# OPTIMIZATION OF LABETALOL HCL FILM BY USING QBD

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## ABSTRACT

The present study was undertaken to develop and optimize Labetalol hydrochloride (HCl) loaded mouth dissolving film (MDF) using a Quality by Design (QbD) approach. Labetalol HCl is an antihypertensive drug with rapid gastrointestinal absorption but limited oral bioavailability due to extensive first-pass metabolism. Mouth dissolving films offer a convenient oral dosage form that rapidly disintegrates in the oral cavity and can improve ease of administration and patient compliance. In the present investigation, the QbD framework was applied by defining the Quality Target Product Profile (QTPP), identifying critical quality attributes (CQAs), performing risk assessment, and selecting critical formulation variables. A solvent casting method was selected for fabrication of the Labetalol HCl loaded MDF. Hydroxypropyl methylcellulose E15 (HPMC E15), polyethylene glycol 4000 (PEG 4000), and sodium lauryl sulfate (SLS) were selected as independent formulation variables. A Box-Behnken Design (BBD) was employed to investigate the influence of these variables on film thickness, folding endurance, and *in-vitro* drug release. Fifteen experimental batches (MQA301–MQA315) were prepared and evaluated, followed by preparation of the optimized formulation, MQA316. The optimized formulation consisted of HPMC E15 (331.947 mg), PEG 4000 (290.000 mg), and SLS (163.748 mg). The software-predicted values for thickness, folding endurance, and drug release were 100.44 µm, 210 folds, and 96.36%, respectively. The observed values for the optimized MQA316 formulation were 99.2 ± 0.4 µm thickness, 209 ± 0.816 folds folding endurance, and 95.90% drug release. The formulation exhibited a disintegration time of 27 ± 0.81 seconds, drug content of 99.17%, surface pH of 6.75 ± 0.07, and acceptable weight variation. SEM analysis revealed a smooth film surface with few small pores. DSC and XRD studies indicated a reduction in drug crystallinity and conversion toward an amorphous state, while FTIR analysis indicated compatibility between the drug and excipients. Accelerated stability testing at 40 ± 2°C/75 ± 5% RH for three months showed no significant deterioration in the evaluated quality attributes. The close agreement between predicted and observed responses demonstrated the suitability of the QbD-based BBD approach for optimization of Labetalol HCl MDF.

**Keywords:** Labetalol hydrochloride; Mouth dissolving film; Quality by Design; Box-Behnken Design; Design of Experiments; HPMC E15; PEG 4000; Sodium lauryl sulfate.

## 1. INTRODUCTION

Quality by design (QbD) is a methodology used to build quality into products, by design. The QbD approach is used to ensure the pharmaceutical development is conducted in arrange to have in the end a systematic understanding of how process parameters affect a product **(Silva *et al.*, 2017).** According to ICH (International Conference Harmonization) Q8, QbD can be defined as “a systematic approach towards development that begins with predefined

objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" **(Patil and Pethe, 2013).** A very common tool or element used in the QbD is the quality target product profile (QTPP), which can be defined as "a dynamic product description that summarizes the quality characteristics expected to guarantee the product performance, stability, safety, and efficiency". Mainly, QTPP includes the critical quality attributes (CQAs) and critical process parameters (CPPs). CQAs might be continued as attributes that characteristic of product quality and CPPs refers to critical process parameters or variables that can impact these characteristics. Therefore, the mix of the CQAs and CPPs allows the explanation of design space. The preparation of FDBF and QTPP may be organized based on earlier reported studies considering the essential requirements for manufacturing as well as techniques available for its characterization to get the desired film properties. A prepared FDBF should be handled without being harmed, ought to be physically stable and give a simple and pleasant administration. These properties may be translated into product quality attributes, such as appropriate organoleptic and mechanical properties **(Borges *et al.*, 2016).**

Transdermal drug delivery systems have gained considerable attention as an alternative to conventional oral administration because they can provide controlled and sustained drug release, avoid gastrointestinal degradation, reduce hepatic first-pass metabolism, and potentially improve patient compliance **(Alkilani *et al.*, 2022).** Among various transdermal systems, polymeric films are attractive because of their flexibility, ease of application, relatively simple manufacturing process, and ability to incorporate drug with suitable penetration-enhancing and film-forming agents. The development of an optimized Labetalol HCl transdermal film may therefore provide a promising approach for achieving prolonged drug release and maintaining more consistent drug concentrations **(Kotnala *et al.*, 2025).**

Labetalol hydrochloride, 2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl]-benzamide, a non-selective α, β-adrenoceptor antagonist which is used in the treatment of hypertension **(Jayanthi, 2018).** It is appreciably soluble in lower and higher pH solutions, with minimum solubility between pH 6 to 10. The drug shows variable bioavailability ranging from 10-80% which may be attributed to its instability in alkaline pH and poor absorption due to precipitation. It is administered in doses ranging from 50-200 mg twice a day due to its shorter half life of 3-6 hrs suggesting the need for sustained release formulation **(Murakami *et al.*, 2021).**

Labetalol HCl is administered orally in conventional tablet dosage forms as well as by other routes when rapid blood-pressure control is required. Following oral administration, the drug is absorbed from the gastrointestinal tract; however, its systemic availability is influenced by extensive hepatic first-pass metabolism **(Abdullah and Yusof, 2019).** Consequently, only a fraction of the administered dose reaches systemic circulation in unchanged form. Variability in absorption and metabolism may contribute to variations in plasma drug concentrations and therapeutic response. In addition, conventional oral dosage forms require swallowing with or without water and may not always be convenient for patients who have difficulty swallowing tablets **(Bow and Blomme, 2026).**

In the present study, a QbD-based approach was employed for the development and optimization of Labetalol HCl polymeric film. Appropriate polymers and other formulation components were selected based on their functional properties, while critical formulation

variables were systematically investigated using Design of Experiments. The developed films were evaluated for physicochemical and mechanical properties, drug content, *in-vitro* drug release, and other relevant performance characteristics. The optimized formulation was subsequently identified based on predefined acceptance criteria for the CQAs. The study aims to demonstrate the applicability of the QbD approach in developing a robust Labetalol HCl film with desirable quality attributes, reproducible performance, and potential suitability for transdermal drug delivery.

## 2. MATERIALS AND METHODS

### 2.1 Chemicals

Labetalol hydrochloride were obtained from Swapnroop Drugs & Pharmaceuticals Aurangabad, India, a reputable supplier of analytical reagents. Loba chemie pvt.ltd. Mumbai, India provided the HPMC E15, SLS, Citric Acid, Vanillin, Xylitol, Propylparaben, Methanol, Potassium dihydrogen phosphate and Disodium hydrogen phosphate. Chemdyes Corporation pvt. Ltd. Gujarat, India provided the PEG 4000.

### 2.2 Preformulation Studies of Labetalol Hydrochloride

The preformulation studies of Labetalol hydrochloride was carried out through organoleptic and physicochemical characterization for the compatibility studies of drug and excipients.

#### 2.2.1 Organoleptic Characteristics

Organoleptic characteristics such as color, texture, and odor of the drug substance were determined **(McMahon, 2008).**

### 2.3 Evaluation of Physicochemical Properties and Analytical Characteristics

Physicochemical properties such as melting point and solubility. Analytical characteristics such as UV-visible spectrophotometric analysis, DSC, XRD, and FT-IR studies were carried out for the quality evaluation and characterization of Labetalol hydrochloride.

#### 2.3.1 Melting Point

The melting point of Labetalol hydrochloride was determined using a melting point apparatus.

#### 2.3.2 Solubility Profile

The solubility of the drug was determined in distilled water, phosphate buffer pH 6.8, and methanol, as per standard protocol and pharmacopoeia **(Segall, 2023).**

#### 2.3.3 UV Spectroscopy

- **Detection of $\lambda_{max}$**

A standard stock solution of drug was prepared by dissolving accurately weighed 5 mg of drug in 5 ml of distilled water (Solution A, i.e., 1000 µg/ml) and then 1ml of this solution was diluted to 10ml with distilled water (Solution B, i.e., 100 µg/ml). From this solution, further dilutions of 5, 10, 15, 20, 25 µg/ml were prepared, and $\lambda_{max}$ was determined by using scanning mode of UV-visible spectrophotometer.

- **Calibration Curve in Methanol**

A standard stock solution of drug was prepared by dissolving accurately weighed 5 mg of drug in 5 ml of methanol (Solution A, i.e., 1000 µg/ml) and then 1ml of this solution was diluted to 10ml with methanol (Solution B, i.e., 100 µg/ml). Different aliquots of solution B were diluted up to 10 ml with methanol so as to get solutions of 5, 10, 15, 20, and 25 µg/ml concentration. Absorbance of each of the above dilutions were measured at the detection wavelength.

➢ **Calibration Curve in Phosphate Buffer pH 6.8**

A standard stock solution of drug was prepared by dissolving accurately weighed 5 mg of drug in 5 ml of phosphate buffer pH 6.8 (Solution A, i.e., 1000 µg/ml) and then 1ml of this solution was diluted to 10ml with phosphate buffer pH 6.8 (Solution B, i.e., 100 µg/ml). Different aliquots of solution B were diluted up to 10 ml with phosphate buffer pH 6.8 so as to get solutions of 5, 10, 15, 20, and 25 µg/ml concentration. Absorbance of each of the above dilution was measured at the detection wavelength **(Zinjad *et al.*, 2019).**

**2.3.4 X-Ray Diffraction (XRD)**

Crystallinity of Labetalol hydrochloride was evaluated by using X-ray diffractometer, using Nifiltered Cu-K a radiation source. The tube voltage of 40 kV, tube current 30 mA and scanning rate 5°C/min over a range of 5-40° of 2θ diffraction angle at room temperature, patterns were formed with a step width of 0.04°C.

**2.3.5 Differential Scanning Calorimetry (DSC)**

Thermal analysis of Labetalol hydrochloride, was carried out using differential scanning calorimetric method. Samples equivalent to approximately 3.7 mg Labetalol hydrochloride was placed in thermetically sealed aluminium pans and heated over the temperature range of 25°C-250°C at a constant rate of 40°C/min under a nitrogen purge (20 ml/min).

**2.3.6 FTIR Spectroscopy**

The FTIR spectrophotometer was used to record the FTIR spectra of Labetalol hydrochloride at room temperature in the 4000-400 $cm^{-1}$ ranges. The sample was made by grinding it with dry KBr powder and compressing the powder in a hydraulic press **(Sládková *et al.*, 2017).**

**2.4 Selection of Process for the Fabrication of MDF**

There were various methods that could be used for the fabrication of MDF. Among those, the solvent casting method was selected as it was easy and most suitable for Labetalol hydrochloride loaded MDF formulation on the basis of literature survey, drug-excipient characteristics and availability of materials. In this method, a water-soluble polymer and plasticizer were dissolved in water, while the remaining excipients were separately dissolved. These solutions were then carefully mixed together with continuous stirring at 40°C and 300 rpm. During this blending process, the drug, dissolved in a suitable solvent, was slowly added while maintaining constant stirring. A vacuum was employed to remove any trapped air. The resulting solution was poured into molds, allowed to dry, and subsequently cut into the desired sizes and shapes **(Singh *et al.*, 2012).**

**2.5 Design and Development of MDF Using QbD Approach**

Steps involve in QbD approach were shown below:

**Step 1:** To establish a quality target product profile **(**QTPP) for the MDF.

**Step 2:** Determination of the critical quality attributes **(**CQAs) of the MDF.

**Step 3:** Incorporated a risk assessment exercise to identify the Critical Process Parameters **(**CPPs).

**Step 4:** Involved drafting an informal design of experiment (DoE) to determine optimal settings.

**2.5.1 Defining the Quality Target Product Profile (QTPP)**

The QTPP refers to a set of predefined characteristics and attributes that the final product was intended to have in order to meet specific quality and performance criteria. The QTPP criteria

for the development of MDF was identified using the results of the literature study and an awareness of the characteristics of the product and process **(Joshi *et al.*, 2012).**

**2.5.2 Identifying the Critical Quality Attributes (CQA)**

The CQAs indicate characteristics that have a significant impact on product performance. It ought to be chosen taking into account QTPP requirements. The CQAs taken into account for the creation of MDF include thickness, surface pH, *In-vitro* disintegration time, folding endurance, *In-vitro* dissolution, tensile strength, etc **(Shantilal *et al.*, 2021).**

**2.5.3 Identification of Critical Material Attributes (CMA) and Critical Process Parameters (CPP)**

The third step in drug development based on QbD was determining CMAs and CPPs. The CMAs and CPPs were identified based on the literature study and their impact on the CQAs. Concentration of Polymer, Plasticizer, Surfactant, and Nature of Excipients were the CMA's optimized parameters. Stirring speed, stirring time, stirring temperature and drying time were the CPPs under investigation. For the purpose of achieving the target quality, CPPs were chosen depending on the process parameter whose variability has an effect on CQAs **(Saxena *et al.*, 2023).**

**2.5.4 Risk Assessment Studies and Screening of Factors for MDF**

Risk assessment studies were carried out to pinpoint CMAs or CPPs with a significant impact on the CQAs of MDF. Potential high-risk factors that could influence the quality of the final MDF formulation were catalogued using an Ishikawa fishbone diagram. Risk levels for both formulation and process parameters were documented in the risk estimation matrix (REM), with each attribute classified as low, medium, or high risk based on its influence on CQAs. Parameters assessed as high risk were further investigated using the DoE to establish the design space **(Mehrotra and Kumar, 2023).**

**2.6 Optimization of Formulation**

The formulation optimization was typically done by simply adjusting each variable separately. However, it is difficult to develop an ideal formulation since the technique provides no information about how the variables interact. Therefore, to reduce the number of runs and errors, a computer-aided optimization process was used and for that Design Expert 13.0.15 (Stat-Ease) was utilized **(Sahoo *et al.*, 2022).**

**2.6.1 Selection of Experimental Design**

There were various experimental designs including full factorial, central composite, boxbehnken, mixture and D-optimal were considered useful for the computer-aided optimization process of MDF. Among those, on the basis of literature survey the most appropriate design was chosen and applied to optimize the MDF formulation of Labetalol HCl **(Patel *et al.*, 2023).**

**2.6.2 Selection of Independent variables and Dependent or Response variables**

Based on the literature review independent variables were selected and the values of the independent variables were taken on the basis of hit and trial method and were set at low (-1) medium (0) and high (+1) levels. While response variables were selected on the basis of significant impact of independent variables on the fabrication and performance of the final MDF formulation **(Liu *et al.*, 2021).**

### 2.6.3 Fabrication and Characterization of Batches of MDF of Labetalol Hydrochloride Suggested by Selected Experimental Design

On the basis of numerous independent variables, the selected experimental design offered several batches of MDF having different combinations. The MDF batches were prepared and evaluated for selected dependent variables. Total fifteen batches were prepared on the basis of recommendation of software and labelled as MQA301-MQA315. The batches were evaluated to formulate an optimized batch MQA316 similarly.

### 2.6.4 Statistical Analysis for MDF Formulation

- **Fit Summary**

The Fit Summary compiles the crucial facts required to choose the ideal model's initial condition. "The Whitcomb Score" was used to select the suggested model or models. The proposed model ought to be regarded as an ideal spot to start for the model fitting **(Soni *et al.*, 2021).**

- **Sequential Sum of Squares**

Sequential sum of square analyses the response's variability so that the error can be reduced. A sequential sum of squares calculates the amount of variance that may be explained (increased regression sum of squares) or alternately, the amount of error that can be decreased (decreased error sum of squares) **(Xu, 2017).**

- **Analysis of Variance (ANOVA)**

The ANOVA studies were generated from the software to evaluate the p-values, F-ratio, and lack of fit. In order to assess how well the experimental data fit, the regression coefficient ($R^2$) and adjusted $R^2$ were calculated. The following regression equation was used for prediction of the responses,

The polynomial equation generated by this experimental design is given as,

$R = \beta0+\beta1\ A+\beta2\ B+\beta3\ C+\beta12\ AB+\beta13\ AC+\beta23\ BC+\beta11\ A2+\beta22\ B2+\beta33\ C2$

Where R was the response and A, B, and C were the response factors and $\beta_0$, $\beta_1$, $\beta_2$ and $\beta_3$ were the linear coefficients of the factors. $\beta_{12}$, $\beta_{13}$ and $\beta_{23}$ were the interaction coefficients and $\beta_{11}$, $\beta_{22}$ and $\beta_{33}$ were the quadratic coefficients **(Reji *et al.*, 2022).**

- **Response Surface Analysis for MDF Formulation**

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

- **3D Response Surface**

Three-dimensional (3D) response surface plots were utilized to understand how the elements studied in mulch interact with each other, influencing their responses and correlations.

- **2D Contour Plot**

The two-dimensional (2D) contour plot was used to demonstrate the connection between the responses, mixture elements, and/or numerical factors.

- **Perturbation Graph**

The perturbation plot simplifies the process of comparing the influence of each factor at a particular point within the design space. When plotting the response, one element was varied across its range, while the remaining variables were held constant. The reference point was set by "Stat-Ease" to be the middle (coded 0) for all the factors by default.

- **Diagnostic Analysis**

Regression quality was evaluated using residual plots. To verify the accuracy of these assumptions and provide guidance on how to improve the model, various residual plot types can be utilised **(Selvamuthu *et al.*, 2018).**

- **Normal Plot of Residuals**

A normal plot of residuals, also known as a normal probability plot of standardized residuals, was a graphical tool used in statistics to assess whether the residuals from a regression or statistical model followed a normal distribution. Residuals were the differences between observed data points and the values predicted by a statistical model.

- **Residuals vs Predicted**

The residuals were plotted against the descending expected response values in this graph, it serves as a visual verification for the constant variance assumption.

Residuals vs Run

The plot was used to view a very helpful plot known as "Outlier t" that displays how many standard deviations a particular run deviates from what one would anticipate from all the others **(Hussain *et al.*, 2022).**

- **Predicted vs Actual**

A comparison graph between the observed (actual) and projected response levels. It aids in identifying observations that the model does not accurately predict.

**2.7 Formulation of Optimized MDF Formulation of Labetalol Hydrochloride**

In order to find out the optimized composition of Labetalol hydrochloride loaded MDF, the desired constraints for response variables were set and accordingly fed into the software. Considering the desired constraint, the software generates distinct formulations. The formulation with maximum desirability was fabricated

**2.8 Characterization of Optimized Labetalol Hydrochloride Loaded MDF**

**2.8.1 Measurement of Thickness**

The thickness of the formulation was determined using a digital vernier caliper (Figure 9). Measurements were taken at 5 distinct points on the film i.e., central and each of the four corners of the film. Subsequently, the mean thickness was calculated. For measurement of uniformity of thickness, 3 films were randomly selected from each batch, and their thickness was measured **(Martin *et al.*, 2017).**

**2.8.2 *In-vitro* Drug Dissolution Study**

An *In-vitro* dissolution study of the MDF was conducted using a USP dissolution apparatus type-I (basket type) as illustrated in the Figure 10. The dissolution medium consisted of 300 mL of phosphate buffer (pH 6.8) and was maintained at 37°C ± 0.5°C with a rotation speed of 50 rpm. Each film was securely placed inside the basket. At specific time intervals (0.5, 1, 2, 4, 8, and 10 minutes), 5 mL aliquots were withdrawn from each vessel, filtered, and subsequently subjected to analysis for Labetalol HCl using a spectrophotometer (Shimadzu-1800) at 302 nm. To maintain the sink condition, the volume in each vessel was replenished with 5 mL of fresh buffer **(Upreti *et al.*, 2014).**

**2.8.3 Estimation of Folding Endurance**

The folding endurance of the MDF was assessed by repeatedly folding it at a specific point until it reached a point of breakage or showed signs of damage. The recorded value for folding endurance indicates the total number of complete folding cycles accomplished before

failure occurred. A greater folding endurance value suggests robust mechanical characteristics and increased resilience for the MDF.

**2.8.4 Estimation of Drug Content Uniformity**

Drug content uniformity was assessed to ensure the even distribution of the drug within the films. This involved dissolving each film completely by stirring it in a volumetric flask filled with 10 ml of 6.8 pH phosphate buffer. The filtered solution was then utilized for measuring the absorbance at 302 nm to estimate the drug concentration, employing a Shimadzu 1800 UV-Spectrophotometer **(Zayed *et al.*, 2020).**

**2.8.5 Estimation of pH**

The pH of the MDF was determined by using a calibrated pH meter. Initially, the film was dissolved in 5 ml of phosphate buffer (pH 6.8). Subsequently, the pH of this solution was measured using a calibrated pH meter. This method was employed to ensure precise measurement of the pH of the MDF, a critical factor in evaluating its suitability for the oral cavity and its potential influence on taste and comfort during usage.

**2.8.6 Estimation of Weight Variation**

The weight variation test validates the uniformity of the fabricated MDF. Three film samples, each with an area of 6 $cm^2$ (2 cm x 3 cm), were individually extracted from each batch. The weight of each sample was measured, and the standard deviation of these measurements was computed. The average weight of the film should not exceed a deviation of ±7.5% **(Ouda *et al.*, 2020).**

**2.8.7 Estimation of Disintegration Time**

It is the point at which film begins to breakdown when exposed to water. The film was placed in a Petri dish containing 25 mL of water, and the time after the film completely disintegrated or collapsed was recorded. 30 seconds or less is thought to be the ideal disintegration time for MDF.

**2.8.8 SEM of Optimized MDF**

SEM allows for high-resolution imaging, which can reveal the surface morphology of the MDF. This is important for understanding its texture, smoothness, presence of any irregularity, and uniform distribution of the drug throughout the film formulation.

**2.8.9 DSC of Optimized MDF**

Thermal characterization was evaluated using the DSC analysis. MDF was cut into fine pieces using a sharp cutter, placed in thermetically sealed aluminium pans, and heated over a temperature range of 25°C–250°C at a constant rate of 40°C/min under a nitrogen purge (20 ml/min) **(Kukal, 2026).**

**2.8.10 FTIR of Optimized MDF**

The FTIR spectrophotometer was used to record the FTIR spectra of Labetalol hydrochloride loaded MDF 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.

**2.8.11 XRD of Optimized MDF**

XRD was performed to study the crystalline behavior of the drug after formulating it into a final formulation. The MDF underwent XRD analysis using an X-ray powder diffractometer equipped with a conventional Cu sealed X-ray tube, operated at a voltage of 40 kV and a current of 30 mA. The XRD profiles were registered within the $2\theta$ range, employing a scanning rate of 4°/min **(Senthilkumar and Vijaya, 2015).**

### 2.8.12 Stability Study of MDF

To ascertain the impact of temperature on MDF stability throughout the specified duration, a stability analysis of the optimized formulation was performed. The formulation, enclosed in between two aluminium layers, was subjected to three months of accelerated stability testing at temperature 40±2°C and 75±5% relative humidity in accordance with ICH guidelines. At certain intervals of time (1 month, 2 months and 3 months.), samples were taken out, and physical and chemical characteristics such as thickness, disintegration time, surface pH, drug content, weight variation, folding endurance and *in-vitro* drug release were examined **(Majeed *et al.*, 2017).**

## 3. RESULT AND DISCUSSION

### 3.1 Preformulation Studies of Labetalol Hydrochloride

### 3.1.1 Organoleptic Characteristics

**Table 1: Organoleptic Characteristics of Labetalol Hydrochloride**

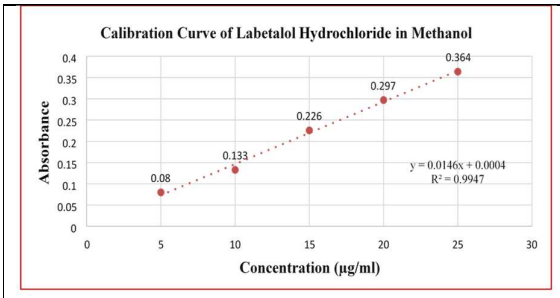
| Properties | Observation |
|---|---|
| Color | White to off-white |
| Texture | Crystalline powder |
| Odor | Odorless |
| Taste | Slightly bitter |

### 3.1.2 Melting Point

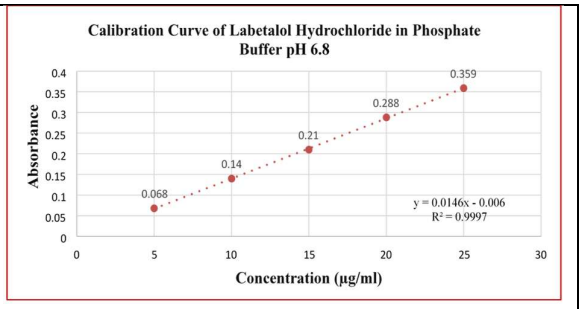
**Table 2: Melting Point of Labetalol Hydrochloride**

| Melting Range | | Average |
|---|---|---|
| Starting point | End point | |
| 183°C | 185°C | 184°C |
| 184°C | 185°C | 184.5°C |
| 182.5°C | 186°C | 184.25°C |

### 3.1.3 Calibration Curve

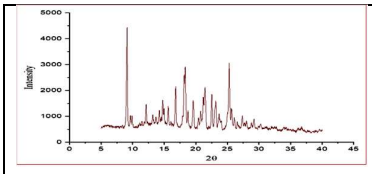



**Graph 1: Calibration Curve of Labetalol Hydrochloride in Methanol**

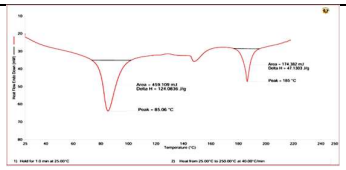



**Graph 2: Calibration Curve of Labetalol Hydrochloride in Phosphate Buffer pH**

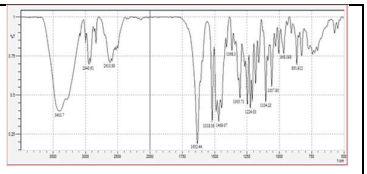
### 3.1.4 XRD, DSC and FTIR of Labetalol Hydrochloride



**Graph 3: XRD of Labetalol Hydrochloride**



**Graph 4:: DSC of Labetalol Hydrochloride**



**Graph 5: FTIR of Labetalol Hydrochloride**

### 3.2 Process for the Fabrication of MDF

There were various methods for the fabrication of MDF as previously mentioned. Among those, the solvent casting method was selected as it was easy and most suitable for Labetalol hydrochloride loaded MDF formulation.

### 3.2 QbD Approach for MDF

#### 3.2.1 Quality Target Product Profile for Labetalol Hydrochloride Loaded MDF

**Table 3: Quality Target Product Profile for the Formulation of MDF**

| QTPP element | Target | Justification |
|---|---|---|
| Dosage form | Mouth dissolving film | This dosage form is suitable for paediatrics and geriatrics, as it is easy to ingest without water, making it ideal for patients with gastrointestinal issues. It's costeffective, portable, stable, and enhances patient compliance by reducing dosing frequency. |
| Dosage design | Immediate release film | Immediate release film plays a crucial role in ensuring timely and effective treatment of cardiovascular conditions, improving patient adherence, and addressing emergency medical needs. |
| Route of administration | Oral | Better patient compliance. |
| Dosage strength | 5 mg Labetalol hydrochloride | It directly affects the efficacy of the drug, making it essential for achieving the desired therapeutic outcome. Insufficient dosage may lead to inadequate heart rate reduction, while excessive dosage can result in adverse effects, such as bradycardia. |
| Stability | At least 12 months at room temperature | Maintain quality, safety and efficacy throughout product life cycle. |
| Drug product quality attributes | Physical appearance<br>• Surface texture<br>• Transparency | Meeting the same compendia or other applicable quality standard |
| | Performance attributes<br>• Surface pH<br>• Moisture content | |
| | • *In-vitro* disintegration time | |
| | Mechanical properties<br>• Folding endurance<br>• Thickness<br>• Tensile strength | |
| | Drug content<br>• *In-vitro* dissolution | |
| | Identification<br>• DSC<br>• XRD<br>• FTIR | |

**Table 4: CQA, CMA and CPP for the Formulation of MDF**

| CQA element | | Target | Justification |
|---|---|---|---|
| Physical attributes | Appearance | Uniform surface texture | Doesn't have any effect on safety and toxicity. |
| Performance attributes | Thickness | 5-200 µm | Thickness of film directly affect the Disintegration and dissolution. Hence, it should be optimum. |
| | Folding endurance | 5-300 times | The target is set to ensure patient acceptability. |
| | Weight variation | SD >/ ±7.5% | The target is set to ensure dose uniformity. |
| | Tensile strength | 9-17g/mm$^2$ | It gives an indication of strength of film. Hence, it should be moderate. |
| | Surface pH | 6.2 to 7.6 | The target is set to ensure patient acceptability. |
| | *In-vitro* disintegration time | 5-30 sec | It has a direct effect on bioavailability. Hence, it should disintegrate within a minute. |
| | *In-vitro* dissolution | Maximum release in less than 10 Minutes | It directly affects the bioavailability. Hence, this attribute was studied throughout the finished dosage form. |
| | Content uniformity | 85-115% | Content uniformity must be within limit to ensure uniform distribution of API. |

| Attributes | | Effect on CQA | Control strategy |
|---|---|---|---|
| CMAs | Concentration of Polymer | Performance attributes | concentration range was selected from preliminary studies. |
| | Concentration of Plasticizer | | |
| | Concentration of Surfactant | | |
| | Nature of Excipients | Appearance | All excipients were water soluble. |
| CPPs | Stirring speed | Physical and performance attributes | 300 RPM |
| | Stirring time | Homogeneity and performance attributes of final product | 115-120 minutes |
| | Stirring temperature | Performance attributes and film homogeneity | 39-40°C |
| | Drying time | Performance attributes and physical efficacy | 6 to 9 hours |

**Table 5: REM for Initial Risk Assessment of Formulation Variables**

| Drug product CQAs | Formulation Variables | | |
|---|---|---|---|
| | HPMC E15 | PEG 4000 | SLS |
| Folding endurance | High | High | Low |
| Thickness | High | Low | Low |
| *In-vitro* drug release | High | Medium | Medium |

**Table 6: Justification for Formulation Variables Inceptive Risk Assessment**

| Formulation Variables | Drug product CQAs | Risk Assessment | Justification |
|---|---|---|---|
| HPMC E15 | Folding endurance | High | Folding endurance of MDF increases as the concentration of HPMC E15 increases. There was direct linear relationship. Hence, the risk was high. |
| | Thickness | High | Thickness increases as the concentration of HPMC E15 increases. There was direct linear relationship |

| | | | |
|---|---|---|---|
| | | | in between. Hence, the risk was high. |
| | *In-vitro* drug release | High | *In-vitro* drug release decreases as the concentration of HPMC E15 increases. Hence, the risk was high. |
| PEG 4000 | Folding endurance | High | Folding endurance decreases as the concentration of PEG 4000 increases as it reduces the brittleness of the MDF. There was direct relationship. Hence, the risk was high. |
| | Thickness | Low | PEG 4000 was used as a plasticizer. As it doesn't exhibit any major impact on Thickness, the risk was low. |
| | *In-vitro* drug release | Medium | *In-vitro* drug release may vary depend on concentration of PEG 4000. Hence, the risk was medium. |
| SLS | Folding endurance | Low | Almost negligible increase in Folding endurance as the concentration of SLS increases. Hence, the risk was low. |
| | Thickness | Low | No major impact was observed on Thickness, so the risk was low. |
| | *In-vitro* drug release | Medium | *In-vitro* drug release may vary depend on concentration of SLS. Hence, the risk was medium. |

### 3.3 Optimization of MDF Formulation

#### 3.3.1 Selection of Experimental Design

Box Behnken design was selected for optimization as it provides information exclusively on the effect of experiment variables and overall experimental error in a minimum number of runs. Being a response surface design, it requires three levels (-1, 0, 1) and offers a total of 15 experimental runs to investigate the impact of independent variables on response variables.

#### 3.3.2 Independent Variables

**Table 7: Independent Variables with Levels**

| Independent Variables | Unit | Low (-1) | High (+1) |
|---|---|---|---|
| Polymer (HPMC E15) | mg | 320 | 400 |
| Plasticizer (PEG 4000) | mg | 210 | 290 |
| Surfactant (SLS) | mg | 90 | 170 |

#### 3.3.3. Response Variables

**Table 8: Response Variables**

| Response Variables | Unit |
|---|---|
| Thickness | µm |
| Folding endurance | folds |
| % Drug releases | % |

#### 3.3.4 Fabrication and Characterization of MDF Batches Suggested by BBD

**Table 9: Different Combinations of MDF Formulations Offered by BBD**

| Run | Batch No. | Independent Variables | | |
|---|---|---|---|---|
| | | X1 | X2 | X3 |
| | | HPMC E15 (mg) | PEG 4000 (mg) | SLS (mg) |
| 1. | MQA301 | 360 | 250 | 130 |
| 2. | MQA302 | 320 | 250 | 90 |

| | | | | |
|---|---|---|---|---|
| 3. | MQA303 | 360 | 210 | 90 |
| 4. | MQA304 | 400 | 250 | 90 |
| 5. | MQA305 | 400 | 290 | 130 |
| 6. | MQA306 | 320 | 290 | 130 |
| 7. | MQA307 | 320 | 250 | 170 |
| 8. | MQA308 | 400 | 250 | 170 |
| 9. | MQA309 | 360 | 290 | 170 |
| 10. | MQA310 | 360 | 250 | 130 |
| 11. | MQA311 | 360 | 210 | 170 |
| 12. | MQA312 | 400 | 210 | 130 |
| 13. | MQA313 | 360 | 290 | 90 |
| 14. | MQA314 | 320 | 210 | 130 |
| 15. | MQA315 | 360 | 250 | 130 |

**Table 10: Results of Dependent Variables Analysis of MDF Batches**

| Run | Batch No. | Response Variables | | |
|---|---|---|---|---|
| | | R1 | R2 | R3 |
| | | Thickness (µm) | Folding endurance | Drug release (%) |
| 1. | MQA301 | 102 ± 0.6324 | 208 ± 2.9439 | 91.706 |
| 2. | MQA302 | 88 ± 1.0954 | 188 ± 0.8165 | 93.608 |
| 3. | MQA303 | 98 ± 0.8944 | 198 ± 1.6329 | 89.176 |
| 4. | MQA304 | 115 ± 1.0954 | 244 ± 2.1602 | 85.508 |
| 5. | MQA305 | 120 ± 0.6324 | 255 ± 2.1602 | 88.276 |
| 6. | MQA306 | 95 ± 3.1622 | 191 ± 1.6329 | 96.406 |
| 7. | MQA307 | 94 ± 1.2649 | 196 ± 1.6329 | 96.368 |
| 8. | MQA308 | 118 ± 0.6324 | 248 ± 2.1602 | 88.162 |
| 9. | MQA309 | 109 ± 1.4142 | 236 ± 2.9439 | 93.12 |
| 10. | MQA310 | 105 ± 0.6324 | 216 ± 2.9439 | 91.628 |
| 11. | MQA311 | 101 ± 1.4142 | 204 ± 3.7416 | 90.968 |
| 12. | MQA312 | 112 ± 1.0954 | 246 ± 1.6329 | 85.084 |
| 13. | MQA313 | 107 ± 0.6324 | 231 ± 1.6329 | 92.624 |
| 14. | MQA314 | 88 ± 1.6733 | 185 ± 0.8165 | 93.436 |
| 15. | MQA315 | 104 ± 0.6324 | 224 ± 1.6329 | 92.048 |

## 3.4 Statistical Analysis of Findings of Response Variables for MDF Batches

### 3.4.1. Fit Summary of MDF Batches

**Table 11: Lack of Fit for Thickness**

| Source | Sequential P-value | Lack of Fit P-value | Adjusted $R^2$ | Predicted $R^2$ | Remark |
|---|---|---|---|---|---|
| **Linear** | **<0.0001** | **0.9306** | **0.9947** | **0.9924** | **Suggested** |
| 2FI | 0.4594 | 0.9395 | 0.9936 | 0.9865 | - |
| Quadratic | 0.9997 | 0.7552 | 0.9948 | 0.9744 | - |
| Cubic | 0.7552 | - | 0.9979 | - | Aliased |

**Table 12: Lack of Fit for Folding Endurance**

| Source | Sequential P-value | Lack of Fit P-value | Adjusted $R^2$ | Predicted $R^2$ | Remark |
|---|---|---|---|---|---|
| **Linear** | **<0.0001** | **0.7294** | **0.9208** | **0.8838** | **Suggested** |
| 2FI | 0.9907 | 0.5871 | 0.8925 | 0.7445 | - |
| Quadratic | 0.9649 | 0.3743 | 0.8364 | 0.2809 | - |
| Cubic | 0.3743 | - | 0.8902 | - | Aliased |

**Table 13: Lack of Fit for % Drug Release**

| Source | Sequential P-value | Lack of Fit P-value | Adjusted $R^2$ | Predicted $R^2$ | Remark |
|---|---|---|---|---|---|
| **Linear** | **<0.0001** | **0.1042** | **0.9679** | **0.9528** | **Suggested** |
| 2FI | 0.8169 | 0.0787 | 0.96.4 | 0.9.84 | - |
| Quadratic | 0.1456 | 0.1072 | 0.9766 | 0.8745 | - |
| Cubic | 0.1072 | - | 0.9957 | - | Aliased |

**Table 14: Sequential Model Sum of Square Tables for Thickness**

| Source | Sum of Square | df | Mean Square | F-value | p-value | Remark |
|---|---|---|---|---|---|---|
| Mean vs Total | 1.614E+05 | 1 | 1.614E+05 | - | - | - |
| **Linear vs Mean** | **1402.50** | **3** | **467.50** | **492.89** | **<0.0001** | **Suggested** |
| 2FI vs Linear | 2.75 | 3 | 0.9167 | 0.9544 | 0.4594 | - |
| Quadratic vs 2FI | 0.0167 | 3 | 0.0056 | 0.0036 | 0.9997 | - |
| Cubic vs Quadratic | 3.00 | 3 | 1.0000 | 0.4286 | 0.7552 | Aliased |
| Residual | 4.67 | 2 | 2.33 | - | - | - |
| Total | 1.628E+05 | 15 | 10854.80 | - | - | - |

**Table 15: Sequential Model Sum of Square Tables for Folding Endurance**

| Source | Sum of Square | df | Mean Square | F-value | p-value | Remark |
|---|---|---|---|---|---|---|
| Mean vs Total | 7.129E+05 | 1 | 7.129E+05 | - | - | - |
| **Linear vs Mean** | **7652.25** | **3** | **2550.75** | **55.26** | **<0.0001** | **Suggested** |
| 2FI vs Linear | 6.50 | 3 | 2.17 | 0.0346 | 0.9907 | - |
| Quadratic vs 2FI | 24.50 | 3 | 8.17 | 0.0856 | 0.9649 | - |
| Cubic vs Quadratic | 384.75 | 3 | 116.25 | 1.82 | 0.3743 | Aliased |
| Residual | 128.00 | 2 | 64.00 | - | - | - |
| Total | 7.210E+05 | 15 | 48068.00 | - | - | - |

**Table 16: Sequential Model Sum of Square Tables for % Drug Release**

| Source | Sum of Square | df | Mean Square | F-value | p-value | Remark |
|---|---|---|---|---|---|---|
| Mean vs Total | 1.248E+05 | 1 | 1.165E+05 | - | - | - |
| **Linear vs Mean** | **159.06** | **3** | **53.02** | **141.58** | **<0.0001** | **Suggested** |
| 2FI vs Linear | 0.4306 | 3 | 0.1435 | 0.3113 | 0.8169 | - |
| Quadratic vs 2FI | 2.32 | 3 | 0.7743 | 2.83 | 0.1456 | - |
| Cubic vs Quadratic | 1.27 | 3 | 0.4222 | 8.49 | 0.1072 | Aliased |
| Residual | 0.0995 | 2 | 0.0497 | - | - | - |
| Total | 1.249E+05 | 15 | 8328.68 | - | - | - |

### 3.4.2 ANOVA Studies

**Table 17: ANOVA for Thickness**

| Source | Sum of Square | df | Mean Square | F-value | p- value | Remark |
|---|---|---|---|---|---|---|
| **Model** | 1402.50 | 3 | 467.50 | 492.89 | <0.0001 | significant |
| A-HPMC E15 | 1250.00 | 1 | 1250.00 | 1317.89 | <0.0001 | - |
| B-PEG 4000 | 128.00 | 1 | 128.00 | 134.95 | <0.0001 | - |
| C-SLS | 24.50 | 1 | 24.50 | 25.83 | 0.0004 | - |
| **Residual** | 10.43 | 11 | 0.9485 | - | - | - |
| Lack of fit | 5.77 | 9 | 0.6407 | 0.2746 | 0.9306 | not significant |
| Pure Error | 4.67 | 2 | 2.33 | - | - | - |
| **Cor Total** | 1412.93 | 14 | - | - | - | - |

**Table 18: Fit Statistics for Thickness**

| Particulars | Observations | Particulars | Observations |
|---|---|---|---|
| **Std. Dev.** | 0.9739 | **$R^2$** | 0.9926 |
| **Mean** | 103.73 | **Adjusted $R^2$** | 0.9906 |
| **C.V.%** | 0.9389 | **Predicted $R^2$** | 0.9875 |
| **-** | - | **Adeq Precision** | 65.6167 |

### 3.4.3 ANOVA for Folding Endurance

**Table 19: ANOVA for Folding Endurance**

| Source | Sum of Square | df | Mean Square | F-value | p- value | Remark |
|---|---|---|---|---|---|---|
| **Model** | 7652.25 | 3 | 2550.75 | 55.26 | <0.0001 | significant |
| A-HPMC E15 | 6786.12 | 1 | 6786.12 | 147.02 | <0.0001 | - |
| B-PEG 4000 | 800.00 | 1 | 800.00 | 17.33 | 0.0016 | - |
| C-SLS | 66.13 | 1 | 66.13 | 1.43 | 0.2565 | - |
| **Residual** | 507.75 | 11 | 46.16 | - | - | - |
| Lack of fit | 379.75 | 9 | 42.19 | 0.6593 | 0.7294 | not significant |
| Pure Error | 128.00 | 2 | 64.00 | - | - | - |
| **Cor Total** | 8160.00 | 14 | - | - | - | - |

**Table 20: Fit Statistics for Folding Endurance**

| Particulars | Observations | Particulars | Observations |
|---|---|---|---|
| **Std. Dev.** | 6.79 | **$R^2$** | 0.9378 |
| **Mean** | 218.00 | **Adjusted $R^2$** | 0.9208 |
| **C.V.%** | 3.12 | **Predicted $R^2$** | 0.8838 |
| **-** | - | **Adeq Precision** | 22.3034 |

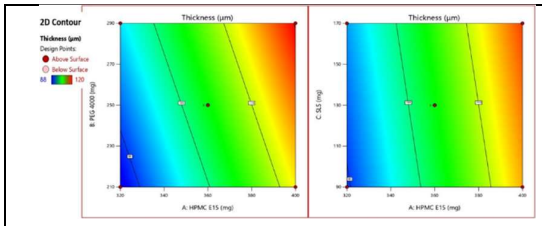
**Table 21: Statistical Analysis of % Drug Release**

| Source | Sum of Square | df | Mean Square | F-value | p- value | Remark |
|---|---|---|---|---|---|---|
| **Model** | 159.06 | 3 | 53.02 | 141.58 | <0.0001 | significant |
| A-HPMC E15 | 134.32 | 1 | 134.32 | 358.56 | <0.0001 | - |
| B-PEG 4000 | 17.32 | 1 | 17.32 | 46.24 | <0.0001 | - |
| C-SLS | 7.34 | 1 | 7.43 | 19.84 | 0.0010 | - |
| **Residual** | 4.12 | 11 | 0.3745 | - | - | - |
| Lack of fit | 4.02 | 9 | 0.4467 | 8.98 | 0.1042 | not significant |
| Pure Error | 0.0995 | 2 | 0.0497 | - | - | - |
| **Cor Total** | 163.18 | 14 | - | - | - | - |

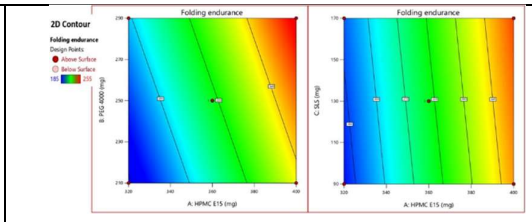
**Table 22: Fit Statistics for % Drug Release**

| Particulars | Observations | Particulars | Observations |
|---|---|---|---|
| **Std. Dev.** | 0.6120 | **$R^2$** | 0.9748 |
| **Mean** | 91.20 | **Adjusted $R^2$** | 0.9679 |
| **C.V.%** | 0.6710 | **Predicted $R^2$** | 0.9528 |
| **-** | - | **Adeq Precision** | 35.2435 |

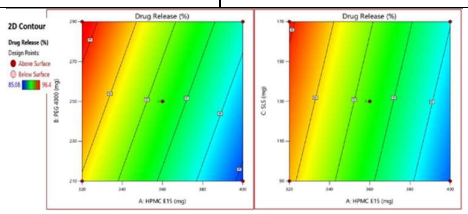
## 3.5 Response Surface Analysis of MDF Batches




**Graph 6: 2D Contour Plots (A) Effect of HPMC E15 & PEG 4000 on Thickness of MDF, (B) Effect of HPMC E15 & SLS on Thickness of MDF**

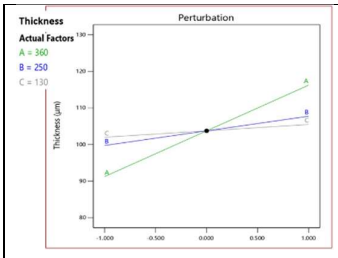



**Graph 7: 2D Contour Plots (A) Effect of HPMC E15 & PEG 4000 on Folding Endurance of MDF, (B) Effect of HPMC E15 & SLS on Folding Endurance of MDF.**

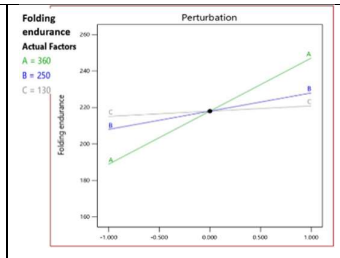



**Graph 8: 2D Contour Plots (A) Effect of HPMC E15 & PEG 4000 on % Drug Release of MDF, (B) Effect of HPMC E15 & SLS on % Drug Release of MDF**

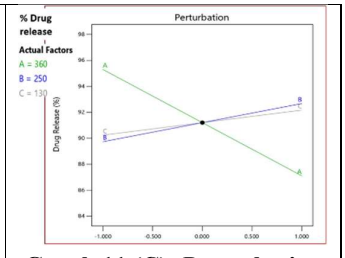
### 3.5.1 Perturbation Graph of Thickness, Folding Endurance and % Drug Release




**Graph 9 (A): Perturbation Graph of Thickness**

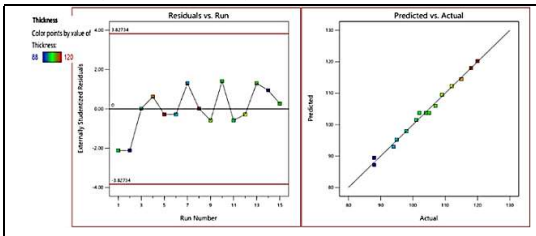



**Graph 10 (B): Perturbation Graph of Folding Endurance**

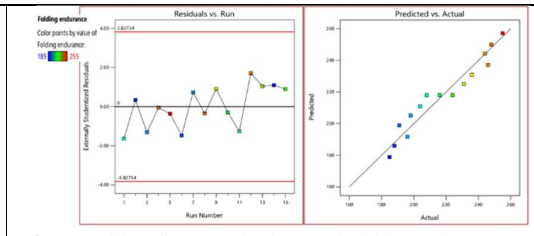



**Graph 11 (C): Perturbation Graph of % Drug Release**

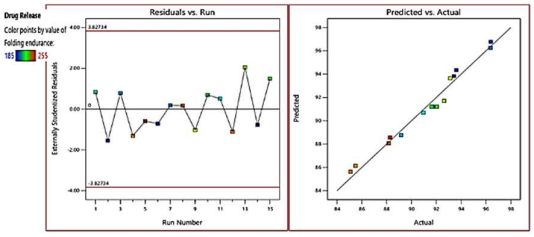
### 3.5.2 Diagnostic Analysis for Assessment of Residuals




**Graph 12: Diagnostic Analysis (A) Residuals vs. Run Plot for Thickness, (B) Predicted vs. Actual Plot for Thickness**




**Graph 13: Diagnostic Analysis (A) Residuals vs. Run Plot for Folding Endurance, (B) Predicted vs. Actual Plot for Folding Endurance**




**Graph 14: Diagnostic Analysis (A) Residuals vs. Run Plot for % Drug Release, (B) Predicted vs. Actual Plot for % Drug Release**

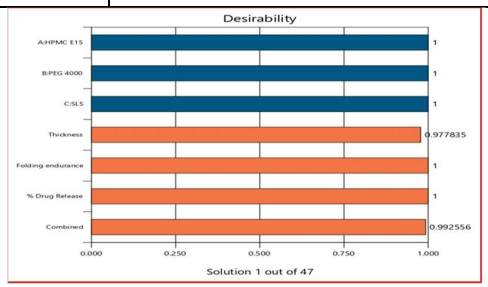
### 3.6 Prediction of Optimized Labetalol hydrochloride loaded MDF Formulation

**Table 23: Desirable Objectives of Response Variables for Optimized MDF Batch**

| Response variables | Criteria |
|---|---|
| Thickness | Target |
| Folding endurance | Target |
| % drug release | Maximum |

**Table 24: Software Predicted Values of Responses with Maximum Desirability**

| Response variables | Predicted values | Desirability |
|---|---|---|
| Thickness (µm) | 100.44 | 0.993 |
| Folding endurance (folds) | 210 | |
| % drug release (%) | 96.36 | |




**Graph 15: The Desirability of Individual Independent and Response Variables Depicted in Bar Graph**

### 3.7 Fabrication of Optimized Labetalol Hydrochloride Loaded MDF Formulation

**Table 25: Suggested Formulation Variables of Labetalol Hydrochloride Loaded MDF with Highest Desirability**

| Variable | Quantity |
|---|---|
| HPMC E15 | 331.947 mg |
| PEG 4000 | 290.000 mg |
| SLS | 163.748 mg |

### 3.8 Characterization of Optimized Labetalol Hydrochloride Loaded MDF Formulation

#### 3.8.1. Measurement of Thickness, Drug Content Uniformity, pH, Weight Variation, Disintegration Tim and Folding Endurance

**Table 26: Thickness, Drug Content Uniformity, pH, Weight Variation, Disintegration Time and Folding Endurance of MDF Batches**

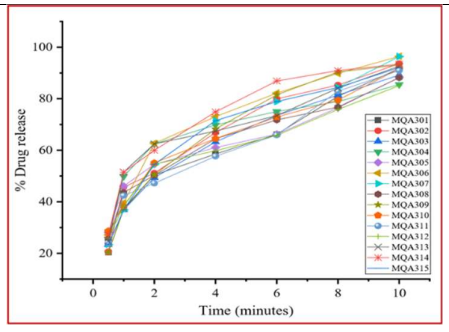
| Batch No. | Thickness (µm) (Mean*± SD) | Folding endurance (folds) (Mean*± SD) | Drug Content Uniformity (%) | pH (Mean*± SD) | Weight Variation (mg) (Mean*± SD) | DT (seconds) (Mean*± SD) |
|---|---|---|---|---|---|---|
| MQA301 | 102 ± 0.632 | 208 ± 2.943 | 96.98 | 6.67 ± 0.032 | 95.50 ± 0.82 | 34.6 ± 1.52 |
| MQA302 | 88 ± 1.095 | 188 ± 0.816 | 98.08 | 6.54 ± 0.030 | 91.17 ± 0.44 | 36 ± 1 |
| MQA303 | 98 ± 0.894 | 198 ± 1.632 | 94.79 | 6.81 ± 0.004 | 92.86 ± 0.27 | 27.6 ± 0.47 |
| MQA304 | 115 ± 1.095 | 244 ± 2.160 | 100 | 6.68 ± 0.012 | 97.15 ± 0.23 | 24.6 ± 1.24 |

| | | | | | | |
|---|---|---|---|---|---|---|
| MQA305 | 120 ± 0.632 | 255 ± 2.16 | 96.16 | 6.71 ± 0.020 | 105.34 ± 0.26 | 23 ± 0.81 |
| MQA306 | 95 ± 3.162 | 191 ± 1.632 | 99.45 | 6.79 ± 0.012 | 94.5 ± 0.35 | 28.6 ± 0.94 |
| MQA307 | 94 ± 1.264 | 196 ± 1.632 | 100.2 | 6.72 ± 0.012 | 95.89 ± 0.53 | 29.3 ± 2.05 |
| MQA308 | 118 ± 0.632 | 248 ± 2.160 | 99.17 | 6.7 ± 0.014 | 102.44 ± 0.43 | 33 ± 1.63 |
| MQA309 | 109 ± 1.414 | 236 ± 2.943 | 96.43 | 6.69 ± 0.008 | 103.60 ± 0.53 | 28.6 ± 1.24 |
| MQA310 | 105 ± 0.632 | 216 ± 2.943 | 97.26 | 6.65 ± 0.016 | 96.71 ± 0.41 | 23 ± 0.81 |
| MQA311 | 101 ± 1.414 | 204 ± 3.741 | 98.63 | 6.78 ± 0.009 | 96.95 ± 0.08 | 30.3 ± 1.24 |
| MQA312 | 112 ± 0.632 | 246 ± 1.632 | 93.97 | 6.62 ± 0.020 | 97.18 ± 0.18 | 24.3 ± 0.47 |
| MQA313 | 107 ± 0.632 | 231 ± 1.632 | 99.72 | 6.66 ± 0.009 | 95.02 ± 0.20 | 26.6 ± 0.94 |
| MQA314 | 88 ± 1.673 | 185 ± 0.816 | 95.61 | 6.83 ± 0.009 | 91.02 ± 0.08 | 25.3 ± 0.94 |
| MQA315 | 104 ± 0.632 | 224 ± 1.632 | 94.52 | 6.64 ± 0.020 | 95.23 ± 0.32 | 26 ± 0.81 |
| MQA316 | 99.2 ± 0.4 | 209 ± 0.816 | 99.72 | 6.77 ± 0.155 | 104.21 ± 0.58 | 27.66 ± 1.24 |

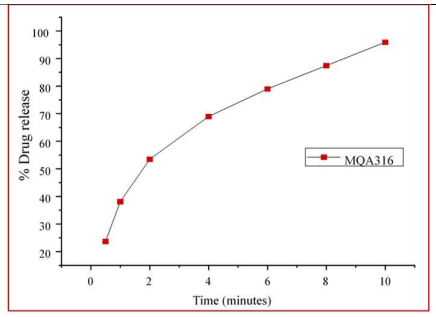
### 3.8.2. *In-vitro* Drug Dissolution Study

**Table 27: % drug release of MDF Batches**

| Batches | % Drug Release (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Time | | | | | | |
| | 30 sec | 1 min | 2 min | 4 min | 6 min | 8 min | 10 min |
| MQA301 | 20.28 | 37.13 | 50.39 | 58.53 | 66.20 | 80.94 | 91.70 |
| MQA302 | 20.64 | 45.70 | 51.14 | 66.85 | 79.93 | 85.29 | 93.60 |
| MQA303 | 23.40 | 36.87 | 49.35 | 63.24 | 73.50 | 81.40 | 89.17 |
| MQA304 | 25.56 | 49.86 | 62.45 | 69.83 | 75.03 | 78.87 | 85.50 |
| MQA305 | 28.08 | 46.06 | 54.50 | 61.03 | 66.21 | 76.51 | 88.27 |
| MQA306 | 27.12 | 39.57 | 62.66 | 73.05 | 82.15 | 89.82 | 96.40 |
| MQA307 | 23.40 | 36.87 | 54.51 | 71.49 | 78.89 | 84.35 | 96.36 |
| MQA308 | 25.56 | 43.62 | 50.22 | 64.48 | 71.76 | 76.75 | 88.16 |
| MQA309 | 20.40 | 37.54 | 50.52 | 68.26 | 81.49 | 90.36 | 93.12 |
| MQA310 | 28.68 | 38.27 | 55.10 | 64.52 | 72.89 | 79.45 | 91.62 |
| MQA311 | 24 | 42.40 | 47.18 | 57.66 | 65.91 | 82.93 | 90.96 |
| MQA312 | 25.92 | 38.23 | 54.58 | 59.79 | 65.79 | 75.84 | 85.08 |
| MQA313 | 24.72 | 51.53 | 62.46 | 67.44 | 73.45 | 84.09 | 92.62 |
| MQA314 | 27.24 | 51.45 | 59.98 | 74.88 | 86.89 | 90.92 | 93.43 |
| MQA315 | 23.40 | 36.87 | 54.51 | 71.49 | 78.89 | 84.35 | 92.04 |
| MQA316 | 23.64 | 38.07 | 53.46 | 68.97 | 78.97 | 87.44 | 95.90 |




**Graph 16: *In-vitro* % Drug Release Profiles for Batches MQA301 to MQA315**




**Graph 17: *In-vitro* % Drug Release Profiles of MQA316.**

### 3.8.3 SEM of Optimized MDF

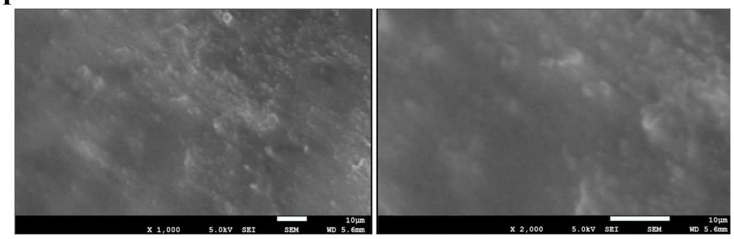
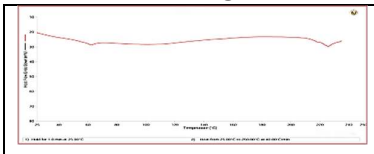
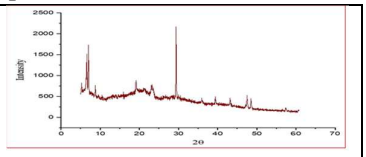


**Figure 1: SEM of Labetalol Hydrochloride Loaded Optimized MDF**



**Graph 18: DSC of Labetalol Hydrochloride Loaded Optimized MDF**

**Graph 19: FTIR of Labetalol Hydrochloride Loaded Optimized MDF**



**Graph 20: XRD of Labetalol Hydrochloride Loaded Optimized MDF**

### 3.8.4 Accelerated Stability Study

**Table 28: Stability Study Data of Optimized MDF Formulation**

| Parameters | Time | | |
|---|---|---|---|
| | 1 Month | 2 Month | 3 Month |
| Thickness (µm) | 98.6 ± 0.8 | 98 ± 0.63 | 97.8 ± 0.4 |
| Disintegration time (sec.) | 27 ± 0.81 | 26.3 ± 0.47 | 26 ± 0.81 |
| Drug content (%) | 99.17 | 98.9 | 98.9 |
| Surface pH | 6.75 ± 0.07 | 6.73 ± 0.01 | 6.72 ± 0.03 |
| Folding endurance (folds) | 207 ± 0.47 | 206 ± 0.81 | 206 ± 0.47 |
| *In-vitro* drug release (%) | 95.48 | 94.65 | 94 |
| Weight variation (mg) | 103.71 ± 0.78 | 103.54 ± 0.66 | 103.41 ± 0.57 |

### 3.9 Validation for Derived Model

**Table 29: Summary of the Data of Optimized MDF Batch (MQA316)**

| Parameters | Observations |
|---|---|
| Thickness (µm) | 99.2 ± 0.4 |
| Disintegration time (sec.) | 27 ± 0.81 |
| Drug content (%) | 99.17 |
| Surface pH | 6.75 ± 0.07 |
| Folding endurance (folds) | 209 ± 0.816 |
| *In-vitro* drug release (%) | 95.90 |
| Weight variation (mg) | 103.71 ± 0.78 |
| SEM analysis | The Labetalol hydrochloride loaded MDF formulation exhibited a smooth surface with a few small pores (section 6.9.8). |
| DSC analysis | The DSC thermogram of pure Labetalol hydrochloride had sharp endothermic peaks at 85.06°C and 185°C. While DSC thermogram of optimized Labetalol hydrochloride loaded MDF formulation showed decrease in intensity of peaks confirming its amorphous form (section 6.9.9). |
| FTIR analysis | The FTIR spectra of pure Labetalol hydrochloride revealed the characteristics absorption bands at 3401.7, 2943.61, 1632.44, 1722.43, 1529.55, 1469.07, 1368.3, 1224.09, and 1104.24. FTIR spectrum of optimized MDF formulation showed remarkable bands with a significant reduction in the intensity of the peaks, indicating there is no unwanted interaction between drug and excipients in the formulation. Hence this confirms the compatibility of the formulation ingredients (section 6.9.10). |

| | |
|---|---|
| XRD analysis | The X-ray diffractogram of Labetalol hydrochloride had shown the characteristic sharp peaks at 9.1187, 16.8147, 18.3423, 21.4748 and 25.2841 on diffraction angle (2θ) suggesting that the drug is present in a crystalline form. While the XRD pattern of optimized formulation showed few characteristic diffraction peaks with reduced intensity indicating the conversion of drug to amorphous or molecular form (section 6.9.11). |

**Table 30: Predicted and Observed Response Variables for Labetalol Hydrochloride Loaded MDF**

| Response variables | Predicted values | Observed values |
|---|---|---|
| Thickness (µm) | 100.44 | 99.2 ± 0.4 |
| Folding endurance (folds) | 210 | 209 ± 0.816 |
| *In-vitro* drug release (%) | 96.36 | 95.90 |

**Discussion**

The present study successfully optimized Labetalol HCl mouth dissolving film using a Quality by Design approach and Box-Behnken Design. HPMC E15, PEG 4000, and SLS significantly influenced the film characteristics, particularly thickness, folding endurance, and drug release. Increasing HPMC E15 increased film thickness and folding endurance but reduced drug release, whereas PEG 4000 and SLS enhanced drug release. The optimized formulation (MQA316) containing HPMC E15 331.947 mg, PEG 4000 290 mg, and SLS 163.748 mg showed satisfactory characteristics, including thickness of 99.2 ± 0.4 µm, folding endurance of 209 ± 0.816 folds, drug content of 99.17%, disintegration time of approximately 27 seconds, and *in-vitro* drug release of 95.90%. The experimental results were closely comparable with the predicted values, confirming the suitability of the developed model. SEM showed a smooth film surface with few small pores, while DSC and XRD indicated reduced crystallinity of the drug in the optimized formulation. FTIR studies showed no significant unwanted interaction between the drug and excipients. Furthermore, the formulation remained stable during three months of accelerated stability testing. Overall, the findings demonstrate that QbD and DoE provide an effective systematic approach for optimizing Labetalol HCl mouth dissolving film with desirable quality attributes.

## 4. CONCLUSION

The MDF of Labetalol hydrochloride was successfully developed and optimized using a computer-assisted QbD approach. The important properties and CQAs were identified, assessed, and controlled in the formulation using a QbD approach. As a result, the predefined QTPP was matched, confirming the formulation's safety and efficacy. The optimized formulation of MDFs of Labetalol HCL, revealed the highest desirability of 0.993 which is close to 1.

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