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Design optimization and evaluatıon of polyvinyl alcohol based oral thin film of apixaban

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ABSTRACT: The current research work aimed to prepare an optimized and evaluate fast-dissolving oral thin film of Apixaban using polyvinyl alcohol as a film former. The oral thin film of Apixaban enhances the solubility, bioavailability, and therapeutic efficacy in thrombus, pulmonary embolism, and venous thromboembolism. The chemical compatibility and thermal analysis were investigated with the help of FTIR, and DSC. The optimization was performed with the Box-Behnken design. The concentrations of film former (PVA: X1), plasticizer (PEG 200: X2), and superdisintegrant (cross povidone: X3) were considered as independent factors and the critical quality attributes for the oral films are disintegration time, dissolution, and folding endurance. The ANOVA comprised of Quadratic model which predicted p-values of 0.0039, 0.0105, and 0.0020 significant. The scanning electron microscopy assessed the texture of the film. An optimized batch P6 disintegrated within 19 seconds, released the drug (99.07 %) within 10 min and had a folding endurance of 116. The results conclude that optimized batch P6 of oral thin film of Apixaban significantly minimizes the deep vein thrombosis, pulmonary embolism, and venous thromboembolism due to fastest onset of action and improved solubility. Thus, the complications associated with the clotting of blood is sharply reduces.

KEYWORDS: Oral thin film; Apixaban; Polyvinyl alcohol; Deep vein thrombosis; Box-Behnken design.

1. INTRODUCTION

Polyvinyl alcohol (PVA) is one of the most biodegradable polymers widely utilized in the biomedical and pharmaceutical fields for offering versatility [1]. When polyvinyl acetate undergoes hydrolysis generates the thermoplastic synthetic polymer known as PVA [2]. PVA possesses excellent mechanical strength, marked film-forming potential, hydrophilicity, biocompatibility, non-toxic, and non-carcinogenic. Moreover, the solubility properties of PVA mainly rely on the particle size distribution, molecular weight, and the nature of the material. The high degree of compatibility and inertness make PVA approved by the US FDA for its utilization in oral delivery. PVA possesses good retention capacity for the solvent and provides structural modification at the extensive level. Hence, PVA-based films are widely utilized for oral, topical, buccal, ophthalmic, and vaginal applications [3, 4].

The highest patient comfort and compliance is achieved through oral drug delivery. Moreover, the non-invasive, economical, and safe methods also make the first choice for patients in the prevention and therapy of diseases [5]. Oral drug delivery poses difficulty in pediatric, geriatric, and bedridden persons as well as patients with dysphagia and surgery of the oral cavity. To overcome this hurdle, oral thin films (OTF) are gaining tremendous popularity for the administration of a large number of active ingredients, prebiotics, probiotics, peptides, nutraceuticals immunomodulators, etc. The OTF provides the administration of the medicament without consuming water, the prompt onset of action, dose accuracy, and ease of carry. Furthermore, the coloring and flavoring agent enhances the acceptability and use comparatively with tablets and capsules [6].

The formation of blood clots (thrombus) in the legs of the deep veins resulted in the progress of Deep vein thrombosis (DVT) which is an unseen condition in the body. The progressive stage of blood clots later resulted in the inflammatory condition followed by the painful situation which provokes the pulmonary embolism (PE) [7]. Furthermore, the advanced stage known as venous thromboembolism (VTE) develops if not treated in advance. The clots during movement enter inside the brain and the condition of

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central venous sinus thrombosis (CVST) occurs. The most routinely used therapy for the prevention of blood clots is oral anticoagulant. One of the most preferred drugs in this condition is direct, and highly selective factor Xa (FXa) inhibitors [8].

Apixaban belongs to the category of direct and orally active potent anticoagulants operated by inhibiting the factor Xa, prothrombinase, and thrombin. Apixaban is useful in several conditions such as the prevention and treatment of stroke, PE, DVT, and CVST. Apixaban is also regularly suggested by the surgeon after knee and hip replacement surgery. The therapeutic efficacy of Apixaban is constrained due to its poor bioavailability of approx. 50 % [9, 10]. Hence, the current research is primarily dedicated to the enhancement of solubility, bioavailability, and prompt therapeutic efficacy of Apixaban via oral thin film technology.

The superiority and care of pharmaceutical products are the essential criteria from regulatory approval and patient concern point of view. These criteria are achieved with the execution of a quality-by-design (QbD) method. Moreover, risk assessment, material, and time-saving with the best possible runs are achieved through the QbD approach [11]. The aim of current research was advancement of a quality-based Apixaban film for the deterrence and management of clotting factors such as DVT, PE, and CVST.

2. RESULTS AND DISCUSSION

2.1. FTIR interaction study

The identity of Apixaban by assessed by FTIR by scanned in 400-5000 cm^{-1}. The spectrum attained was interpreted for the bands and the stretching. The shrill peak was illustrious 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 PVA and cross povidone were investigated and found to be compatible. The spectrums were showed in Figures 1 to 3.

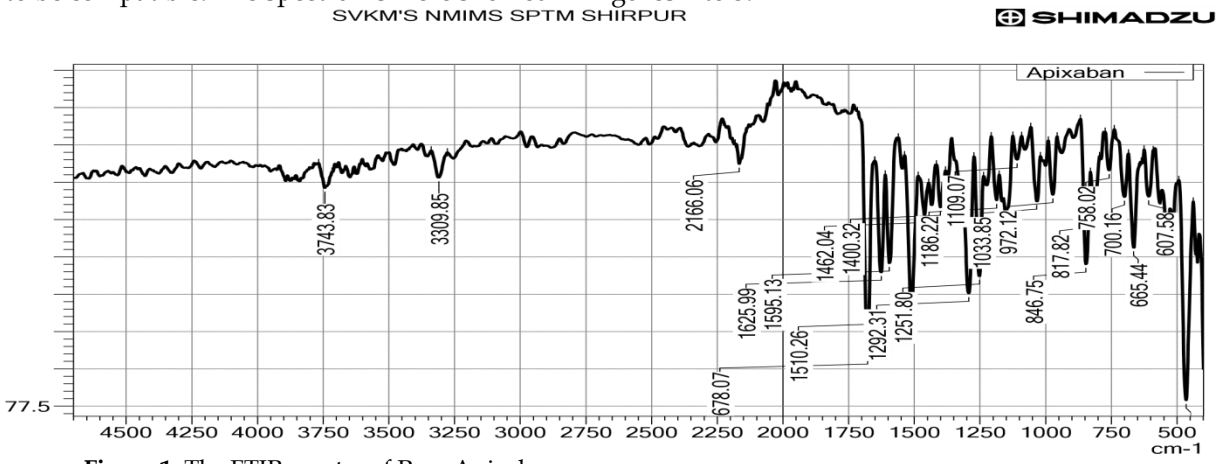

Figure 1. The FTIR spectra of Pure Apixaban

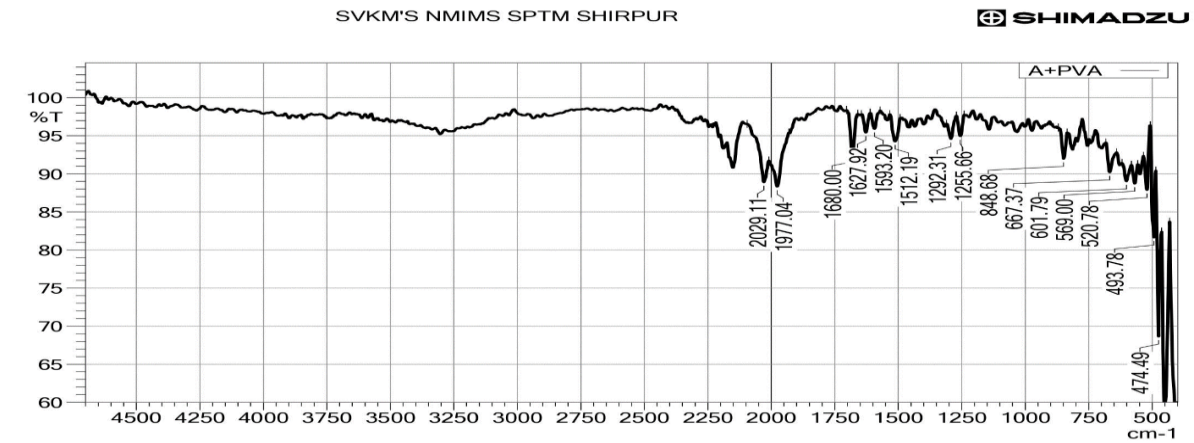

Figure 2. FTIR Spectra of Apixaban and PVA

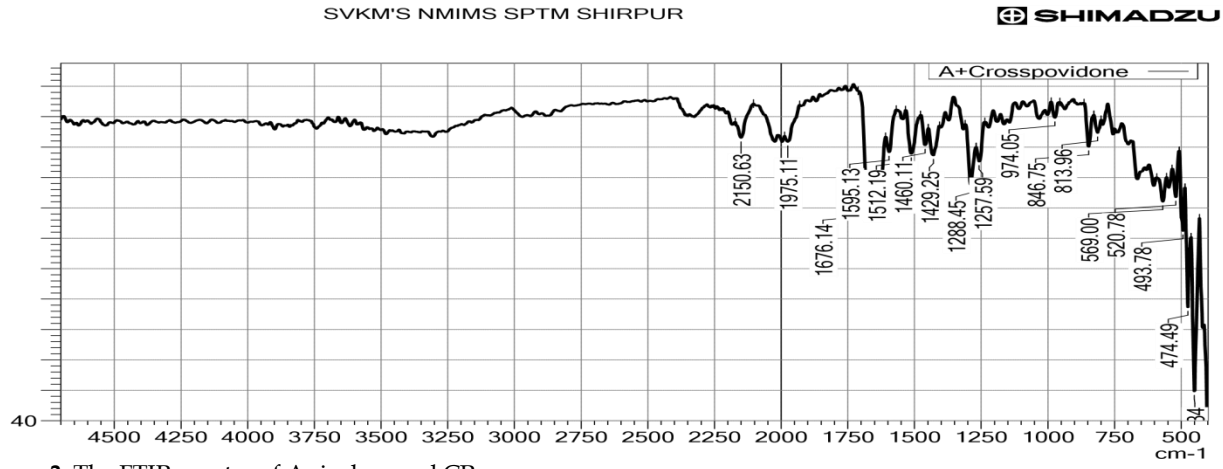

Figure 3. The FTIR spectra of Apixaban and CP

2.2. DSC

The thermal analysis was carried out by differential scanning calorimetry (Mettler, Star SW 13). The DSC thermogram of Apixaban showed in Figure 4 indicated the sharp peak of onset at 237.03 ° C and decomposes completely at a peak of 239.11 ⁰ C. Furthermore, the Apixaban combined with the PVA was also tested by the DSC showed in Figure 5. The presence of a peak in the combined form was separately exposed and Apixaban was found to be compatible with the PVA.

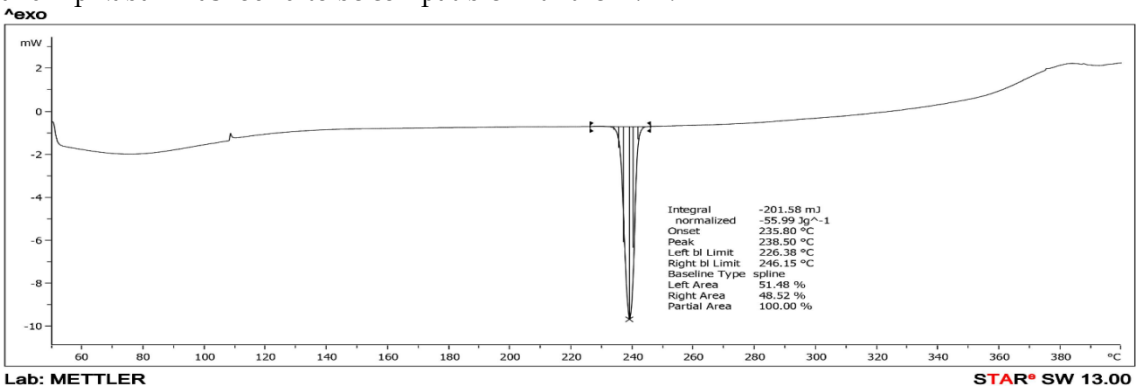

Figure 4. DSC Thermogram of Apixaban

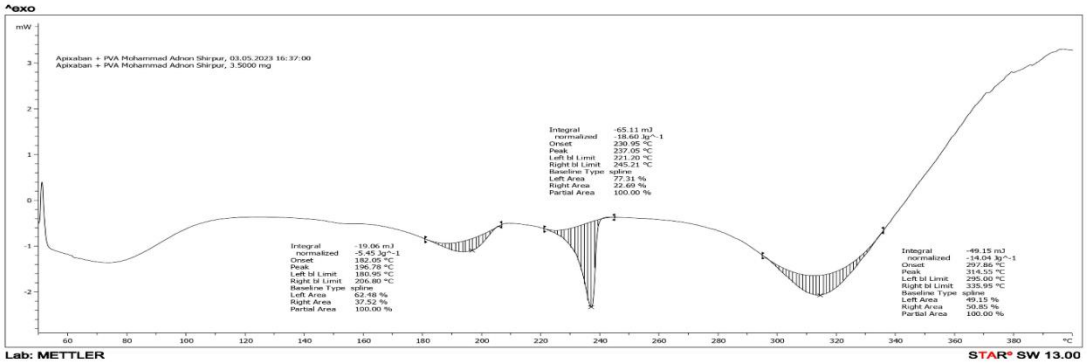

Figure 5. DSC Thermogram of Apixaban and PVA

2.3. Optimization of OTF of Apixaban

The Box-Behnken design model is composed of the selection of formulation ingredients such as film former (PVA: X1), plasticizer (PEG 200: X2), and superdisintegrant (cross povidone: X3). The therapeutic efficacy of the OTF was entirely reliant on the disintegration time, the percentage of drug dissolved and the folding endurance, hence these were accepted as dependent factors. The application of the Box-Behnken

design model predicted 12 trial batches for the progress of OTF depicted in Table 1. Furthermore, the results obtained from the evaluation of OTF batches were fitted into the ANOVA model. These results indicated the quadratic model was significantly retrieved with a p-value > 0.05. The p-values for the disintegration time and dissolution release were found to be 0.0039, 0.0105, and 0.0020 respectively. The ANOVA results for the dependent factors were presented in Table 2 to 4 respectively.

Table 1. The Box-Behnken design for OTF of Apixaban

		Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
Std	Run	A:PVA	B:PEG 200	C:CCS	Disintegration Time	Dissolution	Folding endurance
		mg	ml	mg	sec	%	number
10	1	450	0.8	12	28	98.06	126
6	2	500	0.7	12	27	98.17	121
12	3	450	0.8	15	21	98.89	124
8	4	500	0.7	15	20	98.96	117
4	5	500	0.8	13.5	25	98.58	120
11	6	450	0.6	15	19	99.07	116
7	7	400	0.7	15	20	98.9	118
3	8	400	0.8	13.5	24	98.64	120
9	9	450	0.6	12	27	98.26	115
2	10	500	0.6	13.5	24	98.7	113
1	11	400	0.6	13.5	23	98.75	110
5	12	400	0.7	12	26	98.38	117

Table 2. The BBD of ANOVA model **for the Disintegration Time**

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	103.92	8	12.99	51.96	0.0039	significant
A-PVA	1.12	1	1.12	4.50	0.1240	
B-PEG 200	3.12	1	3.12	12.50	0.0385	
C-CCS	98.00	1	98.00	392.00	0.0003	
AB	0.0000	1	0.0000	0.0000	1.0000	
AC	0.2500	1	0.2500	1.0000	0.3910	
BC	0.2500	1	0.2500	1.0000	0.3910	
A^2	0.1250	1	0.1250	0.5000	0.5305	
B^2	1.13	1	1.13	4.50	0.1240	
C^2	0.0000	0				
Residual	0.7500	3	0.2500			
Cor Total	104.67	11				

Table 3. The BBD **of ANOVA model for the Dissolution**

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.18	8	0.1476	26.64	0.0105	significant
A-PVA	0.0085	1	0.0085	1.52	0.3048	
B-PEG 200	0.0465	1	0.0465	8.39	0.0626	
C-CCS	1.09	1	1.09	196.30	0.0008	
AB	0.0000	1	0.0000	0.0045	0.9507	
AC	0.0182	1	0.0182	3.29	0.1674	
BC	0.0001	1	0.0001	0.0180	0.9016	
A^2	0.0190	1	0.0190	3.43	0.1611	
B^2	0.0085	1	0.0085	1.52	0.3048	
C^2	0.0000	0				
Residual	0.0166	3	0.0055			
Cor Total	1.20	11				

Table 4. The BBD of ANOVA model for the Folding endurance

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	219.92	8	27.49	82.47	0.0020	significant
A-PVA	4.50	1	4.50	13.50	0.0349	
B-PEG 200	162.00	1	162.00	486.00	0.0002	
C-CCS	2.00	1	2.00	6.00	0.0917	
AB	2.25	1	2.25	6.75	0.0805	
AC	6.25	1	6.25	18.75	0.0227	
BC	2.25	1	2.25	6.75	0.0805	
A^2	40.50	1	40.50	121.50	0.0016	
B^2	12.50	1	12.50	37.50	0.0088	
C^2	0.0000	0				
Residual	1.00	3	0.3333			
Cor Total	220.92	11				

The BBD predicted the polynomial quadratic formula for the dependent parameters which were showed in equations 1, 2, and 3 respectively. The symbols A, B, and C represented the concentration of PVA (film former), PEG 200 (plasticizer), and cross povidone (superdisintegrant) respectively. The joint terms AB, AC, and BC as well as square terms A^2, B^2, and C^2 indicated the influence of both independent criteria on the disintegration time, dissolution, and folding endurance. The mathematical signs plus and minus signify that respective independent factors have synergistic and antagonistic outcomes on the dependent factors.

In DT, the extent of PVA and PEG 200 have showed synergistic effects. Whereas, the concentration of CP has an antagonistic effect. The overall disintegration time was observed at 23 seconds. Moreover, the concentrations of PVA and PEG 200 as well as PEG 200 and CP have a synergistic effect on the disintegration time. All the square terms have synergistic effects on the disintegration time. The higher content of PEG 200 prolog the disintegration time and lower accelerated.

In the case of the dissolution release profile, the overall amount of drug dissolved was 98.50 %. The concentration of cross povidone has showed synergistic action while PVA and PEG 200 have showed antagonistic action on the drug released. In the combined form, the concentration of PEG 200 and CP along with PVA and PEG 200 have synergistic action. Similar to the disintegration time, all the square terms have synergistic effects. The greater extent of PEG 200 slighly delay the dissolution process comparatively with the less concentration. This was attributed due to the viscosity of the liquid released in to the solution.

The synergistic effects were indicated by the concentration of PVA and PEG 200 for the folding endurance. The antagonistic effect was showed by the concentration of CP on the folding endurance. The combined parameters and some square terms also showed the antagonistic effects on the folding endurance. Moreover, the results of all unconstrained factors on the constrained responses were also showed with 2-D Contour plots and 3-D response surface plots in the Figure 6 to 11 respectively.

$$DT = +23.00 +0.3750\ A +0.6250\ B -3.50\ C +0.0000\ AB -0.2500\ AC +0.2500\ BC +0.2500\ A^2 +0.7500\ B^2 +0.0000\ C^2 \quad \text{Equation 1}$$

$$Dissolution = +98.50 -0.0325\ A -0.0763\ B +0.3687\ C -0.0025\ AB +0.0675\ AC +0.0050\ BC +0.0975\ A^2 +0.0650\ B^2 +0.0000\ C^2 \quad \text{Equation 2}$$

$$Folding\ endurance = +122.75 +0.7500\ A +4.50\ B -0.5000\ C -0.7500\ AB -1.25\ AC -0.7500\ BC - 4.50\ A^2 -2.50\ B^2 +0.0000\ C^2 \quad \text{Equation 3}$$

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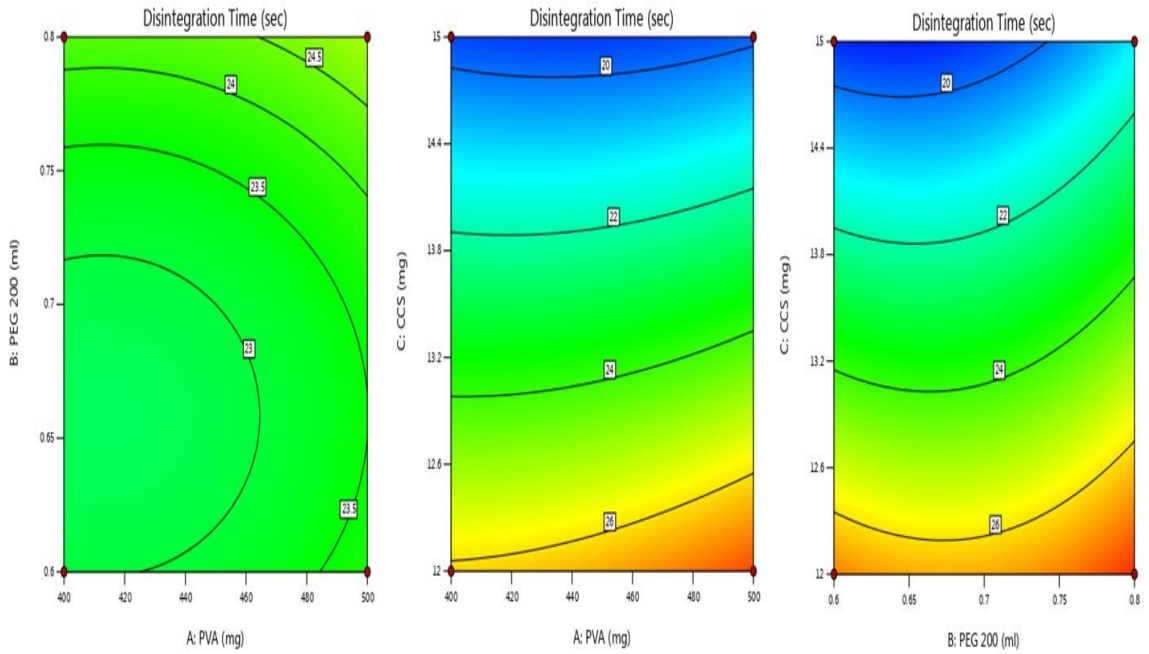

Figure 6. 2-D Contour plot for the disintegration time

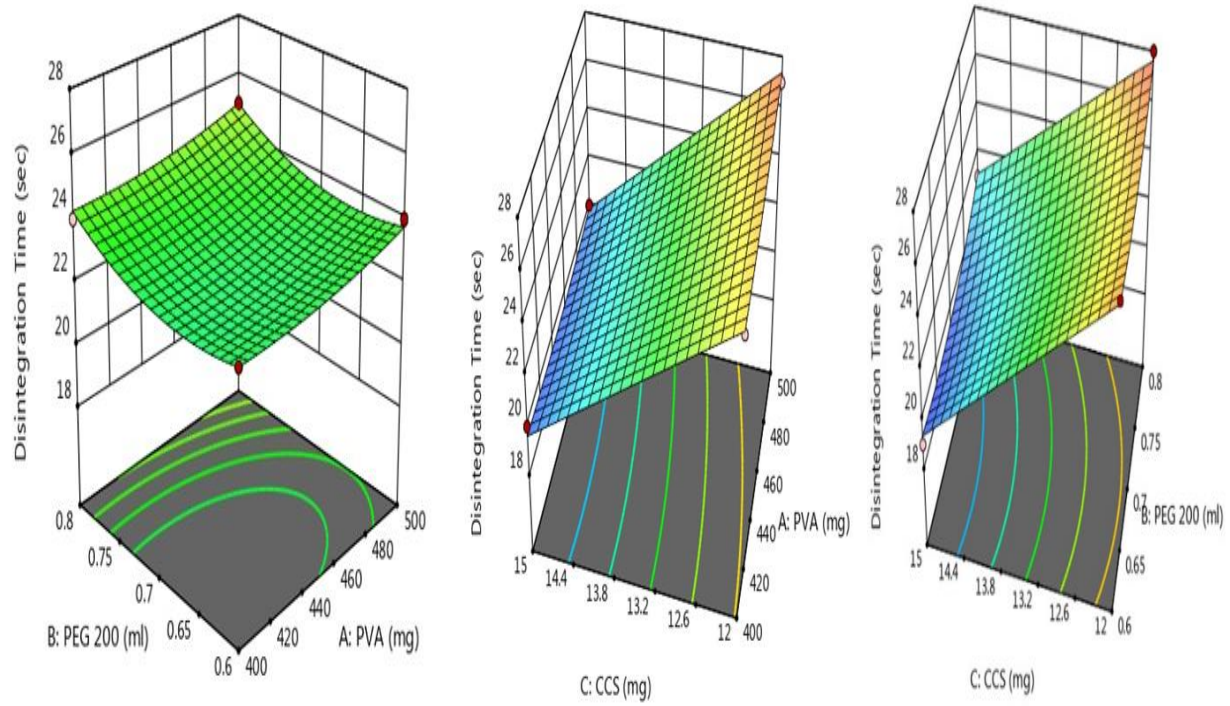

Figure 7. 3-D Response surface plots for disintegration time

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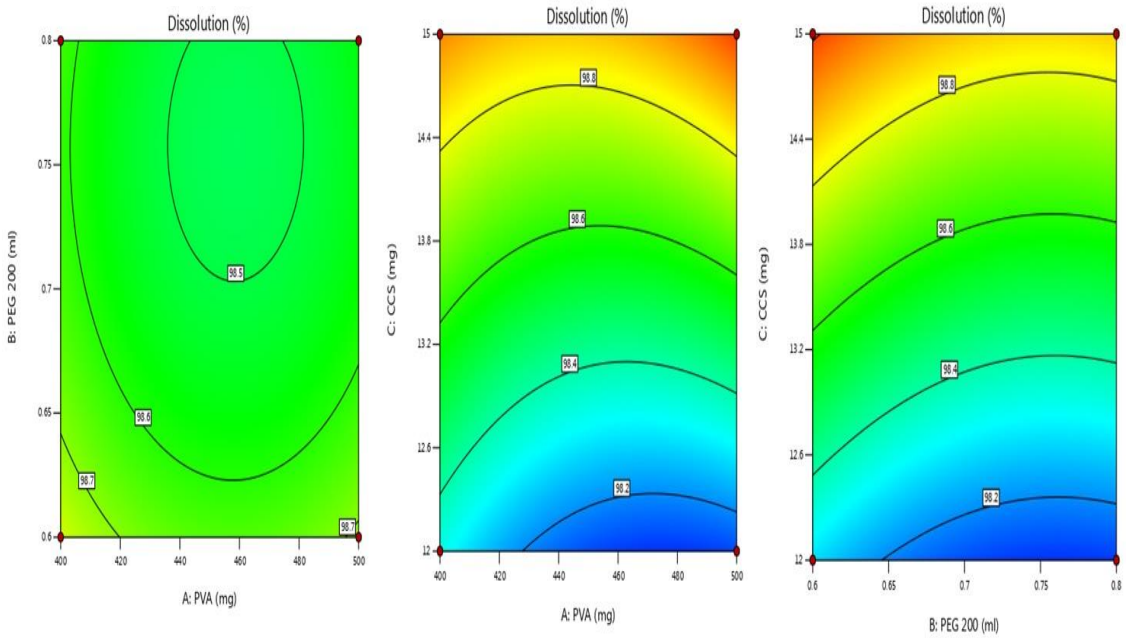

Figure 8. 2-D Contour plot for the dissolution

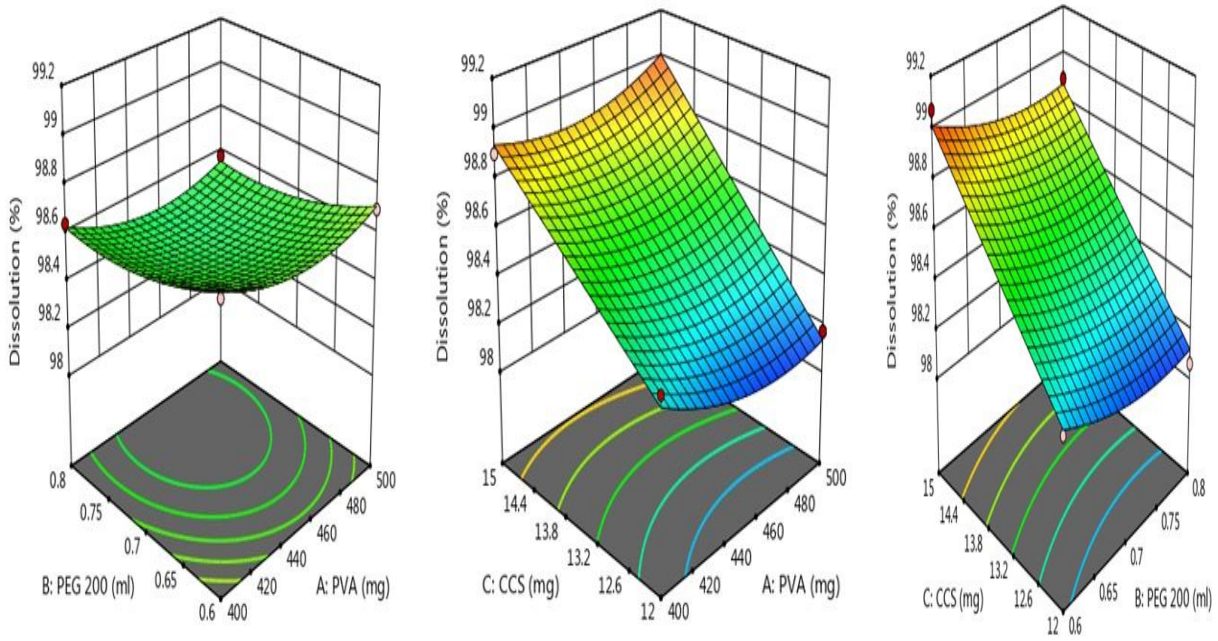

Figure 9. 3-D Response surface plots for dissolution release

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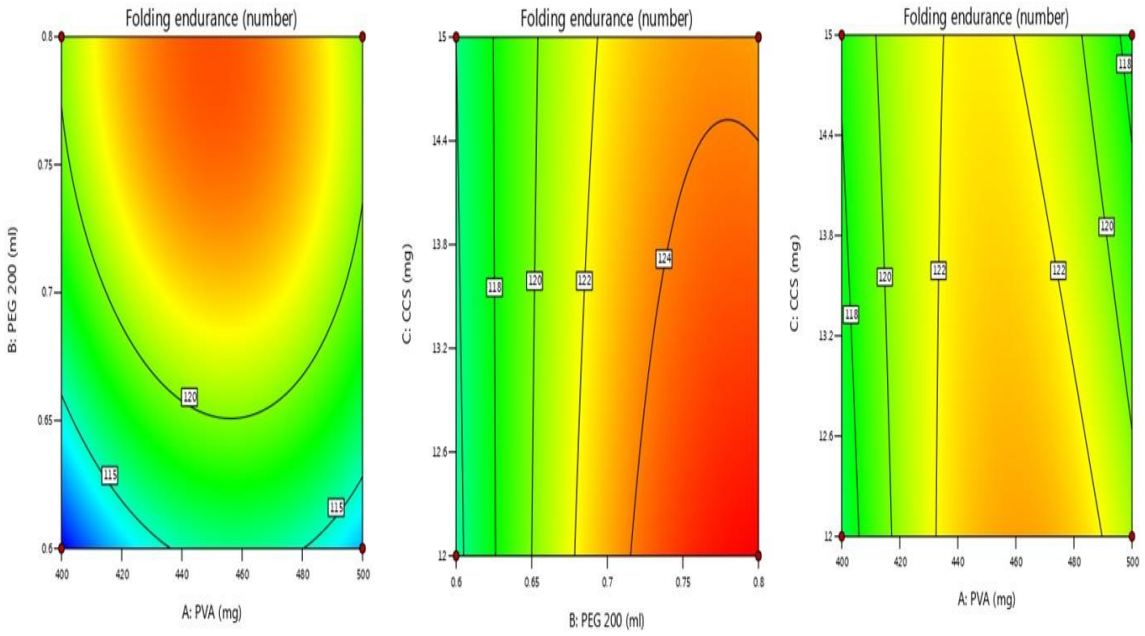

Figure 10. 2-D Contour plot for the folding endurance

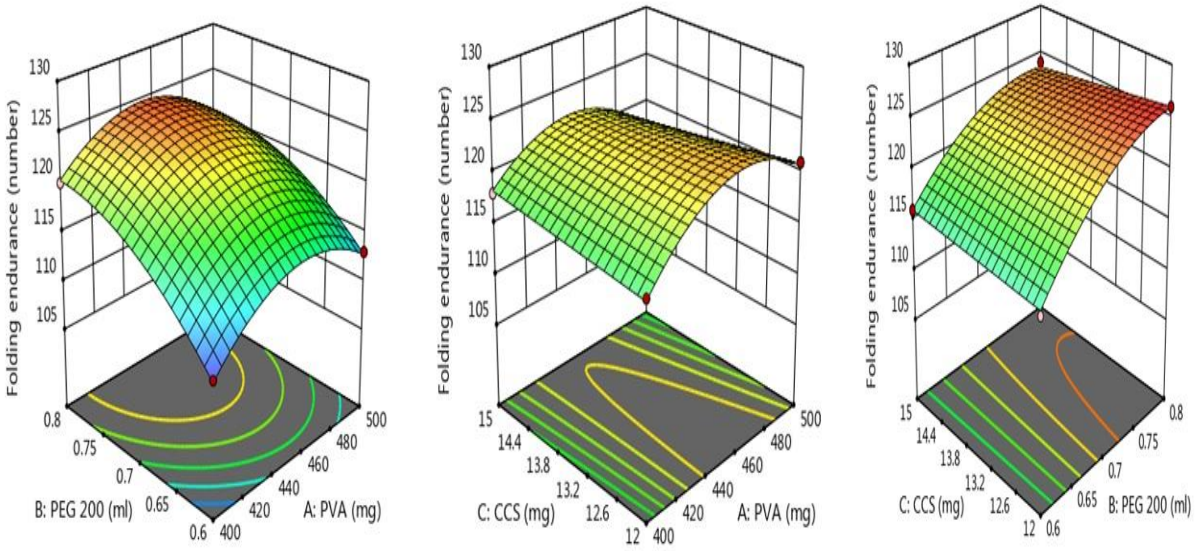

Figure 11. 3-D Response surface plots for folding endurance

2.4. Evaluation of OTF of Apixaban

2.4.1. Quality of film

The PVA films of Apixaban were inspected visually and found to be transparent, smooth and peeled off from the petri dish with the least energy. The entre solubility of PVA in the distilled water created a complete transparent film.

2.4.2. Thickness of OTF

The thickness of films were noted 60 to 74 mm. The divergences in the thickness were attributed due to the unrelated concentration of film former (PVA) and plasticizer (PEG). The alterations in the thickness was attributed due to the extent in individual batches which comprised of PVA and PEG 200. The uniformity amongst the film ensure that thickness is maintained propely.

Figure 12. (a) Image of OTF, 10 (b): Ideal picture of OTF (3 X2 Dimension)

2.4.3. Folding endurance

The OTFs was estimated for their folding capacity and observed in the range of 110 to 126. The PVA films showed strong sturdiness and extended folding endurance. Hence, greater folding endurance of the film ensures greater holding potential and firmness. The essentail quantity of plasticizer provides enough folding endurance which contributed significantly in the drug absorption and permeation.

2.4.4. Analysis of pH

The PVA-based OTFs were analysed for their pH and found 6.4 to 6.8.

2.4.5. Evaluation of moisture content

The estimation of moisture content was related with the stability of the film. An ideal film should hold adequate moisture otherwise dry film disruption occurred speedily. Additionally, the unnecessary amount of moisture give rise to hygroscopicity and liquefy upon contact to the atmosphere. The mean moisture content in the entire films were found to be 10.97% to 13. 81%.

2.4.6. Disintegration time

The disintegration time were identified from 19 second to 28 seconds. The divergences in the disintegration time was foreknown due to the transformed concentration of cross povidone which worked as superdisintegrants. As the concentration of CP rises the disintegration time found to be shorten compared with moderate and lesser amount. The greater extent of CP when comes in contact with the fluid, resulted into the rapid bursting of actives from the film. Moreover, PVA and PEG are water soluble which synergistically reduces the disintegration time due to rapid dissolution mechanism.

2.4.7. In-vitro dissolution study

The drug released profile encompassing Apixaban loaded oral film was showed in the Figure 13 and 14. The marketed tablet of Apixaban was evaluated for the drug released studies. The drug was liberated gradually from the tablet and taken 70 to 85 min for the whole released. Whereas, the complete films from all the batches were liberated within 10 min in the presence of saliva fluids. This specified that film was considered as fast dissolving and speedy release pattern was observed. The highest drug released was 99.07 % observed with F6 batch. The drug released pattern from all the 12 batches were very alike and insignificant variances was ascribed due to the transformed concentration of PVA, PEG 200 and cross povidone.

The concentration of independent varaibles such as PVA, PEG and CP markly affect the release of active ingredient from the film. During intial concentration of PVA along with the altered extent of PEG and CP, the release rate is moderate. Similarly, at highest extent of PVA, the release rate increases marginally due to greater viscosity. At the optimum concentration of PVA, intial concentration of PEG and highest concentration of CP showed prompt release from the OTF.

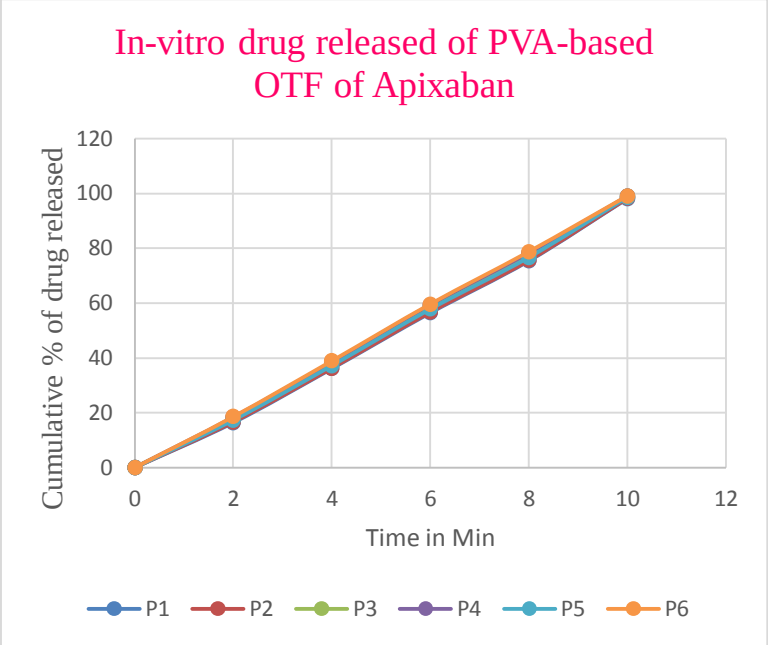

Figure 13. In-vitro drug released of Apixaban from OTF (P1-P6)

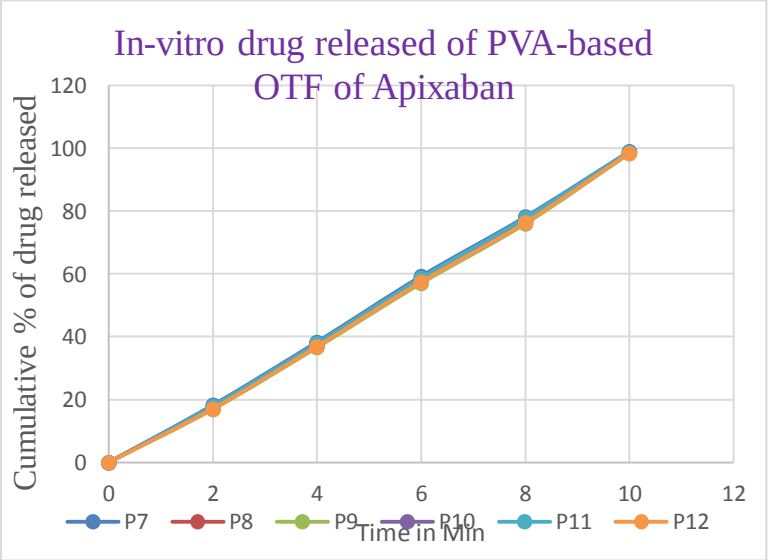

Figure 14. In-vitro drug released of Apixaban from OTF (P7-P12)

2.4.8. Content uniformity

The content uniformity ensures the better therapeutic efficacy from the OTF. The content estimated in all the films were in the range of 97.85 % to 99.02 %.

2.5. Evaluation of surface morphology by scanning electron microscopy (SEM)

The batch F10 was evaluated by SEM and observed uniformity in the film. Hence, apixaban was totally dissolved in the HPMC E15 and PEG 400. The mean particle size by SEM analysis was found to be 1µm. The results of SEM analysis was showed in the Figure 15.

2.6. Stability study

The optimized batch F6 was evaluated consistent with the stability testing parameters and results was depicted in the Table 5. The optimized batch successfully accepted under the described conditions and

results were satisfactory. This batch was further suggested for the technology transfer for the industrial level manufacturing process.

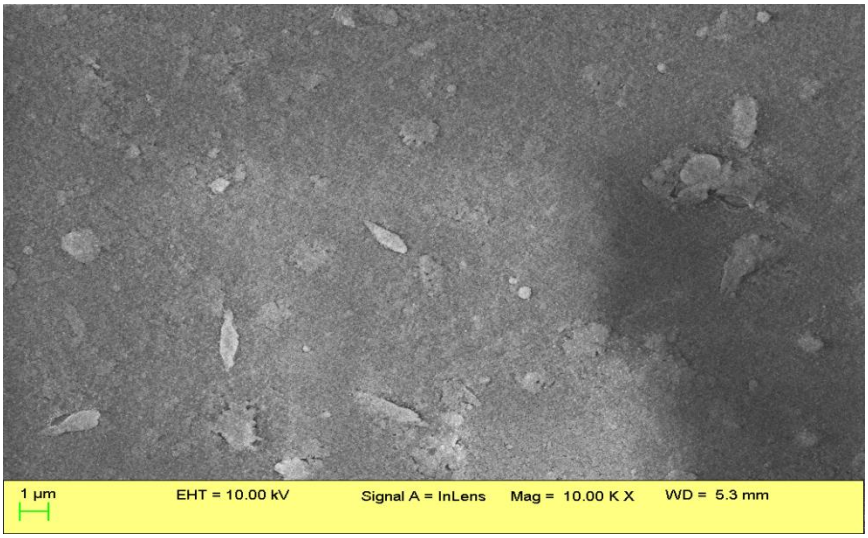

Figure 15. SEM image of an optimized batch F6

Table 5. Evaluation criteria for stability

Criterion	Initial	30 Days	60 Days	90 Days
Disintegration time	19 Sec	19	17	16
Dissolution	99.07%	98.91%	98.79%	98.70%
Folding endurance	116	111	107	102

3. CONCLUSION

The requirement of prompt onset of action in the conditions of DVT, PE and CVST was achieved through the development of fast dissolving oral thin film of Apixaban. Moreover, the greater solubility and superior therapeutic efficacy is attained with the oral thin film of Apixaban. The PVA showed a excellent film forming ability and less permeable for the entry of moisture from the atmosphere. Hence, upon opening of wrapper, the chances of liquification is minimized. The high mechanical strength of OTF was confirmed by their superior folding endurance characteristics. The compatibility of apixaban with several ingredients were confirmed with the FTIR and DSC. The PEG showed marvalous plasticizer potential and cross povidone was resposible for the quick release of active from the film. The Box-Behnken design was operated and entire batches were qualify for the evaluation test. The pH of all OTF lies within the range of 6.4 to 6.8 indicated suitability of dissolution in the presence of oral saliva. The optimized batch F6 was the best batch which disintegrant within 19 seconds and dissolved with 99.07 %. Thus, the prompt onset of action and greater stability is achieved with the OTF of Apixaban which curcumvents the mortality associated with the clotting of blood. The uniformity and amorphous nature was confirmed with the SEM. The PVA-based OTF of Apixaban (F6) is highly recommended for the pilot plant scale up for the commercialization.

4. MATERIALS AND METHODS

Apixaban was supplied by the Natco Pharma, Kothur, Telangana, India. Polyvinyl alcohol was gifted by Merck Chemical, Mumbai. Aspartame and citric acid were purchased from Loba Chemicals, Mumbai. All other ingredients utilized in the research work were of analytical grade only.

4.1. FTIR interaction study

The confirmation of Apixaban and any possible kind of interaction with the formulation ingredients were examined with the FTIR (Affinity-1s, Shimadzu, Japan). The powder samples were scanned in 400-5000 cm^{-1} and interpretation were recorded [12].

4.2. Differential scanning calorimetry (DSC)

The thermogravimetric analysis and nature were assessed with the DSC (DSC, Mettler, Star SW13, UK) by heating the sample in a series of 50-300^0 C beneath the inert nitrogen gas at the flowing rate of 40 ml/min. The thermogram of the samples was recorded [13].

4.3. Preparation of the artificial saliva

The oral cavity containing the saliva is responsible for the disintegration and dissolution of film. The prepared film wants to be checked in vitro with artificial saliva of the same pH. A precisely 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 into the beaker containing distilled water. The DW was added to make up the solution up to 1 liter. Finally, the pH of the solution was tested and adjusted with the phosphoric acid if required.

4.4. Development of OTF of Apixaban

The modified solvent casting method was chosen for the formulation of OTF. The suitable size of the petri dish was taken and sterilized by a hot air oven at 160 ^{0}C for about 2 hrs. Subsequently, the surface area of the whole plate was judge from the 3 x 2 size dimension. Conferring to the surface area, the essential dose of Apixaban was planned. In the first beaker, 10 ml of double distilled water was taken and boiled further. The desired quantity of film former (PVA) was conveyed carefully and allowed to swell for about 3-4 h. 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 [14].

Thereafter, the liquids components were gradually mixed under uninterupted stirring at 2000 rpm. The remaining constituents such as citric acid and aspartame was incorporated and stirred well. The liquid was cast in plate and position in an oven at 40-45^0 C for about 12 hrs. The film was cut into pieces (3x2 size) [15]. The composition of PVA-based OTF was depicted in Table 6.

Table 6. Composition of PVA-based OTF of Apixaban

Sr. No	Batch	PVA (mg)	PEG 200 (ml)	CCS (mg)	Citric acid (mg)	Distilled water
1	P1	450	0.8	12	4	20
2	P2	500	0.7	12	4	20
3	P3	450	0.8	15	4	20
4	P4	500	0.7	15	4	20
5	P5	500	0.8	13.5	4	20
6	P6	450	0.6	15	4	20
7	P7	400	0.7	15	4	20
8	P8	400	0.8	13.5	4	20
9	P9	450	0.6	12	4	20
10	P10	500	0.6	13.5	4	20
11	P11	400	0.6	13.5	4	20
12	P12	400	0.7	12	4	20

4.5. Optimization of Apixaban by Box-Behnken Design (BBD)

The successful development of OTF primarily depended on the three formulation components such as the 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 were implemented. The DoE software predicted 12 trial runs by using BBD. Further, response surface methodology was implemented and quadratic equations were elaborated [16].

4.6.Evaluation of OTF

4.6.1. Appearance of film

The prepared OTF was confirmed for its superiority factors such as transparency, smoothness, and ease of detaching.

4.6.2. Thickness

The thickness of the prepared films was assessed with the digitally calibrated Vernier caliper to ensure uniformity in the film.

4.6.3. Folding endurance

It ensures the flexibility possessed by the film. It was determined by nonstop folding of film at the similar location until it broke [12].

4.6.4. Estimation of pH

The film was retained in contact with the distilled water and permitted to transform into solution inside the petri dish. The liquid achieved was measure by digital pH (Lab India, Pico model) [17].

4.6.5. Determination of moisture content

Approximately 1 g of films were mounted on the digital moisture analyzer which was set at a temperature of 105 ^{0} C. After onset the moisture available in the films was noted [18].

4.6.6. Disintegration time

The film diamension (3x2) was kept in the 10 ml of artificial saliva. The time requisite to entirely disintegrate was witness in triplicate [19].

4.6.7. In-vitro dissolution study

The estimation performed at 37 ±0.5^0 C with USP type II dissolution apparatus (Electolab India, 8 stations, Inspire-08). The dissolution media utilized was simulated saliva. The content of 5 ml were quited at 1 min and change with 5 ml of salivary fluids to attain equilibrium. The contents determined by UV visible spectrophotometer [20].

4.6.8. Content uniformity

A film of Apixaban was placed in the artificial saliva solution. The content was characterized with a UV-visible spectrophotometer at 264 nm [21].

4.6.9. Evaluation of surface morphology

The best batch was assessed by scanning electron microscopy to check its uniformity (SEM) [22].

4.7. Stability study

The OTF was store in the aluminum pouch. This pouch was placed at 40^0 C and 75 % RH for 90 days (Remi India, SC-12 plus). The contents were quited after every 30 days and analyze [23].

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