Implementation of Quality by Design in Generic Drug Product Development: A Case Study Using Diclofenac Sodium Sustained Release Tablets

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ABSTRACT

The current study aims to implement Quality by Design (QbD) principles in the development of generic products to establish a robust, consistent, and regulatory-compliant formulation. Diclofenac Sodium was selected as a model drug to develop a sustained-release tablet formulation. Voveran® SR 100mg Tablets were used as the reference-listed drug (RLD), and the Quality Target Product Profile and Critical Quality Attributes were delineated. Key formulation variables affecting drug release and hardness were identified using initial risk assessment. A 2^{5-1} fractional factorial design was employed for screening significant factors influencing the formulation attributes. The formulations were further optimized using a Central Composite Design to define a design space, ensuring steady drug release and hardness. The desirability approach was used to confirm the optimal conditions and make the point predictions. The actual values aligned very closely with the predictions made by the model. The optimized formulations demonstrated drug release of 80-100% after 12 hours and hardness between 70-130 newtons. The optimized formulation showed excellent similarity with RLD, with an F2 value of more than 50. This study underscores the efficacy of QbD in pharmaceutical development, demonstrating its role in achieving predefined quality standards and regulatory compliance while fostering continuous improvement.

Keywords: Quality by Design; Design of Experiment; Formulation Optimization; Fractional Factorial Design; Central Composite Design; Desirability; Diclofenac.

INTRODUCTION

The pharmaceutical industry is subject to stringent regulatory oversight due to the critical impact of drug quality on patient health. Over the decades, the approach to pharmaceutical quality management has evolved significantly, transitioning from end-product testing to proactive quality assurance integrated throughout the product lifecycle. One of the most significant advancements in this field is the adoption of the Quality by Design (QbD) framework.[1,2]

Quality by Design (QbD) is a systematic, science-based approach to pharmaceutical development that emphasizes understanding and controlling formulation and manufacturing processes. This methodology, introduced by quality management pioneer Joseph M. Juran, advocates for the design and optimization of processes to ensure sustainable product quality. [3] The U.S. Food and Drug Administration (FDA) has incorporated QbD principles into its current Good Manufacturing Practices (cGMP) guidelines, and the International Council for Harmonization (ICH) has supported these principles through guidelines Q8, Q9, and Q10.[4,5]

QbD involves defining a Quality Target Product Profile (QTPP), identifying Critical Quality Attributes (CQAs), assessing risks associated with formulation and process variables, and employing Design of Experiments (DoE) to optimize the formulation . This structured

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approach not only ensures that pharmaceutical products meet desired quality standards but also facilitates regulatory compliance and continuous improvement throughout the product lifecycle. [6–10]

Diclofenac sodium is a widely used non-steroidal anti-inflammatory drug (NSAID) with well-documented anti-inflammatory, analgesic, and antipyretic properties. It is commonly used to treat various conditions, such as rheumatoid arthritis and ankylosing spondylitis. Sustained-release formulations of diclofenac sodium offer the advantage of improved patient compliance by reducing dosing frequency and minimizing side effects.[11–13]

This study aims to implement Quality by Design (QbD) and Design of Experiments (DoE) methodologies in the development of a generic sustained-release (SR) drug product comprising diclofenac sodium as the model drug. Diclofenac sodium was selected due to its low solubility and widespread therapeutic use. The reference-listed drug (RLD) Voveran® SR 100 mg Tablet was chosen for its established efficacy and safety profile both of which serve as a benchmark for developing conventional generic formulation. By systematically applying QbD principles, this research seeks to demonstrate the robustness, consistency, and regulatory compliance of the optimized formulation.

RESULTS

Analysis of RLD:

The results of the physicochemical characterization of the RLD, Voveran® SR 100 Tablet are given in Table 1. The dissolution profile of RLD in pH 6.8 phosphate buffer is presented in Figure 1.

Table 1 Physicochemical properties of RLD- Voveran® SR 100 Tablets

Sr. no.	Property	Observation
1	Batch No.	BTG1842
2	Description	Light brown to brown colored, film-coated, biconvex round-shaped tablets bearing the inscription 'SR 100' on one side and plain on the opposite side.
3	Strength	100 mg
4	Diameter	9 mm
5	Thickness	3.04 mm
6	Score	No score
7	Average weight	300 mg
8	Hardness	5 kg/cm
9	Assay	98.37 %
10	Dissolution Profile	900mL Phosphate Buffer, Apparatus II (Paddle) 50RPM
	Time (h)	% Drug Released
	0	0
	1	0
	2	1.99
	3	11.16
	4	21.13
	5	31.89
	6	43.06
	7	51.43
	8	62.19
	9	72.16
	10	78.54
	12	88.90

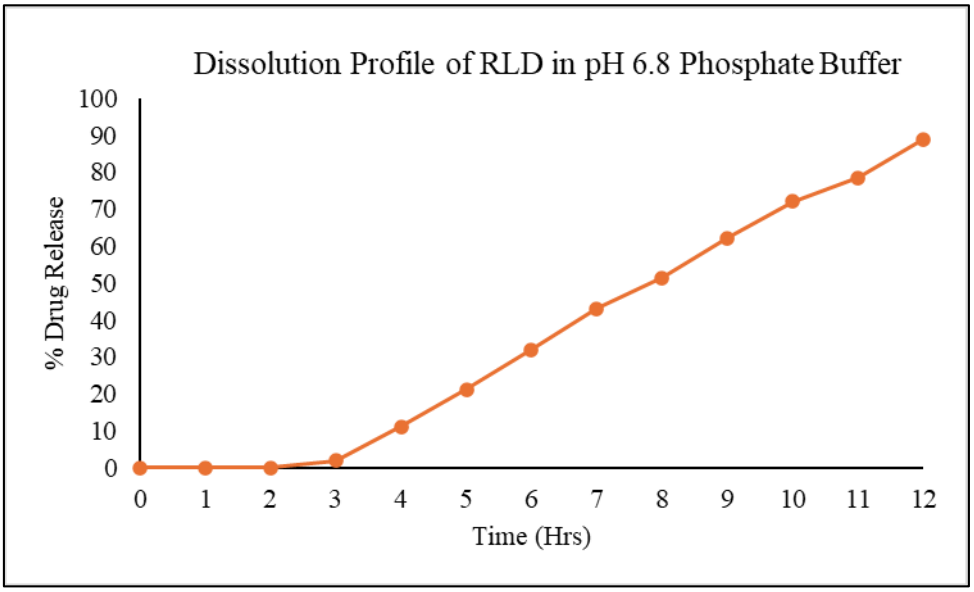

Figure 1 Dissolution profile of Voveran SR 100mg Tablets in pH 6.8 Phosphate Buffer

Selection of Quality Target Product Profile (QTPP)

Considering the physicochemical, clinical, and pharmacokinetic (PK) attributes, along with the in vitro dissolution profile of the RLD, the QTPP for the development of Diclofenac SR tablets is outlined in Table 2.

Table 2 QTPP for Diclofenac SR tablets

QTPP Elements		Target	Justification
Dosage form		Sustained Release Tablet	Pharmaceutical equivalence requirement: Same dosage form
Route of administration		Oral	Pharmaceutical equivalence requirement: Same route of administration
Dosage strength		100 mg	Pharmaceutical equivalence requirement: Same strength
Drug product quality attributes	Physical Attributes (Description, Tablet Weight, Hardness, Thickness, Friability, Disintegration Time) y	Pharmaceutical equivalence requirement: Meeting the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality)	
	Assay		
	Content Uniformity		
	Degradation Products		
	Drug Release		

Identification of Critical Quality Attributes (CQAs)

CQAs for current development, Diclofenac SR tablets, are listed in Table 3

Table 3 CQAs for Diclofenac SR tablets.

Quality Attributes of the Drug Product		Target	Is it a CQA?	Justification
Physical Attributes	Appearance	Color and shape acceptable to the patient. No visual tablet defects were observed.	No	Color, shape, and appearance don't directly influence safety and efficacy, rendering them non-critical attributes. Their targets are established primarily for patient acceptability.
	Friability	Not more than 1.0% w/w	No	The target is established based on compendial standards. Since friability doesn't influence safety or efficacy, it isn't classified as a CQA.
Assay		90-100% of label claim	Yes	Fluctuations in the assay can influence safety and efficacy, making the assay a critical parameter.
Content Uniformity		Meets Pharmacopeial requirements	Yes	Variability in content uniformity will affect safety and efficacy. Content uniformity is critical.
Degradation Products		Complies with ICH Q3B	No	The degradation products directly influence safety. However, diclofenac sodium is a well-known molecule with good stability in solid dosage forms. Thus, degradation products were not considered as CQA.
Drug Release		Similar Dissolution profile as RLD	Yes	The Dissolution profile is essential to achieve similar pharmacokinetics; therefore, it is critical.

Initial risk assessment for formulation Variables

Risk assessment for formulation variables is given in Table 4, and justification for the same is discussed in Table 5.

Table 4 Initial risk assessment for formulation variables

Drug Product CQAs	Formulation Variables			
	Concentration of Diluents	The concentration of Release Controlling Polymer	Binder Concentration	Glidant andlubricant concentration
Assay	Medium	Low	Low	Low
Content Uniformity	Medium	Low	Low	Low
Drug Release	Medium	High	Medium	Medium

Table 5 Justification for initial risk assessment of formulation variables

Formulation Variables	Drug Product CQAs	Justification
Concentration of Diluents	Assay	The concentration of diluents is an essential factor for designing a tablet formulation. The flow properties of the blend depend on the concentration of diluents, and poor flow properties may lead to uneven distribution of diclofenac sodium in the blend and tablets; thus, the risk is assigned as medium.
	Content Uniformity	
	Drug Release	The current drug product is a matrix tablet designed for sustained release of diclofenac sodium. The release control from such formulation depends on the matrix's integrity. Lactose monohydrate is a water-soluble substance[14], while microcrystalline cellulose is known to have disintegration properties[15]. Thus, a higher lactose concentration can cause faster erosion of the matrix, while a high concentration of microcrystalline cellulose may cause disintegration of the matrix. Thus, the concentration of diluents is considered critical, and risk is assigned as medium.
Concentration of Release Controlling Polymer	Assay	The release-controlling polymer is intended for achieving sustained release, and its concentration is not directly related to assay and content uniformity. Thus, the risk is assigned as low.
	Content Uniformity	
	Drug Release	Release-controlling polymer is solely responsible for imparting the sustained release properties to the current formulation. Therefore, a low concentration of release-controlling polymer can lead to a faster release profile, and a very high concentration can hinder drug release. Thus, the concentration of release-controlling polymer is very critical, and risk is assigned as high.
Binder	Assay	In the present formulation, the binder serves to provide cohesiveness to the mixture. Its concentration doesn't directly impact the assay or content uniformity; thus, the risk is assigned as low.
	Content Uniformity	
	Drug Release	While the release-controlling polymer primarily governs the sustained drug release, the binder can influence dissolution due to its effect on blend compaction characteristics. Consequently, the associated risk is categorized as medium.
Glidant and lubricant	Assay	Glidants and lubricants function to enhance flow characteristics and avoid issues like sticking and picking. Their presence doesn't directly influence the assay or content uniformity, leading to a classification of low risk.
	Content Uniformity	
	Drug Release	Both talc and magnesium stearate are hydrophobic, and diclofenac sodium is a BCS class II molecule. Therefore, a higher concentration of glidant and lubricant may impart hydrophobicity to the drug substance and further reduce the solubility of diclofenac sodium, impacting the dissolution. Thus, the risk is assigned as medium.

FORMULATION DEVELOPMENT OF DICLOFENAC SR TABLET:

Selection of Components of Drug Product:

The selection of formulation components was performed through a review of relevant literature[16,17]. Polyethylene oxide was chosen as the release-modulating polymer, attributed to its commendable hydration capacity and extended-release characteristics[18]. Moreover, this polymer is recognized for its non-toxicity and non-irritant nature[19]. The excipients selected for the formulation development with their corresponding applications and reported ranges are shown in Table 6.

Table 6 Components of formulation with reported ranges.

SR. No.	Ingredient	Function	Reported range (% w/w)
1	Diclofenac Sodium	API	-
2	Polyethylene oxide	Release controlling polymer	5.0-85.0
3	Microcrystalline cellulose (MCC)	Diluent	20.0-90.0
4	Lactose monohydrate	Diluent	Up to 80
5	Povidone K30	Binder	0.5-5.0
6	Talc	Glidant	1.0-10.0
7	Magnesium stearate	lubricant	0.25-5.0

Formulation Screening by Design of Experiment approach:

The formulation screening trials were conducted to understand the factors that have significant impact on the dissolution profile and hardness of the tablets. The 2^{5-1} factorial design was selected and total of sixteen experiments were performed in this study. The details of the formulation compositions are given in Table 7.

Table 7 Layout for 2^{5-1} design with experimental runs

Formulation	Factor 1 Polyethylene Oxide (mg)	Factor 2 Povidone K 30 (mg)	Factor 3 MCC (mg)	Factor 4 Talc (mg)	Factor 5 Magnesium Stearate (mg)	Response 1 Drug Release (%)	Response 2 Hardness (N)
F1	75	15	60	15	9	77.59	147.8
F2	75	6	60	15	3	86.17	112.1
F3	45	6	40	15	3	103.67	58.1
F4	45	6	60	3	3	105.85	99.9
F5	45	15	40	15	9	95.16	80.5
F6	75	15	40	3	9	76.31	89.7
F7	75	15	60	3	3	77.36	137.6
F8	75	15	40	15	3	76.4	86.6
F9	45	15	60	3	9	96.26	127.4
F10	75	6	60	3	9	86.16	102.9
F11	45	6	40	3	9	104.42	53
F12	45	15	60	15	3	96.18	120.3
F13	45	6	60	15	9	105.4	95.8
F14	75	6	40	15	9	85.4	67.3
F15	45	15	40	3	3	95.92	71.3
F16	75	6	40	3	3	85.24	61.1

The physicochemical attributes such as weight variation, friability, and assay of the formulations F1 to F16 were evaluated. The results were found to meet the Pharmacopoeial standards and displayed minimal variation. The *in vitro* dissolution profiles of these formulations are presented in Figure 2.

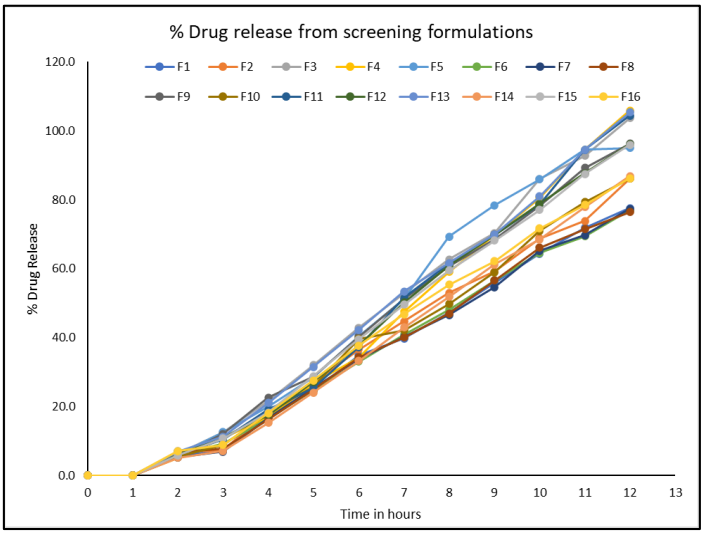

Figure 2 In vitro dissolution profiles of the screening formulations.

Various drug release kinetics for each formulation F1 to F16 were assessed based on the drug release profiles. These models included zero order, Hixson-Crowell, first order, Korsmeyer-Peppas Higuchi, and the n exponent value[20,21]. The model fitness data for drug release kinetics is given in Table 8, the fitness data indicates that all dissolution profiles adhered to a zero-order release, which is deemed optimal for sustained-release formulations.

Table 8 The model fitness data (Correlation coefficient value) for dissolution profiles.

Formulation	Zero-order	First order	Higuchi	Korsmeyer-Peppas	HixonCrowell	n exponent value
SF1	0.9726	0.9258	0.8282	0.9380	0.9467	2.2986
SF2	0.9722	0.9016	0.8281	0.9374	0.9357	2.3409
SF3	0.9763	0.8570	0.8351	0.9171	0.9187	2.2947
SF4	0.9616	0.7897	0.8066	0.9389	0.8766	2.3622
SF5	0.9740	0.8652	0.8306	0.9215	0.9210	2.3093
SF6	0.9745	0.9316	0.8317	0.9317	0.9508	2.2536
SF7	0.9722	0.9263	0.8278	0.9399	0.9468	2.3075
SF8	0.9721	0.9292	0.8280	0.9377	0.9480	2.2913
SF9	0.9746	0.8445	0.8312	0.9196	0.9115	3.3070
SF10	0.9702	0.8963	0.8237	0.9338	0.9299	2.3130
SF11	0.9662	0.8233	0.8156	0.9352	0.8950	2.3548
SF12	0.9683	0.8430	0.8197	0.9339	0.9078	2.3636
SF13	0.9743	0.8184	0.8306	0.9231	0.9003	2.3191
SF14	0.9645	0.8890	0.8122	0.9503	0.9236	2.3912
SF15	0.9709	0.8427	0.8238	0.9315	0.9085	2.3520
SF16	0.9734	0.9109	0.8394	0.9333	0.9409	2.3274

Statistical Interpretation of Screening DoE Study:

The responses obtained from the screening trials (F1 to F16) were analyzed using various regression models, including linear, two-factor interaction, quadratic, and cubic models, to evaluate the relationship between the studied factors and their effects on the DP-CQA. The linear regression model was found to be significant for both drug release and tablet hardness. This indicates that the selected responses are directly influenced by the individual factors studied, and the interaction between these factors does not have a significant impact on DP-CQA[22]. The half normal plot a graphical tool used in statistical analysis to identify the significance of factors in a designed experiment[23] and Pareto plots based on the Pareto Principle (80/20 rule), which suggests that roughly 80% of problems are often caused by 20% of the factor were plotted to understand the factors that have significant impact of selected responses[24].

The half-normal plot and Pareto chart for dissolution, depicted in Figure 3A, indicate that polyethylene oxide, povidone K 30, and microcrystalline cellulose significantly influence drug release, with contributions of 81.82%, 17.86%, and 0.25%, respectively. These findings were statistically validated using the analysis of variance (ANOVA) test. p-values below 0.05 (Table 9) confirm the significance of polyethylene oxide, povidone K 30, and microcrystalline Cellulose in the model, while other factors are non-significant. Main effect analysis plots revealed an inverse relationship between polyethylene oxide, povidone K 30, and drug release, whereas microcrystalline cellulose exhibited a direct proportional relationship to drug release.

Similarly, for drug release, polyethylene oxide, povidone k 30, and microcrystalline cellulose were significant factors in the half-normal and Pareto charts (Figure 3B). microcrystalline cellulose had the highest influence, contributing to 70.31% of the total impact, followed by povidone K 30 and polyethylene oxide with contributions of 22.12% and 4.85%, respectively. The ANOVA results presented in Table 10 further confirmed the significance of polyethylene oxide, microcrystalline cellulose, and povidone K 30 (p-values < 0.05), with other factors and interactions being non-significant.

Table 9 ANOVA for the Linear model for Drug Release

Source	Sum of Squares	df	Mean Square	F-value	p-value	Significance
Model	1769.20	5	353.84	3376.30	< 0.0001	Significant
A-Polyethylene Oxide	1448.37	1	1448.37	13820.19	< 0.0001	Significant
B-Povidone K 30	316.22	1	316.22	3017.30	< 0.0001	Significant
C-MCC	4.46	1	4.46	42.58	< 0.0001	Significant
D-Talc	0.1502	1	0.1502	1.43	0.2589	Non-significant
E-Magnesium Stearate	0.0005	1	0.0005	0.0048	0.9460	Non-significant

Table 10 ANOVA for the Linear model for hardness

Source	Sum of Squares	df	Mean Square	F-value	p-value	Significance
Model	12297.94	5	2459.59	87.20	< 0.0001	Significant
A-Polyethylene Oxide	610.09	1	610.09	21.63	0.0009	Significant
B-Povidone K 30	2782.56	1	2782.56	98.65	< 0.0001	Significant
C-MCC	8845.40	1	8845.40	313.60	< 0.0001	Significant
D-Talc	40.96	1	40.96	1.45	0.2559	Non-significant
E-Magnesium Stearate	18.92	1	18.92	0.6709	0.4318	Non-significant

From the fractional factorial screening DoE, the concentrations of polyethylene oxide, povidone K 30, and microcrystalline cellulose were selected for optimization. The concentrations of talc and magnesium stearate were found to have no impact on DP-CQAs.

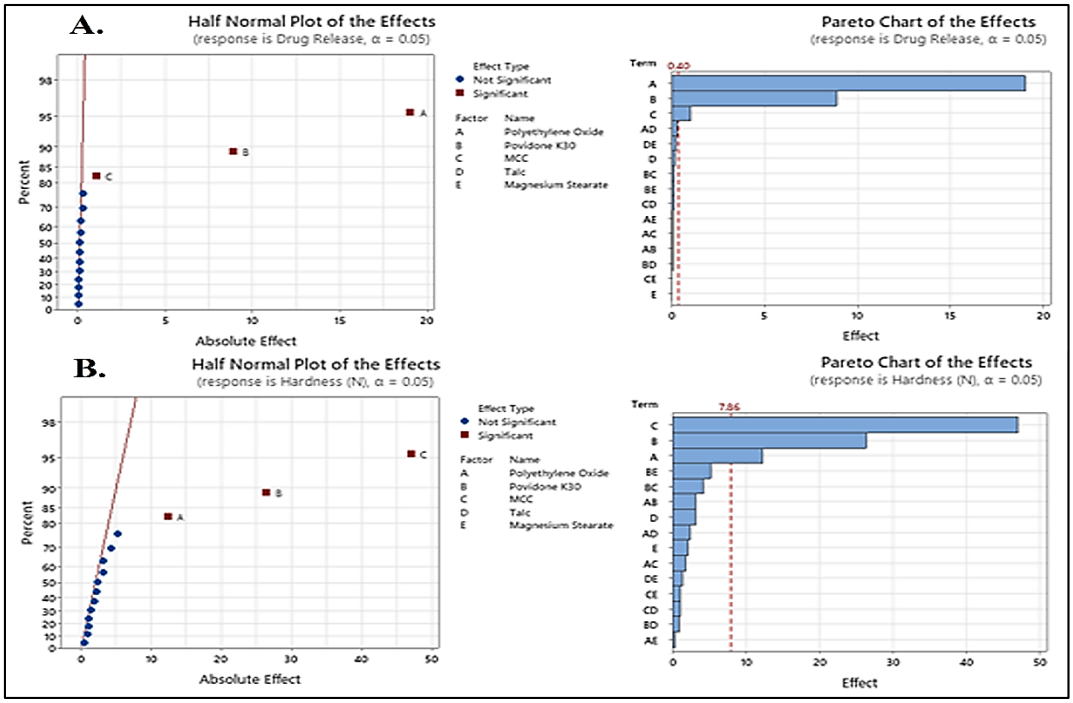

Figure 3 Half Normal Plot and Pareto Charts for A. Drug Release B. Hardness

Optimization of Formulation:

Optimization was conducted using a Central Composite Design (CCD) with three crucial variables identified from the screening phase. The primary goal was to define a design space where variations in parameters would not significantly alter the studied responses. The layout for the optimization study is provided in Table 11.

Table 11 Optimization Trials and Responses

Formulation	Factor 1	Factor 2	Factor 3	Response 1	Response 2
	A: Polyethylene Oxide	B: Povidone K 30	C: MCC	Drug Release	Hardness
	mg	mg	mg	%	N
OF1	45.00	15.00	40.00	95.38	68.50
OF2	60.00	10.50	66.81	85.15	131.50
OF3	75.00	15.00	40.00	70.25	88.50
OF4	60.00	10.50	33.18	83.80	63.50
OF5	85.22	10.50	50.00	63.46	112.50
OF6	60.00	10.50	50.00	83.99	97.00
OF7	60.00	10.50	50.00	82.79	93.50
OF8	60.00	10.50	50.00	82.71	96.50
OF9	34.77	10.50	50.00	103.43	81.00

Formulation	Factor 1	Factor 2	Factor 3	Response 1	Response 2
	A: Polyethylene Oxide	B: Povidone K 30	C: MCC	Drug Release	Hardness
OF10	45.00	6.00	40.00	96.13	64.50
OF11	75.00	15.00	60.00	71.22	130.50
OF12	60.00	10.50	50.00	83.07	97.00
OF13	60.00	10.50	50.00	83.89	98.00
OF14	45.00	15.00	60.00	96.23	111.00
OF15	60.00	10.50	50.00	83.72	96.00
OF16	75.00	6.00	40.00	72.92	84.00
OF17	60.00	2.93	50.00	85.83	92.50
OF18	45.00	6.00	60.00	98.53	108.50
OF19	60.00	18.06	50.00	81.75	100.00
OF20	75.00	6.00	60.00	73.01	125.50

Statistical analysis of the responses evaluated using various regression models to establish the relationships between independent and dependent variables. The linear model was found significant with a sequential p-value <0.0001 for both drug release and hardness. The linear model indicated that drug product CQAs are not impacted by the interaction between the studied factors. The regression model equations for drug release and hardness are shown in Equation 1 and Equation 2, respectively. These equations enable the prediction of drug release and tablet hardness values at given concentrations of the independent variables.

Drug Release =+132.55758 -0.810808 Polyethylene Oxide -0.233885 Povidone K 30 +0.048184 MCC…… Equation 1

Hardness = -49.78290 +0.629626 Polyethylene Oxide +0.465694 Povidone K 30 +2.08234 MCC…… Equation 2

An ANOVA test (Table 12 and Table 13) confirmed the efficiency of the linear model, with p-values < 0.05, indicating the significance of all model terms. Adequacy measures showed reasonable agreement, and the non-significant lack of fit p-value confirmed the suitability of the model for predicting the responses.

Table 12 ANOVA table for Drug release Central Composite Design study.

Source	Sum of Squares	df	Mean Square	F-value	p-value	Significance
Model	2038.25	3	679.42	1372.29	< 0.0001	Significant
A-Polyethylene Oxide	2019.96	1	2019.96	4079.92	< 0.0001	Significant
B-Povidone K 30	15.12	1	15.12	30.55	< 0.0001	Significant
C-MCC	3.17	1	3.17	6.40	0.0223	Significant
Residual	7.92	16	0.4951			
Lack of Fit	6.28	11	0.5712	1.74	0.2807	Not significant
Pure Error	1.64	5	0.3278			
Cor Total	2046.17	19				
Std. Dev.	0.7036		R^2		0.9961	
Mean	83.86		Adjusted R^2		0.9954	
CV %	0.8390		Predicted R^2		0.9940	
			Adeq. Precision		129.9926	

Table 13 ANOVA table for Hardness Central Composite Design study.

Source	Sum of Squares	df	Mean Square	F-value	p-value	Significance
Model	7198.99	3	2399.66	1476.07	< 0.0001	Significant
A-Polyethylene Oxide	1218.07	1	1218.07	749.25	< 0.0001	Significant
B-Povidone K 30	59.96	1	59.96	36.88	< 0.0001	Significant
C-MCC	5920.96	1	5920.96	3642.08	< 0.0001	Significant
Residual	26.01	16	1.63			
Lack of Fit	14.18	11	1.29	0.5446	0.8138	Not significant
Pure Error	11.83	5	2.37			
Cor Total	7225.00	19				
Std. Dev.	1.28		R^2		0.9964	
Mean	97.00		Adjusted R^2		0.9957	
CV %	1.31		Predicted R^2		0.9948	
			Adeq. Precision		122.8124	

The 3D surface plots (Figure 4) generated from the regression models displayed a linear relationship between the independent variables (polyethylene oxide, povidone K 30, and MCC) and the response variables. The concentration of polyethylene oxide and povidone K30 was found to be inversely proportional to the drug release indicating decrease in the drug release with increase in concentrations; whereas the MCC concentration was found to be directly proportional to the drug release meaning increase in MCC concentration increased the drug release.

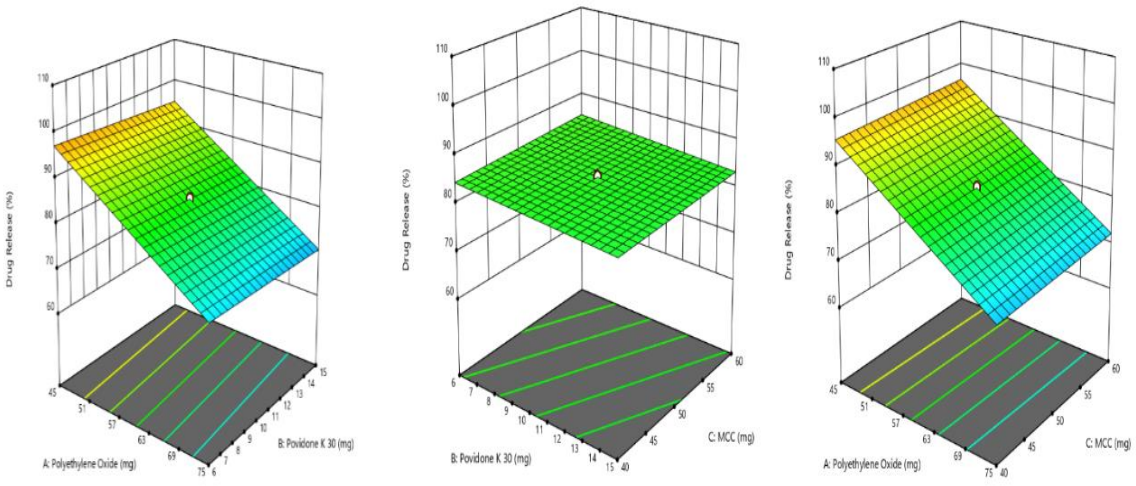

Figure 4 3D Surface plots for drug release

Similarly, 3D surface plots (Figure 5) for hardness showed a linear relationship between the independent variables and hardness. The concentrations of MCC, polyethylene oxide, and povidone K 30 were directly proportional to hardness indicating increase in concentration of these excipient shows increase in the tablet hardness values.

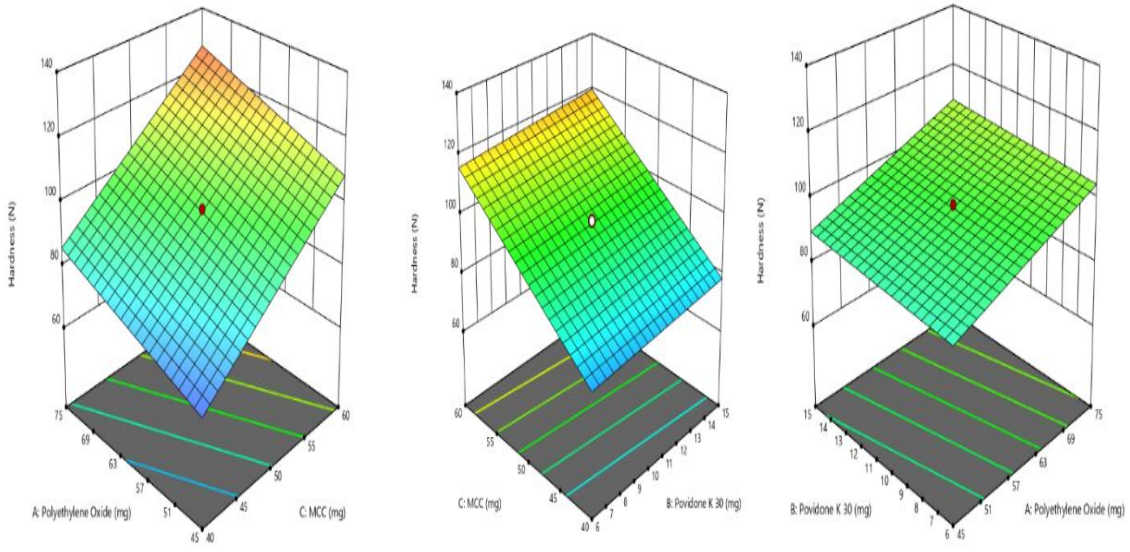

Figure 5 3D Surface plots for hardness

The desirability approach was adopted to achieve the desired formulation outcomes. The optimized range for dissolution after 12 h was set between 80-100% and tablet hardness values between 70-130 N. These values were fitted into a desirability model, and the ideal concentrations of the independent variables for optimal performance were predicted. Three formulations (Table 14) were manufactured based on these predictions, and theoretical values were compared with actual results. Predicted and actual values (Table 15) aligned closely, defining a design space for the formulation that allows for response predictions with changes in input variables. The red zone in Figure 6 represents the input variable range with a desirability score of 1, i.e., the design space that will produce optimal responses.

Table 14 Composition and results for optimized batches with one desirability

Sr. No.	Polyethylene Oxide	POVIDONE K30	MCC	Drug Release	Hardness
F1	49.13	14.29	54.40	92.00	101
F2	64.75	9.12	44.76	80.00	88
F3	48.90	14.35	50.07	91.96	91

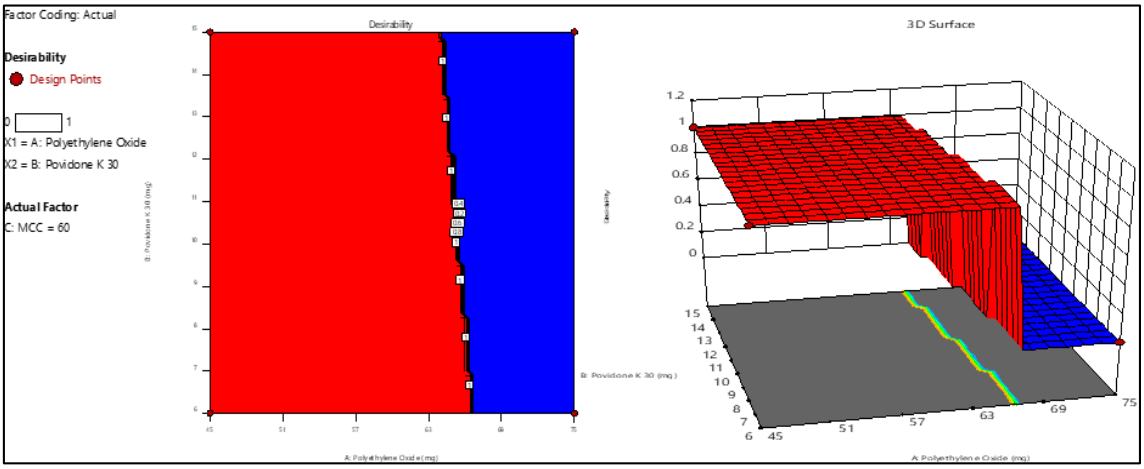

Figure 6 Desirability plot displaying Zone in red where all optimum responses can be achieved.

Table 15 Predicted vs. Actual Responses

Formulation	F1		F2		F3	
	Hardness	Drug Release	Hardness	Drug Release	Hardness	Drug Release
Predicted value	101	92	88	80	91	91.96
Actual value	100	92.72	86	79.49	90	91.73

The similarity of the Optimized formulation with the RLD

The composition of the optimized formulation is provided in Table 16. The dissolution profile of the optimal formulation was compared with the Reference Listed Drug (RLD) by calculating the dissimilarity factor (F1) and similarity factor (F2). The results are presented in Table 17, with a graphical representation shown in Figure 7.

Table 16 Composition of Optimized Formulation

Sr. no.	Ingredients	Quantity per tab (mg)
1	Diclofenac Sodium	100.0
2	Microcrystalline cellulose	60.0
3	Lactose monohydrate	65.0
4	Polyethylene Oxide	45.0
5	POVIDONE K30	6.0
6	Talc	15.0
7	Magnesium stearate	9.0
Total Tablet weight		**300.0**

Table 17 Comparative dissolution profiles of Optimized formulation and RLD

Time in Hours	Voveran® Tablets 10 mg	Optimized Formulation
	% Drug Release	
1	0	0
2	0	0
3	1.99	1.21
4	11.16	12.92
5	21.13	22.46
6	31.89	30.75
7	43.06	40.06
8	51.43	50.51
9	62.19	61.44
10	72.16	70.79
11	78.54	79.82
12	88.90	88.14
Difference factor (f1)	-	2.35
Similarity factor (f2)	-	88.93

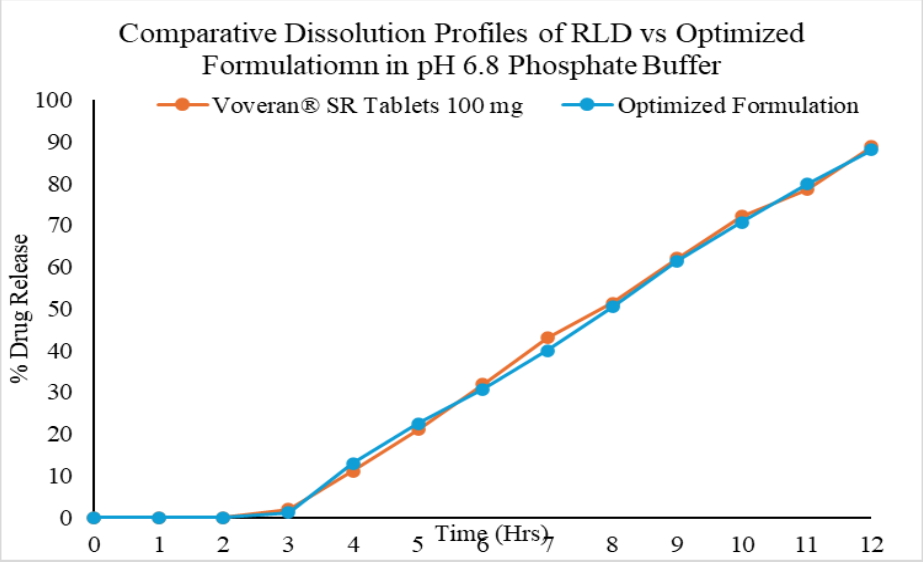

Figure 7 Comparative dissolution profiles of optimized formulation and RLD

DISCUSSIONS:

The successful implementation of the Quality by Design (QbD) framework in the development of Diclofenac Sodium SR tablets provided a robust and systematic approach to product formulation. The comprehensive characterization of Voveran® SR 100 mg,

the reference-listed drug (RLD), facilitated the definition of a Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs), ensuring that key performance criteria were met. The focus on drug release and mechanical properties, such as hardness, was essential to matching the RLD and ensuring product consistency.

Key formulation variables, polyethylene oxide, povidone K30, and microcrystalline cellulose were identified through a 2^{5-1} fractional factorial design. The statistical analysis highlighted that Polyethylene Oxide significantly contributed to sustained drug release, while Povidone K30 and MCC influenced both dissolution and hardness. Polyethylene Oxide, serving as the release-modulating polymer, exhibited an inverse relationship with drug release, where higher concentrations prolonged the release, aligning with its role in matrix formation. Povidone K30, as a binder, contributed to formulation cohesiveness but also played a critical role in modulating drug release by enhancing the compactability of the blend. MCC, known for its disintegrant properties, was found to have a direct proportional effect on both drug release and hardness, confirming its dual role as a diluent and disintegrant in the tablet matrix.

During the Central Composite Design optimization phase, the interactions among the three critical variables were explored in depth. The statistical models and 3D surface plots confirmed that Polyethylene Oxide and Povidone K30 were inversely related to drug release, while MCC exhibited a positive correlation. The hardness of the tablets showed a linear increase with higher concentrations of all three variables, underscoring their influence on the mechanical strength of the formulation. The optimization process successfully delineated a design space that ensured minimal variability in drug release (80-100% after 12 hours) and tablet hardness (70-130 N).

The optimized formulations were evaluated against the RLD, and the calculated similarity factor (F2 = 88.93) demonstrated that the dissolution profiles of the optimized tablets closely matched those of Voveran® SR 100 mg, confirming pharmaceutical equivalence. This alignment of experimental results with model predictions validated the reliability of the QbD approach in achieving consistent, high-quality outcomes. Moreover, the risk assessment of the final formulation indicated that the potential variability in drug release and hardness had been reduced to a low level, ensuring product robustness and regulatory compliance.

The successful application of the QbD framework in this study not only ensured the development of a bioequivalent sustained-release formulation but also provided insights into the critical role of excipient interactions in modulating drug release and tablet hardness. These findings highlight the importance of using a systematic approach to optimize formulation variables, ensuring the reproducibility and consistency of generic pharmaceutical products.

The implementation of the Quality by Design (QbD) framework in developing a generic SR formulation of Diclofenac Sodium demonstrated the robustness and efficiency of this systematic approach. The initial phase of this study involved the comprehensive characterization of the RLD, Voveran® SR 100 mg Tablets, establishing a baseline for the QTPP and CQA). The defined QTPP ensured that the new formulation met pharmaceutical equivalence requirements—the identification of CQAs through risk assessment allowed for a focused approach in the subsequent formulation development. The key attributes influencing the formulation, such as assay, content uniformity, and drug release, were thoroughly evaluated. The screening Design of Experiments (DoE) facilitated the identification of the significant variables, namely Polyethylene Oxide, Povidone K30, and Microcrystalline Cellulose (MCC), which were found to impact drug release and hardness significantly.

During the screening phase, a 2^{5-1} fractional factorial design allowed for the identification of the primary factors affecting drug release and hardness. The optimization phase utilized CCD to define a design space where

variations in the parameters would not significantly alter the studied responses. The CCD approach enabled a comprehensive evaluation of the interaction and quadratic effects of the independent variables. Statistical analysis of the responses indicated that the linear model was significant for both drug release and hardness. The desirability approach was instrumental in determining the optimal range for dissolution and hardness, resulting in three optimized formulations. The predicted values were closely aligned with the actual experimental outcomes, reinforcing the reliability of the optimization model. Comparative analysis with the RLD, using dissimilarity (F1) and similarity factors (F2), confirmed the equivalence of the optimized formulation. This approach not only facilitated regulatory compliance but also established a strong foundation for continuous improvement in pharmaceutical development. The updated risk assessment for formulation variables based on the optimization results is given in Table 13.

Table 13 Updated risk assessment for formulation variables

Drug Product CQAs	Formulation Variables			
	Concentration of Diluents	The concentration of Release Controlling Polymer	Binder Concentration	Glidant andlubricant concentration
Assay	Low*	Low	Low	Low
Content Uniformity	Low*	Low	Low	Low
Drug Release	Low*	Low*	Low*	Low*

* The risk was reduced to low

CONCLUSION

The successful application of QbD methodologies in the development of a generic SR formulation of Diclofenac Sodium highlights the efficacy of these systematic approaches in pharmaceutical development. The comprehensive characterization of the RLD, coupled with rigorous screening and optimization phases, allowed for the identification and fine-tuning of critical formulation variables. The resulting optimized formulation demonstrated a dissolution profile and mechanical properties comparable to the RLD, confirming its equivalence and meeting regulatory standards.

This study underscores the importance of QbD principles in ensuring the robustness, consistency, and regulatory compliance of pharmaceutical products. By defining a clear design space and utilizing predictive regression models, the development process not only achieved the desired quality attributes but also established a framework for continuous improvement. The findings provide a valuable reference for future generic drug development, demonstrating that a structured, science-based approach can lead to the successful formulation of high-quality pharmaceutical products.

EXPERIMENTAL

Materials:

Diclofenac sodium was generously provided by Kirti Pharmaceuticals, Nashik. India All additional excipients were sourced from local vendors. All reagents utilized for analytical procedures were of analytical grade.

Selection of Manufacturing Process:

The formulation of Diclofenac Sustained Release Tablets commenced utilizing the direct compression technique. This method was chosen for its simplicity, enhanced scalability, and cost efficiency. Diclofenac sodium and all the excipients were mixed, and the resulting blend was compressed using 9 mm round biconvex punches fitted to a Single Rotary Compression

machine(Royal Artist, Mumbai, India)

Formulation Development for Diclofenac Sodium Sustained Release Tablet:

The Design of Experiment (DoE) screening methodology was applied to identify key input variables that impact the DP-CQAs. A $^{25-1}$ fractional factorial design with a resolution V was chosen for the preliminary experiments.

In vitro dissolution profile:

The in-vitro dissolution study was performed in pH 6.8 Phosphate buffer using USP type-II (Paddle) at a speed of 50 RPM in Electrolab Dissolution apparatus. The content of Diclofenac was determined using a UV Spectrophotometer (Jasco, Japan)

Optimization of formulation and building Design space:

Prototype formulation developed from screening experiments was optimized using Response surface methodology (RSM), a widely practiced approach in developing and optimizing drug delivery. Based on the principle of design of experiments (DOE), the methodology encompasses various experimental designs, generation of polynomial equations, and mapping the response over the experimental domain to determine the optimum formulation(s). The central composite design was selected for the optimization model building, while the desirability approach was used to predict the responses from optimized formulations. The statistical validity of the polynomials was established based on the analysis of variance (ANOVA) provision in the Design Expert software (Version 12 Stat-Ease, Inc.).

STATEMENTS AND DECLARATIONS

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Conflict of interest:

The authors declare that there is no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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تطبيق الجودة من خلال التصميم في تطوير المنتجات الدوائية الجنيسة: دراسة حالة باستخدام أقراص ديكلوفيناك الصوديوم ممتدة المفعول

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ملخص

تهدف هذه الدراسة إلى تطبيق مبادئ الجودة من خلال التصميم (QbD) في تطوير المنتجات الجنيسة من أجل وضع تركيبة متينة ومتسقة ومتوافقة مع المتطلبات التنظيمية .تم اختيار ديكلوفيناك الصوديوم كدواء نموذجي لتطوير تركيبة أقراص ممتدة المفعول .استُخدمت أقراص فوفيران ®إس آر 100مغ كدواء مرجعي مسجّل (RLD)، وتم تحديد ملف تعريف الجودة المستهدف وسمات الجودة الحرجة .جرى تحديد المتغيرات الرئيسية في التركيبة التي تؤثر على انطلاق الدواء وصلابته باستخدام التقييم الأولي للمخاطر .وتم اعتماد تصميم عاملي كسري 1-25لفحص العوامل المهمة المؤثرة في صفات التركيبة .بعد ذلك جرى تحسين التركيبات باستخدام تصميم مركب مركزي لتحديد مساحة تصميمية تضمن ثبات انطلاق الدواء وصلابته .استُخدم نهج الاستحسان لتأكيد الظروف المثلى وتوليد تنبؤات دقيقة .وقد تقاربت القيم الفعلية بشكل كبير مع تنبؤات النموذج .أظهرت التركيبات المحسنة انطلاقًا للدواء يتراوح بين 80و 100%بعد 12ساعة وصلابة تتراوح بين 70و 130نيوتن .كما أظهرت التركيبة المحسنة تشابهًا ممتازًا مع الدواء المرجعي، حيث سجلت قيمة F2أكبر من 50.تؤكد هذه الدراسة فعالية النهج القائم على الجودة من خلال التصميم في تطوير الأدوية، مبرزة دوره في تحقيق معايير الجودة المحددة سلفًا والامتثال للتنظيمات مع دعم التحسين المستمر.

الكلمات الدالة: الجودة من خلال التصميم؛ تصميم التجربة؛ تحسين التركيبة؛ التصميم العاملي الكسري؛ التصميم المركب المركزي؛ الاستحسان؛ ديكلوفيناك.

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