

## RESEARCH ARTICLE



# Multivariate Analysis and Computational Predictability of Modified Release Formulation of Chirally Pure Metoprolol Succinate

Vikram S. Gharge<sup>1</sup>, Mukesh B. Shinde<sup>1,\*</sup>, Satish L. Jadhao<sup>1</sup>, Nikhil P. Sadamat<sup>1</sup> and Nilkant S. Biradar<sup>1</sup>

<sup>1</sup>Research and Development Department, Zuventus Healthcare Ltd., India

**Abstract:** This study employs computational techniques to predict the performance of a modified release matrix formulation of chirally pure S (–) metoprolol succinate, using a quality by design (QbD) approach. The research defines the quality target product profile and critical quality attributes of the S (–) metoprolol succinate matrix formulation. To assess risks, an Ishikawa diagram and failure mode and effects analysis following International Conference on Harmonization Q8 guidelines were conducted. The formulation screening process utilized Plackett–Burman design, followed by optimization through Box–Behnken design. The modified release formulation was developed using high shear granulation, incorporating a combination of high and low viscosity hydroxypropyl methylcellulose (HPMC) polymers along with other excipients. The impact of polymer composition and stearic acid on the release profile of S (–) metoprolol succinate was investigated, revealing their significant influence on the drug delivery system’s desired effect. Specifically, the variables X1: HPMC K4M and X2: HPMC K100M were identified as key factors affecting drug release (Y1). Statistical analysis (ANOVA) confirmed the significance of the selected model, with predicted outcomes aligning well with observed results, comparable to the reference product Seleken® XL range. Both drug content and release performance were found to be similar to the innovator formulation. In summary, this investigation underscores the potential of employing a QbD approach with a combination of low and high viscosity HPMC polymers to achieve precise single-dose delivery of S (–) metoprolol succinate.

**Keywords:** matrix formulation, quality by design (QbD), S (–) metoprolol succinate

## 1. Introduction

Quality by design (QbD) represents a systematic approach to developing pharmaceutical formulations, beginning with predefined objectives, comprehensive product understanding, process control, and quality risk management, all aimed at achieving cost reduction as a major outcome [1]. To enhance regulatory approval procedures, the International Conference on Harmonization (ICH) and the Food and Drug Administration have implemented a QbD-based submission framework. This approach assists the pharmaceutical industry in overcoming regulatory barriers and reducing developmental costs [2]. QbD-based product development relies on guidelines such as ICH Q8, Q9, and Q10 [3, 4]. In the case of S (–) metoprolol succinate, a  $\beta$ 1-selective receptor antagonist is used for heart diseases, and its receptor selectivity depends on blood concentration [5]. However, long-term usage of this drug can lead to Cardiovascular System complications in patients with asthma [6]. To mitigate these issues, formulating S (–) metoprolol succinate as a prolonged release (PR) matrix formulation can reduce drug concentration fluctuations in the blood and enhance its  $\beta$ 1 selectivity [7]. Compared to immediate-release

tablet dosage forms, swellable matrix formulations are preferable, as they provide stable drug plasma levels within a therapeutic range for an extended period, leading to fewer side effects and improved patient compliance [8]. Such matrices ensure reproducible gastric transit kinetics of S (–) metoprolol succinate, resulting in better control of bioavailability and therapeutic efficacy [9]. The biopharmaceutical classification system (BCS) categorizes S (–) metoprolol succinate as a Class I drug due to its high solubility and permeability across epithelial membranes [10]. While it is rapidly absorbed along the gastrointestinal tract, incomplete bioavailability of approximately 50% may occur due to complex formation or presystemic clearance [11]. Consequently, frequent administration of the drug, up to four times daily depending on the indication, is required [12].

Various strategies have been explored to address this challenge, including bilayer tablets, osmotic pumps, hot melt extrusion, and coated pellets with uniform size [13–20]. Among these, swellable matrix systems have proven promising for oral controlled drug delivery, offering ease of manufacture, cost-effectiveness, and the ability to accommodate drugs with diverse physicochemical properties at various concentrations [21, 22].

Controlling drug release in swellable matrix systems relies on three mechanisms: water penetration into the system, swelling and matrix formation, and drug diffusion from the matrix. The kinetics of drug release are influenced by the relative movement and position of the erosion front, diffusion front, and swelling front [23].

\*Corresponding author: Mukesh B. Shinde, Research and Development Department, Zuventus Healthcare Ltd., India. Email: [mukesh.shinde@zuentus.com](mailto:mukesh.shinde@zuentus.com)

The development of a PR formulation of S (–) metoprolol succinate using a QbD approach is the main objective of this work. The study aims to: (1) establish the quality target product profile (QTPP) and critical quality attributes (CQAs) of the formulation during initial development, (2) employ risk assessment tools to identify potential factors affecting QTPP, (3) screen these factors using the Plackett–Burman design, (4) optimize the formulation through the Box–Behnken design, (5) apply analysis of variance (ANOVA) to identify the best-fit model and understand the drug release mechanism, and (6) Compare the optimized formulation with the marketed formulation Seleken® XL 25 mg (Batch No. STY007), manufactured by AstraZeneca Sweden. The swellable matrix system as a drug delivery system is expected to meet the objective of patient satisfaction with the convenience of a single dose of S (–) metoprolol succinate. Moreover, a QbD-based development process facilitates easy scale-up, simple production well-defined targets, and cost-effectiveness.

## 2. Materials and Methods

S (–) metoprolol succinate was used from Zuventus Healthcare Ltd. All excipient like microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC) K4M, HPMC K100M, povidone (PVP K-30), isopropyl alcohol, stearic acid, colloidal silicon dioxide, magnesium stearate, and all other chemicals used were of analytical reagent grade from Zuventus Healthcare Ltd.

### 2.1. Innovator product characterization

The physicochemical attributes of the innovator tablets, including thickness, hardness, drug content, and dissolution profile, were assessed using methods outlined in the United States Pharmacopeia.

### 2.2. QTPP and CQAs of formulations

QTPP and CQAs constituted fundamental elements within QbD, forming the cornerstone for developing a test product [1]. QTPP serves as a comprehensive description of the drug product's essential attributes. The selection of QTPP relies on factors such as the physicochemical properties of the active drug, therapeutic approach, intended application, as well as the product's safety and effectiveness (Table 1). In the context of the current study, the assay and drug release profile of Swellable Matrix tablets were identified as CQAs [24] (Table 2).

### 2.3. One factor at a time (OFAT) study trials of S (–) metoprolol succinate PR tablets formulation

Based on information extracted from literature, product leaflets, and the innovator's formulation details, the blueprint for initial prototype batches was established [6]. Initial experimentation was conducted to assess diverse polymer combinations capable of yielding a tailored release profile for S (–) metoprolol succinate. Excipient selection was based on current understanding and adhered to the regulatory guidelines for inactive ingredients in oral solid dosage forms [25, 26].

### 2.4. Risk assessment

The ICH Q9 guidance documents outline two fundamental elements of risk assessment: the visualization of risk identification through an Ishikawa diagram and the examination of risk analysis using the failure mode and effects analysis (FMEA) method, as described by Wilkinson [27]. The Ishikawa diagram is employed to map potential risk parameters that impact the CQAs of formulation. Additionally, in accordance with existing literature and preliminary experiments, the FMEA technique was utilized to scrutinize the various risk factors. Each potential failure mode is assigned

**Table 1**  
**Quality target product profile for S (–) metoprolol succinate PR tablets formulation**

QTPP element	Target	Justification
Dosage form	Prolonged release tablets	Requirement as per pharmaceutical equivalence for finished formulation
Route of administration	Oral	Requirement as per pharmaceutical equivalence the finished formulation
Dosage strength	25 mg	Requirement as per pharmaceutical equivalence the finished formulation
Drug product quality attributes	Physical attributes: Should comply as per specification Identification: Should comply as per specification Assay: NLT 90.0% & NMT 110.0% of label claim Drug release 1st h – NMT 25% of the label claim 4th h – 20%–40% of the label claim 8th h – 40%–60% of the label claim 20th h – NLT 80% of the label claim Degradation products: (a) Any individual impurity: NMT 0.5% (b) Total impurities: NMT 0.75%	Requirement as per pharmaceutical equivalence of the finished formulation  Meeting the same regulatory or other applicable (quality) standards (i.e., assay, identity, purity)
Stability	24-month shelf-life	As per ICH guidelines
Product packing system	Required packing system, to achieve the desired shelf life and to ensure tablet physical parameter during transport	Alu Alu blister pack selected similar to innovator

**Table 2**  
**CQAs of S (-) metoprolol succinate PR tablets formulation**

CQAs	Target	Justification
Appearance	White, spherical convex tablet	The appearance is not considered as critical factor in current formulation
Assay	100% of its label claim	Assay is a crucial factor that influences the formulation's effectiveness. Variable values signify a product that is less effective
Hardness of tablet (N)	40–80 N	To resist breakage of granules and control of release of drug through matrix tablet
Drug release (%)	1st h – NMT 25% of the label claim 4th h – 20%–40% of the label claim 8th h – 40%–60% of the label claim 20th h – NLT 80% of the label claim	Modified release of drug up to 20 h was considered to obtain desired plasma concentrations

numerical values based on its detectability ( $D$ ), severity ( $S$ ), and probability ( $P$ ). These numerical values are then multiplied together for each risk, resulting in a risk priority number ( $RPN$ ).

$$RPN = S \times D \times P \quad (1)$$

Commencing the FMEA involved classifying inputs into distinct categories encompassing formulation, production methodology, quantity, personnel, drug properties, and environmental factors. A  $RPN$  threshold of 50 was established, wherein any variable surpassing this threshold was deemed a potential critical factor warranting consideration.

## 2.5. Preparation of swellable matrix tablet by high shear granulation

Swellable matrix tablet of S (-) metoprolol succinate was prepared by high shear granulation technique using polymers such as combination of high and low viscosity HPMC in combinations with other excipients. Accurately weighed quantities of sifted drug and intragranular materials HPMC K4M, HPMC K100M, and microcrystalline cellulose were thoroughly mixed and granulated in rapid mixer granulator (SAI-10LICB, Sainath Boilers & Pneumatics, India) using Povidone in mixture of isopropyl alcohol and purified water (75:25). The wet granules were sieved through #10 sieve and dried in Rapid Fluid Bed Dryer (Unifluid Nano, S.B. Panchal & Corporation, India) at 55 °C till Loss on Drying (Moisture Analyzer, HC 103, Mettler Toledo, USA) reaches to 2.5%w/w. Dried granules were sieved through #20 sieves. The final granules were blended with extra granular materials (Stearic Acid, Colloidal Silicon Dioxide, Magnesium Stearate) and compressed using 11 mm standard concave punches, on 13 station rotary tablet press (Model-CMBD 3, Cadmach, Ahmedabad, India).

## 2.6. Plackett–Burman screening design

The objective of this experimental design was to identify the key factors that significantly impact CQAs. A total of five factors were examined through twelve experimental runs, with each factor being assessed at both low (-1) and high (+1) levels. The creation and randomization of the design matrix, employing Minitab 17 software (Version 17.07.1 USA), facilitated a statistically rigorous investigation. The statistical significance of these findings was determined by the significance level, often represented as  $\alpha$  or alpha, following the insights of Wilkinson [27]. The entire study was conducted in triplicate to ensure robustness. The dependent variable of interest, in this case, was the percentage of drug release ( $Y_1$ ).

## 2.7. Box–Behnken optimization study design

The optimization process for formulation involved the utilization of a Box–Behnken design, which encompasses three factors, each with three levels. The low and high levels of these factors were directly derived from the (OFAT) study, while the medium levels were set at the midpoint. The design matrix was generated and randomized using Minitab 17 software, which was also employed for subsequent statistical analysis.

Following a thorough regression analysis for each response variable, the resulting polynomial model was formulated as follows:

$$Y_1 = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 \quad (2)$$

In the context of this study,  $Y$  represents the response variable, while  $X_1$ ,  $X_2$ , and  $X_3$  represent the primary influential variables. Additionally,  $X_1X_2$ ,  $X_1X_3$ , and  $X_2X_3$  denote interaction effects, and  $X_{12}$ ,  $X_{22}$ , and  $X_{32}$  represent quadratic effects. The parameter  $b_0$  denotes the baseline value, and coefficients  $b_1$  to  $b_3$  capture the effects of the respective variables.

To assess the significance of these factors on the responses, the  $p$ -values of  $b_1$  to  $b_3$  were determined. Furthermore, ANOVA was employed to ascertain the model's significance.

The optimization of variables and responses, both in terms of formulation and process, was achieved through polynomial equations. These equations were utilized to optimize drug release (%) ( $Y_1$ ) for formulation. The established numerical model facilitated the exploration of the optimal levels of  $X_1$ : HPMC K4M (mg/tab),  $X_2$ : HPMC K100M (mg/tab), and  $X_3$ : stearic acid (mg/tab).

## 2.8. Establishment of design space

The design space encompasses a multidimensional arrangement and interplay of input variables and process parameters that have been substantiated to ensure the desired quality, as indicated by Selen et al. [28] and Issa et al. [29]. In the current investigation, the combination of surface response methodology and optimization was employed to establish the design space. This design space was identified within the shared domain of successful operational ranges for CQAs, specifically the drug release (%) parameters: 1-h release not exceeding 25%, 4-h release between 20% and 40%, 8-h release ranging from 40% to 60%, and 20-h release not falling below 80%.

## 2.9. Physical characterization of the tablets

The compressed tablets physicochemical attributes including thickness (Vernier caliper, 500 196-30, Mitutoyo Corporation, Japan), hardness (Hardness Tester, EHT-SPR, Electro Lab, India), drug content, and dissolution profile were assessed using methods outlined in the United States Pharmacopeia.

## 2.10. Dissolution study

The dissolution examination was conducted employing a USP dissolution test apparatus (TRUST E-14, Electro Lab, India) of Type II (Paddle type). The experiment was executed with the paddle rotating at a speed of 50 rpm, utilizing 500 ml of pH 6.8 phosphate buffer as the dissolution medium. For each test, six tablets were introduced into the medium. Samples were extracted at various time intervals, filtered through a 0.22  $\mu\text{m}$  filter to maintain sink conditions, and retained for analysis. Quantification of the release of S (–) metoprolol succinate was conducted through high-performance liquid chromatography (Model-e2695, Waters instrument, USA). The analytical setup employed a Waters Spherisorb C8 column measuring 125  $\times$  4.0 mm with a particle size of 5  $\mu\text{m}$ . A mobile phase consisting of a mixture of buffer solution and acetonitrile (at a ratio of 750:250) was utilized. The detection wavelength was set at 280 nm, and the flow rate was maintained at 1.0 ml/min throughout the 5-min run time.

## 3. Results and Discussion

### 3.1. Innovator product characterization

All the observed evaluation of innovator formulation (Seleken® XL 25 mg, Batch No. STY007, Mfg. AstraZeneca Operations Sweden) is given in Table 3.

### 3.2. QTPP and CQAs for formulation

The QTPP and CQAs pertaining to S (–) metoprolol succinate PR tablets are illustrated in the following Table 4, accompanied by justifications for the chosen quality attributes [30]. Based on the biopharmaceutical (BCS) classification of the drug substance and an in-depth understanding of the drug product, the drug release profile (Y1) was specified with the following ranges: 1 h (not exceeding 25%), 4 h (20% to 40%), 8 h (40% to 60%), and 20 h (not less than 80%). Additionally, the assay was identified as a

**Table 3**  
Physical and chemical parameter assessment for innovator formulation

Strength	25 mg
Physical characterization	
Dimensions (mm)	10.6 $\times$ 5.6
Thickness (mm)	3.75–3.76
Hardness (N)	105.6
Assay %	98.82%
Dissolution profile of tablets	
1 h	9.90
4 h	26.72
8 h	48.63
20 h	87.27

CAQs for formulation, aligning with the work by Fahmy et al. [31]. These attributes were deemed crucial in achieving the desired dosing regimen and efficacy of S (–) metoprolol succinate [32].

### 3.3. OFAT study trials for formulation

The preliminary trial batches of formulation underwent assessment, and the outcomes from these findings, HPMC K4M and HPMC K100M, emerged as the controlled release polymers that yielded drug release profiles conforming to predetermined temporal intervals. The synergy achieved through the combination of HPMC K4M and HPMC K100M was recognized as the optimal choice for advancing the subsequent phases of development.

### 3.4. Risk assessment

By amalgamating data from the innovator's product literature, scientific insights, and expert discussions, an Ishikawa diagram (depicted in Figure 1) was constructed. This diagram aimed to delineate and pinpoint potential risk factors that exert an influence on the subject at hand.

CQAs for the formulation of S (–) metoprolol succinate PR tablets encompass drug release (%) (Y1), as sourced from references [7]. The risk analysis tool yielded a RPN threshold for potential risk factors, as detailed in the work by Wang et al. [24]. Upon conducting FMEA, five noteworthy failure modes were identified (X1: HPMC K4M, X2: HPMC K100M, X3: Povidone

**Table 4**  
QTPP and CQAs pertaining to S (–) metoprolol succinate PR tablets

QTPP elements	Target	Its CQA	Justification
Rout of administration	Oral	No	Present dosage form is intended for oral delivery
Dosage form	Prolonged release tablet	No	To achieve a consistent plasma concentration of drug substance
Strength of active	25 mg	No	Amount of a drug substance to achieve desired pharmacodynamics effect
Drug release profile	1 h: NMT 25% 4 h: 20–40% 8 h: 40–60% 20 h: NLT 80%	Yes	Pharmacopoeial requirements for a modified release formulation to achieve the specified plasma concentration
Assay	Should be 100% of its label claim	Yes	Assay is a crucial factor that influences the formulation's effectiveness. Variable values signify a product that is less effective
Stability	Should fulfill ICH requirements	NO	Product requirements
Packaging system	Product requirements	NO	Maintain efficacy and safety on storage

Figure 1  
Ishikawa diagram

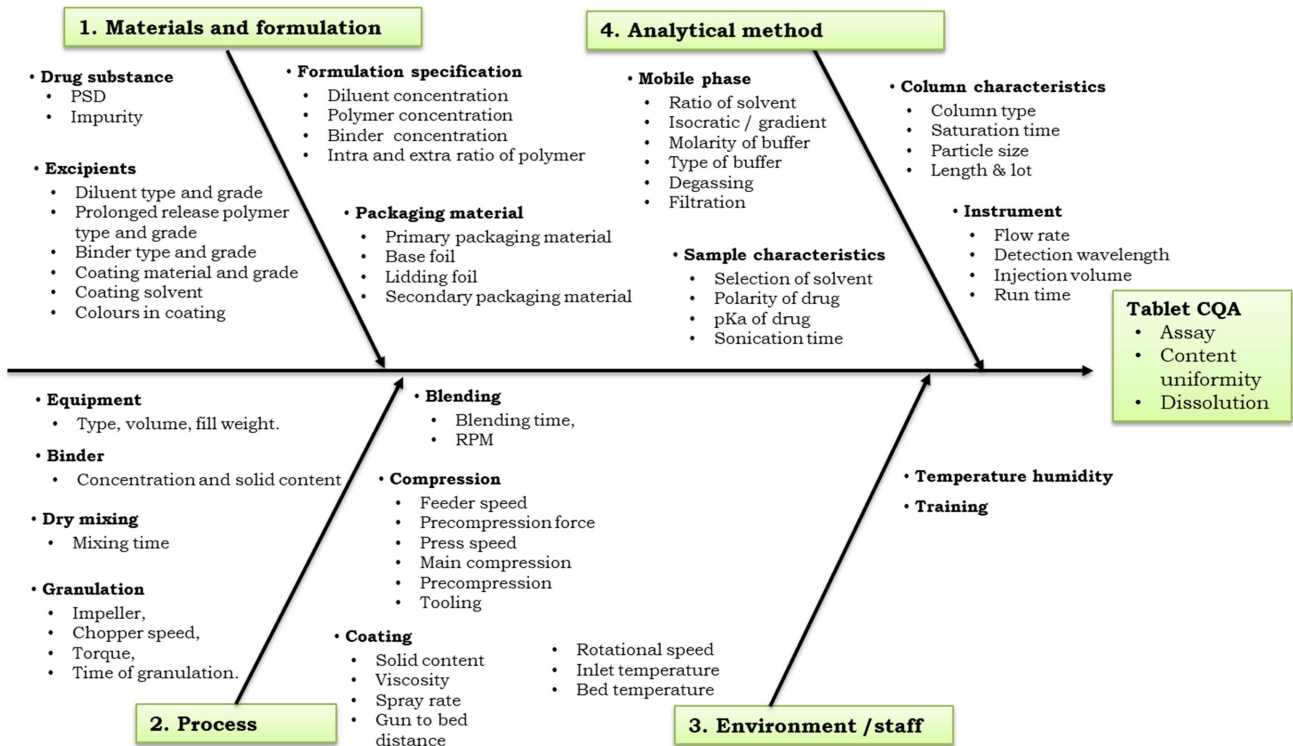
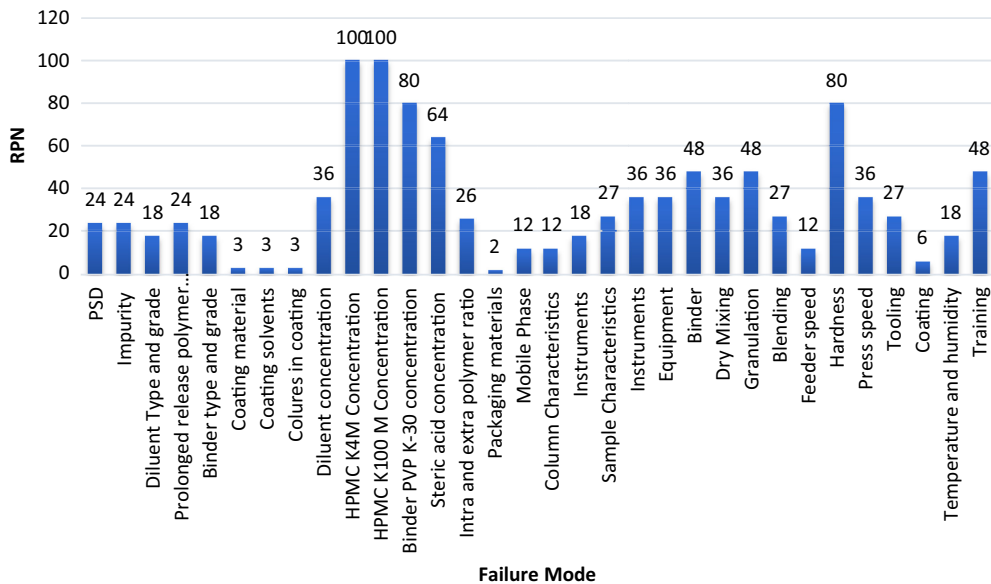


Figure 2

RPN scores for process dependent variables in S (-) metoprolol succinate modified release tablets



(PVP K-30), X4: stearic acid, and X5: Hardness), each carrying the potential for a negative impact on drug release (Figure 2). These factors were selected for further investigation, while other factors with lower RPN values were excluded from subsequent study phases (Table 5).

### 3.5. Plackett–Burman screening design

The Plackett–Burman statistical experiment with five factors at two levels was utilized to assess high-risk factors. The experiment involved 12 runs, the results of which are presented in Tables 6 and 7. The drug release

**Table 5**  
**RPN score for potential failures modes of S (-) metoprolol succinate modified release tablets**

Item and function/process step	Potential failure mode	Severity	Probability	Detection	RPN	
Drug substance	PSD	3	4	2	24	
	Impurity	3	4	2	24	
Excipients	Diluent type and grade	3	3	2	18	
	Prolonged release polymer and grade	4	3	2	24	
	Binder type and grade	3	3	2	18	
	Coating material	1	3	1	3	
	Coating solvents	1	3	1	3	
	Colures in coating	1	3	1	3	
Formulation specifications	Diluent concentration	3	4	3	36	
	HPMC K4M concentration	5	4	5	100	
	HPMC K100 M concentration	5	4	5	100	
	Binder PVP K-30 concentration	5	4	4	80	
	Steric acid concentration	4	4	4	64	
	Intra and extra polymer ratio	3	3	4	26	
Packaging materials	Packaging materials	1	2	1	2	
Analytical method	Mobile phase	2	3	2	12	
	Column characteristics	2	3	2	12	
	Instruments	3	2	3	18	
	Sample characteristics	3	3	3	27	
	Instruments	4	3	3	36	
	Equipment	4	3	3	36	
Process	Binder	3	4	4	48	
	Dry mixing	3	4	3	36	
	Granulation	4	3	4	48	
	Blending	3	3	3	27	
	Feeder speed	2	2	3	12	
	Hardness	5	4	4	80	
	Press speed	4	3	3	36	
	Tooling	3	3	3	27	
	Coating	1	2	3	6	
	Environment and staff	Temperature and humidity	3	2	3	18
		Training	4	3	4	48

for 1 h was 11.36–21.18%; for 4 h 31.50–49.80%; for 8 h 42.5–67.8%; and for 20 h 70.1–94.5%.

Observing the results,  $X_1$  (HPMC K4M) positively influenced drug release ( $Y_1$ ) at 1 h and 4 h time points where  $p$ -value < 0.05. Meanwhile,  $X_2$  (HPMC K100M) negatively impacted drug release at 8 h and 20 h time points. This negative effect can be attributed to the high viscosity of HPMC K100M, resulting in a slower drug release due to hindered penetration of the dissolution medium [33, 34].

The impact of  $X_3$  (Povidone, PVP K-30) on drug release was found to be insignificant, likely because of its hydrophilic nature, causing it to dissolve quickly upon contact with the dissolution medium.

The impact of  $X_4$  (stearic acid) on drug release was found to be negatively affecting drug release ( $Y_1$ ) at 1 h time points where  $p$ -value < 0.05 likely because of its hydrophobic nature.

$X_5$  (Hardness,  $N$ ) within the range of 80–160 N was identified as a crucial process parameter affecting core tablet properties, but it had an insignificant effect on drug release.

Coefficients from Tables 6 and 7 revealed  $X_3$  (PVP K-30) and  $X_5$  (Hardness,  $N$ ) as insignificant thus set at constant values of 250 mg/tab and 120 N, respectively.

From the screening,  $X_1$  (HPMC K4M),  $X_2$  (HPMC K100M), and  $X_4$  (stearic acid) were found to significantly impact drug release. These parameters were further analyzed for their interactions and effects on QTPP using Box–Behnken optimization study.

### 3.6. Box–Behnken optimization study design

To explore the impact of  $X_1$ : HPMC K4M,  $X_2$ : HPMC K100M, and  $X_3$ : stearic acid on the drug release ( $Y_1$ ) of formulation, a Box–Behnken design employing a three-factor, three-level configuration was employed (Table 8).

The polynomial equation for drug release ( $Y_1$ ) was established through regression analysis, represented as:

$$Y_1 = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 \quad (3)$$

In this equation,  $Y_1$  denotes the response variable, the main effects of the factors are represented by  $X_1$ : HPMC K4M,  $X_2$ : HPMC K100M, and  $X_3$ : stearic acid, the interaction effect of factors is  $X_1X_2X_3$ , and the quadratic effects are captured by  $X_1^2$ : HPMC K4M<sup>2</sup>,  $X_2^2$ : HPMC K100M<sup>2</sup>, and  $X_3^2$ : stearic acid<sup>2</sup>. The constant was denoted as  $b_0$ , and the coefficients of the factors are represented by  $b_1$ ,  $b_2$ , and  $b_3$  (Table 9).

To assess the significance of these factors on the response, the  $p$ -values of  $b_1$ ,  $b_2$ , and  $b_3$  were determined. Additionally, an ANOVA was employed to ascertain the significance of the overall model, as detailed in the work by Yerlikaya et al. [25].

**Table 6**  
**Observation for Plackett–Burman screening design**

Batch no	Formulation variables				Process variables X5	Response (% drug release)			
	X1	X2	X3	X4		Y1			
	HPMC K4M (mg/tab) L:40; H:80	HPMC K100M (mg/tab) L:80; H:120	Povidone PVP K 30 (mg/ tab) L:20; H:60	Stearic acid (mg/tab) L:7; H:14	Hardness (N) L:80; H:160	1 h	4 h	8 h	20 h
SMS-PB1	40	80	20	14	160	21.15 ± 0.97	42.72 ± 1.68	66.8 ± 0.98	91.8 ± 1.56
SMS-PB2	80	120	20	14	80	11.36 ± 1.28	33.8 ± 1.26	59.5 ± 0.66	82.8 ± 1.39
SMS-PB3	40	120	20	7	80	19.1 ± 1.09	44.5 ± 1.56	62.6 ± 1.23	83.5 ± 1.58
SMS-PB4	80	80	60	14	80	16.4 ± 1.06	35.5 ± 1.58	62.8 ± 1.32	87.9 ± 1.55
SMS-PB5	40	120	60	14	80	17.11 ± 0.99	49.8 ± 1.54	62.6 ± 1.56	88.6 ± 1.39
SMS-PB6	80	80	20	7	160	19.15 ± 0.69	38.5 ± 1.36	61.5 ± 1.55	93.6 ± 1.85
SMS-PB7	80	120	20	14	160	11.26 ± 0.59	31.5 ± 1.38	42.5 ± 1.34	70.1 ± 1.39
SMS-PB8	80	120	60	7	160	12.45 ± 0.87	38.5 ± 1.39	49.6 ± 1.69	78.5 ± 1.56
SMS-PB9	40	120	60	7	160	18.22 ± 2.01	39.5 ± 1.52	56.8 ± 1.56	89.5 ± 1.45
SMS-PB10	40	80	60	14	160	21.18 ± 1.69	35.6 ± 1.66	52.1 ± 1.45	82.5 ± 1.39
SMS-PB11	80	80	60	7	80	18.6 ± 1.78	39.5 ± 1.22	58.9 ± 1.89	89.5 ± 1.52
SMS-PB12	40	80	20	7	80	19.4 ± 1.59	45.6 ± 1.09	67.58 ± 1.73	94.5 ± 1.84

**Note:** HPMC hydroxypropyl methylcellulose; L: low level of the factor; H: high level of the factor.

**Table 7**  
**Coefficients for drug release (%) (Y1) and its estimated effects (coded units)**

Effect	Coef				SE coef				T value				p-value							
	1 h	4 h	8 h	20 h	1 h	4 h	8 h	20 h	1 h	4 h	8 h	20 h	1 h	4 h	8 h	20 h				
X1	-5.490	-6.74	-2.95	-3.83	17.615	39.59	57.61	85.65	0.153	1.21	1.51	1.51	115.25	32.70	38.25	56.56	0.000	0.000	0.000	0.000
X2	-5.397	0.03	-8.01	-8.63	-2.698	0.01	-4.01	-4.32	0.153	1.21	1.51	1.51	-17.96	-2.78	-0.98	-1.27	0.000	0.032	0.366	0.253
X3	-0.577	0.30	-4.28	-0.80	-0.288	0.15	-2.14	-0.40	0.153	1.21	1.51	1.51	-1.89	0.12	-1.42	-0.26	0.108	0.906	0.205	0.800
X4	-2.410	-2.86	0.89	-3.40	-1.205	-1.43	0.44	-1.70	0.153	1.21	1.51	1.51	-7.88	-1.18	0.29	-1.12	0.000	0.282	0.778	0.304
X5	-0.760	-3.73	-5.45	-4.30	0.380	-1.86	-2.72	-2.15	0.153	1.21	1.51	1.51	-2.49	-1.54	-1.81	-1.42	0.047	0.174	0.121	0.205

**Table 8**  
Results for Box–Behnken optimization design (Mean  $\pm$  SD,  $n = 3$ )

Batch no	X1	X2	X3	Y1			
	HPMC K4M (mg/tab) L:50;M:60;H:70	HPMC K100M (mg/ tab) L:70;M:80;H:90	Stearic acid (mg/ tab) L:6;M:7;H:8	1 h	4 h	8 h	20 h
MS-BB-1	60	90	6	19.5 $\pm$ 1.23	32.87 $\pm$ 1.29	50.9 $\pm$ 0.56	84.6 $\pm$ 1.11
MS-BB-2	50	90	7	21.22 $\pm$ 1.35	32.5 $\pm$ 1.37	46.8 $\pm$ 0.78	84.5 $\pm$ 1.02
MS-BB-3	70	70	7	17.5 $\pm$ 0.97	40.5 $\pm$ 1.28	59.8 $\pm$ 0.59	85.6 $\pm$ 1.28
MS-BB-4	60	70	8	21.15 $\pm$ 0.89	36.72 $\pm$ 0.89	60.8 $\pm$ 0.69	88.8 $\pm$ 1.38
MS-BB-5	70	80	8	13.11 $\pm$ 1.23	36.8 $\pm$ 0.82	55.6 $\pm$ 0.89	89.6 $\pm$ 1.57
MS-BB-6	50	70	7	21.26 $\pm$ 1.37	41.5 $\pm$ 0.73	62.5 $\pm$ 1.59	90.1 $\pm$ 1.33
MS-BB-7	70	80	6	17.4 $\pm$ 0.79	38.6 $\pm$ 0.45	56.5 $\pm$ 1.37	81.5 $\pm$ 1.09
MS-BB-8	60	80	7	18.18 $\pm$ 0.75	35.6 $\pm$ 0.69	52.1 $\pm$ 0.83	82.5 $\pm$ 0.96
MS-BB-9	60	70	6	19.15 $\pm$ 0.89	38.5 $\pm$ 0.1.13	58.5 $\pm$ 0.78	83.6 $\pm$ 1.06
MS-BB-10	70	90	7	15.6 $\pm$ 0.69	34.5 $\pm$ 1.29	51.9 $\pm$ 0.59	85.5 $\pm$ 1.51
MS-BB-11	50	80	6	19.4 $\pm$ 0.43	35.5 $\pm$ 1.69	60.8 $\pm$ 0.39	82.9 $\pm$ 1.45
MS-BB-12	60	80	7	16.1 $\pm$ 1.29	33.5 $\pm$ 1.43	54.6 $\pm$ 0.72	83.5 $\pm$ 1.27
MS-BB-13	60	90	8	15.45 $\pm$ 0.53	32.5 $\pm$ 0.73	49.6 $\pm$ 0.89	85.5 $\pm$ 0.99
MS-BB-14	50	80	8	21.5 $\pm$ 1.02	39.5 $\pm$ 0.97	55.9 $\pm$ 0.76	85.6 $\pm$ 0.78
MS-BB-15	60	80	7	15.36 $\pm$ 1.67	33.8 $\pm$ 0.88	51.5 $\pm$ 1.24	82.8 $\pm$ 0.97

**Table 9**  
Estimated regression coefficients for drug release (%) (Y1) (quadratic)

Factors	Coef (Coded)				SE coef (Coded)				T				<i>p</i> -value*			
	1 h	4 h	8 h	20 h	1 h	4 h	8 h	20 h	1 h	4 h	8 h	20 h	1 h	4 h	8 h	20 h
X1	16.547	34.300	52.73	82.933	0.625	0.744	1.16	0.791	26.48	46.09	45.45	104.85	0.000	0.000	0.000	0.000
X2	-2.471	0.175	-0.275	-0.113	0.383	0.456	0.710	0.484	-6.46	0.38	-0.39	-0.23	0.001	0.717	0.715	0.826
X3	-0.911	-3.106	-5.300	-1.000	0.383	0.456	0.710	0.484	-2.38	-6.82	-7.46	-2.06	0.063	0.001	0.001	0.094
X1*X1	0.694	2.701	2.38	1.383	0.563	0.671	1.05	0.713	1.23	4.03	2.28	1.94	0.273	0.010	0.072	0.110
X2*X2	1.654	0.249	0.13	2.108	0.563	0.671	1.05	0.713	2.94	0.37	0.13	2.96	0.032	0.726	0.904	0.032
X3*X3	0.612	0.599	2.08	0.583	0.563	0.671	1.05	0.713	1.09	0.89	1.99	0.82	0.327	0.413	0.103	0.450
X1*X2	-0.465	0.750	1.95	1.375	0.541	0.644	1.00	0.685	-0.86	1.16	1.94	2.01	0.430	0.297	0.110	0.101
X1*X3	-1.597	-1.450	1.00	1.350	0.541	0.644	1.00	0.685	-2.95	-2.25	1.00	1.97	0.032	0.074	0.365	0.106
X2*X3	-1.513	0.353	-0.90	-1.075	0.541	0.644	1.00	0.685	-2.79	0.55	-0.90	-1.57	0.038	0.608	0.411	0.177

Note: X1 HPMC K4M; X2: HPMC K100M; X3: stearic acid \**P*-value <0.05 significant.

### 3.7. Evaluation of the design space

The design space for formulation was defined with the goal of achieving specific drug release profiles (Y1): 1 h (not more than 25%), 4 h (20% to 40%), 8 h (40%–60%), and 20 h (not less than 80%), respectively.

### 3.8. Characterization of PR tablets

The tablets were of a weight of 400 mg  $\pm$  2%, exhibiting an average diameter of 11  $\pm$  0.05 mm and a thickness of 4.6  $\pm$  0.2 mm. Their hardness ranged from 80 to 160 N, while the friability percentage was less than 0.02%. The drug content for all batches fell within the range of 95–105%. All recorded measurements met the desired standards, indicating satisfactory outcomes.

## 4. Conclusion

In this research, the development of S (–) metoprolol succinate PR tablets was undertaken using a QbD approach. The utilization of an Ishikawa diagram and FMEA aided in the identification of risk factors that influence the quality of the drug products. A Plackett–Burman

design was employed to identify significant factors, while a Box–Behnken optimization design was utilized to refine the range of variables. The CQA of the S (–) metoprolol succinate PR tablets was determined to be drug release. Among the formulation variables, namely X1 (HPMC K4M), X2 (HPMC K100M), and X3 (stearic acid), it was found that they significantly impact the drug release profile. The results of model confirmation tests demonstrated a close alignment between predicted outcomes and actual observations, thus affirming the precision and robustness of the model. The formulation of matrix tablets was optimized to achieve the desired drug release characteristics, effectively minimizing the number of required trials. This approach not only reduces development time, costs, and labor but also offers valuable insights for future conventional matrix tablet manufacturing endeavors. This comprehensive analysis serves as a guide for upcoming matrix tablet manufacturers, facilitating informed decision-making in the product development process.

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## Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

## Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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