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OPTIMIZATION AND EVALUATION OF FEXOFENADINE HYDROCHLORIDE SUBLINGUAL FILMS

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ABSTRACT

This study focuses on the optimization and evaluation of fexofenadine hydrochloride sublingual films aimed at treating allergic rhinitis. Films were prepared using the solvent casting method and optimized with Box-Behnken design, a response surface methodology, to refine the formulation parameters. Variables such as polymer concentration, plasticizer content, and disintegrant concentration were systematically varied to determine their effects on film properties. The optimized films demonstrated favourable characteristics including appropriate thickness, disintegration time, folding endurance, and in-vitro drug release profile. These results suggest that the solvent-cast sublingual films of fexofenadine hydrochloride are effective for sublingual delivery, providing a promising solution for allergic rhinitis management with potential benefits in patient compliance and therapeutic onset. Future research will involve in vivo testing and clinical trials to validate the efficacy and safety of these films.

Keywords: Optimization, Bioavailability, Sublingual Film, Design of Experiments, Fexofenadine Hydrochloride

1. INTRODUCTION

Allergic rhinitis (AR) is characterized by sneezing, nasal congestion, nasal itching and rhinorrhoea (nasal discharge) and is caused by Immunoglobulin E (IgE)-mediated reactions to inhaled allergens. These immune reactions involve mucosal inflammation that is driven by type 2 cells. AR seems to be the consequence of environmental exposures acting on a predisposed genetic background. AR is often comorbid with asthma and/or conjunctivitis. AR is one of the most common chronic conditions in high-income countries, with a prevalence of up to 50% in some countries **[1-3]**. By contrast, the prevalence is relatively low in low income and middle income countries, although prevalence is increasing steadily in these countries. AR is a global health problem that causes major burden and disability worldwide. Indeed, AR contributes to missed or unproductive time at work and school, sleep problems and, in children, decreased involvement in outdoor activities. The diagnosis of AR is made by medical history and examination (physical examination and, if needed, nasal endoscopy) plus, in some patients, tests for allergen-specific IgE (skin prick tests or tests for serum- specific IgE) **[4, 5]**. Available treatments include allergen avoidance, pharmacotherapy with H_1 antihistamines or Intranasal Corticosteroids (INCS) and Allergen-specific Immunotherapy (AIT). Many patients are dissatisfied with their treatment, for example, because management does not take the patient's needs into consideration, no cure is available, adherence to long-term therapy is poor and/or because the patient does not fully understand the condition **[6-8]**.

The oral route of drug administration is widely regarded as the most convenient, economical, and safest method. Among oral solid dosage forms, tablets and capsules are the most popular. However, many patients, particularly pediatric and geriatric individuals, encounter difficulties in swallowing tablets and hard gelatin capsules, leading to non-adherence to prescribed medications. Dysphagia, or difficulty swallowing, affects nearly 35% of the general population. Additionally, swallowing tablets or capsules can be problematic in certain situations, such as during motion sickness, sudden allergic reactions, coughing, fear of choking, or when water is not readily available. To address these challenges, several oral mucosal drug delivery systems (OMDDS) have been developed. An OMDDS refers to a method of administering medications or drugs through the mucous membranes of the oral cavity, including the lining of the mouth, gums, cheeks, or sublingual area **[9]**. OMDDS is widely applicable as a novel site

for drug administration, offering both immediate and controlled release actions while preventing first-pass metabolism and enzymatic degradation due to gastrointestinal microbial flora. These systems provide both local and systemic effects, leveraging the highly permeable nature of the oral mucosa to facilitate direct absorption of drugs into the bloodstream, thereby bypassing the digestive system and avoiding degradation by stomach acids and enzymes. Various formulations like mucoadhesive tablets, buccal patches, films, gels, and sprays are utilized to deliver medications, offering advantages such as rapid onset of action, increased bioavailability, reduced dosing frequency, and improved patient compliance. The rich vasculature and avoidance of the first-pass metabolism contribute to the effectiveness of this route for delivering a wide range of drugs, including analgesics, hormones, and vaccines, making oral mucosal drug delivery an area of significant interest in pharmaceutical research and development **[10]**.

The term "sublingual," which literally translates to "under the tongue," refers to the mucosal membrane that covers the floor of the mouth and the ventral surface of the tongue, as depicted. Sublingual drug delivery denotes a method where drugs are positioned beneath the tongue, allowing direct absorption through the blood vessels in that region. This delivery mode exploits the highly permeable nature of the sublingual mucosa, enabling rapid entry of drug substances into the bloodstream, bypassing the digestive system's metabolic processes. This route offers advantages in terms of fast onset of action, high bioavailability, and avoiding degradation in the gastrointestinal tract, making it a preferred choice for certain medications **[11]**.

2. MATERIALS AND METHODS

2.1 Materials

Fexofenadine hydrochloride was received as a gift sample from Sirmour remedies private limited, Sirmour, Himachal Pradesh, India. HPMC E-15 (hydroxypropyl methyl cellulose), PEG 400 (polyethylene glycol), Crospovidone, Tween 80, Citric Acid, Sodium Saccharine, and Menthol were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. All other chemicals and reagents used were of analytical grade and used without further purification.

2.2 METHODS

2.2.1 Optimization of Fexofenadine Hydrochloride Sublingual Film formulation by Design of Experiment Approach

DoE is a systematic study to determine the interaction between material and/or process parameters on the performance of final formulation.

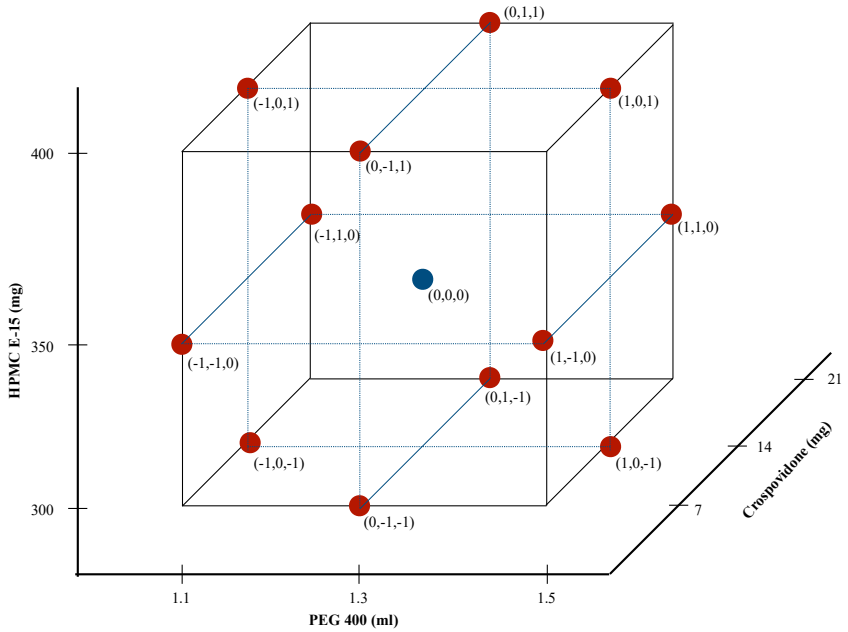


Figure 1: The Box–Behnken design representing three independent variables at three levels (–1, 0, +1)

In the present study, a three-factor, three-level experimental design (Box–Behnken design) approach was utilized to investigate the influence of various independent variables on dependent variables.

Software trial version 23.1.6, Stat-Ease 360, Minneapolis, MN was employed to perform design of experiments. The critical formulation components significantly affecting the quality and performance of final product at three different levels, i.e. -1 (low), 0 (medium), and +1 (high) were considered as independent variables **(Figure 1 and Table 1)** and evaluation parameters desired in final product were selected as dependent variables **(Table 2)**.

Table 1: Independent Variables with Levels

S. No.	Variables	Unit	Low (-1)	Medium (0)	High (+1)
1.	(X1) Polymer (HPMC E-15)	mg	300	350	400
2.	(X2) Plasticizer (PEG-400)	ml	1.1	1.3	1.5
3.	(X3) SDA (Crospovidone)	mg	7	14	21

Table 2: Dependent Variables

S. No.	Variables	Unit
1.	(Y1) Thickness	mm
2.	(Y2) Folding Endurance	Number of Folds
3.	(Y3) Disintegration Time	Seconds

The experimental design matrix output provided by Stat-Ease 360 software proposed 15 experimental runs (B1 to B15) having three replicates of centre point as shown in **Table 3**.

Table 3: Combinations of Sublingual Film Batches suggested by Box–Behnken Design

Run	Batch No.	Independent Variables		
		X1	X2	X3
		HPMC E-15 (mg)	PEG-400 (ml)	Crospovidone (mg)
1.	B1	300	1.5	14
2.	B2	400	1.5	14
3.	B3	350	1.1	21
4.	B4	400	1.1	14
5.	B5	350	1.5	21
6.	B6	400	1.3	21
7.	B7	400	1.3	7
8.	B8	300	1.1	14
9.	B9	300	1.3	21
10.	B10	350	1.3	14
11.	B11	300	1.3	7
12.	B12	350	1.3	14
13.	B13	350	1.3	14
14.	B14	350	1.1	7
15.	B15	350	1.5	7

2.2.2 Fabrication of Fexofenadine HCl Sublingual Films:

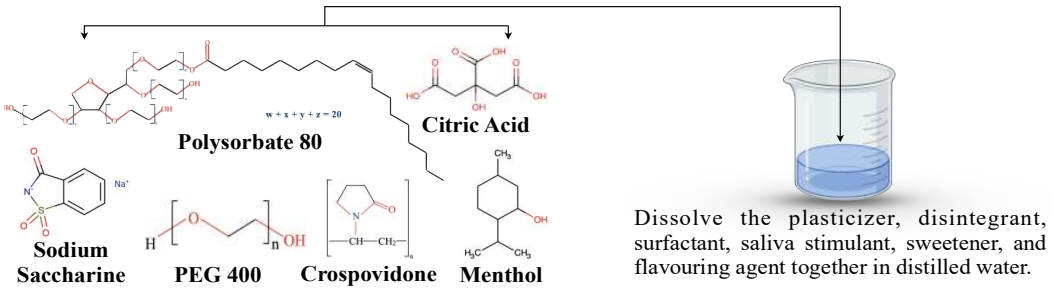
The 15 different combinations of optimization trial batches of Fexofenadine HCl sublingual films suggested by the software were prepared using solvent casting method as stepwise shown in **Figure 2**. The polymer was soaked in three-fourths of the solvent overnight and stirred for 15 minutes to form a uniform dispersion. Meanwhile, plasticizer, disintegrant, saliva stimulant, sweetener, and flavouring agent were dissolved together in water. Fexofenadine HCl was then dissolved in ethanol and added to the excipient mixture. This combined blend was then incorporated into the polymeric solution under continuous stirring (50 rpm) for an hour at 55°C. The final solution was cast into moulds (48 cm^2), dried at room temperature, peeled from the moulds, and cut into 2 cm x 4 cm squares **[12-15]**.

Step 1- Polymer Solution Preparation:

HPMC E-15 soaked in distilled water overnight

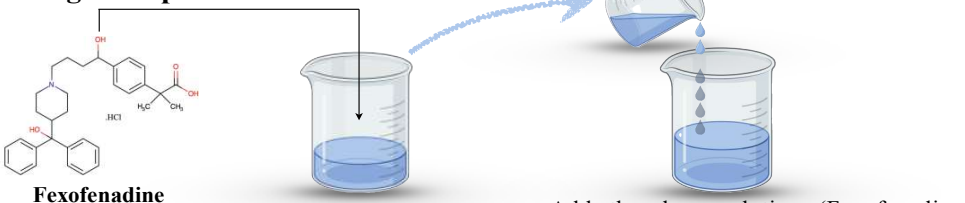
Make the dispersion uniform by stirring using a magnetic stirrer for 15 minutes

Step 2- Excipient Mixture Preparation:



Dissolve the plasticizer, disintegrant, surfactant, saliva stimulant, sweetener, and flavouring agent together in distilled water.

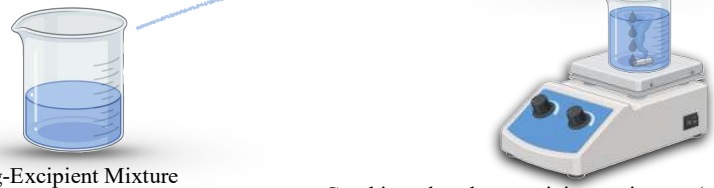
Step 3- Drug Incorporation:



Dissolve Fexofenadine Hydrochloride in ethanol.

Add the drug solution (Fexofenadine Hydrochloride in ethanol) to the excipient mixture from step 2.

Step 4- Incorporation into Polymeric Solution:



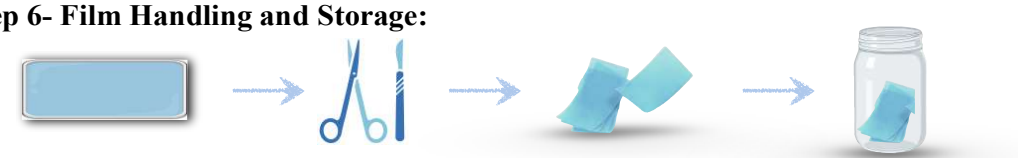
Drug-Excipient Mixture

Combine the drug-excipient mixture (step 3) with the polymeric solution (step 1) under continuous stirring for one hour. This ensures even distribution of all components.

Step 5- Casting and Drying:

Pour the final casting solution into the moulds (48 cm^2). Allow the films to dry completely at room temperature.

Step 6- Film Handling and Storage:



Once dry, carefully peel the films from the moulds. Use a sharp tool to cut the films into desired size (2 cm x 4 cm). Store the prepared sublingual films in transparent airtight glass containers.

Figure 2: Steps involved in the processing of Fexofenadine HCl sublingual films

2.2.3 Characterization of Fexofenadine HCl Sublingual Films for Response Variables:

The 15 trial batches were characterized for response variables and the observations were recorded as shown in **Table 4**.

- **Thickness**

A digital vernier caliper was used to measure the thickness of the film formulation. Five measurements were taken on each film: one in the centre and one at each of the four corners. The average thickness was then calculated for each film. To assess thickness uniformity across the batch, three films were randomly chosen, and their thickness was measured **[16]**.

- **Folding Endurance:**

The folding endurance was measured by repeatedly folding them at the same spot until they broke or showed visible damage. The folding endurance is the total number of folds a film can withstand before breaking. A higher folding endurance value indicates the film is stronger and more flexible **[17]**.

- ***In-vitro* Disintegration Study:**

The test measured how long the film takes to break down in water. Each film was placed in a dish containing 20 ml of water, and the time it took for the film to completely disintegrate or fall apart was recorded. Ideally, sublingual films should disintegrate within 30 seconds or less **[18]**.

- **Statistical Data Analysis:**

The results of response variables were fed into Design Expert software (Stat-Ease Inc., Minneapolis, MN) for statistical fitting into linear, two factors interaction (2FI), quadratic, and cubic models to check the agreement with sequential p-value, lack of fit p-value, and R^2 values.

- **Response Surface Analysis:**

The relationship between independent and response variables was further elucidated by constructing 3D response surface graphs for each response variable and effect of independent variables on each response variable was studied.

2.2.4 Evaluation of Optimized Formulation of Fexofenadine Hydrochloride Sublingual Film:

- ***In-vitro* Drug Release Study:**

In vitro drug release of Fexofenadine HCl sublingual films was evaluated using a modified dissolution apparatus. The dissolution medium consisted of 20 ml of phosphate buffer (pH 6.8) placed in a 100 ml beaker, suspended in the dissolution flask. A USP type I dissolution apparatus was employed, with the stirrer operating at 50 rpm without the basket attachment. Samples were withdrawn at predetermined intervals (30, 60, 90, 120, 150, 180, 210, 240, 270, and 300 seconds). The drug content in each sample was measured spectrophotometrically at a wavelength of maximum absorbance (λ_{max}) of 252 nm using a UV-Visible 1800 spectrophotometer **[19-21]**.

- **Drug Content Uniformity:**

The study assessed drug content uniformity to guarantee consistent drug distribution within the films. This involved dissolving each film entirely in a volumetric flask containing 10 ml of 6.8 pH phosphate buffer. The filtered solution was then used to measure absorbance at 252 nm for estimating drug concentration, employing a Shimadzu 1800 UV-Visible Spectrophotometer.

- **Weight Variation:**

A weight test was performed using digital weighing balance to ensure consistent film quality within each batch of sublingual films. Three film samples, each with a defined area of 8 cm^2 (2 cm by 4 cm), were taken from each batch and weighed individually. Standard deviation was used to analyse the variation in these weights. The average weight of the samples must not exceed deviation of ± 7.5% **[22]**.

- **Surface pH:**

To check the surface pH of a sublingual film, the film was placed on a clean, flat surface and moistened with a few drops of distilled water to form a thin layer. The water was allowed to equilibrate with the film's surface for a few minutes. Then, the pH was measured using a calibrated digital pH meter by gently placing the electrode on the moistened film. The pH value obtained was recorded. This method was employed to ensure precise measurement of the pH of the films, a critical factor in evaluating its suitability for the oral cavity and its potential influence on taste and comfort during usage **[23]**.

- **Scanning Electron Microscopy (SEM):**

SEM allows for high-resolution imaging, which can reveal the surface morphology of the sublingual film. This is important for understanding its texture, smoothness and presence of any irregularity **[24]**.

- **Differential Scanning Colorimetry (DSC):**

Thermal characterization of sublingual film formulation was evaluated using the differential scanning colorimetry (DSC-6000, Remi Elektechnik ETD, Mumbai, India). Sublingual Film was cut into fine pieces using a sharp cutter, placed in thermetically sealed aluminium pans, and heated over a temperature range of 25–250°C at a constant rate of 40°C/min under a nitrogen purge (20 ml/min) **[25-27]**.

- **FT-IR Spectroscopy (FTIR):**

The FT-IR spectrophotometer (D8 Advance, Bruker, USA) was used to record the FT-IR spectra of Fexofenadine Hydrochloride sublingual film at room temperature in the 4000-400 cm^{-1} range. The sample was made by grinding it with dry KBr powder and compressing the powders in a hydraulic press **[28-30]**.

3. RESULT AND DISCUSSION

The fifteen different combinations of Fexofenadine Hydrochloride sublingual film formulation suggested by the Box-Behnken design were prepared and characterized for response variables. The results obtained from the response surface variables were further utilized for statistical and response surface analysis to understand the influence of several independent parameters interacting at various levels as well as the correlation between each independent variable and the response variable were all independently assessed for every response variable of the formulation.

Table 4: Results of Characterization of Sublingual film batches for Response variable

Run	Batch No.	Dependent or Response Variables		
		Thickness (mm)	Folding Endurance (Folds)	Disintegration Time (Seconds)
1.	B1	0.063 ± 0.0014	252 ± 1.73	39 ± 1.52
2.	B2	0.095 ± 0.0041	285 ± 2	46 ± 2
3.	B3	0.074 ± 0.0030	260 ± 1.73	42 ± 3
4.	B4	0.09 ± 0.0041	281 ± 2.64	47 ± 1.73
5.	B5	0.081 ± 0.0036	273 ± 2.64	41 ± 2.64
6.	B6	0.093 ± 0.0040	280 ± 3.60	45 ± 1.73
7.	B7	0.092 ± 0.0041	278 ± 1	49 ± 2
8.	B8	0.059 ± 0.0030	247 ± 3.60	40 ± 1.73
9.	B9	0.06 ± 0.0030	249 ± 1	32 ± 1
10.	B10	0.077 ± 0.0040	266 ± 2	39 ± 2.64
11.	B11	0.061 ± 0.0030	249 ± 2	39 ± 1
12.	B12	0.078 ± 0.0041	270 ± 1.73	40 ± 2
13.	B13	0.079 ± 0.0040	270 ± 2	39 ± 1
14.	B14	0.073 ± 0.0030	262 ± 3.60	45 ± 2
15.	B15	0.08 ± 0.0041	274 ± 3	43 ± 2.64

3.1 Statistical Data Analysis:

➢ **Fit Summary of Sublingual Film Batches:**

The fit summary for Thickness demonstrated the linear model's strong significance ($P < 0.0001$) and an impressive Adjusted $R^2 = 0.9932$, while the 2FI, quadratic, and cubic models displayed lower significance and reduced adjusted R^2 values, with the cubic model being aliased, suggesting the linear model as the most suitable due to its robust fit, predictability, and significance. For Folding Endurance, the linear model exhibited high significance ($P < 0.0001$) and a strong Adjusted R^2 of 0.9465, while the other models lacked significance and had lower adjusted R^2 values, with the cubic model being aliased, favouring the linear model for its notable fit, predictability, and significance. In the case of Disintegration Time, the linear model revealed significant predictive power (Adjusted $R^2 = 0.7651$, Predicted $R^2 = 0.6752$), whereas other models varied in significance and explanatory capabilities, with the cubic model being highly significant but aliased, making the linear model the preferable choice due to its robust fit and predictability.

Table 5: Results of Characterization of Sublingual Film batches for Response variable

Response Variable	Model	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	Source
Y1: Thickness	Linear	< 0.0001	0.5856	0.9932	0.9909	Suggested
	2FI	0.8018	0.4880	0.9916	0.9845	-
	Quadratic	0.3900	0.4733	0.9923	0.9692	-
	Cubic	0.4733	-	0.9933	-	Aliased
Y2: Folding Endurance	Linear	< 0.0001	0.4154	0.9465	0.9214	Suggested
	2FI	0.9873	0.3051	0.9276	0.8279	-
	Quadratic	0.3631	0.2918	0.9356	0.6968	-
	Cubic	0.2918	-	0.9669	-	Aliased
Y3: Disintegration Time	Linear	0.0002	0.0627	0.7651	0.6752	Suggested
	2FI	0.9262	0.0446	0.6943	0.3661	-
	Quadratic	0.1268	0.0642	0.8293	0.0610	-
	Cubic	0.0642	-	0.9815	-	Aliased

3.2 Response Surface Analysis of Sublingual Film Formulation:

The three-dimensional response surface plots constructed for each response variable demonstrate the impact of changes to independent factors and their interactions on response variables of the sublingual film.

- **Impact of Variables on Sublingual Film Thickness as determined by 3D Surface Graphs:**

The plots depict the relationship between the thickness of films and the concentrations of various factors, specifically polymer, plasticizer, and super disintegrating agent. In **Figure 3 (a) and (b)**, thickness is shown as a function of polymer and plasticizer, with a notable increase in thickness as the polymer amount increases. Thickness varies with polymer and super disintegrating agent, where thickness increases with higher polymer amounts and decreases as the super disintegrating agent increases. Critical design points, indicated by red and blue markers, show regions above and below the surface, emphasizing the significant impact of polymer concentration on thickness in both scenarios.

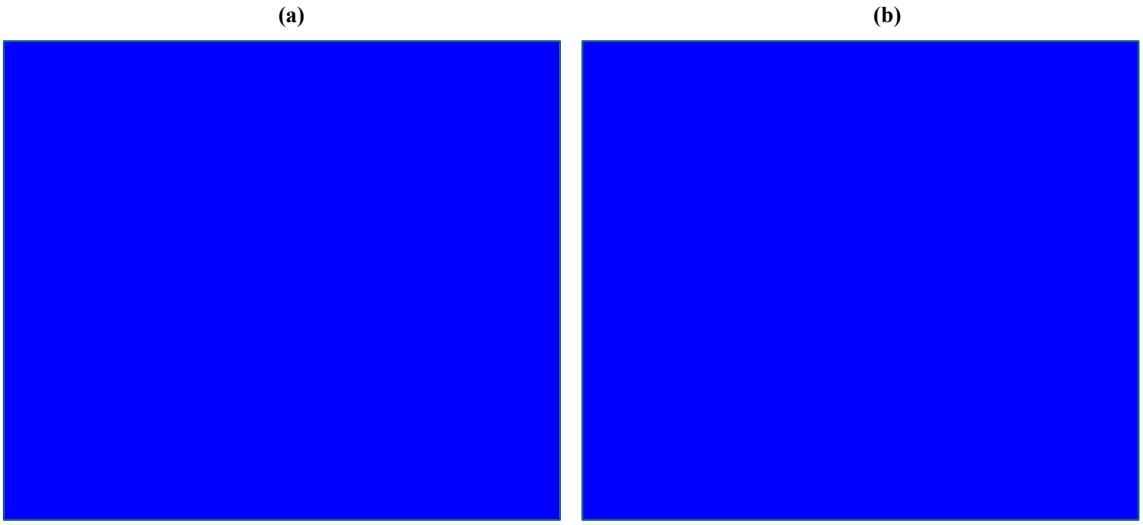


Figure 3: 3D-response surface plots showing effect of (a) HPMC E-15 and PEG 400 and (b) HPMC E-15 and Crospovidone on thickness of Fexofenadine HCl Sublingual Films

- **Impact of Variables on Sublingual Film Folding Endurance as determined by 3D Surface Graphs:**

The graphs illustrate the effect of polymer, plasticizer, and super disintegrating agent concentrations on folding endurance. In **Figure 4 (a) and (b)**, folding endurance increases as the polymer amount increases, while the plasticizer ranges from 1.1 ml to 1.5 ml, showing a peak endurance around the higher polymer and plasticizer concentrations. Folding endurance also increases with higher polymer amounts, but decreases as the super disintegrating agent increases from 7 mg to 21 mg.

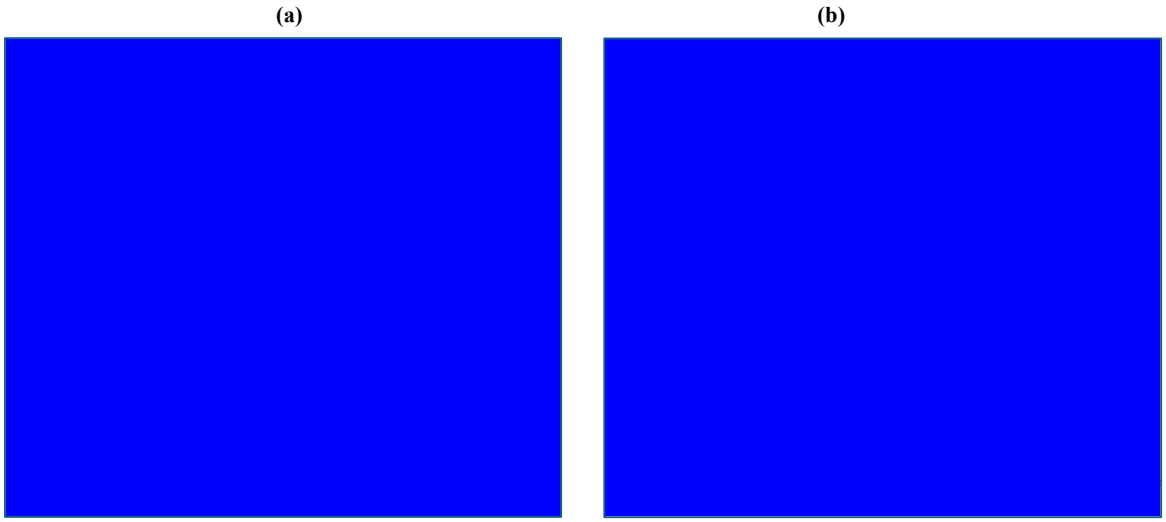


Figure 4: 3D-response surface plots showing effect of (a) HPMC E-15 and PEG 400 and (b) HPMC E-15 and Crospovidone on Folding Endurance of Fexofenadine HCl Sublingual Film

- **Impact of Variables on Sublingual Disintegration Time as determined by 2D Contour Plotting and 3D Surface Graphs:**

Figure 5 (a) and (b) illustrates the relationship between the amounts of polymer and plasticizer on the disintegration time of film, measured in seconds. The plot shows a clear trend where increasing both polymer and plasticizer amounts leads to longer disintegration times. **Figure 5 (a) and (b)** demonstrates the effect of varying amounts of polymer and super disintegrating agent on the disintegration time measured in seconds. The plot reveals that increasing the super disintegrating agent concentration leads to shorter disintegration time.

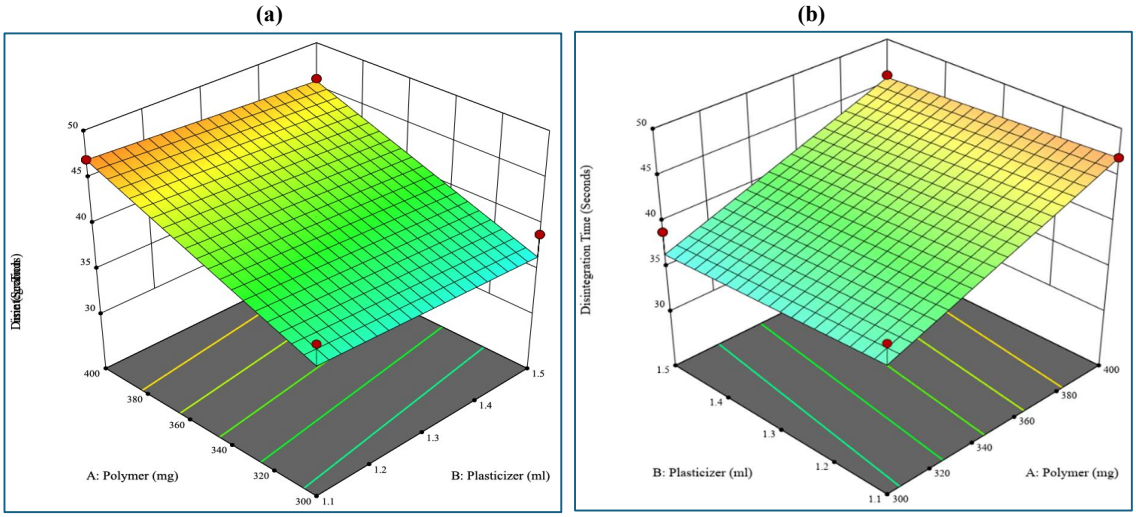


Figure 5: 3D-response surface plots showing effect of (a) HPMC E-15 and PEG 400 and (b) HPMC E-15 and Crospovidone on Disintegration Time of Fexofenadine HCl Sublingual Films

3.3 Prediction of Optimized Fexofenadine HCl Sublingual Film:

The desired criteria were defined in the software design expert version 13.0.15 (Stat easy) as indicated in Table 6 below to reach the ideal formulation. Using these parameters along with the output from optimization batches, the software produced 100 unique formulas that were all getting close to a desirability score of 1. The formulation with the highest desirability of 1 was determined to be the anticipated ideal formulation. **Figures 6 and 7** displayed the desirability ramps and bar graphs that predicted the formulation with the highest desirability.

Table 6: Desirable Objectives of Response Variables for Optimized Batch.

S. No.	Response Variables	Criteria
1.	Thickness	Minimize
2.	Folding Endurance	In Range
3.	Disintegration Time	In Range

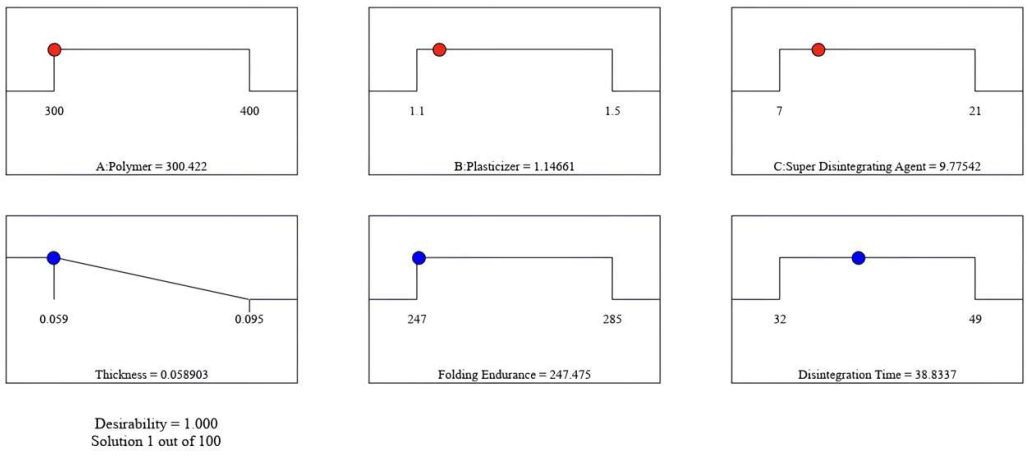


Figure 6: Desirability and Predicted Values of Response Variables with Respective Degree of Independent Variable

Table 7: Predicted and observed response variables for Fexofenadine HCl Sublingual Film

S. No.	Optimized Formula Composition		Response		
	Variable	Quantity	Evaluation Parameter	Software Predicted	Experimentally Observed
1.	HPMC E-15	300.42 mg	Thickness	0.058 mm	0.060 mm
2.	PEG-400	1.14 ml	Folding Endurance	247	248
3.	Crospovidone	9.77 mg	Disintegration Time	38 seconds	40 seconds

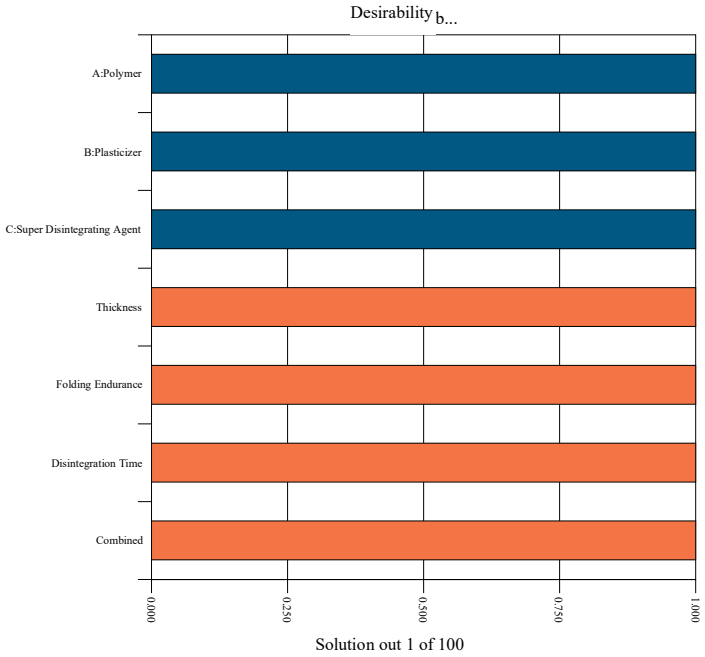


Figure 7: Desirability of Individual Independent and Response Variables Depicted in Bar Graph

Figure 8: Optimized Fexofenadine HCl Sublingual Film Batch

3.4 Characterization of Optimized Ivabradine HCl loaded MDF Formulation

It became clear that there was very minute difference between the software-predicted and experimentally observed response data for the optimized formulation of Fexofenadine HCl sublingual film, with only small relative percentage errors that were well within the acceptable range.

Table 8: Characterization of Optimized Fexofenadine Hydrochloride Sublingual Film

S. No.	Response Variables	Batch Number	Observations
1.	Thickness (mm)	Optimized Batch (B16)	0.060 mm
2.	Folding endurance (folds)		248
3.	Disintegration Time (seconds)		40 seconds
4.	Drug Content Uniformity (%)		100.23 ± 1.03
5.	Surface pH		6.78 ± 0.09
6.	Weight Variation (mg)		163 ± 1
7.	*In-vitro* % Drug Release (%)		95.40

- **Thickness:**

The thickness of the batches (B1 to B15) was evaluated and are presented in **Table 4**, with results indicating that all batches conformed to the accepted thickness range, demonstrating good patient acceptability and consistency with established limits. The thickness of optimized batch B16 was found to be 0.060 mm.

- **Folding Endurance:**

The folding endurance of all fifteen batches B1 to B15 were reported to be in the range of 247-285. Based on the results from these formulations, all of them exhibited folding endurance values that conformed to the limits indicated in **Table 4**. The folding endurance of optimized batch B16 was found to be 248 folds.

- ***In-vitro* Disintegration Study:**

The disintegration time of all fifteen batches was evaluated and found to in range of 32 to 49 seconds as shown in **Table 4**. The disintegration time of optimized batch B16 was found to be 40 seconds.

- ***In-vitro* Drug Release Study:**

The study investigated the maximum amount of Fexofenadine HCl that could be released from the films. All formulations underwent testing until a point of no further drug release was observed within a 300 seconds timeframe. Since this 300 seconds mark applied to all formulations, the testing was stopped at that point. The drug release of optimized batch is graphically depicted in **Figure 9**.

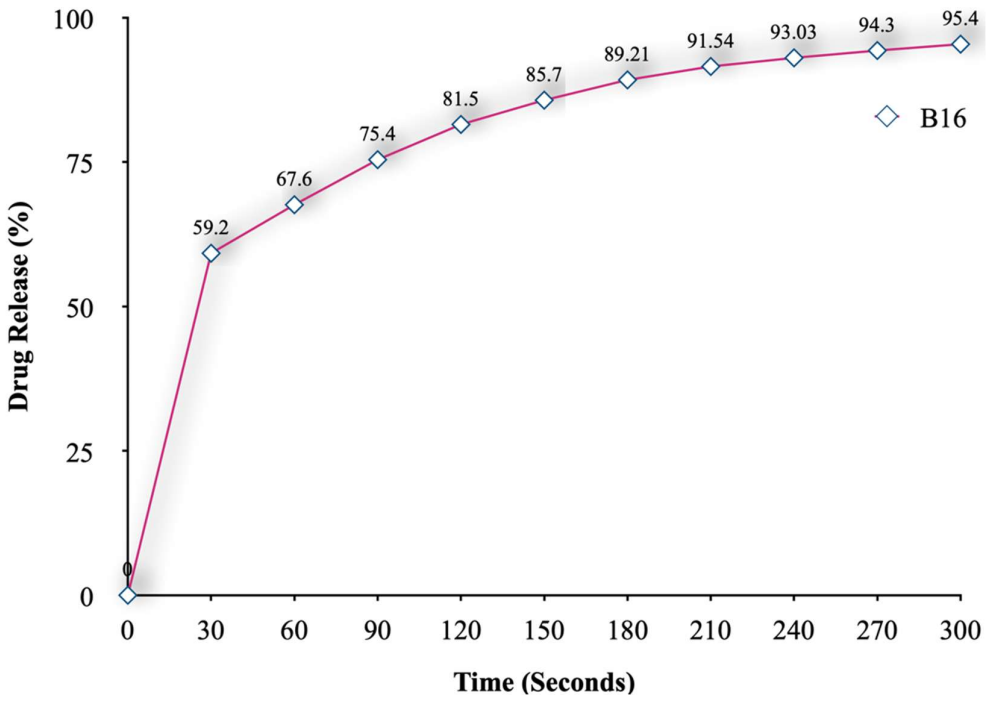


Figure 9: ***In-vitro*** **% drug release profiles of optimized Fexofenadine Hydrochloride Sublingual Film**

- **Drug Content Uniformity:**

Drug content uniformity refers to how consistently the drug is distributed throughout the sublingual film batch. The drug content uniformity of sublingual film batches was determined. Drug content uniformity of the optimized sublingual film formulation was found to be 100.23 ± 1.03 % which indicates uniformity of mixing. Drug content was within the limit of 95% to 105 %.

- **Weight Variation:**

The average weight of the optimized sublingual film formulation was found to be 163 ± 1 which complies with the limit of not more than ± 7.5% standard deviation.

- **Surface pH:**

The pH of the optimized sublingual film formulation was found to be 6.78 ± 0.09 which complies within the limits of pH 6 to 7.

- **SEM of Optimized Sublingual Film**

The morphological study of the optimized Fexofenadine HCl sublingual film was carried out by scanning electron microscopy (SEM) at a prescribed magnification. The Fexofenadine HCl sublingual film exhibited a smooth surface with a few small pores, as illustrated in **Figure 10**. This signifies a uniform distribution of Fexofenadine HCl sublingual film.

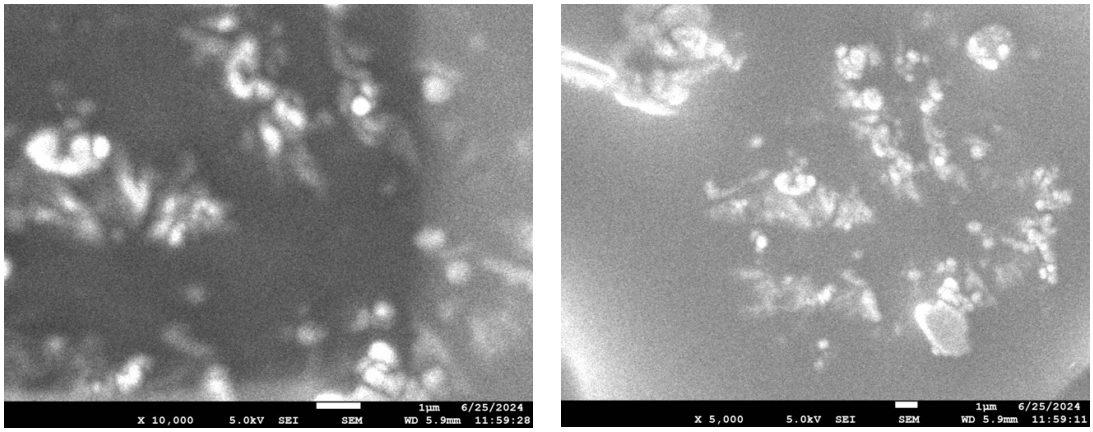


Figure 10: SEM of Optimized Fexofenadine HCl Sublingual Film

➢ **DSC of Optimized Sublingual Film**

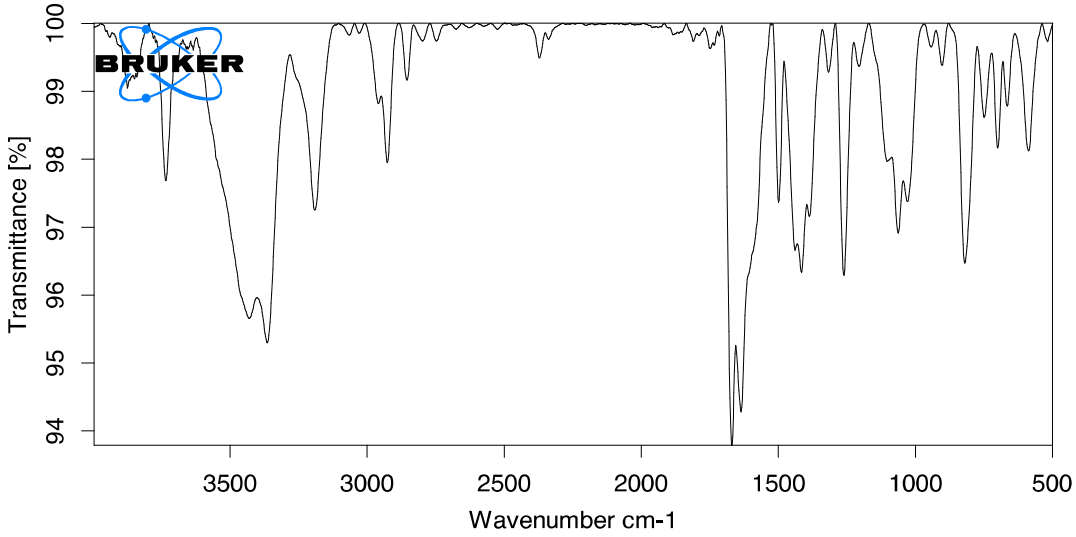
The DSC thermogram of pure Fexofenadine HCl and Fexofenadine HCl Sublingual Film is depicted in **Figure 11**. Thermogram of pure Fexofenadine HCl had sharp endothermic peaks at 213.83 °C, corresponding to its melting point and indicating the crystalline nature of the drug. While DSC thermogram of optimized Fexofenadine HCl sublingual film formulation showed decrease in intensity of peaks confirming its amorphous state, successful entrapment of drug and uniform distribution within the formulation.

Figure 11: DSC of Fexofenadine HCl and optimized Fexofenadine HCl Sublingual Film

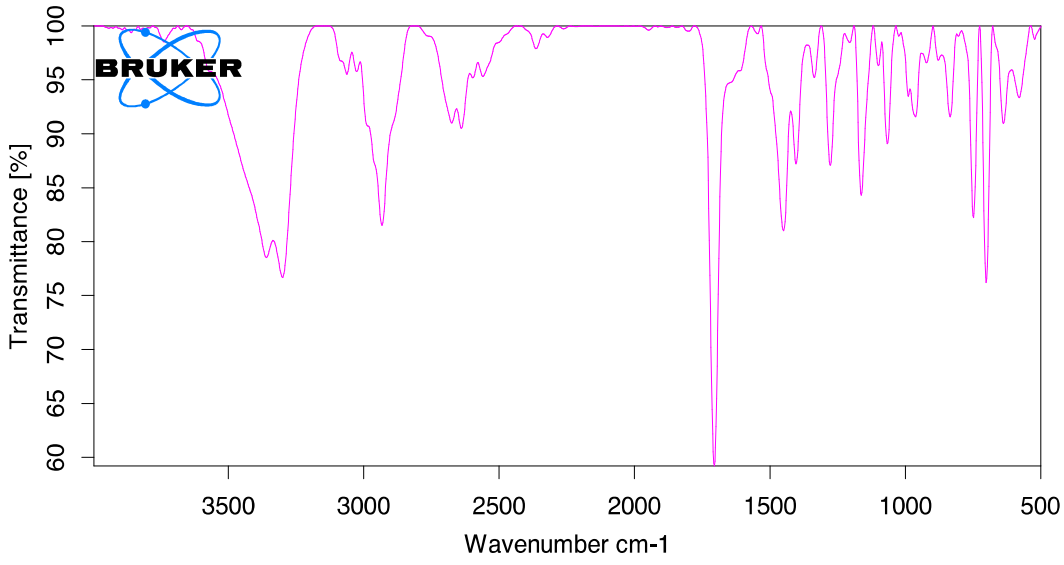
➢ **FTIR of Optimized Sublingual Film:**

The primary application of FTIR spectra is to ascertain how a drug interacts with any excipient. As demonstrated in **Figure 12 (a)**, the optimized Fexofenadine Hydrochloride sublingual film formulation's FTIR spectrum revealed notable drug FTIR bands, but the intensity of the peaks had

significantly decreased, suggesting that there was no undesired interaction between the drug and excipients in the formulation. Therefore, this result validates that the constituents in the formulation are compatible.



(a)



(b)

Figure 12: FTIR of (a) Fexofenadine HCl (b) Optimized Fexofenadine HCl Sublingual Film

- **Stability Studies:**

An accelerated stability test was conducted on an optimized batch of Fexofenadine Hydrochloride Sublingual Film for three months at a high temperature (40 ± 2°C) and humidity (75 ± 5 %) to assess its ability to maintain quality. The dissolution profile analysis of the sublingual film both before and after it underwent accelerated stability studies were analysed. The results of stability study are depicted in **Table 9**. The formulation holds steady for the designated duration.

Table 9: Stability Study Data of Optimized Sublingual Film

S. No.	Parameters	Time		
		1 Month	2 Month	3 Month
1.	Thickness (mm)	0.060	0.059	0.059
2.	Folding Endurance (Number of Folds)	246	244	244
3.	Disintegration Time (Seconds)	39	38	38
4.	*In-vitro* Drug release (%)	94.90	93.51	92
5.	Drug Content (%)	99.19	98.24	98.10
6.	Weight Variation (mg)	162	160	159
7.	Surface pH	6.78	6.73	6.70

CONCLUSION

The Fexofenadine HCl sublingual film underwent systematic optimization using Design Expert software by employing a three-factor, three-level BBD. This approach efficiently established the relationship between chosen variables and response criteria, yielding a precise prediction with 15 optimization trial batches. The resultant polynomial equations and 3D response surface plots illustrated the significant influence of each variable on various responses. The software-predicted optimized formulation, validated through statistical evaluation and adherence to desired response constraints, comprised 300.42 mg HPMC E-15, 1.14 ml PEG 400, and 9.77 mg Crospovidone. Experimental characterization closely matched the predicted values, showing a mean thickness of 0.060 mm, folding endurance of 248 folds, and disintegration time of 40 seconds. These findings validated the efficacy of the formulation optimization strategy. Solid-state characterization via SEM, DSC, and FT-IR affirmed the uniform distribution of the drug throughout the film formulation. Accelerated stability studies were conducted for three months confirmed the stability and robustness of the optimized sublingual film (B16). Consequently, this Fexofenadine HCl sublingual film represents a promising alternative for administration, potentially enhancing patient compliance. However, further in-depth studies on pharmacokinetics are required to establish the clinical effectiveness of the Fexofenadine HCl sublingual film.

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