IJPSR (2020), Volume 11, Issue 11 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 November 2019; received in revised form, 03 March 2020; accepted, 21 March 2020; published 01 November 2020

QUALITY BY DESIGN APPROACH TO OPTIMIZE OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM

P. C. Jagtap [*1], P. Vijayalakshmi [2] and K. S. Bhise [3]

Department of Pharmaceutical Sciences [1], Jawaharlal Nehru Technological University Hyderabad - 500085, Telangana, India.
Department of Pharmaceutics [2], Teegala Krishna Reddy College of Pharmacy, Rangareddy, Hyderabad - 500097, Telangana, India.
Department of Pharmaceutics [3], MCE's Allana College of Pharmacy, Azam Campus, Camp, Pune - 411001, Maharashtra, India.

Keywords:

Controlled porosity osmotic tablet, Full factorial design, Quality by Design, Optimization, *Garcinia indica*

Correspondence to Author:
Prajakta Chandrakanat Jagtap

Research Scholar,
Department of Pharmaceutical Sciences, Jawaharlal Nehru Technological University Hyderabad - 500085, Telangana, India.

E-mail: jagtapprajakta86@gmail.com

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 3^2 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.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(11).5561-71

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(11).5561-71

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 coating [3-5].

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 activities [6-9]. The ethanolic extract of *Garcinia indica* fruit rinds exhibited significant antioxidant and cytotoxic activity [10-12]. 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 industry [13-14]. 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 3^2 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, HPβ-Cyclodextrin was procured from Loba chem. Pvt. Ltd., Mumbai. The rest of the chemicals and reagents were of analytical grade.

Methods: Inclusion complexes of *Garcinia indica* extract with HP β-CD were prepared by the solvent evaporation method [15]. 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 [16].

Preparation of CPOP Tablets: The inclusion complex of *Garcinia indica* with HP β-CD was used in the preparation of CPOP tablets due to poor solubility of the drug. The inclusion complex was prepared using the solvent evaporation method. CPOP tablets were prepared by wet granulation techniques with varying amounts of osmogen. The composition with an optimized amount of osmogen was depicted in **Table 1**.

Accurately weighed quantity of each ingredient was passed through sieve # 85. The ingredients were manually blended homogenously 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 ºC for sufficient time (3-4 h). The dried granules were passed through sieve #30 and blended with talc and magnesium stearate. The homogenous 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+ HPβCD	300
NaCl	120
Sodium Starch glycollate	4
Dicalcium Phosphate	24
Talc	1
Mg stearate	1
Total wt	450

Coating of Core Tablets: [17] 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/cm^{2,} respectively. Inlet and outlet air temperatures were 35 ºC and 55 ºC, respectively. Coated tablets were dried at 50 ºC. 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 product [20]. 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 quality[21]. 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	Appearance is not directly linked to safety and efficacy. The target is set to ensure patient acceptability and to match the reference product
	Size	No	For patient acceptance and compliance with the regimens. The tablet dimensions are set close to reference product dimensions
	Friability	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
	Hardness	Yes	Hardness will affect friability, disintegration, and dissolution that can impact bioavailability. Both formulation and process variables affect the hardness
The concentration of osmotic agent		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
The concentration of coating polymer and coating thickness		Yes	Improper concentration may affect dissolution
Amount of pore-forming agent		Yes	Variability in the amount of pore-forming agent will direct effect on the membrane integrity and drug release from the coated tablet
Assay and content uniformity		Yes	Variability in assay and content uniformity will affect safety and efficacy. It impacts both formulation and process variables
Dissolution		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: 3^2 factorial design was employed to optimize the concentration of HPMC (X1) and % weight gain (X2) as the factors studied at three levels each. All other formulations and processing variables were kept invariant throughout the study. **Table 4** 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 CENTRAL COMPOSITE 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 CCD 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 Release: [25] 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 Study: [26] 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 ºC 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 ß-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 3^2 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 osmotic tablet was subjected to *in-vitro* drug release studies in simulated gastric and intestinal fluid.

Fig. 1 represents the dissolution study performed in Phosphate Buffer pH 6.8. Hence 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.

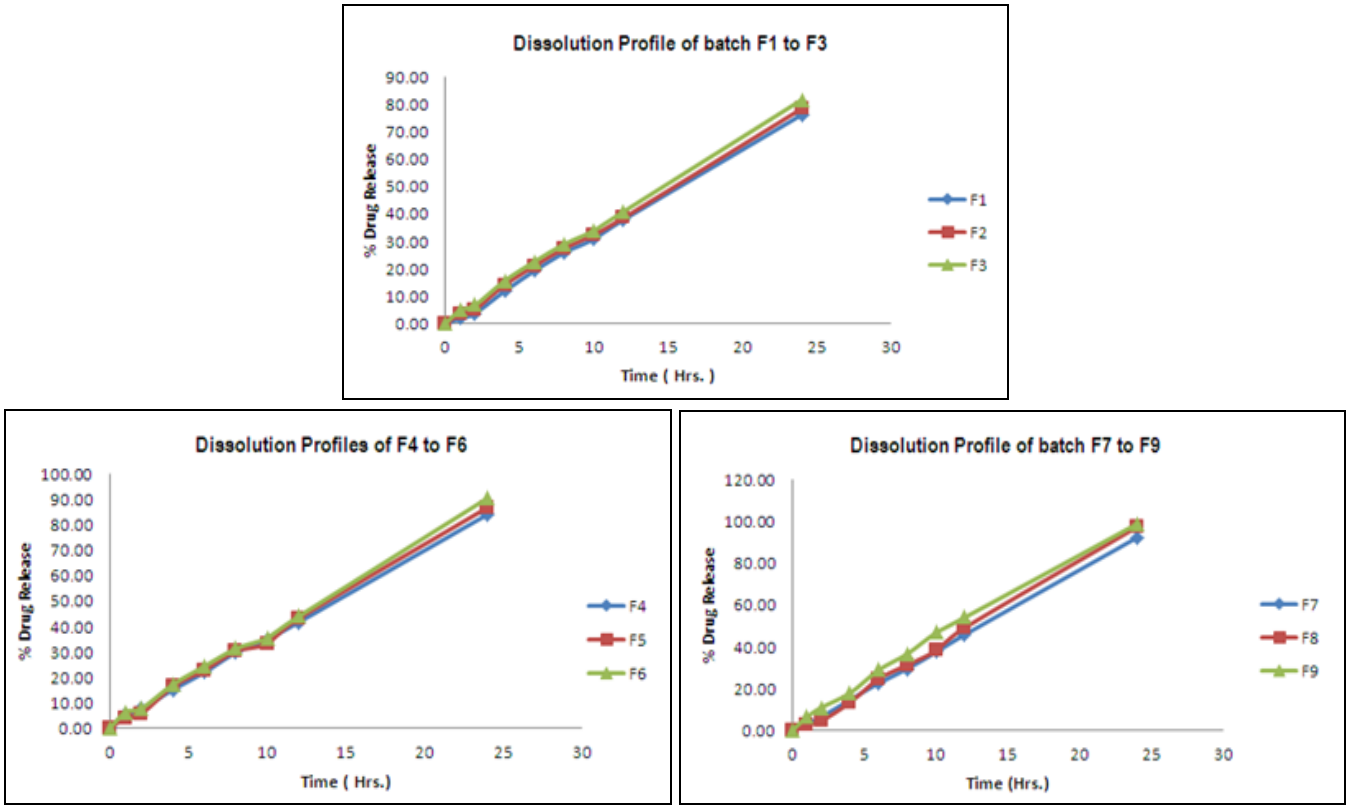


FIG. 1: *IN-VITRO* DRUG RELEASE STUDY OF FACTORIAL BATCHES

TABLE 7: MODEL SUMMARY STATISTICS FOR Y1 AND Y2

Source	Y1				Y2				
	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	Remark
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 R^2 value was in good agreement with the adjusted R^2 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 * A^2 – 0.461 * B^2

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

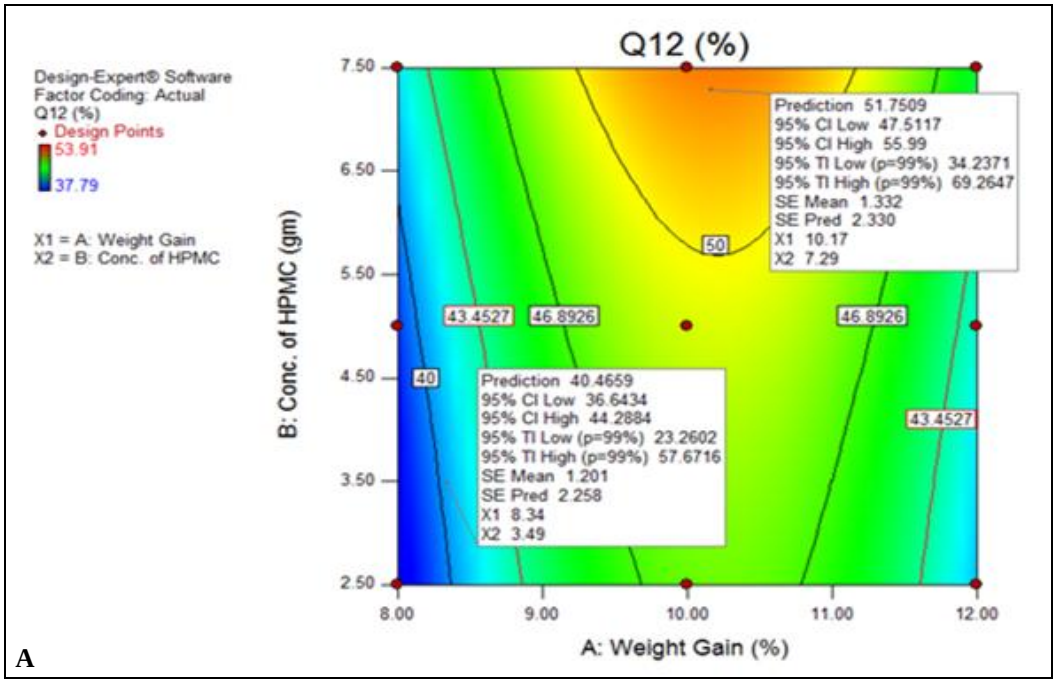
TABLE 8: RESULT OF ANALYSIS OF VARIANCE (ANOVA)

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; R^2- 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.



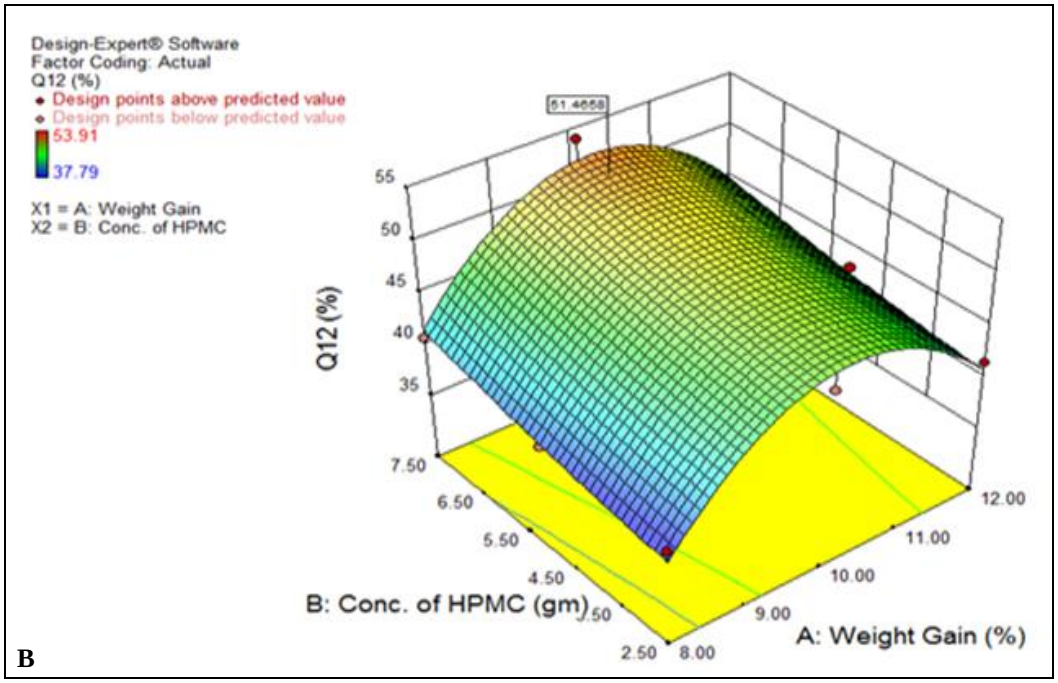


FIG. 2: (A) COUNTOUR PLOT AND (B) RESPONSE SURFACE PLOT SHOWING EFFECT OF FORMULATION VARIABLES ON % DRUG RELEASE Q12 (Y1)

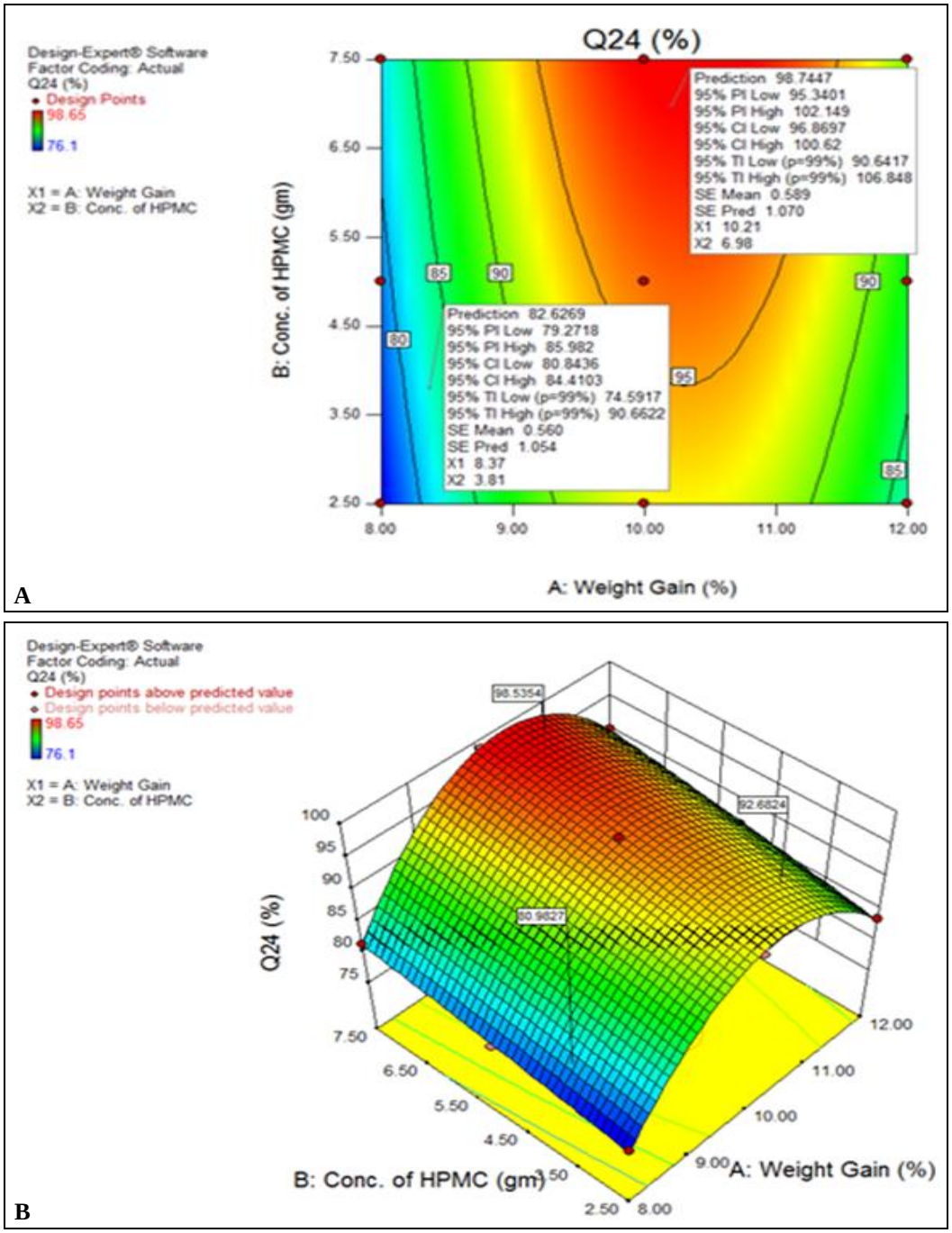


FIG. 3: (A) CONTOUR PLOT AND (B) RESPONSE SURFACE PLOT SHOWING EFFECT OF FORMULATION VARIABLES ON % DRUG RELEASE Q24 (Y2)

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

combination of concentration HPMC and % weight gain to the acceptable operating ranges for formulating CPOP tablets concerning the target product profile. When critical variables operated within the established design, space compliance to CQAs would be assured. The design space is shown in **Fig. 4**, also called an overlay plot, which is a shaded region with yellow color, indicates that region of successful operating ranges.

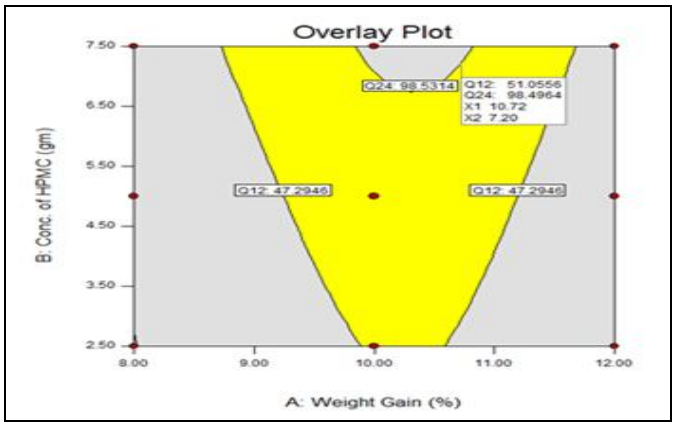


FIG. 4: OVERLAY PLOT OF RESPONSE VARIABLES

Characterization of Optimized Formulation:

Effect of pH on Optimized Formulation: Release studies of the optimized formulation were conducted to study the effect of pH on drug release using a pH change method. The release media was simulated gastric fluid (SGF, pH 1.2), Phosphate buffer (pH 6.8), and Phosphate buffer (pH 7.2). **Fig. 5** showed release of drug from the optimized formulation, and it is evident that the release profile is similar in all the media, demonstrating that the developed formulation has a pH-independent release.

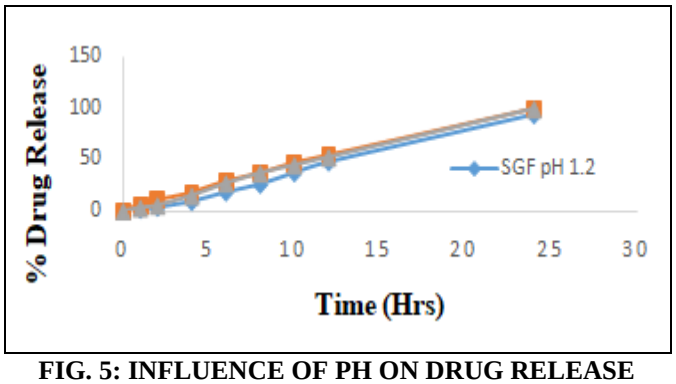


FIG. 5: INFLUENCE OF PH ON DRUG RELEASE

Effect of Agitation Intensity on Optimized Formulation: Fig. 6 represents the release profile of the drug from the optimized formulation is independent of the agitation intensity of the release media and hence, it can be expected that the release from the developed formulation will be independent of the hydrodynamic conditions of the body.

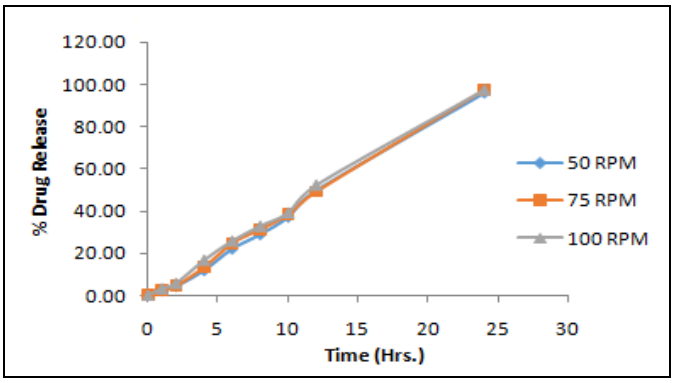


FIG. 6: INFLUENCE OF AGITATION INTENSITY

Kinetics of Drug Release for Factorial Batches: Dissolution profiles of the optimized formulation F6 was fitted to various mathematical models (zero-order, first-order, Higuchi, Korsmeyer Peppas, and Hixson Crowell Model) to describe the kinetics of drug release as showed in **Fig. 7**. It is evident from the data that Zero Order Kinetic and Korsmeyer-Peppas model was the best fit model for batch F6. The value of n is indicative of the release mechanism. Here $0.5 < n < 1$ so, anomalous (non-fickian) diffusion was seen. The observations were summarized in **Table 10**.

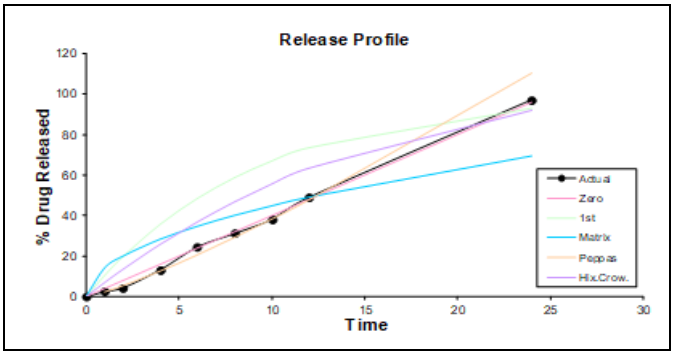


FIG. 7: KINETIC OF DRUG RELEASE PROFILE OF OPTIMIZED FORMULATION F6

TABLE 10: KINETICS OF DRUG RELEASE OF OPTIMIZED FORMULATION F6

Formulation code	Model	R	K
F6	Zero-order	0.9987	4.4474
	First order	0.9781	-0.1208
	Matrix	0.9165	16.0722
	Korsmeyer Peppas	0.9980	5.7985
	Hixson Crowell	0.8816	-0.0418

Stability Study: The optimized formulation F6 was subjected to the stability study at 40 °C and 75 % RH for 6 months as per ICH guidelines. Drug

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 factorial design was a successful tool for the optimization of tablets based on the osmotic drug delivery system to achieve colonic delivery.

ACKNOWLEDGEMENT: I wish to express my sincere gratitude to Principal Dr. (Mrs.) Kiran Bhise and the Management of M.C.E. Society's Allana College of Pharmacy, Pune, for allowing me to carry out the research work and for their support throughout the work. I would like to express my gratitude towards Dr. Vijayalakshmi Prakya, Principal, Teegala Krishna Reddy College of Pharmacy, Hyderabad, and Jawaharlal Nehru Technical University, Hyderabad, Telangana, India for continuous support and guidance.

CONFLICTS OF INTEREST: All authors stated that there are no conflicts of interest.

REFERENCES:

1. Lachman L, Lieberman AH and Kaning LJ: The theory and practice of industrial pharmacy. 3rd ed. Bombay: Indian Varghese Publishing House 1987: 293-4.
2. Ansel HC, Allen LV and Popovich NC: Pharmaceutical dosage form and drug delivery system. 8th ed. Baltimore: Lippincott Williams and Wilkins 2005: 162.
3. Sahoo CK, Sahoo NK, Rao SRM, Sudhakar M and Satyanarayana K: A review on controlled porosity osmotic pump tablets and its evaluation Bulletin of Faculty of Pharmacy, Cairo University 2015; 53: 195-205.
4. Kanagale P, Lohray B, Misra A, Davadra P and Kini R: Formulation and optimization of porous osmotic pump-basedd controlled release system of oxybutynin. AAPS Pharm Sci Tech. 2007.
5. Makhija S and Vavia P: Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine I. cellulose acetate as a semipermeable membrane. J Control Release 2003; 89: 5-18.
6. Jagtap P, Bhise K and Vijayalakshmi P: A phytopharmacological review on *Garcinia indica*. Int J of Herbal Medicine 2015; 3(4): 02-07.
7. Deore AB, Sapakal VD, Dashputre NL and Naikwade NS: Antiulcer activity of *Garcinia indica* Linn fruit rinds. Journal of Applied Pharmaceutical Science 2011; 01(05): 151-55.
8. Khatib NA, Pawase K and Patil PA: Evaluation of anti-inflammatory activity of *Garcinia indica* fruit rind extracts in Wistar rats. Int J Res Ayurveda Pharm 2010; 1(2): 449-54.
9. Ahmad A, Sarkar SH, Aboukamee A, Ali S, Bernhard B, Sebastian S and Yiwei L: Anticancer action of garcinol *in-vitro* and *in-vivo* is in part mediated through inhibition of STAT-3 signaling. Advance Access publication September 2012; 13: 1-7.
10. Jagtap P, Vijayalakshmi P and Bhise K: Phytochemical characterization and cytotoxic evaluation of methanolic extract of *Garcinia indica* Fruit Rind. Int J of Pharmacognosy 2017; 4(11): 372-77.
11. Darji KK, Shetgiri P and D'mello PM: Evaluation of antioxidant and antihyperlipidemic activity of extract of *Garcinia indica*. IJPSR 2010; 1(12): 175-81.
12. Shahi SR, Deore SV and Dabir PD: QBD Approach in formulation and evaluation of sumatriptan succinate bilayer buccal tablets. European Journal of Pharmaceutical and Medical Research 2016; 3(9): 257-65.
13. Upasani A, Kshirsagar S and Bhalekar M: Design and Optimization of sustained release matrix tablet of Opipramol HCl, by using quality by design approach. Asian J Pharm Clin Res 2014; 7(5): 227-34.
14. Patel H, Parmar S, and Patel B: A comprehensive review on Quality by Design (QbD) in pharmaceuticals. Int J Pharm Sci Rev Res 2013; 21(1): 223-36.
15. Ghosh T, Ghosh A, Thimmasetty J, Kumar A and Sushil K: Development and biopharmaceutical evaluation of controlled porosity osmotic formulations of silymarin β-cyclodextrin inclusion complex. IJPPR Human 2016; 7(1): 276-92.
16. Jagtap PC, Prakya V and Bhise KS: Design and Development of controlled porosity osmotic tablets of *Garcinia indica* extract. Journal of Drug Delivery & Therapeutics 2018; 8(4): 161-69.
17. Jagtap P, Awargaonkar A, Kuchekar S and Bhise K: Formulation and evaluation of controlled porosity osmotic pump tablet of ranitidine hydrochloride. Research Journal of Pharmacy and Technology 2010; 3(4): 1205-08.

18. Shah HP, Shailesh T, Prajapati ST and Patel CN: Quality by design enabled development and optimization of gastroretentive floating matrix tablets of dipyridamole. Asian Journal of Pharmaceutics 2017; 11(2): 1-10.
19. Mahima R, Gupta A and Rathore D: Quality by Design (QbD) Approach for Formulation Development of Hydralazine Hydrochloride Tablets. J Chem Pharm Res 2016; 8(5): 336-41.
20. Lachmann L, Lieberman HA and Kanig JL: Theory and Practice of Industrial Pharmacy, Bombay: Indian. Varghese Publishing House 1991: 315-16.
21. Sharma R, Jain S, Tiwari R and Tiwari K: Design and statistical optimization of solubility modulated monolithic osmotic tablet of metformin hydrochloride (SCOT). Der Pharmacia Lettre 2015, 7(3): 48-60.
22. Bhalekar MR, Madgulkar AR, Sheladiya DD, Kshirsagar SJ, Wable ND, Desale SS: Statistical optimization of sustained release venlafaxine HCI wax matrix tablet. Indian J Pharm Sci 2008, 70(4): 472-76.
23. Ratnakar NC and Gohel MC: Statistical optimization of controlled porosity osmotic tablet of milnacipran HCl. Asian Journal of Pharmaceutics 2016; 10(3).
24. Gondaliya D and Pundarikakshudu K: The fabrication and evaluation of the formulation variables of a controlled porosity osmotic drug delivery system with diltiazem hydrochloride. Pharmaceutical Technology 2003; 58-68.
25. Moore JW and Flanner HH: Mathematical Comparison of Dissolution Profiles. Pharm Techno 1996; 20: 64-74.
26. Carstensen JT: Drug stability: Principle and practices, Marcel Dekker, New York, 2nd ed. 1995; 538-50.

How to cite this article:
Jagtap PC, Vijayalakshmi P and Bhise KS: Quality by design approach to optimize osmotically controlled drug delivery system. Int J Pharm Sci & Res 2020; 11(11): 5561-71. doi: 10.13040/IJPSR.0975-8232.11(11).5561-71.