg) of HPMC E15 showed the best results in terms of both DT and dissolution and transparency. The lowest disintegration time of 15 sec was achieved with a concentration of 500 mg and dissolution of 99.11%. Further, a rise in the extent of slightly less transparent and higher DT time compared with 500 mg of HPMC E15.

Similar to the film former, the influence of Plasticizer (PEG 200) was evaluated. The higher extent of plasticizers showed an increase in disintegration time and slightly less dissolution rate compared with lower concentrations. The rise in concentration increases the viscosity of the film, which slightly delays the DT and dissolution. The lower extent of plasticizer enabled rapid

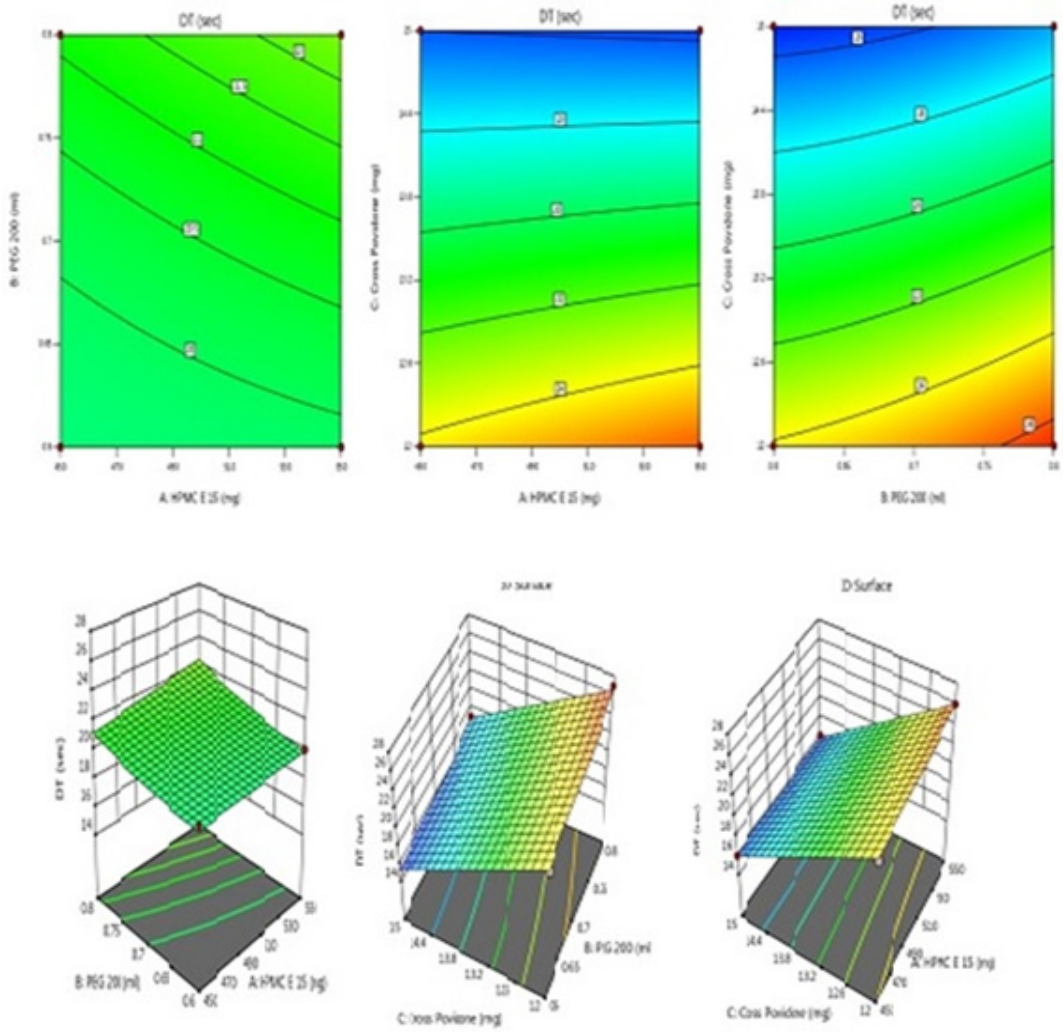

Figure 4: 2-D Contour plots and 3-D RSM for the Disintegration time.

Table 2: The Box-Behnken design for OTF of Apixaban.

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A: HPMC E 15	B: PEG 200	C: Cross Povidone	DT	Dissolution
		mg	mL	mg	sec	%
1	1	500	0.8	15	17	98.54
7	2	550	0.6	13.5	20	98.06
2	3	450	0.8	13.5	21	97.79
6	4	450	0.7	15	16	98.52
4	5	550	0.7	15	16	99.11
8	6	550	0.8	13.5	22	98.67
12	7	450	0.7	12	24	98.23
5	8	450	0.6	13.5	20	98.43
10	9	500	0.8	12	27	98.5
3	10	550	0.7	12	26	98.3
9	11	500	0.6	15	15	99.11
11	12	500	0.6	12	24	98.42

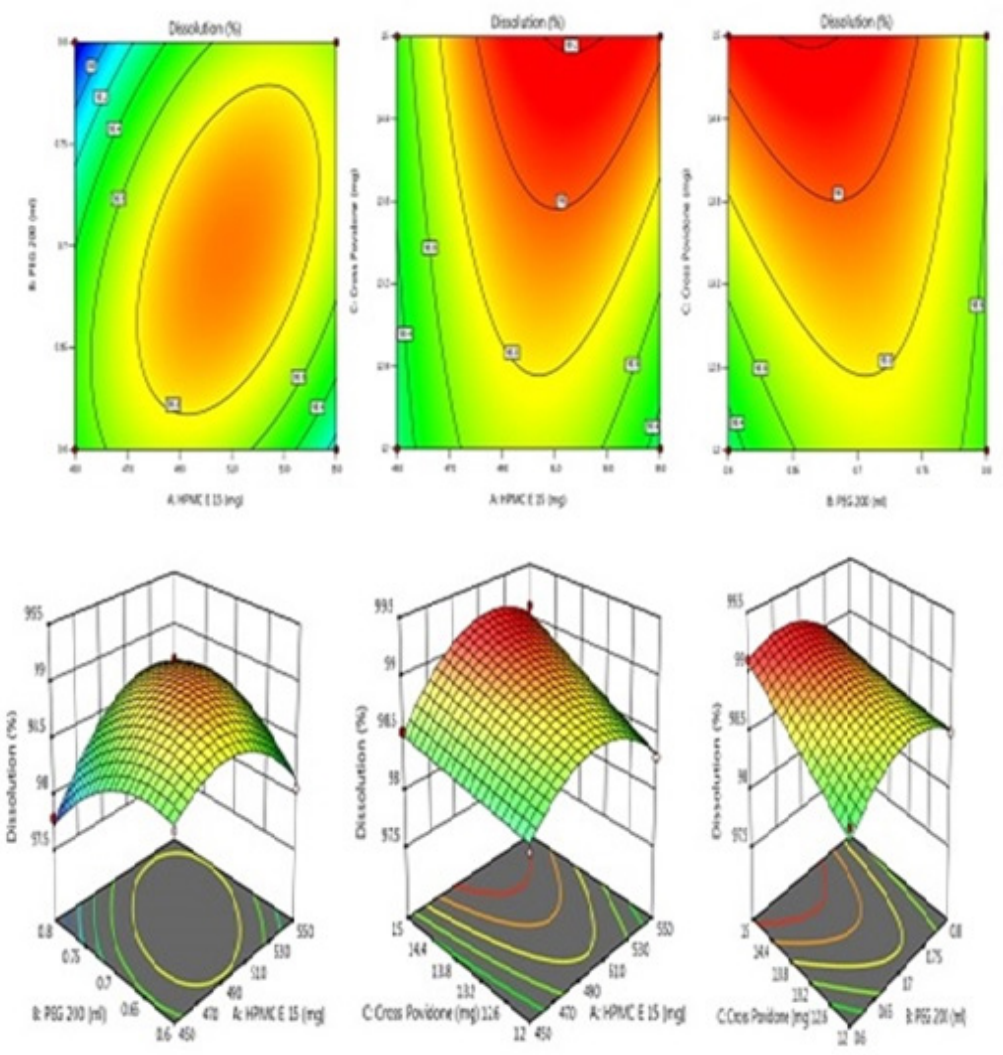

Figure 5: 2-D Contour plots and 3-D RSM for the Dissolution release.

Table 3: The ANOVA of BBD for the dependent factor DT.

Source	Sum of Squares	d_f	Mean Square	F-value	*p*-value	
Model	181.92	8	22.74	90.96	0.0017	Significant
A-HPMC E 15	1.13	1	1.13	4.50	0.1240	
B-PEG 200	8.00	1	8.00	32.00	0.0109	
C-Cross Povidone	171.12	1	171.12	684.50	0.0001	
AB	0.2500	1	0.2500	1.0000	0.3910	
AC	1.0000	1	1.0000	4.00	0.1393	
BC	0.2500	1	0.2500	1.0000	0.3910	
A^2	0.0000	1	0.0000	0.0000	1.0000	
B^2	0.1250	1	0.1250	0.5000	0.5305	
C^2	0.0000	0				
Residual	0.7500	3	0.2500			
Cor Total	182.67	11				

Table 4: The ANOVA of BBD for the dependent factor Dissolution.

Source	Sum of Squares	d_f	Mean Square	F-value	*p*-value	
Model	1.54	8	0.1928	12.47	0.0311	Significant
A-HPMC E 15	0.1711	1	0.1711	11.07	0.0448	
B-PEG 200	0.0338	1	0.0338	2.19	0.2358	
C-Cross Povidone	0.4186	1	0.4186	27.08	0.0138	
AB	0.3906	1	0.3906	25.27	0.0152	
AC	0.0676	1	0.0676	4.37	0.1276	
BC	0.1056	1	0.1056	6.83	0.0794	
A^2	0.3281	1	0.3281	21.22	0.0192	
B^2	0.1830	1	0.1830	11.84	0.0412	
C^2	0.0000	0				
Residual	0.0464	3	0.0155			
Cor Total	1.59	11				

disintegration and dissolution than to the moderate and higher extents. Furthermore, the effect of the superdisintegrant showed altered disintegration time with its concentration. The higher concentration of cross-povidone showed a faster disintegration and dissolution than with moderate and lower concentrations. The possible reason attributed to the faster release is the rapid bursting effect at higher concentrations of cross-povidone.

Evaluation of OTF of Apixaban

Quality of film

The prepared films of Apixaban were inspected visually and found to be transparent, smooth, and peeled off from the petri dish with the minimum applied energy. The best image of OTF was showed in Figure 6.

Thickness of OTF

The thickness of the films was 65±1.05 to 78±0.84 mm. The dissimilarities in the thickness were credited to the different concentrations of the film former and plasticizer.

Folding endurance

The OTFs were estimated for their folding capacity and observed in the range of 63±0.32 to 80±0.25.

Estimation of pH

The OTF was checked for its pH and found to be in the range of 6.2±0.15 to 6.7±0.16.

Determination of moisture content

The measurement of moisture content was a useful parameter in determining the stability of the film. An ideal film should retain enough moisture; otherwise, dry film breaks out quickly.

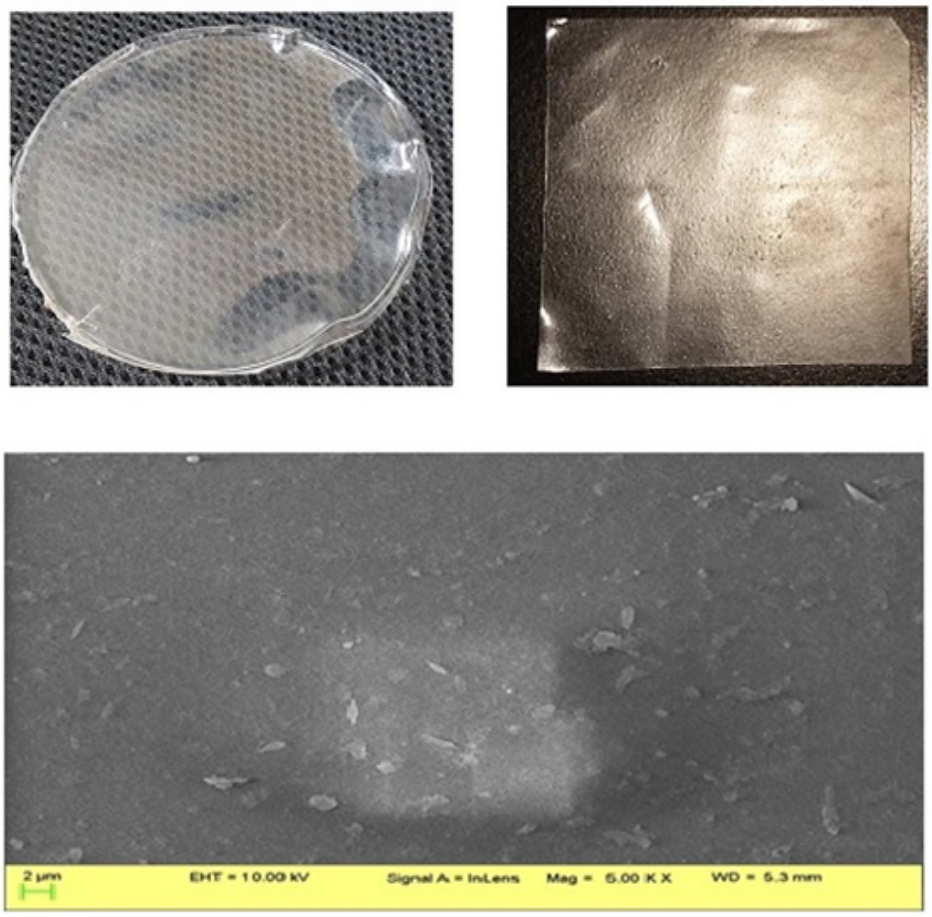

Figure 6: OTF image of Film and SEM.

Furthermore, an excessive amount of moisture resulted in hygroscopic properties and liquefaction upon exposure to the atmosphere. The mean moisture content in the entire film was found to be 9.78%±0.37 to 14. 34±0.55%.

Disintegration time

The disintegration time was identified from 15±0.10 sec to 27±0.14 sec. The dissimilarities in the disintegration time were foreseen due to the changed concentration of cross-povidone which worked as superdisintegrants. As the concentration of CP rises, the disintegration time is found to be shortened compared with moderate and lesser amounts.

In vitro dissolution study

The drug-released profile containing Apixaban-loaded oral film was showed in Figure 7. Before the *in vitro* dissolution, the marketed tablet of Apixaban was assessed for the drug-released studies. The drug was released slowly from the tablet, and took 75 to 85 min for the complete release. Whereas, the entire films from all the batches were liberated within 10 min in the presence of saliva fluids. This indicated that the film was considered fast dissolving, and a quick release pattern was observed. The highest drug release was 99.11±0.86% observed with the F5 batch. The drug release pattern from all 12 batches was very similar, and slight differences were attributed to the altered concentration of HPMC E15, PEG 200, and cross-povidone.

Content uniformity

The content uniformity ensures better therapeutic efficacy from the OTF. The content estimated in all the films was in the range of 97.58%±1.21 to 99.17%±0.96%.

Scanning Electron Microscopy (SEM)

The surface characteristics of an optimized batch F10 were evaluated by SEM, and uniformity in the film. Hence, it was confirmed that Apixaban was dissolved in the film former and PEG 400. The average particle size by SEM analysis was 10 µm. The outcomes of the SEM analysis was showed in Figure 6.

Stability study

The optimized batch A10 was assessed according to the stability testing parameters and successfully passed under the described conditions, and the results were satisfactory. The evaluation parameters at Zero days showed a disintegration time of 15±1.10 sec, dissolution of 99.11%±0.86, and folding endurance

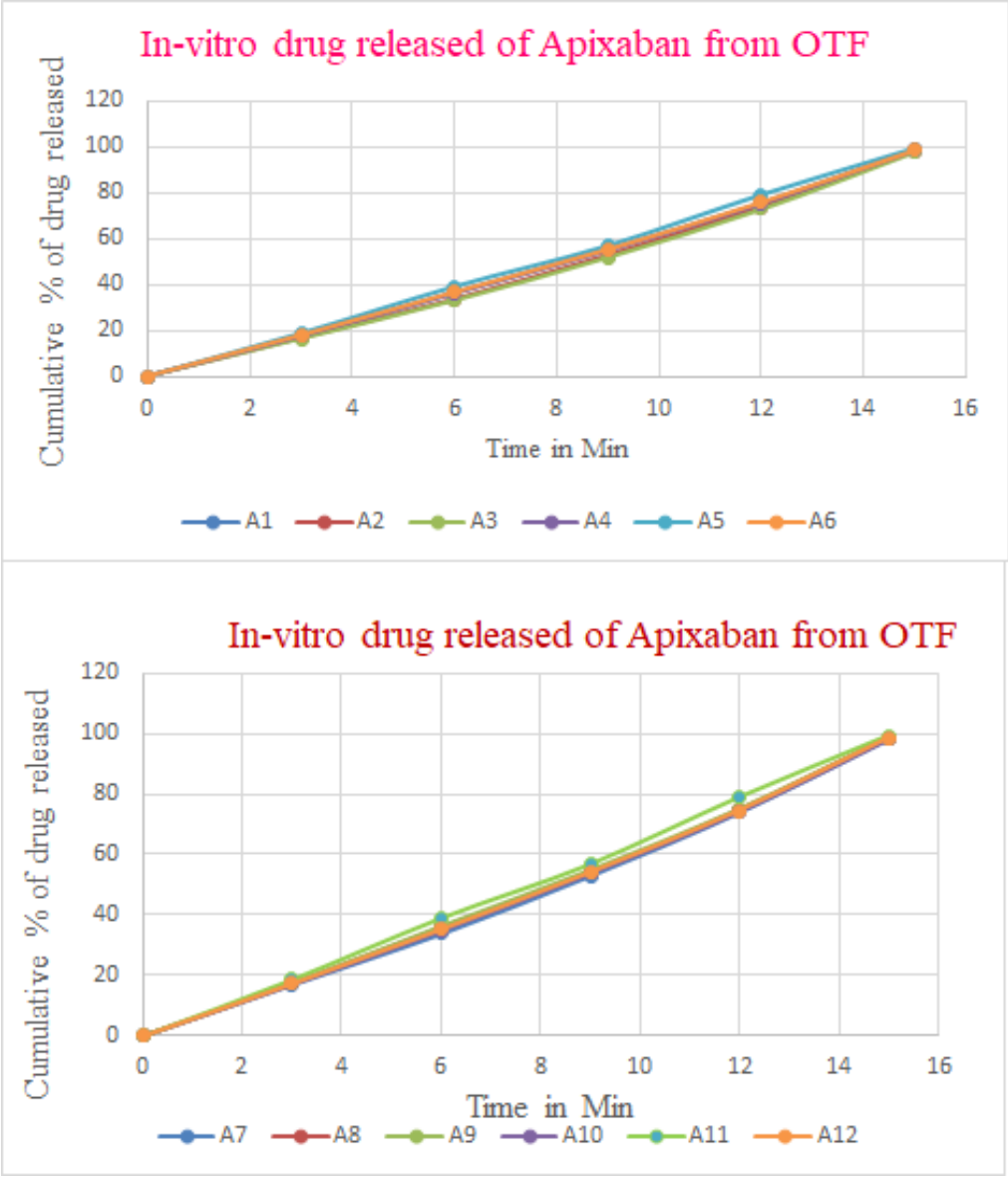

Figure 7: *In vitro* drug release of Apixaban from OTF (A1-A6) and (A7-A12).

of 82±0.57. After 90 days, the DT of the film was 15±1.25 sec, dissolution of 98.79±0.98%, and folding endurance of 70±1.04.

CONCLUSION

Oral anticoagulants are administered to provide prompt relief from several blood clotting conditions such as DVT, PE, VTE, etc. These conditions required a prompt onset of action for the prevention of any unwanted situation. Hence, to combat such hurdles, the oral thin film was designed, which released the medicament within a minute and provided better therapeutic efficacy than the conventional dosage forms. Moreover, the administration of OTF is very simple, with high patient comfort and compliance. The HPMC E15 has provided excellent film-forming ability, and PEG played the role of plasticizer as well as solubilizer. The BBD suggested 12 runs with random trials, with a minimum run, and was found to be more economical than other models. The optimized batch F10 was the best batch, which disintegrant within 16 sec and dissolved with 99.11%. Hence, it was concluded that the OTF of Apixaban is highly recommended for the treatment of DVT, PE, and VTE.

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ABBREVIATIONS

OTF: Oral thin film; **DoE:** Design of Expert; **BBD:** Box-Behnken Design; **QbD:** Quality by design; **DVT:** Deep vein thrombosis; **PE:** Pulmonary embolism.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Apixaban is widely recommended for prevention and therapy of DVT, PE and VTE. The conventional tablet shows delayed therapeutic efficacy due to slow dissolution rate and low bioavailability. The current research developed sublingual oral thin film which provide fastest onset of action, which is an utmost need for the patients suffering from coagulation in blood. The sublingual film bypasses the presystemic metabolism and releases the medicament quickly. The optimized batch disintegrates after 16 sec and dissolution rate of 99.11%. This remarkable achievement is possible only with oral thin film. Moreover, OTF does not require water for the administration, is easy to carry, and highest patient comfort. The morbidity and mortality can be reduced with oral thin film.

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