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QUALITY BY DESIGN APPROACH TO OPTIMIZE OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT: The present investigation deals with the development of the controlled porosity osmotic pump (CPOP) tablet of *Garcinia indica* fruit rind extract used in the management of colon cancer by implementing the concept of Quality by Design (QbD). The quality target product profile (QTPP) and Critical Quality Attributes (CQA) of the *Garcinia indica* tablets were defined based on preliminary studies. The effects of critical parameters were investigated by executing the design of experimentation (DOE) using 3² factorial design. The inclusion complexes of *Garcinia indica* and HP-βCD were added with an optimized amount of sodium chloride in the core of the tablet and coated with cellulose acetate. Multiple regression analysis and ANOVA were employed to identify and to estimate the effect of important parameters and establish their relationship with CQAs. The results of multiple linear regression analysis revealed that CPOP tablets should be prepared using an optimum % weight gain of the tablet (X1) and concentration of pore-forming agents in the coating (X2) to achieve a zero-order drug release. The contour plot suggests that independent variables X1 and X2 were found by 10.6% and 7.2 gm. respectively, for a maximized response. The drug release was inversely proportional to the membrane weight but directly related to the initial level of pore former in the membrane. The study indicated that the feasibility of extending the zero-order release pattern of *Garcinia indica* fruit rind extract was better achieved with controlled porosity osmotic pump tablet for the treatment of colon cancer.

INTRODUCTION: Controlled-porosity osmotic pump (CPOP) is the type of osmotic tablet in which the delivery orifices are formed by the incorporation of a leachable component into the coating solution.

After coming into contact with water, this soluble additive dissolves, resulting in an in situ formation of a microporous semipermeable membrane^{1, 2}. The method to create the delivery orifice is relatively simple with the elimination of the common laser drilling technique and hence it is also cost-effective.

The release rate depends upon the solubility of the drug in the tablet core, the osmotic pressure gradient across the membrane, the coating thickness, and the level of a leachable component in the coating³⁻⁵.

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Garcinia indica (dried rind known as 'kokum'), family Clusiaceae, a tropical fruit, can be viewed as a wonder berry that has a myriad of health benefits and also pharmacologically studied for its anti-oxidative, chelating, free radical scavenging, anticancer, anti-inflammatory, and antiulcer activities⁶⁻⁹. The ethanolic extract of *Garcinia indica* fruit rinds exhibited significant antioxidant and cytotoxic activity¹⁰⁻¹². Therefore, the extract was used for further formulation development studies.

The application of Quality by Design (QbD) in pharmaceutical product development is now a thrust space for the regulatory authorities and the pharmaceutical industry¹³⁻¹⁴. In this study, a QbD approach was used for a better understanding of the relationship of critical formulation and process parameters to CQAs relating to the quality product profile of the CPOP tablet of *Garcinia indica*. The inclusion complexes of *Garcinia indica* were added with an optimized amount of sodium chloride in the core of the tablet and coated with cellulose acetate.

The effects of critical parameters were investigated by executing the design of experimentation (DOE) using 3² factorial designs. Tablets were evaluated for *in-vitro* drug release, membrane integrity, the effect of pH and agitation intensity, *etc.* Different Response surface graphs, counterplots, ANOVA test is applied to understand the correlation and significance of critical parameters on QTPP. Based on the impact of critical formulation variables on QTPP, the proposed design space was utilized to obtain robust formulation.

MATERIALS AND METHODS: Fresh kokum fruits were collected and authenticated by the Botanical Survey of India, Pune, Maharashtra, India. Cellulose Acetate was procured from Signet Chemicals Corporation Pvt. Ltd., Mumbai, NaCl, HPMC, HP β -Cyclodextrin was procured from Loba chem. Pvt. Ltd., Mumbai. The rest of the chemicals and reagents were of analytical grade.

Preparation of CPOP Tablets¹⁶: Inclusion complexes of *Garcinia indica* extract with HP β -CD were prepared by the solvent evaporation method¹⁵. Compatibility studies of inclusion complexes were carried out using FTIR and DSC studies. The level of osmotic agent used in the core

was optimized in the previous study and depicted in **Table 1**.

Accurately weighed quantity of each ingredient was passed through sieve # 85. The ingredients were manually blended homogeneously in a mortar. The mixture was moistened with a non-aqueous solution and granulated through sieve # 30 and dried in a hot air oven at 60 °C for sufficient time (3-4 h). The dried granules were passed through sieve #30 and blended with talc and magnesium stearate. The homogeneous blend was then compressed into tablets with standard concave punches using eight-station rotary compression machines (Mini press, Karnavati, India).

TABLE 1: COMPOSITION OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS OF *GARCINIA INDICA*

Ingredients	Quantity (mg)
GI+ HP β CD	300
NaCl	120
Sodium Starch glycollate	4
Dicalcium Phosphate	24
Talc	1
Mg stearate	1
Total wt	450

Coating of Core Tablets¹⁷: Cellulose acetate (3% w/v) in a mixture of acetone containing known levels of plasticizer (castor oil) and varying level of the pore-forming agent (HPMC) was used as a coating solution. The coating of tablets was performed by using R & D coater. Hot air is supplied to tablet bed by rotating lower speed 10-15 rpm initially. The coating of tablets was carried out with the rotation speed of 15-30 rpm. The spray rate and atomizing air pressure were 1-2 ml/min and 1-2 kg/cm², respectively. Inlet and outlet air temperatures were 35 °C and 55 °C, respectively. Coated tablets were dried at 50 °C. The process was continued until 10% weight gain of the tablets. The coated tablets were rotated for a further 15 min under the blower.

Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA):¹⁸⁻¹⁹ The quality target product profile (QTPP) is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product²⁰. QTPP elements were depicted in **Table 2**.

TABLE 2: PREPARATION OF QTPP

QTPP Elements	Target Product	Quality Profile (TPQP)	Justification
Dosage form		Tablet	Tablet because of ease of administration and patient compliance
Dosage design	Osmotically controlled release		Drug release is independent of pH and agitation intensity
Route of Administration		Oral	Dosage form designed to be administered orally
Dosage strength		300 mg	Commonly acceptable strength
Appearance		Coated tablet	For extended drug release
% Friability		NMT 1.0%	Pharmaceutical quality standard requirements
Hardness		NMT 6 kg/cm ²	Pharmaceutical quality standard requirements
Stability	Short term stability of accelerated condition at 40°C/75% RH and long-term condition (24 months) at 25°C/60% RH		Minimum period (3Months and 6 Months) decided to study the stability of an optimized formulation
Extended Drug Release		≥12 hrs up to 24 h	Up to 16 hrs extended release of a model drug

Identification of Critical Quality Attributes: A critical quality attribute (CQA) is a physical, chemical, biological, or microbiological property or

characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality²¹. CQAs were represented in **Table 3**.

TABLE 3: CRITICAL QUALITY ATTRIBUTES

Quality Attributes of the Drug product	CQA (Yes/No)	Justification
Physical Attributes	Appearance	No
	Size	No
	Friability	Yes
	Hardness	Yes
The concentration of osmotic agent	Yes	Appearance is not directly linked to safety and efficacy. The target is set to ensure patient acceptability and to match the reference product For patient acceptance and compliance with the regimens. The tablet dimensions are set close to reference product dimensions
The concentration of coating polymer and coating thickness	Yes	Friability is critical and directly linked to integrity during packaging and transport of the drug product. The drug product is uncoated tablets. Thus, friability will be monitored throughout product and process development
Amount of pore-forming agent	Yes	Hardness will affect friability, disintegration, and dissolution that can impact bioavailability. Both formulation and process variables affect the hardness
Assay and content uniformity	Yes	The concentration of osmotic agents is required to produce osmotic pressure for the drug release. So it's the critical parameter directly linked to the product quality
Dissolution		Improper concentration may affect dissolution
		Yes
	Yes	Variability in the amount of pore-forming agent will direct effect on the membrane integrity and drug release from the coated tablet
	Yes	Variability in assay and content uniformity will affect safety and efficacy. It impacts both formulation and process variables
	Yes	Failure to meet the dissolution specification can impact the bioavailability of the drug product. Both, formulation as well as process variables affects the dissolution profile. Hence, dissolution is critical and will be evaluated during formulation and process development

Experimental Design: 3² factorial design was employed to optimize the concentration of HPMC (X1) and % weight gain (X2) as the factors studied at three levels each as depicted in **Table 4**. All other formulations and processing variables were kept invariant throughout the study. **Table 5** summarizes an account of the 9 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. % drug release at 12 h (Y1) and 24 h (Y2) were taken as response variables. Response surfaces were constructed

using the Design Expert Software (Version 10.0, Stat-Ease Inc., Minneapolis, U.S.A.).

TABLE 4: VARIABLES AND THEIR LEVELS IN 3² FACTORIAL DESIGN

Independent Variables	Levels		
	Low	Medium	High
X1= Weight Gain (%)	8	10	12
X2 = Conc. of HPMC (gm)	2.5	5	7.5
Transformed value	-1	0	+1
Dependable variable	Y1 = % Drug release at 12 h (Q12) Y2 = % Drug release at 24 h (Q24)		

Data Transformation: The data transformation showed in **Table 5** simplifies the calculations for model development. The data generated by the experimental design was utilized for drawing

contour plot, for obtaining an optimized region within the factorial space and thereby produce an optimized formulation.

TABLE 5: COMPOSITION OF DESIGN BATCHES IN CODED AND TRANSFORMED FORM

Batch code	Coded values		Transformed values	
	X1	X2	Weight Gain	HPMC
F1	-1	-1	8	2.5
F2	-1	0	8	5
F3	-1	1	8	7.5
F4	0	-1	10	2.5
F5	0	0	10	5
F6	0	1	10	7.5
F7	1	-1	12	2.5
F8	1	0	12	5
F9	1	1	12	7.5

Characterization of CPOP Tablets ²⁰:

Weight Variation Test: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of twenty tablets were calculated.

Thickness: The thickness of the core tablets was measured by using a screw gauge. Ten tablets from each batch were randomly selected and used. Thickness is expressed in millimeters.

Hardness: The hardness of randomly selected tablets was tested using Monsanto hardness tester.

Drug Content: The powder is made after triturating 10 CPOP tablets from each batch with mortar and pestle. The powder weight equivalent to one tablet was dissolved in a 100 ml volumetric flask filled with pH 6.8 phosphate buffer and kept on a rotary shaker for 24 h in order to completely extract the drug. The mixture was filtered, and the drug was assayed spectrophotometrically at 253 nm.

In-vitro Release Studies ²¹: The release rate of *Garcinia indica* from CPOP tablets was determined according to the USP using a rotating paddle method. The dissolution test was performed using 900 ml of acidic buffer (pH 1.2) for the first 2 h and phosphate buffer (pH 6.8) for the subsequent 24 h. The stirring speed of the paddle was 100 rpm, and the temperature was maintained at 37 °C ± 0.5 °C. A 5 ml samples were withdrawn at various time intervals and filtered through a 0.45 µm membrane filter. The absorbance of these solutions was analyzed at λ_{max} 253 nm.

Statistical Analysis ²²: Statistical analysis of the batches prepared according to 3² factorial design was performed by multiple regression analyses using Microsoft Excel. Two-way analysis of variance (ANOVA) was performed using the Design-Expert software to evaluate the contribution of each factor with different levels to the response. To graphically demonstrate the influence of each factor on the response, the response surface plots were generated using the Design-Expert software.

Checkpoint Analysis ²³: A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken at 3 points, 1 from each contour plot & the theoretical values of % CDR were calculated by substituting the values in the polynomial equation. CPOP tablets were prepared experimentally at 3 checkpoints and evaluated for the responses.

Optimization Data Analysis: The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors).

Characterization of Optimized Formulation ²⁴:

Effect of pH: An osmotically controlled release system delivers its contents independent of external variables. The *in-vitro* drug release of optimized formulation was carried out in simulated gastric fluid (SGF, pH 1.2), phosphate buffer (pH 4.6) and phosphate buffer (pH 6.8).

Effect of Agitation Intensity: To study the effect of agitation intensity of the release media, release studies of the optimized formulation were carried

out at various rotational speeds *i.e.*, 50, 75, and 100 rpm in USP type-II dissolution apparatus.

Kinetics of Drug Release²⁵: The release data of the formulations were analyzed zero-order kinetics, first-order kinetics, Higuchi model and Korsmeyer-Peppas and Hixson-Crowell equations to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model.

Stability Study²⁶: The optimized formulation was packed in the strips of thick Aluminum foil laminated with PVC and stored in ICH certified stability chambers (Thermo lab, Stability chamber, Scientific Equipment's, Pvt. Ltd.) maintained at 40 °C and 75% RH for 6 months. The tablets were drawn periodically and evaluated for the appearance, drug content and dissolution profile.

RESULTS AND DISCUSSION: Inclusion complexes of *Garcinia indica* extract with HP β -CD were prepared. Drug polymer interactions were studied by FTIR and DSC. It was observed that there was no interaction between the drug and excipients as the characteristic peaks remained as such. DSC Study indicated that there were no

significant changes in the endotherm peak observed between drug and formulation.

QTPP and Critical Quality Attributes: Based on QTPP, CQAs were determined, such as drug dissolution, concentration of pore-forming agent, concentration of cellulose acetate and % weight gain of coated tablets for the dosage form. In the preliminary studies, the optimized concentration of osmotic agents was found to be 80%. A 3² factorial design was utilized in the present study for the optimization of coating parameters. In this design, two factors were evaluated, each at three levels, and experimental trials was carried out at all nine possible combinations.

Evaluation of Factorial Batches: All tablets of the factorial design batches were with a smooth surface, circular curved faced with good texture. All factorial batches were evaluated for weight variation and thickness of the film. The uniform thickness of the tablets throughout the batches ensures good tablet strength. There were no marked variations in the thickness of tablets within each formulation (<5%) indicating uniform behavior of granules throughout the compression process. Film thickness varies with a total weight gain of the tablet. Further observations were noted in **Table 6**.

TABLE 6: EVALUATION OF FACTORIAL BATCHES

Formula code	Coating thickness (mm)	Average* weight (mg)	Hardness (kg/cm ²)	Drug content* (%)	% Drug release
F1	0.22 ± 0.015	471.03 ± 0.67	6.73 ± 0.21	99.31 ± 0.061	76.10
F2	0.20 ± 0.127	475 ± 0.76	7.05 ± 0.17	98.25 ± 0.045	78.33
F3	0.21 ± 0.08	473.95 ± 0.32	6.56 ± 0.09	99.16 ± 0.031	81.54
F4	0.27 ± 0.05	474.02 ± 0.68	7.75 ± 0.07	99.96 ± 0.025	92.15
F5	0.28 ± 0.06	474 ± 0.75	7.30 ± 0.22	97.23 ± 0.091	97.20
F6	0.27 ± 0.135	475.96 ± 0.33	7.21 ± 0.34	99.98 ± 0.053	98.65
F7	0.30 ± 0.738	473.01 ± 0.66	7.33 ± 0.32	99.29 ± 0.076	83.81
F8	0.30 ± 0.916	475 ± 0.74	7.09 ± 0.15	99.98 ± 0.018	86.58
F9	0.31 ± 0.06	473.94 ± 0.31	6.97 ± 0.53	98.61 ± 0.031	90.24

* Mean ± S.D. (n = 3)

In-vitro Drug Release Study of Factorial Batches: The in vitro drug release characteristics were studied in 900ml of 0.1N HCl (pH 1.2) for a period of first 2 h and 3 to 24 h in phosphate buffer pH 6.8 using USP type II dissolution apparatus (Paddle type). The graphical representation of drug release study of the batches F1 to F9 is shown in **Fig. 1**. It was found that drug release increases as the concentration of HPMC increases, and it decreases as the thickness of the tablet increases. F6 batch was the optimized batch that showed maximum drug release, *i.e.*, 98.65%.

Statistical Analysis:

DOE Analysis and Selection of Model: In the present study, both the responses are suggested to be analyzed using the Quadratic model. Since all the criteria of closest adjusted R-squared and predicted R-squared value lowest PRESS value and significant p-value are satisfied. Model summary statistics are given in **Table 7**. As shown in the equation, a statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

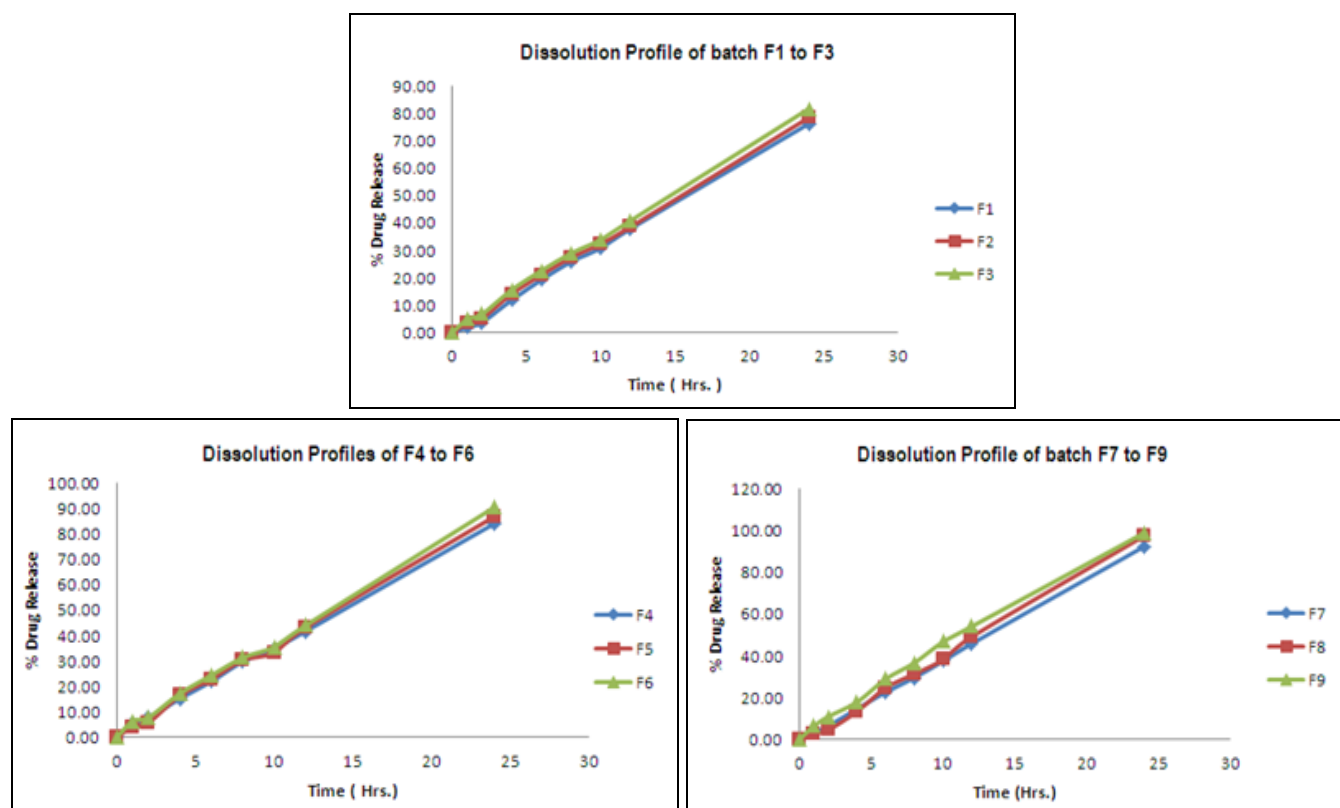


FIG. 1: IN-VITRO DRUG RELEASE STUDY OF FACTORIAL BATCHES

TABLE 7: MODEL SUMMARY STATISTICS FOR Y1 AND Y2

Source	Y1				Y2				Remark
	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	
Linear	0.2419	-0.0107	-0.5880	338.17	0.3086	0.0782	-0.3857	707.59	Nil
2FI	0.2425	-0.2121	-1.8184	600.18	0.3091	-0.1054	-1.4443	1248.16	Nil
Quadratic	0.9485	0.8627	0.8153	133.02	0.9953	0.9875	0.9642	18.30	Suggested
Cubic	0.9994	0.9949	0.8828	24.95	0.9955	0.9642	0.1844	416.47	Alise

Analysis of variance (ANOVA) of the responses indicated that response surface models developed for % drug release were significant and adequate, without significant lack of fit. It was observed that the %drug release indicates a high degree of correlation between the experimental and predicted responses. Also, the predicted R² value was in good agreement with the adjusted R² value, resulting in reliable models. The results of the ANOVA is depicted in Table 8.

Mathematical relationships generated for the studied response variables are expressed as equation Q24 = -259.99 + 67.97 * A + 1.191 * B + 0.049500 * AB -3.308 * A² - 0.461 * B²

A polynomial equation was found to be statistically significant (P<0.0001), as determined using ANOVA, as per the provision of design expert software.

TABLE 8: RESULT OF ANALYSIS OF VARIANCE (ANOVA)

Source of variation	Sum of Squares (SS)	df	Mean Square (MS)	F Value	p-value	Press	R-Squared	Adj R-Squared	Pred R-Squared	Adequate precision
Response Y1, % Drug Release at 12 h										
Model	201.98	5	40.40	11.05	0.0378	133.02	0.9485	0.8627	0.7753	9.737
Residual	10.96	3	3.65							
Cor Total	212.95	8								
Response Y2, % Drug Release at 24 h										
Model	508.25	5	101.65	127.48	0.0011	40.41	0.9953	0.9875	0.9642	20.691
Residual	2.39	3	0.80							
Cor Total	510.64	8								

DF indicates: degrees of freedom; F-Fischer's ratio; R²- regression coefficient

Analysis of Responses using Graphical Method:

To demonstrate the effect of % weight gain and the amount of pore-forming agent HPMC graphically, the contour and response surface plots were generated for the dependent variables Y1 and Y2. The response surface plot indicates that for 51.75 % drug release in 12 h. The % weight gain and concentration of HPMC are 10.17% and & 7.29 gm. The response surface plot indicates that for 98.74% drug release in 24 h. It shows that as weight gain increases the % drug release decreases.

As the concentration of HPMC increases, the drug release increases.

Checkpoint Analysis: For confirmation, a fresh formulation was prepared at the optimum values of the independent variables, and the resultant tablets were evaluated for the % drug release at 12 h and 24 h. The observed values of % drug release were found to be 54.84% at 12 h and 99.77% at 24 h, which were in close agreement with the predicted values.

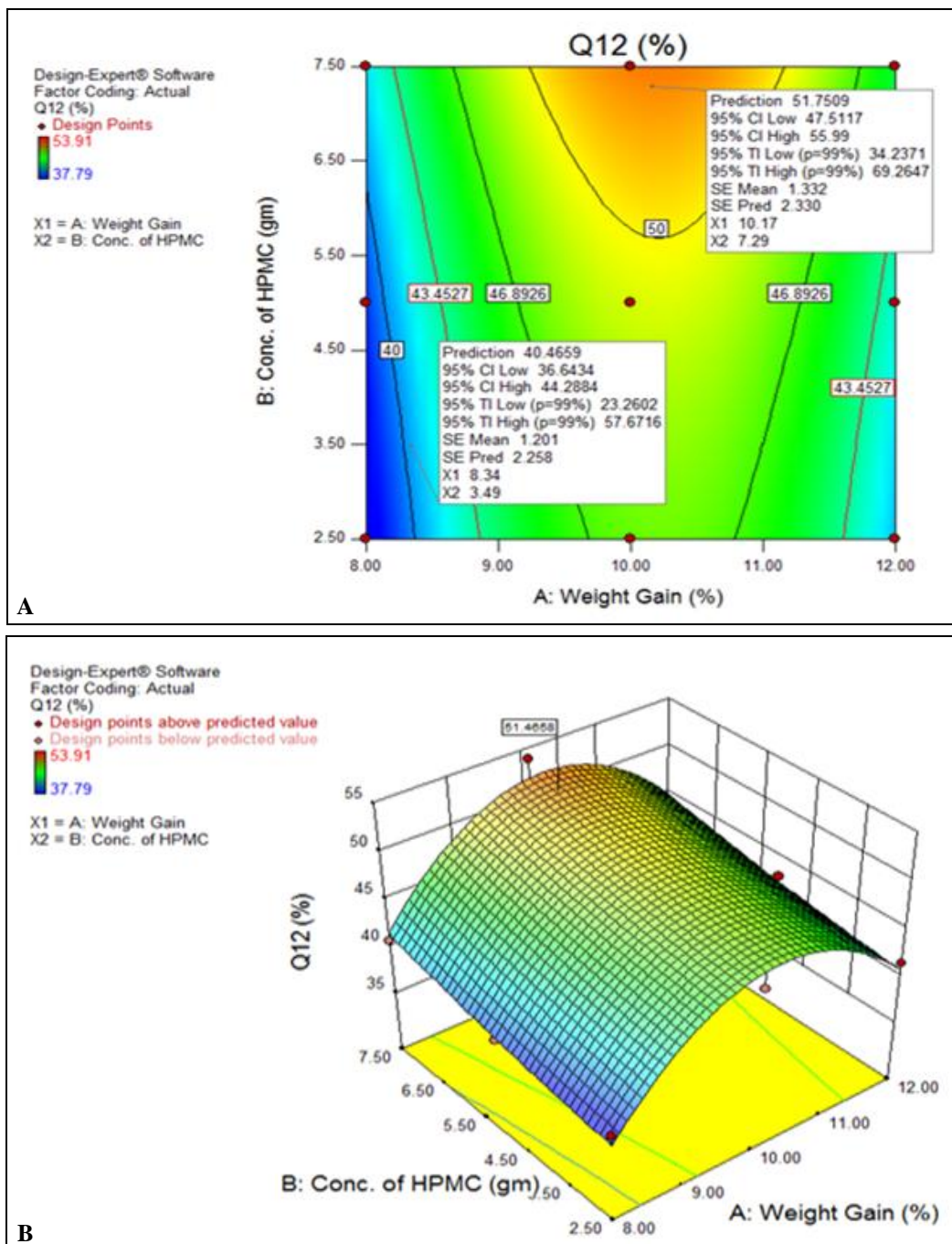


FIG. 2: (A) COUNTOUR PLOT AND (B) RESPONSE SURFACE PLOT SHOWING EFFECT OF FORMULATION VARIABLES ON % DRUG RELEASE Q12 (Y1)

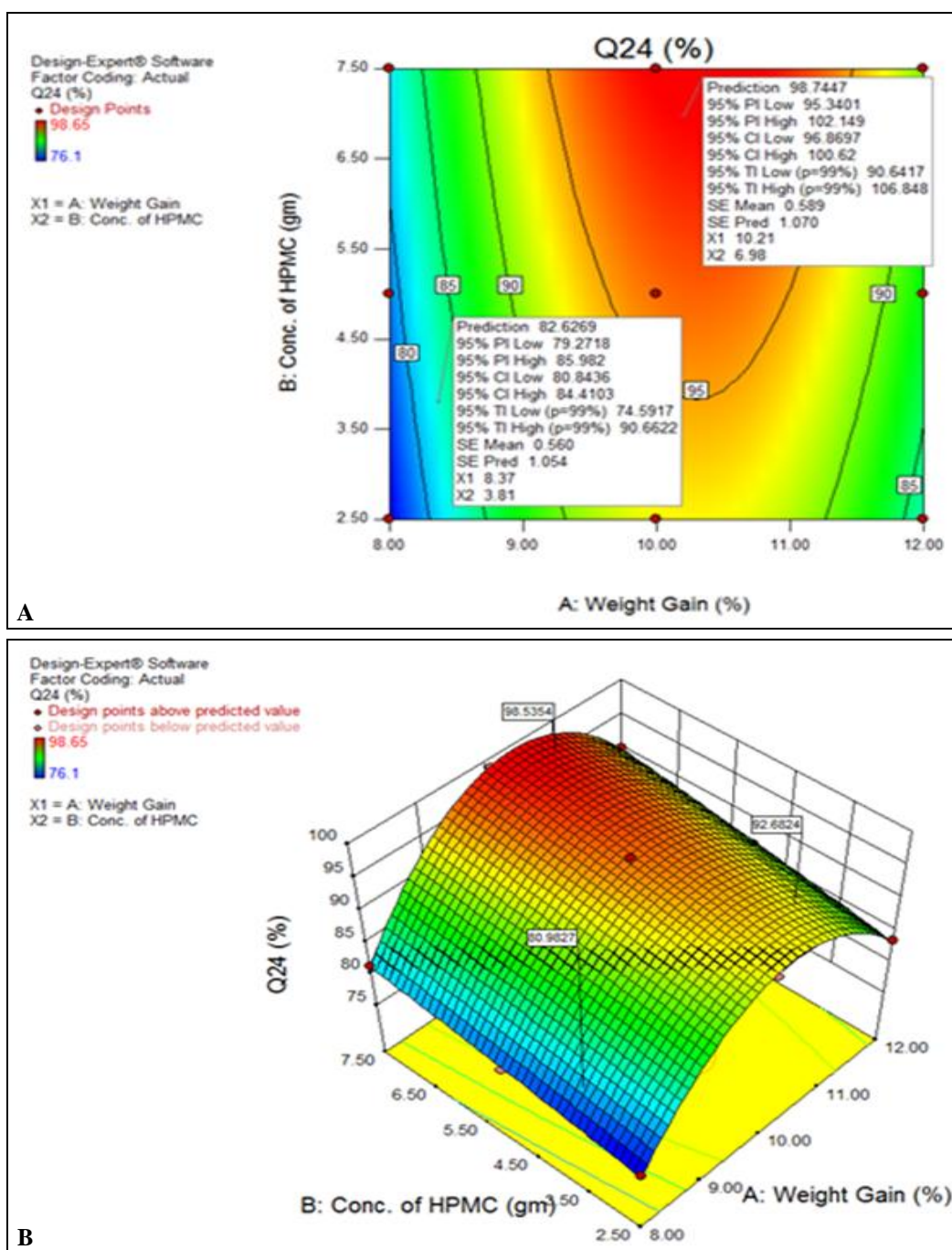


FIG. 3: (A) CONTOUR PLOT AND (B) RESPONSE SURFACE PLOT SHOWING EFFECT OF FORMULATION VARIABLES ON % DRUG RELEASE Q24 (Y2)

TABLE 9: EXPERIMENTAL AND PREDICTED VALUES FOR OPTIMIZED FORMULATION

Dependent Variables	Optimized Formulation	
	Experimental values	Predicted values
Weight gain	10.6	10.63
Conc. of HPMC	7.2	7.27
Q12	54.84	51.32
Q24	99.77	98.78

Establishing Design Space and Control Strategy: The concentration of pore former (HPMC) and % weight gain were found to be

critical on responses drug release. Based on the requirement of product quality, the criteria considered for responses were a minimum of 50 to 55% drug release within 12 h and more than 95% drug should be released in 24 h. Software predicted about 100 solutions of X1, and X2 to obtain the desired response with prediction value 1.00. In optimization Fig. 2 & Fig. 3 desirability 1 indicated that optimum formulation was achieved at 10.63% weight gain and 7.27 gm of HPMC. This study leads to the design space from a multi-dimensional

release profile and visual appearance like dimension, color change, thicknesses were monitored for 6 months; no significant changes

were observed. From the data presented in **Table 11**, the drug content remained more than 95% for 6 months.

TABLE 11: STABILITY STUDY

Parameters	Formulation code F6				
	Initial	1 month	2 months	3 months	6 months
Visual appearance	No Change	No Change	No Change	No Change	No Change
Drug content	99.98 ± 0.018	99.89 ± 0.62	99.85 ± 0.43	98.82 ± 0.34	97.11 ± 0.14
% Drug Release	98.56 ± 0.82	97.57 ± 0.79	97.18 ± 0.84	96.96 ± 0.88	96.90 ± 0.32

CONCLUSION: The desired release of *Garcinia indica* from CPOP was achieved through careful monitoring of the selected formulation variables—such as the level of an osmotic agent in the core, membrane weight gain, and level of pore former in the membrane. The drug release was inversely proportional to the membrane weight gain but directly related to the initial level of pore former in the membrane. Drug release from the developed formulations was independent of pH and agitation intensity. It was concluded that QbD approach was successfully implemented for the optimization of tablets based on the osmotic drug delivery system to achieve colonic delivery.

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