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Original Article

Quality by Design Assisted Development of Fast Dissolving Buccal Film of Ivabradine

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ABSTRACT

Background: Buccal drug delivery is a novel drug delivery system ensure fast onset of action and avoids the first pass metabolism and ultimately improves the bioavailability. **Aim:** The present investigation is oriented towards design and development of Fast Dissolving Buccal Film (FDBF) of Ivabradine HCl (BCS Class I drug) by applying Quality by Design (QbD) concept. **Materials and Methods:** The Quality Target Product Profile was defined for the proposed formulation, CQA's were identified and risk assessment was carried to identify the most critical factors associated with the formulation development. Main Effect Screening design was applied by using independent variable as HPMC and Kopulan-PG, PEG 400, Tween 80 as material attributes that have an impact on responses such as Folding endurance, Disintegration time, % Drug content and % Drug release at 15 min. The stability data obtained for the optimal formulation was computed in the JMP stability toolbox to predict the expiration date. **Results:** The results of the main effect screening design of 12 formulations indicated that the combined action of three factors had a significant impact on Ivabradine release and could predict the ideal formulation with the necessary Quality target product profile (QTPP). The statistically significant models were determined for % drug release at 15 min (R2=0.97) disintegration time (R2=0.99), folding endurance (R2=0.99) and drug Content (%) (R2=0.98). The optimal formulation confirms the expiration date of 25 months. **Conclusion:** The selected factors and responses have a strong association and are significant enough for formulation optimization, because the highest global desirability value obtained was 0.80.

Keywords: Ivabradine, Fast Dissolving Buccal Film, Quality by Design, HPMC, Kopulan PG. Risk Assessment.

INTRODUCTION

Ivabradine, a Hydrogen cyanide channel blocker, used in the treatment of stable symptomatic heart failure caused by dilated cardiomyopathy in pediatric patients and lowering the likelihood of adult patients being hospitalized for worsening heart failure. The funny current (If) in the sinoatrial nodal tissue is specifically inhibited by it, making its mechanism distinct from that of other negative chronotropic agents. As a result, the rate of diastolic depolarization is slowed, which in turn lowers heart rate.[1] The oral bioavailability of drug is 40% due to the initial metabolism in the liver and intestine.

The core principle of QbD is that, the quality can be "designed in" to the processes by using an optimization approach to thoroughly understand how the system responds in terms of quality to specific factors and by using control techniques to maintain continuous quality control. Recently, the FDA began to advocate for the use of QbD in the pharmaceutical industry. QbD has the potential to aid in the creation of high-quality products and pharmaceutical research.[2]

A process can be better understood by identifying its sources of variability, managing variability through process design and predicting product quality attributes using design space. However, we are still on the journey and are still gathering the experience and metrics required to connect and demonstrate the benefits of QbD.[3]

The planning and management of the manufacturing process, according to QbD, promotes consistency in the product quality. The specifications for drug products should typically base on product performance and be clinically relevant. For QbD to work, it is important to comprehend how formulation and process variables impact product quality. Using these discussions and some particular features of the development of generic products

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as a starting point, a target product profile will be established. Additionally, compilation of relevant historical data into a knowledge space about the drug substance, potential excipients and process operations plays a crucial role in the product development. To identify knowledge gaps that call for additional research we utilize the risk assessment. In order to meet a target product quality profile, product's critical material (quality) characteristics that must be controlled.[4]

As oral route administration poses many challenges, such as orally disintegrating tablets have handling problems as it is fragile in nature.[5] The other oral route administration face problems with bioavailability of drugs mainly due to first pass metabolism, enzymes in GI fluids, pH condition in GIT, GIT membrane bound enzymes etc. The oral mucosal layer has a larger surface area than the ocular and nasal mucosal layers; it may pass low molecular weight medicines through the mucosal epithelium.[6] High regional blood flow and the oral mucosa's higher permeability (4-1000 times greater than of skin) allow for quick absorption, which enhances the drug's bioavailability.[7,8] Additionally, FDBF inhibits first pass metabolism, increasing the amount of drug availability in the blood.[9,10] This improves the drug's bio availability while also providing a constant state plasma drug level, which improves therapeutic efficiency. Furthermore, this channel is more porous than the skin and is easier to access.[11]

The FDBF novel drug delivery system offers better therapeutic effect and it is considered as an ideal dosage form of interest for many API's. Because of scale up difficulties it fails to reach market in large scale as acceptable formulation. The application of Quality by design concept in the development of the formulation will emphasize on the better understanding of the formulation variables with respect to attainment of Critical quality attributes. The most influential formulation variables like plasticizers (glycerol, propylene glycol), permeation enhancers (dimethyl sulfoxide, eucalyptus oil), polymers (HPMC, Carbopol) pH modifiers (tartaric acid) were identified and examined through the extensive risk assessment and by the application of appropriate experimental design.

MATERIALS AND METHODS

Materials

Ivabradine HCl was a kind gift sample from Hetero Labs, Hyderabad. Pullulan (Kopulan PG) was obtained from Kumar organic products limited. HPMC 15 cps and PEG 400 was procured from LOBA CHEMIE Pvt. Ltd., and SPECTROCHEM Pvt. Ltd., respectively. Mannitol, peppermint oil, citric acid and Tween 80 were obtained from SD Fine chem Pvt. Ltd.,

Methods

Identifying QTPP and CQA

A QbD strategy was initiated with the right selection and the assignment of QTPP, which includes proactive summary for maximizing the developed formulation's better to the greatest possible extent. The first step in the pharmaceutical development of FDBF containing Ivabradine HCl is the QTPP's assignment of important process and the formulation features (Table 1). Major goal of a patient-centric strategy is to employ FDBF in a way that is safe and effective, facilitating patient compliance and a quick commencement of medication activity. Critical process parameter for FDBF should be reliable, repeatable and produce a product that satisfies the necessary specifications. Each factor was graded as high, medium, or low risk based on the risk and the severity (Table 2).

Risk Assessment

Thorough understanding about Critical material attributes and Critical process attributes will be established through risk assessment process. Figure 1 depicts an Ishikawa fish-bone diagram showing the probable high-risk elements that could affect the quality of final formulation of product. The list takes

Table 1: QTPP Table for Ivabradine FDBF.

QTPP Elements	Target	Justification
Dosage form	Buccal Film	Ease of administration and improved bioavailability.
Dosage type	FDBF	Immediate release and fast onset of action.
Route of administration	Oral cavity	For the effective drug dissolution and to avoid a first-pass metabolism.
Dosage Strength	5 mg	Unit dose of Ivabradine HCl comprise to exhibit therapeutic efficiency.
Pharmacokinetic parameter	C_{max}, T_{max}, AUC.	Ensure quick onset of action and efficacy.
Stability	At least 24-month shelf life at room temperature.	Evaluate the drug's and excipient's degradation pattern.
Container closure system	Aluminium foil sachet.	It is necessary to achieve desired shelf life of the product.

Table 2: CQA's Table for Ivabradine HCl FDBF.

Quality attributes of drug product	Target	Critical quality attribute	Justification
Appearance	Acceptable color and shape. No visual film defects.	No	Safety and effectiveness are not impacted by colour, shape, or appearance. Thus, these are not essential. The objective is defined to ensure the patient acceptance.
Odor	No unpleasant odor.	No	Odor does not directly impact safety and efficacy; it can have an impact on patient acceptance.
Size	2 cm x 2 cm	No	Ease of administration.
Flavor and taste	No unpleasant taste	Yes	Although the taste does not directly effect safety and efficacy, an API's bitter flavour may have an impact on patient acceptance.
Disintegration time	≤30 sec	Yes	The quick onset of action and efficacy are directly affected by a disintegration time of the film.
Assay	100% w/w of label claim	Yes	Safety and efficacy will be affected by content variability.
Dissolution	More than 85% in the target time.	Yes	Bioavailability is affected when the dissolving specification is not achieved.

into account the finer points of important material characteristics or process variables for the development of an FDBF containing Ivabradine HCl.

Construction of Ishikawa Diagram and Risk Estimation Matrix

To organize the risk analysis process for identifying the root causes and underlying sub causes affecting the CQAs, an Ishikawa diagram was created. To identify high-risk steps that might have an impact on the CQAs of FDBFs, a risk assessment process that includes Critical Materials Attributes (CMAs) and Critical Process Parameters (CPPs) was conducted. An Ishikawa (fish-bone) diagram for CLH FDBFs and depicts the cause-and-effect relationship between the potential factors that might affect CQAs of FDBF.

Risk assessment studies have identified key formulation parameters as critical contributors to certain Critical Quality Attributes (CQAs). Among the numerous process and formulation parameters screened, polymer concentration (X1), plasticizer (X2) and surfactant (X3) were highlighted as critical. These parameters pose a high risk to specific CQAs, including film Folding Endurance (Y1), Disintegration Time (Y2), Drug Content (Y3) and Percentage Drug Release (Y4) (Figure 2).

Failure mode effect analysis

For FDBF, we determined the RPN by assigning Probability, Severity and Detectability values to each failure mode (RPN=P*S*D). A failure mode effect study of materials for the FDBFs well illustrated in Table 3.

Drug excipient compatibility: FTIR Spectroscopy

FTIR spectra were captured in the 4000-400cm^{-1} wavenumber range. This analysis gives a unique finger print region for the sample which is helpful in identification of unknown sample.[12]

Design of Experiment (DoE)

A comprehensive study called Design of Experiment (DoE) used to ascertain how the performance of the final formulation is affected by interaction between material and process characteristics. The influence of various independent variables on dependent variables was examined in the current study by using a Main Effect Screening Design technique. The design was devised using Statistical software JMP 16.2 pro (Statistical Analysis Software; SAS Institute Inc., North Carolina, US). In the current study, The Analysis of Variance (ANOVA) was used to determine the relationship between the independent variables (factors) such as HPMC 15cps/Kopulan PG (X1) and PEG 400 (X2) and Tween 80 (X3) and the dependent variables (response) like Folding endurance (Y1), Disintegration time (Y2), Percentage drug release (Y3) and Percentage Drug Content (Y4). The factors (X1, X2 and X3) and their values were entirely chosen based on preliminary tests. DoE runs with defined dependent variables along with other components required to develop the FDBF. Each formulation batch underwent a random series of experiments. Each formulation was developed in accordance with the total of 12 experimentation runs that were allocated.

Main Effect Screening Design

A Chi-square criterion describes a main effects screening design as one with good balance properties. For main effect models, such designs have favorable statistical characteristics.

If an experiment contains discrete or categorical numeric components or if the number of runs is constrained, this might not be possible to develop an orthogonal design for main effect screening. A main effects screening design, however, can be created.

Algorithm is used to generate the design attempts to construct an orthogonal array of strength two. When interactions are minimal, strength-two orthogonal arrays allow for orthogonal main effect estimation. The screening designs are perfect for these arrays. Strength-two orthogonal arrays include regular Resolution 3 fractional factorial designs and Plackett-Burman designs. All possible level combinations were considered when considering design-related factors (Tables 4 and 5). The programme does its best to distribute the level pairings equally. A new balanced column is created at random after a predetermined number of columns have been generated. A metric is established to reflect the level of equilibrium attained for pairs involving the new column. The algorithm switches levels within the new column in an effort to reduce this measurement.

Table 3: RPN calculation for FDBF.

Functions	Critical Material Attributes	Defective mode (critical event)	Justification of failure mode in CQA with respect to QTPP	P	S	D	RPN
Drug	pKa	Higher or lower the optimum range.	It is crucial to maintain optimal drug solubility and absorption, as variations in pKa may impact the drug's ionization state, influencing its therapeutic effectiveness and bioavailability through the buccal route.	4	4	3	48
Polymer	Concentration of polymer	Higher or lower the optimum range.	It is essential to ensure the desired mechanical and drug release properties, as variations in polymer concentration can directly impact the film's structural integrity, drug-polymer interactions and overall performance.	4	4	4	64
Plasticizer	Amount of plasticizer.	Higher or Lower optimum.	It is critical to maintaining the film's flexibility, as variations in plasticizer quantity may impact the film's mechanical properties, drug release kinetics and overall performance.	4	4	4	64
Surfactant	Type of surfactant.	Hydrophilic in nature.	It is crucial to ensure proper hydration, dissolution and disintegration of the film. Variations in the hydrophilic character of the surfactant may impact water uptake and distribution within the film, influencing disintegration time and overall product performance.	4	4	3	48
		Lipophilic in nature.	It is crucial to maintain appropriate drug solubility and distribution within the film, as variations in the lipophilic character of the surfactant may influence drug-polymer interactions and impact drug release kinetics, potentially affecting the overall therapeutic efficacy of the buccal film.	4	4	3	48
	Amount of surfactant.	Higher or Lower the optimum range.	It is essential to ensure proper film breakdown, as variations in surfactant quantity may affect hydration dynamics, dissolution and overall disintegration time, influencing the film's performance.	4	4	4	64
Flavoring agent	Amount of flavoring agent.	Higher or lower the optimum range.	Variations in the amount of flavoring agent may affect the sensory attributes of the buccal film, potentially impacting patient adherence and overall product satisfaction but no direct impact on the efficacy and safety of product.	3	3	3	27

Table 4: Variables and their limits in Main Effect Screening Design.

Variables	Limits			
Polymer	HPMC 15 cps 40%	Kopulan PG 40%	HPMC 15 cps 50%	Kopulan PG 50%
PEG 400	7.5			
Tween 80	1		5	

Table 5: Responses in the Main Effect Screening Design.

Responses	Goal	Lower limit	Upper limit
Folding endurance.	Maximize	200	300
Disintegration time (in sec).	Minimize	20	60
% Drug content.	Maximize	80	100
% Drug release in 15 min.	Maximize	80	100

Table 6: Formulation Table of Ivabradine HCl FDBF.

Formulation	Kopulan-PG (% w/w)	HPMC 15 cps (% w/w)	PEG 400 (% w/w)	Citric acid (% w/w)	Mannitol (% w/w)	Tween 80 (% w/w)	Peppermint Flavor	Water
F1	50	-	10	4	5	5	2	q.s
F2	-	50	5	4	5	5	2	q.s
F3	-	50	7.5	4	5	1	2	q.s
F4	40	-	10	4	5	1	2	q.s
F5	50	-	7.5	4	5	1	2	q.s
F6	40	-	5	4	5	1	2	q.s
F7	40	-	7.5	4	5	5	2	q.s
F8	50	-	5	4	5	1	2	q.s
F9	-	50	10	4	5	5	2	q.s
F10	-	40	10	4	5	1	2	q.s
F11	-	40	5	4	5	5	2	q.s
F12	-	40	7.5	4	5	5	2	q.s

Design Evaluation and Design Diagnostic

The design was assessed using the JMP's design diagnostics tools and a correlations colour map (Figure 3). Users can view the absolute values of correlations among effects in the main effect screening design's correlations colour map, which is a part of the design evaluation outline.

An absolute correlation of one is indicated by the deep red colouring. The diagonal red cells depict model term correlations among themselves. Other cells are either light blue or deep blue in colour. The correlations between the quadratic terms are represented by the light blue squares.

Preparation of Fast Dissolving Buccal Film (FDBF)

A solvent-casting process was used to prepare FDBF of Ivabradine HCl using Kopulan PG, HPMC 15 cps, PEG-400 and other suitable ingredients as mentioned in Table 6. PEG-400 (5, 7 and 10% w/w), Kopulan PG and HPMC 15 cps in different proportions (40 and 50% w/w) and were combined with required quantity of distilled water and stirred continuously for 30 min. After that, the solution was set aside for an hour to allow trapped air bubbles in the mixture to escape. Ivabradine HCl, citric acid, mannitol, Tween 80 (1 and 5% w/w) and peppermint oil flavour were dissolved in additional 10 mL of water and added to the already made polymeric solution drop by drop while stirring continuously kept on magnetic stirrer for 2 hr in 30°C. The solution was removed and the air bubbles were allowed to escape for 30 min. On the Petri dish with a diameter of 9 cm, a cooled solution was poured and dried for 24 hr at room temperature. Carefully removing a dried film off from Petri plate, it was examined for appearance and integrity. Finally, appropriate films with a therapeutic dose of ivabradine HCl were cut into the desired size (2 x 2 cm) (5 mg).

Prior to further analysis, films were wrapped in aluminium foil and kept at a room temperature.[13]

Checking the CQAs

Folding Endurance

A crucial parameter that reveals the mechanical property of film is folding endurance. A good film should be able to withstand the least amount of wear and tear and keep its integrity while being used. It was calculated by folding the film more than 200 times at one specific point. A high number of folding endurances suggests that a film has good mechanical strength.[14]

Disintegration time

It's the time at which a film will break when it comes in contact with water. It was calculated by placing the film (2x2 cm^2) in a Petri-plate (3.5-inch internal diameter,1 inch height) with 25 mL of water maintained at a temperature of 37°C and the time taken by the film to completely disintegrate or collapse was noted in triplicates.[15]

Percentage Drug Content

To ensure that the drug is evenly distributed throughout the films, an estimation of their content was made. Each film was thoroughly dissolved by stirring it in a volumetric flask containing 10 mL

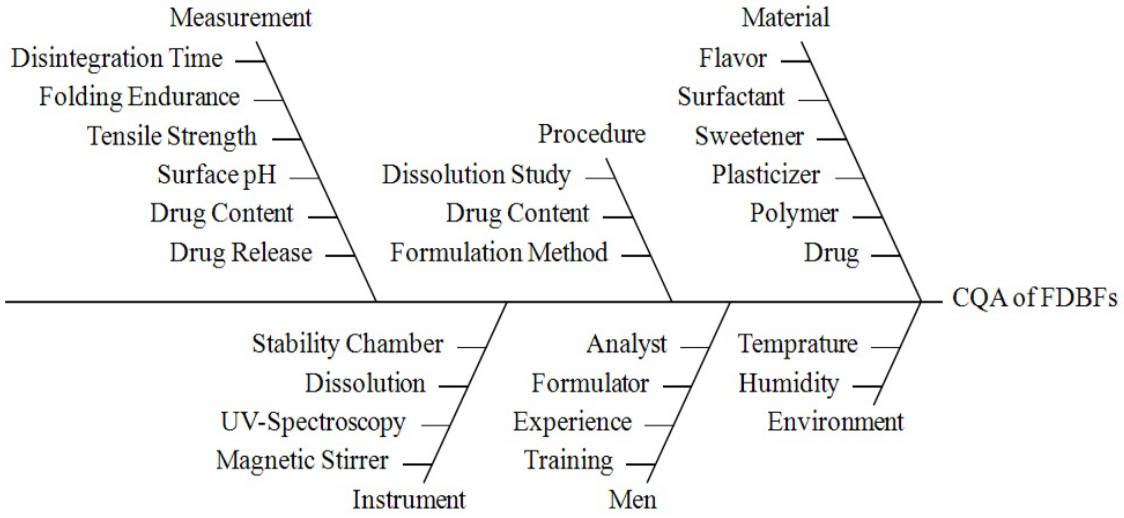

Figure 1: Ishikawa diagram for FDBF's.

Critical Material Attributes	Critical Quality Attributes			
	Folding Endurance	Disintegration time	Content uniformity	% Drug release
Drug	Low	Low	High	Medium
Polymer	High	High	High	High
Plasticizer	High	High	Medium	High
Surfactant	High	High	Low	High
Flavoring agent	Low	Low	Low	Low
Sweetening agent	Low	Low	Low	Low

Figure 2: Risk Estimation Matrix for FDBF's.

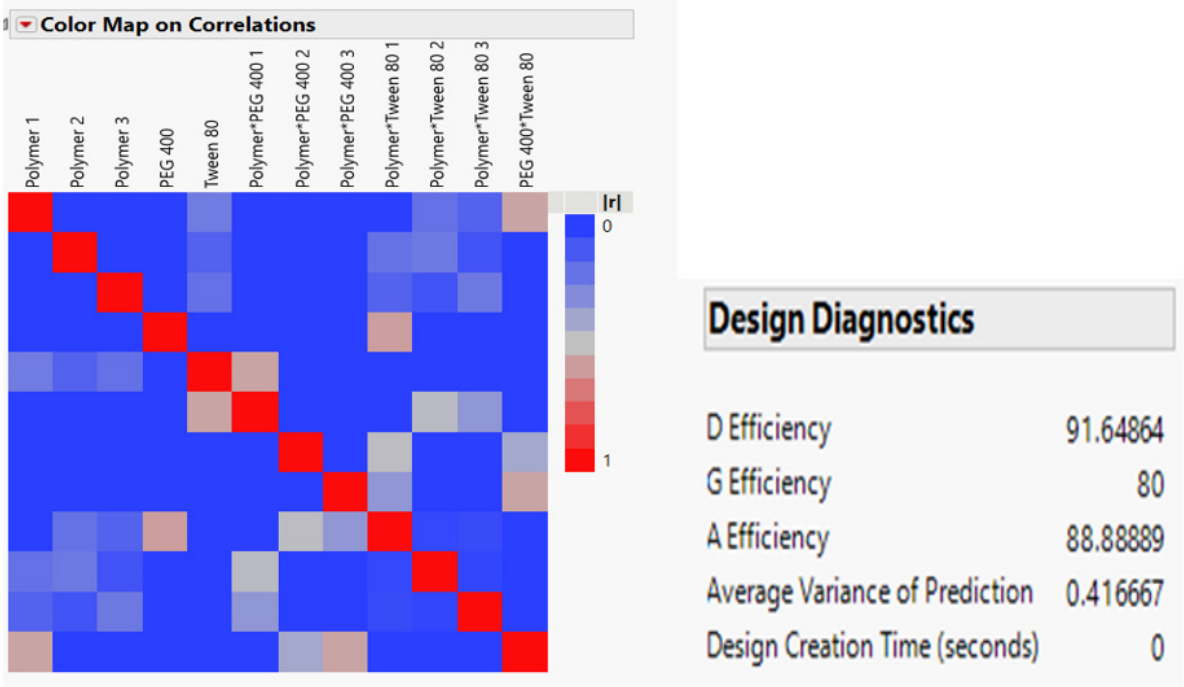

Figure 3: Color Map on Correlations and design diagnostic.

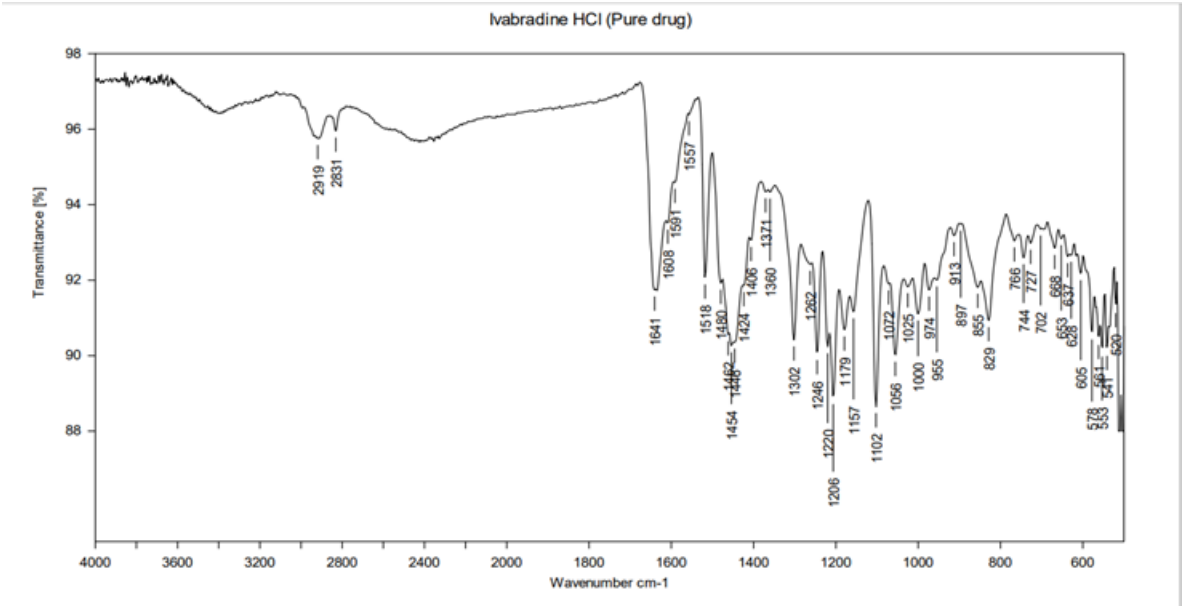

Figure 4: FTIR for Pure drug Ivabradine HCL.

of phosphate buffer (pH 6.8). The concentration of the drug was determined spectrophotometrically (UV-Spectrophotometer, Shimadzu 1700) by measuring absorbance at 281 nm after the solution was filtered.[16]

Estimation of Percentage Drug Release at 15 min

The USP-XXVI dissolution apparatus type-I was used to conduct the *in vitro* dissolution study of FDBFs (basket type). 900 mL of phosphate buffer (pH 6.8) was used as the dissolution medium, which is rotated at a speed of 50 rpm and kept at a constant temperature of 37+/-0.5ºC. Each film was transferred inside the basket firmly. Aliquots of 5 mL from each vessel were taken at predetermined intervals, i.e., 1, 2, 4, 8, 10, 12 and 15 min and then they were filtered and tested for Ivabradine HCl using a Spectrophotometer (Shimadzu-1700) at 281 nm. To maintain the sink condition, fresh buffer (5 mL) was added to the vessels.[17]

Model fit

The various responses obtained for all the 12 formulations of Ivabradine FDBF were incorporated in the design to check the model fit. The data was analyzed statistically by fitting multiple regression models with the intercept set to zero. Statistically

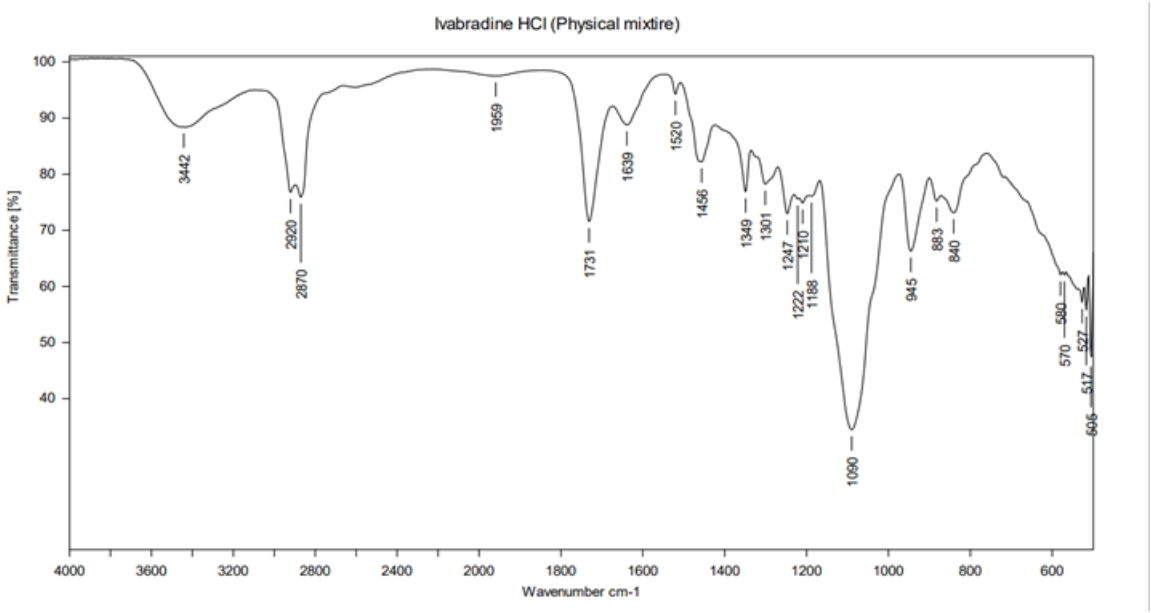

Figure 5: FTIR for Ivabradine HCL and excipients.

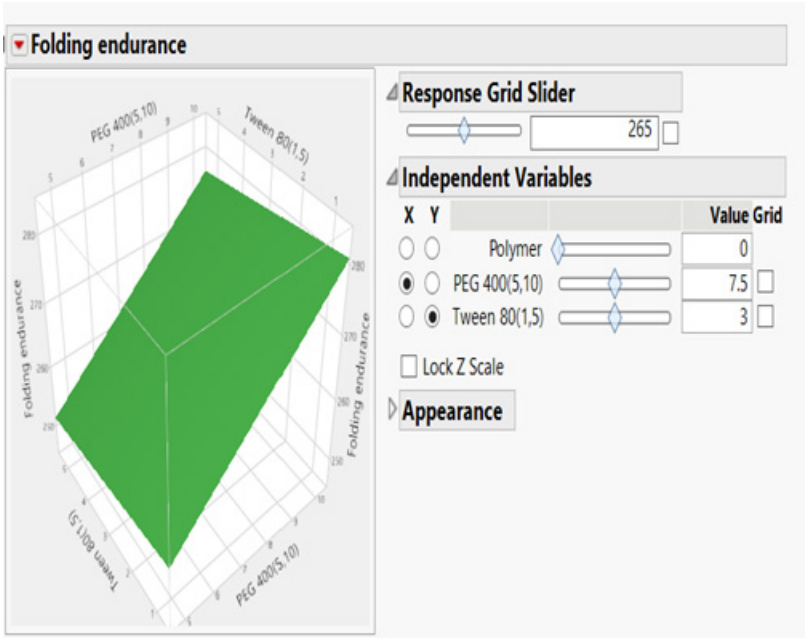

Figure 6: Surface Plot for folding endurance.

significant models were determined for folding endurance, disintegration time, % drug content and % drug release at 15 min. Variables with p values <05 was considered statistically significant. The JMP software was used for the design, analysis and plotting of the various Three-Dimensional (3D) and surface plots. The effects summary obtained for the whole model and the prediction profiler obtained for the individual responses was utilized for the optimization of independent variables factored in the design. With the models developed and validated, the design space was finally set through all individual acceptance regions for each CMA. As per the prediction profiler, the confirmatory experiments for individual response were carried out to validate the model.

Optimization of IVA FDBF-Global Desirability Approach

The simultaneous optimization of IVA-FDBF was done with the help of the Surface profiler and Prediction Profiler obtained for the Main effect screening design. A kind of search-based optimization method making use of desirability functions has been used to find optimal input settings globally. The overall approach is to first convert each response Y into an individual desirability function D. In the present research work, the

Table 7: CQA's for all 12 formulations.

Formulation	Folding Endurance	Disintegration time (sec)	Drug content (percentage)	Drug release at 15 min (percentage)
F1	267±3.605	23±1.74	96.20±0.2	95.90±0.05
F2	265±1.487	29±0.289	97.92±0.594	95.48±0.43
F3	253 ±1.267	26±2.154	94.98±0.03	93.72±0.11
F4	260±2.431	22±0.877	95±0.541	94.24±0.24
F5	244±1.631	22±1.731	97.99±0.015	94.36±0.121
F6	262±1.784	30±0.041	94.19±0.025	94.32±0.022
F7	275±1.527	24±1.594	95.73±0.005	96.50±0.355
F8	254±1.923	24±0.08	97.96±0.02	95.58±0.363
F9	280±2.143	30±1.583	94.15±0.05	95.67±0.184
F10	258±1.547	20±1.734	96.25±0.76	95.15±0.876
F11	276±0.51	28±0.145	94.93±0.04	94.56±0.052
F12	278±2.791	35±0.478	94.90±0.095	94.10±0.288

Table 8: Summary of Model Fit.

Statistical Parameters	Folding endurance	Disintegration time (sec)	% Drug content	% Drug release in 15 min
R Square value	0.9901	0.9936	0.98	0.97
Root Mean Square Error	1.5184	0.4714	0.2815	0.1915
P value	0.0001	0.0001	0.0001	0.0001
Observations	12	12	12	12

Table 9: Confirmatory experimental results as per the prediction profiler.

Responses	Desirability	Predicted value	Experimental value	% Difference
Folding endurance	0.5672	277.5	280	0.89
Disintegration time (in sec)	0.9868	26.5	28	0.05
% Drug content	0.8113	95.88	96.27	0.40
% Drug release in 15 min	0.7452	96.22	98.04	1.87

optimization of formulation was done by desirability function approach (numerical approach). The Optimization was done by attaining the global desirability function for all the responses and which ranges from 0 to 1. The Optimized Formulation (OF) of IVA-FDBF was prepared as per the prediction profiler. The prepared optimized formulation was characterized as per the procedure. The experimental values obtained were compared with the predicted values.

Prediction profiler

The Prediction Process (PP) is a method designed to facilitate the identification of the optimal formulation composition based on target responses. It stands out as an easily applicable technique for predicting the response surface. Specifically developed for Critical Quality Attributes (CQAs), the PP primarily focuses on anticipating values for responses that are of particular concern. In this approach, the predicted values for relevant CQAs are presented in individual plots or graphs. These graphical representations, known as forecasting traces, illustrate the anticipated variability in responses when one variable is slightly altered while keeping the other variables constant at their original values.

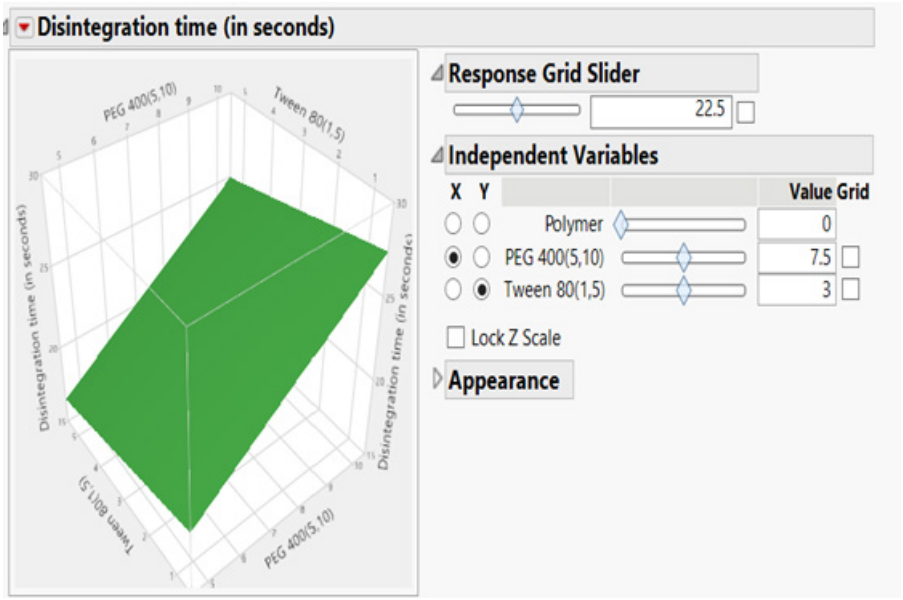

Figure 7: Surface Plot for Disintegration time.

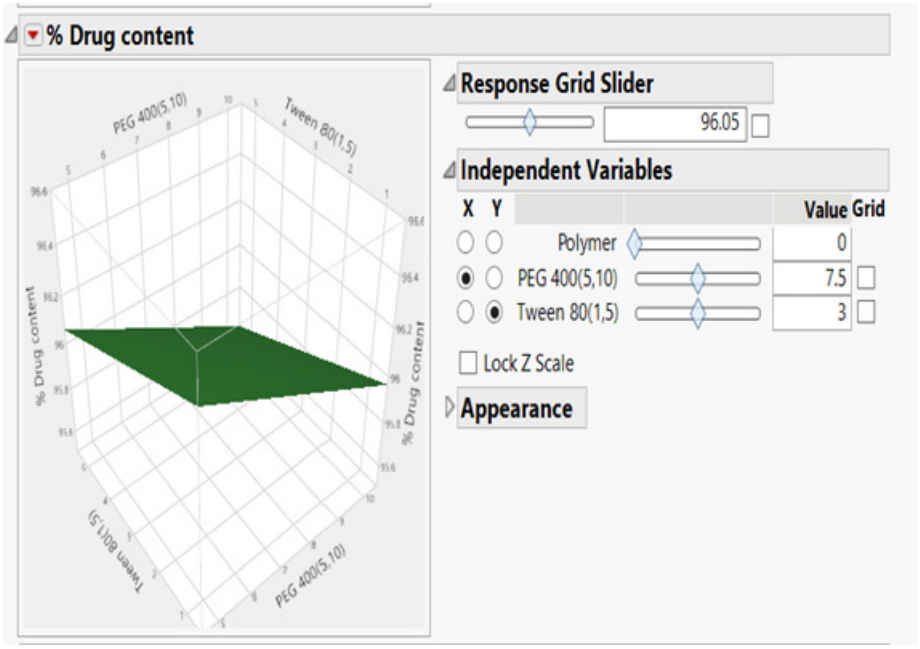

Figure 8: Surface Plot for % Drug Content.

Matching the predicted and experimental values of Optimal formulation (Checking the CQA's)

The predicted responses with maximized desirability of all CQA's such as folding endurance, disintegration time, % drug content, % drug release in 15 min were compared against experimental values and % difference is evaluated.

Evaluation of optimized FDBFs

Physical characterization of oral films

The physical attributes, including color (evaluated through visual inspection), transparency (examined against white light), softness (assessed by touch), peel ability (the ease of film removal after formation and drying) and homogeneity (visually inspected against white light), were assessed for the optimized formulation.[18]

Measurement of Thickness

The thickness of the prepared FDBF film was measured using a screw gauge. Measurements were taken at four different corners of the films and the mean average of these measurements was subsequently calculated.[19]

Estimation of percentage moisture loss

The moisture absorption of the film was determined by placing pre weighed films in a desiccator saturated with a KCL salt solution, ensuring a constant relative humidity of 84%. After 24 hr at room temperature, each film was reweighed. The amount of moisture absorbed by each film was calculated using the following equation.[20]

$$\text{Percentage Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ X } 100$$

Estimation of Surface pH

Each film was adequately moistened with 1 mL of double-distilled water before being given 30 sec in a Petri dish. A pH electrode was in contact with the wet film's surface and a pH metre (pH system 362, Systronics) digitally displayed the pH.[21]

Differential scanning calorimetry

Using differential scanning calorimetry, the thermal behaviour of the drug Ivabradine HCl and optimised batch of Ivabradine Buccal film was examined using DSC 822c, Mettler Toledo. Ivabradine HCl, which had an approximate weight of 2 mg, was added to a pan and hermetically sealed with an aluminum lid. A cutter was used to cut film into tiny pieces. Then, each sample was scanned with nitrogen gas at a flow rate of 20 mL/min and a constant heating rate of 10°C/min at temperatures ranging from 30 to 350°C.[22]

Accelerated Stability study

Following the ICH Q1A (R2) guidelines, accelerated stability studies were performed for optimized FDBF formulation. The formulation was stored under conditions of 25±2°C temperature and a relative humidity of 60±5%. Packaging was done using a polyethylene strip. The formulation was periodically extracted at intervals of 0, 3, 6 and 9 months for assessment of parameters including appearance, folding endurance, disintegration time and drug content.[23]

Prediction of Expiry date

The stability analysis was used in setting dates of the formulation on real time scale and four assay points were taken into consideration for the model fit.

The stability or degradation analysis of the formulated batches was done in accordance with ICH Q1E. As per this guideline a pooled batch sample comprising three batches was used to compute the expiration date. The expiration date was computed using JMP stability tool box using the Stab macro as per the FDA guideline. As per this, three models were fitted as shown below.

Model 1: Utilized discrete slopes and intercept for batches computed.

Model 2: Utilized discrete slopes and common intercept for the batches computed.

Model 3: Utilized common slopes and common slopes for the batches computed.

The goodness of the fit (regression) of the batches computed for the assigned p-value ($p<0.25$) of the above three models was verified and the batches with best goodness of fit was taken as the earliest crossing date of the sample tested.

RESULTS AND DISCUSSION

The QbD method was employed to investigate the FDBF's QTPP and CQAs. The factors that have the most influential effects on the formulation quality of films are most consideration. Thus, the CQAs of Ivabradine HCl FDBF have been found to be folding endurance, disintegration time, percentage drug content and percentage drug release. The experimental design was employed to examine how each independent variable affected individual responses.

Quality Target Product Profile (QTPP)

QTPP was used to determine the preferred dosage form and crucial quality characteristics for Ivabradine HCl (FDBF). Ivabradine HCl's QTPP includes the effective and safe administration of FDBF, which enables quick drug action and boosts patient compliance. The method used to prepare FDBFs was reliable and repeatable, so the finished product satisfies the essential requirements for a drug product. Table 1 lists the QTPP and provides justifications for each choice.

Identification of CQA's

The Quality by Design (QbD) has focused extensively on process design, comprehension and control, equal importance is attributed to the design understanding and control of the product attributes. This is vital as these factors ultimately influence the product's ability to meet patients' requirements and maintain efficacy over its shelf life. Therefore, the consideration of input materials becomes essential, encompassing the identification of their critical attributes, such as physical, chemical, biological or microbiological properties.

Risk Assessment

The risk assessment tools like fishbone diagram, Risk estimation matrix table and Failure mode and effects analysis was extensively utilized in the identification of most critical factors associated with the development of FDBF. The RPN score calculated for each factor enables the identification of process defects

and the quantitative estimation of undesirable effects related to quality and efficacy. As per the RNP score the most critical factors associated with the development of FDBF were Polymer, plasticizer and Surfactant.

Compatibility study- FTIR Spectroscopy

It was clear from Figure 4 that the IR characteristic peaks of the drug Ivabradine hydrochloride indicated the authenticity of the molecule. It was also determined from Figure 5 that there was no chemical interaction. The obtained spectrum clearly shows that there were no appreciable changes in the frequencies, showing that the drug is compatible with all of the excipients used in the formulation.

Checking the CQAs

Physical characterization

All polymeric compositions of Ivabradine HCl loaded films were discovered to be colourless, translucent, soft, peelable, dry, homogeneous and tack free. The prepared films had no stains or dark spots. Comparing films made with Kopulan PG and HPMC 15 cps, the films containing HPMC 15 cps were more flexible and softer, films made with polymer Kopulan PG was stiff and rough. After being pressed for a minute between layers of paper, all films were discovered to be tack free. Additionally, when all films were visually inspected, they all displayed homogeneity and uniform thickness.

Folding Endurance

All 12 formulations of Ivabradine FDBF that were prepared exhibit folding endurance (Table 7) ranging between 244 and 280, signifying excellent mechanical strength and ensuring favorable flexibility. The plasticizer (PEG 400) and the film former (HPMC 15 cps) in addition to Kopulan PG are identified as contributors to the film's flexibility. Achieving a proper concentration of both PEG 400 and HPMC 15 cps is crucial for producing an FDBF with desirable quality.

The study findings indicate that both PEG 400 and HPMC 15 cps positively impact folding endurance (Figure 6). PEG 400 is considered the primary contributor to folding endurance, as it is believed to relax linear polymeric chains, potentially through the formation of hydrogen bonds. This relaxation increases flexibility, leading to higher folding endurance numbers in the final FDBF product.

Disintegration Time

For oral thin films, a desired onset of action is indicated by the Disintegration Time (DT). DT of all Ivabradine HCl prepared FDBF was under 30 sec. Both factors' Polymers: HPMC 15 cps and Kopulan PG and PEG 400 (X1 and X2) contributed to a significantly increase in DT (Y2). The factor Tween 80 (X3) increases the wettability of the optimized film.

A surface plot in Figure 7 shows the influence of various factors on the disintegration time. When regulating the FDBF disintegration time, both factors would be taken into account. However, a high concentration of HPMC 15 cps or Kopulan PG, PEG 400 and Tween 80 would result in films that met the requirements for quick dissolution.

Drug Content (%)

The Figure 8 represents the effect of each factor on the dependent variable drug content. Drug content (%) of all FDBFs ranged from 94.15 to 97.99, demonstrating consistent distribution of Ivabradine all over the film. A high-quality drug ensures dose uniformity and proportionality. The allowed drug content range is 85-115%.

Percentage drug release at 15 min

More than 93.72% of the drug was dissolved within 15 min during *in vitro* dissolution study of all 12 formulations of Ivabradine FDBFs. The plasticizer concentration and the film-forming polymer affect the dissolution process. However, as plasticizer concentration increase along with a rise in drug dissolution, the impact of the plasticizer was comparatively greater (Figure 9).

Model Fit

Statistical analysis of characterization data using regression models revealed significant models for folding endurance, disintegration time, % drug Content, % drug release at 15 min. The actual by predicted plot obtained for the selected CQAs is presented in the Figure 10. The R square value and p- value obtained for each critical quality attribute represents the goodness of the fit.

Effect Summary of CQA's

The interactive report can be shown by selecting Effect Summary (Table 8). The values for the LogWorth (or FDR LogWorth) for the model's impacts are plotted. The report also includes controls that let you add or delete model effects. Automatic updates are made to the model fit report based on modifications made to the Effects Summary report. All the critical factors crossing the blue vertical line indicates goodness of the model fit (Figure 11). The Table 9 summarizes the predicted and experimental values as per the prediction profiler (Figure 12).

Optimized FDBFs formulation

Characterization of optimized batch of FDBF

Thickness

Ivabradine HCl' optimized FDBF (Figure 13) had a thickness of 0.0233 mm±0.03. The plasticizer and film-forming polymer could be responsible for the FDBF's thickness. The findings indicated that the critical parameter HPMC 15 cps is what determines film thickness. Increased concentration of HPMC 15 cps had a

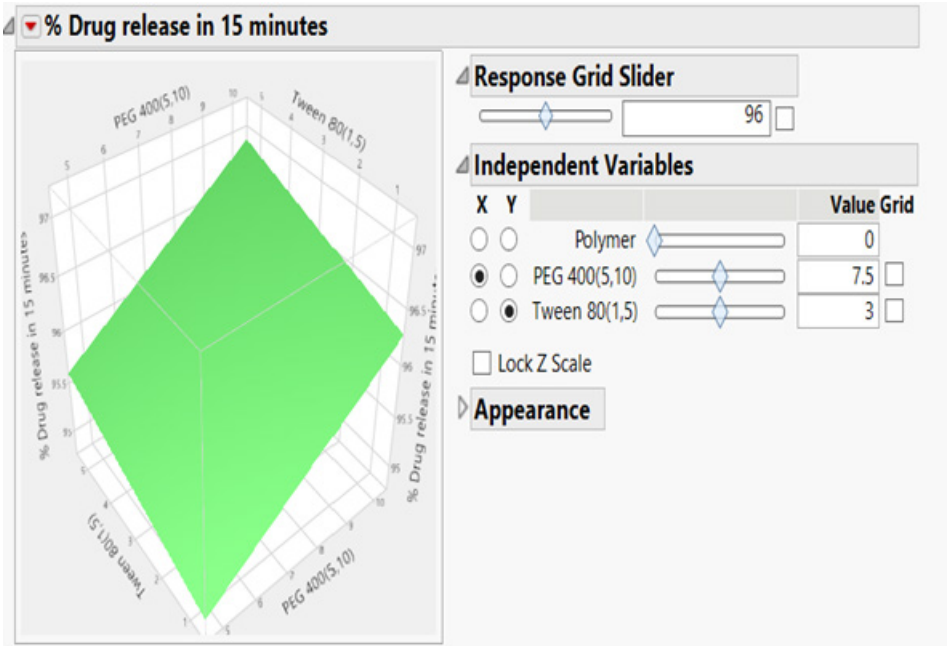

Figure 9: Surface Plot for % drug release at 15 min.

Table 10: **Stability study profile.**

Time in months	Appearance			Folding endurance			Disintegration time (Sec)			% Drug content		
	B1	B2	B3	B1	B2	B3	B1	B2	B3	B1	B2	B3
0	✓	✓	✓	277	275	273	28	26	27	96.27	95.18	96.18
3	✓	✓	✓	274	268	269	29	27	28	96.03	95.23	96.01
6	✓	✓	✓	268	268	267	29	28	29	95.62	94.84	95.48
9	✓	✓	✓	256	255	258	30	28	30	94.13	93.68	94.09

✓ Transparent white, B- Batch.

Table 11: **Degradation analysis data of Optimized-FDBF.**

Models	Display	Intercept	Slope	R Square	Earliest Crossing Time
Model 1	( )	Different	Different	0.98903	16.20712
Model 2	(x)	Different	Common	0.988426	25.03814
Model 3	( )	Common	Common	0.887302	38.69298

Table 12: **Simple Linear Path-Model Summary.**

Parameters	Model 1	Model 2	Model 3
% Drug Content Scale	Linear	Linear	Linear
Time In Months Scale	Linear	Linear	Linear
SSE	0.097198	0.102547	0.998564
Nparm	6	4	2
DF	6	8	10
R Square	0.98903	0.988426	0.887302
MSE	0.0162	0.012818	0.099856

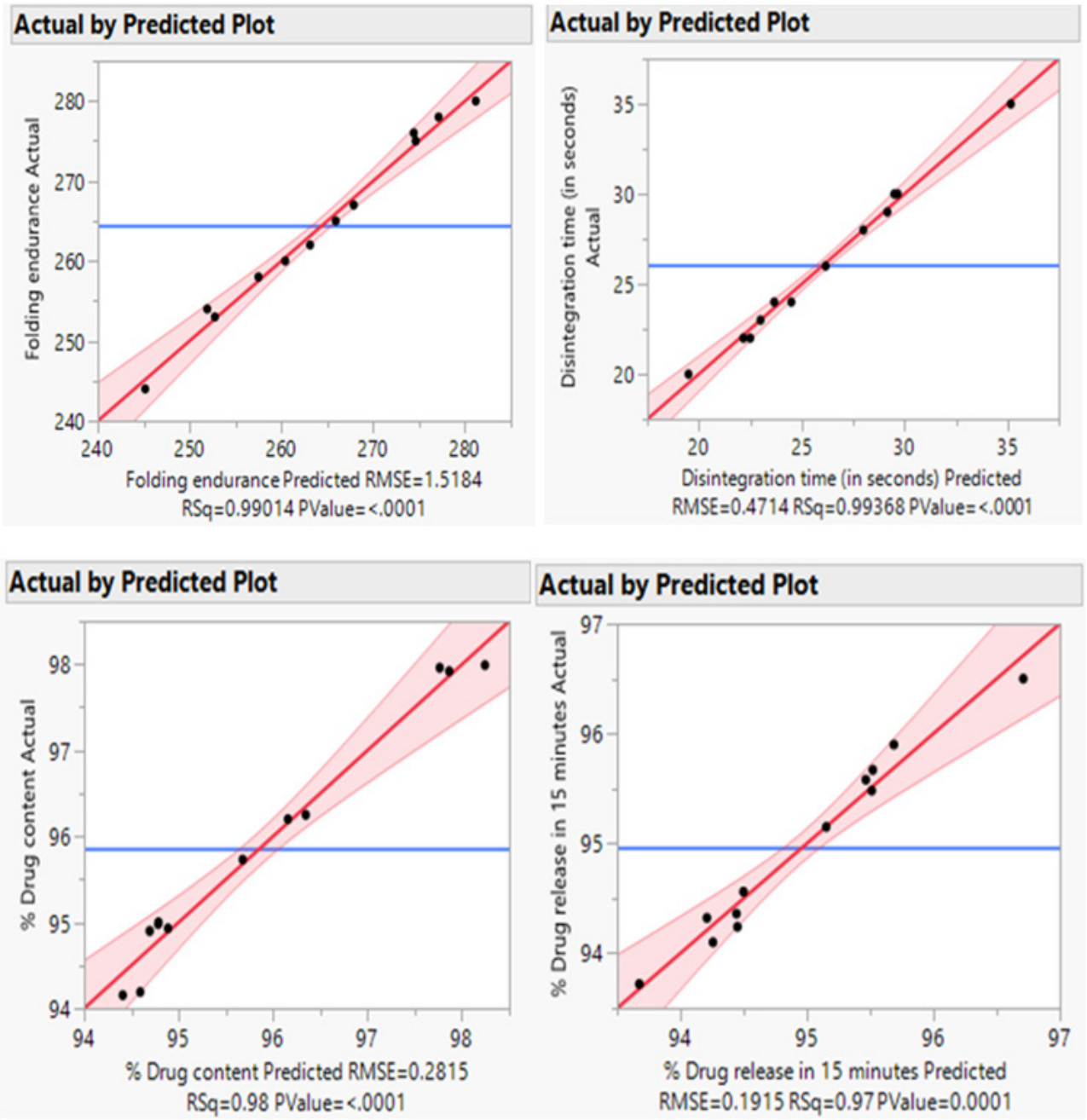

Figure 10: Actual by Predicted Plot for Folding endurance, Disintegration time, Drug content and Drug release.

significant and obvious impact on film thickness. The plasticizer is also thought to take up more space and is in charge of breaking and restructuring the polymer chain, which gives FDBF required thickness.

Moisture Absorption (%)

The film undergoes characteristics changes upon moisture absorption, leading to the formation of a sticky film that may adhere to the patient's hands or the interior of the packaging container. Moreover, moisture presence in the film can impact its disintegration and dissolution tendencies, emphasizing the importance of avoiding moisture. The optimal Moisture absorption of the Film was reported at 2.1%, indicating minimal moisture absorption. Despite being optimized, moisture absorption of the film is acknowledged as a moderately Critical Quality Attribute (CQA) due to its potential impact on product longevity and storage requirements.

Surface pH

The surface pH of optimised formulations was found to be 6.46, which is close to neutral pH values and as a result, no mucosal

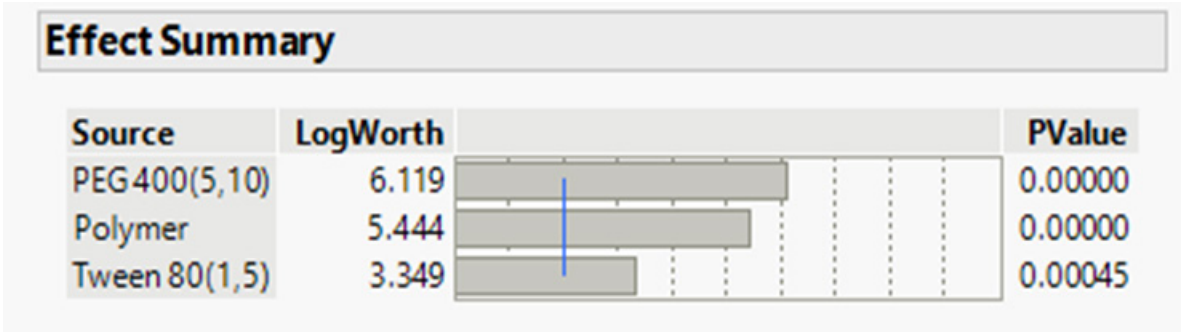

Figure 11: Effect Summary of CQA's.

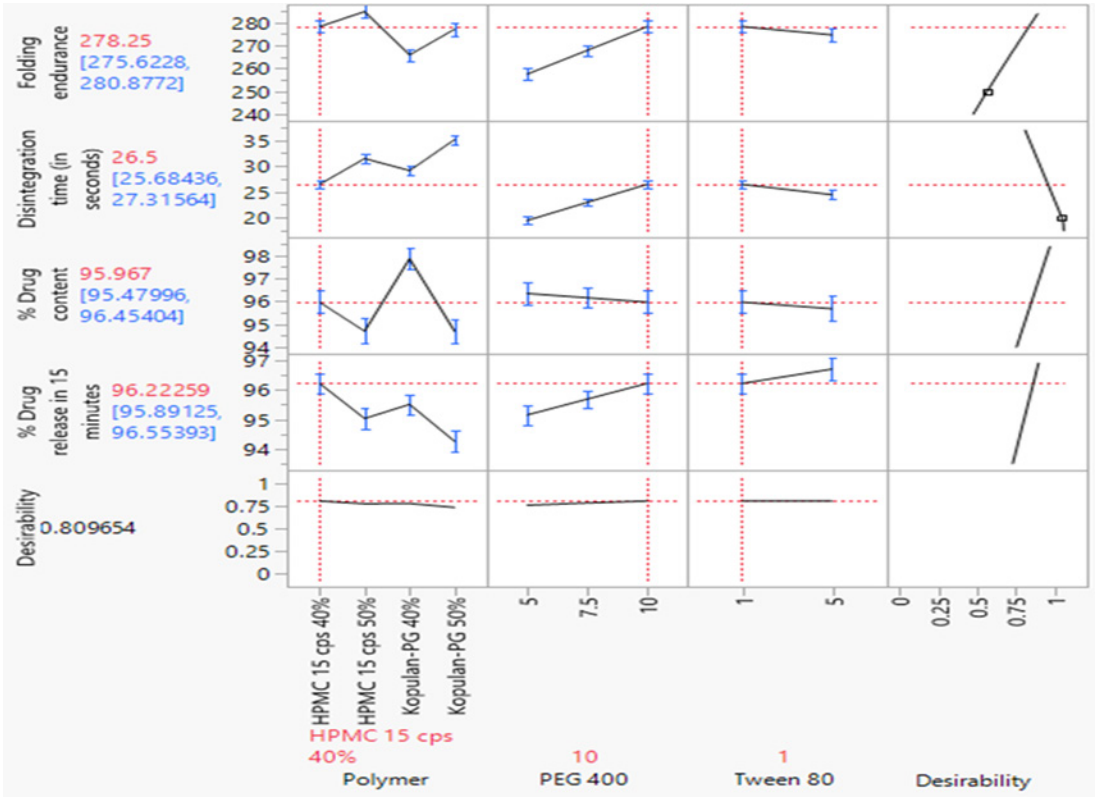

Figure 12: Prediction profiler after optimization.

Figure 13: Optimised batch of Ivabradine FDBF.

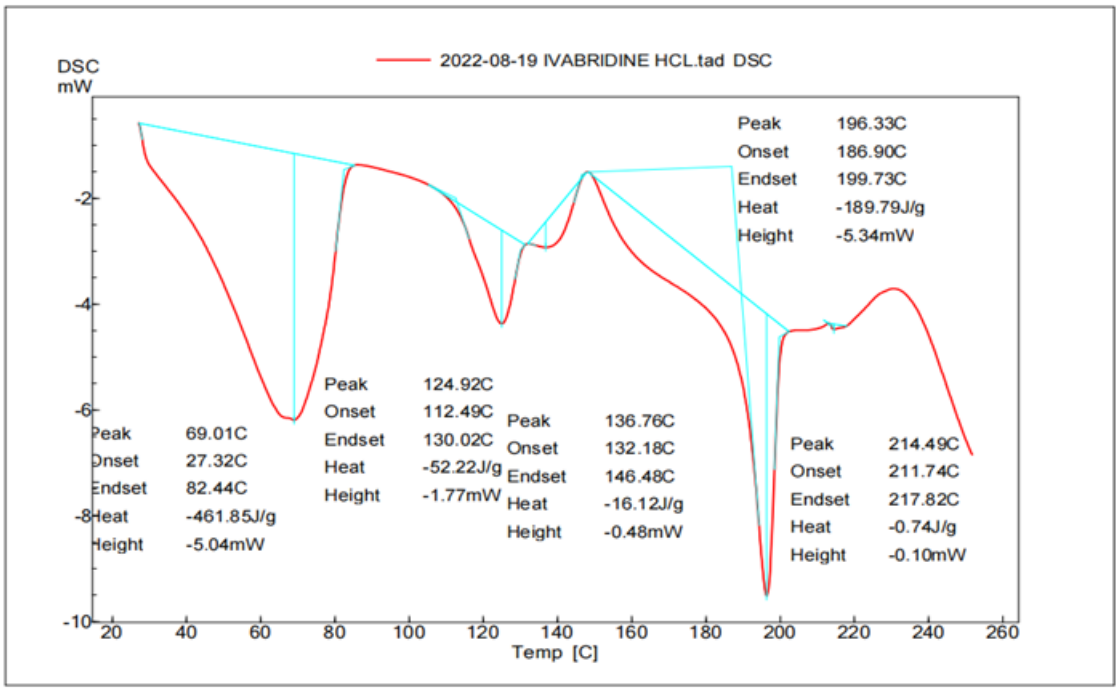

Figure 14: DSC Thermograph of Pure drug Ivabradine HCL.

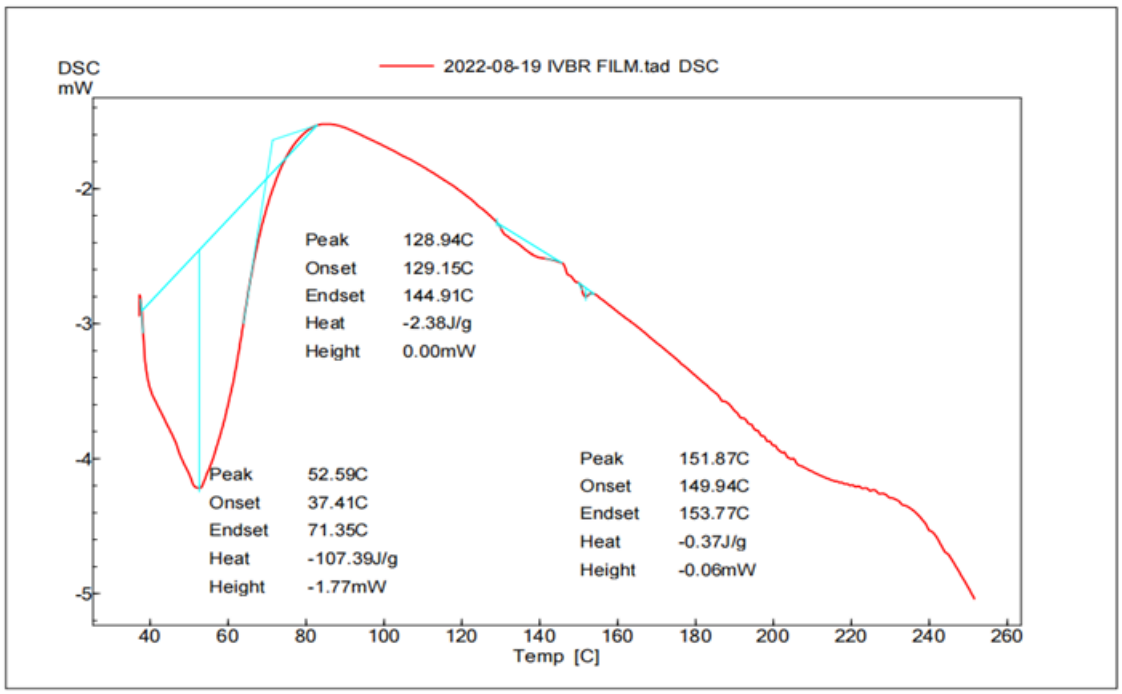

Figure 15: DSC Thermograph of Ivabradine FDBF from optimized batch.

irritation was expected, which promotes patient comfort and compliance.

Differential Scanning Calorimetry (DSC)

Drug Ivabradine HCl and optimized formulation FDBF were undergone DSC scanning and results are depicted in the Figures 14 and 15.

A pure drug's DSC thermograph Ivabradine HCL exhibits the sharp endothermic peak at 196.33°C, which corresponds to the drug's melting point. However, the peak is shadowed in the thermograph of Ivabradine FDBF, this could be due to the conversion of drug to its amorphic form and HPMC is a crystallization inhibitor. As a result, the peak is masked by the excipient effects.

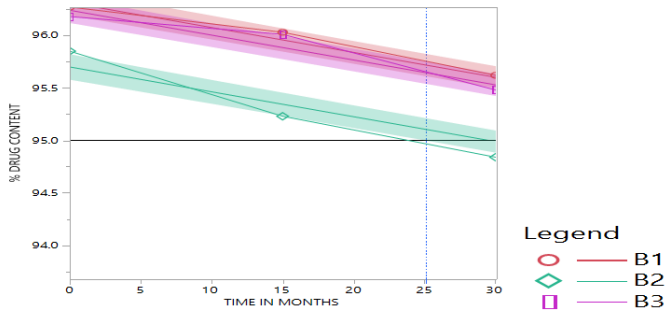

Figure 16: Overlay plot for the degradation analysis of Optimized-FDBF.

Stability Study

Under the selected conditions of temperature (25±2°C) and humidity (60±5% RH), the optimized-FDBF formulation demonstrated both physical and chemical stability (Table 10). A thorough investigation of various factors, including drug content, folding endurance, disintegration time and physical characteristics, showed no significant differences. This suggests that the formulation remains stable under the specified environmental conditions, indicating its suitability for storage and potential use.

Prediction of Expiration date

The overlay plot obtained for degradation analysis is presented in the Figure 16. The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes (Tables 11 and 12). The model suggests the earliest crossing time at 25.03814 with 95% confidence. ICH Guidelines indicate an expiration time of 25.03814 months.

CONCLUSION

The quality by design approach used successfully in order to develop and optimize FDBF of Ivabradine HCl. ANOVA study revealed the model fit the stated work well; in addition, Prediction Profiler aids in predicting the ideal set of factors that will produce the desired targeted responses. The trials with the suitable experimental model was aided by JMP® software. Excellent characteristics of the optimized FDBF includes the drug release of 98.04% in 15 min. Drug is distributed uniformly throughout the film formulation. Additionally, stability testing supported the robustness of the optimized Ivabradine HCl FDBF. With higher patient compliance, FDBF could be viewed as the promising alternative for its administration.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ANOVA: Analysis of variance; **API:** Active pharmaceutical ingredient; **BCS:** Biopharmaceutical classification system; **CMA:** Critical material attributes; **CPP:** Critical process parameters; **CQA:** Critical quality attributes; **DOE:** Design of experiment; **DSC:** Differential scanning colorimetry; **FDA:** Food and drugs administration; **FDFF:** Fast Dissolving Buccal Film; **GIT:** Gastro intestinal tract; **HPMC:** Hydroxy propyl methyl cellulose; **HCN:** Hydrogen cyanide; **PEG:** Poly ethylene glycol; **QbD:** Quality by design; **QTPP:** Quality target product profile.

SUMMARY

This study aimed to develop a fast-dissolving buccal film of the BCS Class I anti-anginal drug Ivabradine hydrochloride using the Quality by Design (QbD) approach. QbD is a systematic method that starts with predefined goals and involves understanding product and process management. Design of Experiments (DOE) was used to assess the relationship between various variables affecting the Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA). Main effect screening design was utilized to identify critical variables affecting the desired response, and risk assessment was conducted using tools like fishbone diagrams and risk evaluation matrix.The software tools were employed to evaluate statistically the efficiency and suitability of the design. Twelve different formulations were tested for parameters like drug content, disintegration time, folding endurance, and drug release. Data from these tests were integrated using the Main effect Screening Design (MESD), and statistically significant models were obtained for key quality attributes. The optimized formulation demonstrated desirable characteristics in physical and chemical tests, indicating successful application of QbD in developing the Ivabradine hydrochloride formulation.

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