

**Formulation Design and Optimization of Hydrophilic Matrix based Sustained Release Tablet of Clarithromycin using a Design of Experiment (DoE)**

**Abstract**

A well-defined and strictly controlled dissolution rate plays vital role in optimization of sustained release dosage form. For this purpose, a computer optimized technique, based on a response surface methodology (RSM) utilizing a quadratic equation and factorial design has been widely used for designing and optimization of different pharmaceutical formulations, which requires smaller number of experimental runs and is less time consuming than conventional formulation methods. The aim of the present study was to design and evaluate once daily sustained release clarithromycin tablet, using two molecular weight grades hydrophilic polymers, i.e. Methocel<sup>®</sup> K15M CR and Methocel<sup>®</sup> K100M CR as release retarding materials, utilizing a Design of Experiment (DoE) approach. The tablets were manufactured by response surface methodology based on 3<sup>2</sup> full factorial design utilizing a polynomial equation where both polymers used as independent variables, along with other requisite excipients. The cumulative percentages of drug released at 2, 12 and 24 hr were selected as dependent variables and restricted to 0-20%, 45-70%, and 80-100%, respectively. Regression and response surface analyses were performed using Design Expert<sup>®</sup> software and found that the release pattern of clarithromycin from the matrix followed non-linear model at 2 and 12hrs but at 24hrs, the pattern was linear. From the overlay plot, one of among different proposed was prepared practically for further investigation and then evaluated for physical and biopharmaceutical properties. The predicted error for observed response of *in vitro* dissolution studies was found to be -0.57, -1.78 and 0.49% at 2, 12 and 24hr, respectively. Finally, modelling of the *in vitro* drug release data suggested that, the drug release from the optimized formulation followed Higuchi model and anomalous/non-Fickian type release mechanism.

**Keywords**

Factorial Design; Clarithromycin; Hydrophilic Matrix; Sustained Release; DoE

## 1. Introduction

“Quality by Design (QbD) is an organized and methodical approach to develop pharmaceutical products based on rational scientific principles”<sup>[1]</sup>. ICH Q8 guidance mentioned the concept of QbD by stating “quality cannot be tested into products i.e. quality should be built in by design”. An understanding of the product and manufacturing process and variables is necessary to define the desired product performance and critical quality attributes (CQA), which enables the organization to establish an optimum product formulation and manufacturing process<sup>[2,3]</sup>. The various formulation and process parameters that dictate the ultimate quality are identified and classified with the help of the design of experiment (DoE)<sup>[4]</sup>. As recognized by ICH Q8, process analytical technology (PAT) may be used to ensure that the process remains within an established range of design parameters<sup>[2]</sup>. In recent years, there has been a lot of works in the development of tablet formulations especially oral sustained release drug delivery system (SRDDS) using QbD/DoE<sup>[5]</sup>.

Sustained release, also known as extended release drug delivery systems are those which can provide drug release for a prolonged period of time and maintain a constant or nearly constant plasma drug concentration when administered<sup>[6-8]</sup>. There are several advantages of SRDDS including more precise control over plasma drug concentration, patient compliance, better drug utilization due to slower release etc<sup>[6-8]</sup>.

Clarithromycin, a semi-synthetic macrolide antibiotic, is derived by the methylation of natural antibiotic erythromycin at its 6 position. When clarithromycin is given at a lower dose (250mg), it shows half-life of 3-4hrs; whereas, at a higher dose it exhibits non-linear pharmacokinetics to give a higher half-life of 7-8 hrs, which is associated with increased risk of adverse effects<sup>[9]</sup>. If it is given in sustained release tablet dosage form, the risk of adverse effects can be reduced due to slower release from the tablet matrix producing a more precise and controlled plasma drug concentration.

A sustained release tablet provides a substantially constant rate of drug release from the tablet in the gastro-intestinal tract over a prolonged period of time<sup>[6-8]</sup>. Use of hydrophilic matrix is well-recognized in designing of sustained release dosage form of many drugs and two marketed

versions of hydroxypropyl methylcellulose (HPMC) named as Methocel<sup>®</sup> K100M CR and Methocel<sup>®</sup> K15M CR are commonly used in the formulation as rate controlling polymers [10-13].

“Designing a formulation with optimized quality in a short time period and minimum number of trials is an important issue during development of any pharmaceutical dosage forms. A well-defined and strictly controlled dissolution rate plays vital role in optimization of sustained release dosage form. For this purpose, a computer optimized technique, based on a response surface methodology (RSM) utilizing a quadratic equation and factorial design has been widely used for designing and optimization of different pharmaceutical formulations, which requires smaller number of experimental runs and is less time consuming than conventional formulation methods” [14]. “Furthermore, these statistical approaches help identification and classification (critical or non-critical) of various formulation and process parameters affecting product stability; as a result, a product is understood well to overcome future product failures” [14]. The present study was designed to examine the formulation and process variables and thereby optimization of those variables for a sustained release clarithromycin 500mg tablet by using Design Expert software based on polynomial equations.

## **2. Materials and Method**

### *2.1. Chemicals and Reagents*

Clarithromycin USP (Potency = 99.46%) was a generous gift from Incepta Pharmaceuticals Limited, Savar, Bangladesh. Hydroxypropyl methylcellulose (Methocel<sup>®</sup> K15M CR and Methocel<sup>®</sup> K100M CR, Colorcon, USA), microcrystalline cellulose (Avicel PH 102, Colorcon, USA), magnesium stearate (Wilfrid Smith Ltd., UK), and talc (Wilfrid Smith Ltd., UK) were purchased from the local market. All the solvents and chemicals were of reagent grade.

### *2.2. Preliminary studies*

Preliminary studies were performed using three hydrophilic matrix polymers *viz.* Methocel<sup>®</sup> K4M, K15M and K100M CR with different predetermined active-polymer ratios and then the overall physico-chemical properties and dissolution profiles of the prepared formulations were investigated as per protocols. Later on, depending upon the results obtained latter two,

Methocel<sup>®</sup> K15M and K100M CR, were selected for further investigation. Table-1 shows the overall ranges of polymers used to evaluate clarithromycin tablet preparations.

**Table 1** Composition of clarithromycin matrices during initial studies.

Name of the ingredients	Justification of use	Amount (mg)
Clarithromycin	Active ingredient	500 <sup>a</sup>
Methocel <sup>®</sup> K100M CR	Rate retarding polymer	250 – 500
Methocel <sup>®</sup> K15M CR	Rate retarding polymer	30 – 200
Methocel <sup>®</sup> K4M CR	Rate retarding polymer	100 – 350
Aerosil 200	Glidant	as required <sup>b</sup>
Magnesium Stearate	Lubricant	as required <sup>b</sup>
Avicel PH 102	Filler	as required <sup>b</sup>

<sup>a</sup> Based on 100% potency.

<sup>b</sup> Based on the final weight of the tablet preparation.

### 2.3. Preparation of tablets

The formulations of the tablets with their codes are listed in Table 2.

**Table 2** Formulations of Clarithromycin 500 mg once daily sustained release tablet.

Name of the ingredients	Amount (mg)
Clarithromycin	500 <sup>a</sup>
Methocel <sup>®</sup> K100M CR	330-440
Methocel <sup>®</sup> K15M CR	55-110
Aerosil 200	11
Magnesium Stearate	11
Avicel PH 102	q.s. to 1100

<sup>a</sup> Based on 100% potency.

The active ingredient, polymers, filler, glidant and lubricant were properly weighed and passed through a sieve of mesh size #40. The weighed active ingredient and excipients (except aerosil-200 and magnesium stearate) blended in a laboratory mixer for about 10 min. Finally magnesium

stearate and aerosil were added and mixed for another 2 min. The appropriate amount of the blended mass was then compressed using a laboratory hydraulic press equipped with a 20 mm caplet shaped punch and die set at a compression force of 5 tons. For further studies, all the preparations were stored in separate airtight polyethylene bags at room temperature.

#### 2.4. *In vitro* release studies

The *in vitro* drug release studies were performed as per clarithromycin extended-release tablets (Test-2) official dissolution method, instructed in USP37-NF32, using USP type I apparatus (Electrolab, India) at 100 rpm and the dissolution medium was 900 mL 0.05M phosphate buffer containing 0.5% sodium lauryl sulfate of pH 6.8, maintained at  $37\pm 0.05^\circ\text{C}$  [15]. The cumulative percentage of drug releases at different time intervals (1hr, 2hr, 4hr, 8hr, 12hr and 24hr) were measured by UV-visible spectrophotometer at 205 nm wavelength using the calibration curve of standard solution. The test was performed with six tablets of each formulation and the percentage of drug released over time was calculated. Official release profile of clarithromycin as described in Test-2 is provided in Table 3.

**Table 3** Standard release profile of clarithromycin.

Time (hr)	Amount dissolved (%)
2	NMT <sup>a</sup> 20
12	45-70
24	NLT <sup>a</sup> 80

<sup>a</sup> NMT = Not more than; NLT = Not less than

#### 2.5. *Experimental design*

$3^2$  full factorial design was used to evaluate the influence of the formulation variables on the drug release from tablet matrix. The amounts of Methocel<sup>®</sup> K100M CR (A) and Methocel<sup>®</sup> K15M CR (B) were selected as covariates at three levels each determined after preliminary trials (Table 2). The percentages of the drug released at 2, 12, and 24 hr were used as dependent variables. Design-Expert software (V. 10, Stat-Ease Inc., Minneapolis, USA) was used for the generation of the  $3^2$  full factorial design experiment (Table 4).

**Table 4** Variables in 3<sup>2</sup> full factorial design.

Formulation variables (% by weight of polymers)	Levels used actual (coded)		
	Low (-1)	Medium (0)	High(+1)
A = Methocel <sup>®</sup> K100M CR	30%	35%	40%
B = Methocel <sup>®</sup> K15M CR	5%	7.5%	10%
Response variables	Constraints		
Q <sub>2</sub> = Cumulative % drug release after 2 hrs	0% ≤ Q <sub>2</sub> ≤ 20%		
Q <sub>12</sub> = Cumulative % drug release after 12 hrs	45% ≤ Q <sub>12</sub> ≤ 70%		
Q <sub>24</sub> = Cumulative % drug release after 24 hrs	80% ≤ Q <sub>24</sub> ≤ 100%		

### 2.6. Optimization of the formulation

For optimization, the desirable ranges of these responses were restricted to the official specification as presented in Table 3 [15]. “The optimized levels of each independent variable were based on the desirability criterion and graphical analysis” [16]. “A new batch of tablets with the predicted levels of the formulation factors was prepared to confirm the validity of the optimization procedure. Finally, the optimized formulation was evaluated for its physical properties, and the release profile was explored and explained by different kinetics models, i.e. zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell models” [17-20].

## 3. Results and Discussion

### 3.1. Full factorial design

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1A + b_2B + b_3AB + b_4A^2 + b_5B^2$$

Where, Y is the dependent variable, b<sub>0</sub> is the intercept representing the arithmetic average of quantitative outcome of nine runs, b<sub>1</sub> to b<sub>5</sub> are the coefficient computed from the observed experimental value of Y, and A and B are the coded level of the independent variables (Methocel<sup>®</sup> K100M CR and Methocel<sup>®</sup> K15M CR). The A and B represent the average result of

changing individual factor at a time from its low to high values. The interaction terms (AB) show how the response changes when two factors are simultaneously changed. The polynomial terms ( $A^2$  and  $B^2$ ) are included to investigate nonlinearity.

The dissolution profile for nine batches presented in Table 5 showed a variation i.e., initial 2hr release ranging from 13.05% to 27% and drug released after 12 hr ranging from 60.06 to 70.03% and drugs released after 24 hr ranging from 71.01 to 91.89%.

**Table 5** The composition and observed responses from randomized runs in  $3^2$  full factorial design.

Formulation	Factor		Responses		
	A (mg)	B (mg)	Q <sub>2</sub>	Q <sub>12</sub>	Q <sub>24</sub>
Run-1	330	55	27	75.06	91.89
Run-2	330	82.5	26.91	73.71	88.47
Run-3	330	110	23.67	70.11	87.03
Run-4	385	55	25.29	78.03	89.37
Run-5	385	82.5	24.39	71.91	80.91
Run-6	385	110	20.07	68.94	84.42
Run-7	440	55	16.74	63.27	78.03
Run-8	440	82.5	15.39	63.18	80.10
Run-9	440	110	13.05	60.06	71.01

Apart from compendial requirement, we have also measured the release profile of clarithromycin at 1, 4 and 8 hr to precisely calculate the drug release kinetics of it. The obtained results are presented in Table 6 and Fig. 1.

**Table 6** Zero order release profile of nine formulations (F1 to F9) of clarithromycin matrix tablets.

Time	Cumulative % of drug released
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(hour)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	22.95	15.39	16.74	16.29	13.78	17.91	13.95	10.89	9.09
2	27	26.91	23.67	25.29	24.39	20.07	16.74	15.39	13.05
4	38.45	39.69	31.59	32.13	36.81	28.8	27.63	25.74	24.66
8	53.37	58.68	50.31	60.21	56.54	40.23	42.93	39.42	38.43
12	75.06	73.71	70.11	78.03	71.91	68.94	63.27	63.18	60.06
24	91.89	88.47	87.03	89.37	80.91	84.42	78.03	80.1	71.01

The data indicates that the release profile of the drug is strongly dependent on the selected independent variables. The fitted equations relating the responses ( $Q_2$ ,  $Q_{12}$  and  $Q_{24}$ ) to the transformed factors are as follows:

$$Q_2 = 24.20 - 5.40A - 2.04B - 0.090AB - 2.85A^2 - 1.32B^2$$

$$Q_{12} = 72.74 - 5.40A - 2.88B + 0.44AB - 5.12A^2 - 0.079B^2$$

$$Q_{24} = 83.21 - 6.38A - 2.80B$$

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive) with the results of analysis of variance (ANOVA) to identify insignificant factors (Table 7).

**Table 7** Summary of results of regression analysis.

	$Q_2$		$Q_{12}$		$Q_{24}$	
	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value
Intercept	24.20	-	72.74	-	83.21	-
A	-5.4	<0.0001	-5.4	0.0019	-6.38	0.0012
B	-2.04	0.0014	-2.88	0.0179	-2.81	0.0541
AB	-0.09	0.7916	0.44	0.6571	-	-
$A^2$	-2.85	0.0024	-5.12	0.0126	-	-
$B^2$	-1.32	0.0337	-0.079	0.9501	-	-
$R^2$	0.9262	-	0.5842	-	0.6499	-

The terms with  $p < 0.05$  were considered statistically significant. The considerable numbers of coefficients in the  $Q_2$ ,  $Q_{12}$  and  $Q_{24}$  were found to be insignificant at  $P > 0.05$  hence do not contribute significant information to the prediction of  $Q_2$ ,  $Q_{12}$  and  $Q_{24}$ . A suitable polynomial model was selected based on the estimation of several statistical parameters such as the multiple correlation coefficient ( $R^2$ ), adjusted multiple correlation coefficient (adjusted  $R^2$ ) and the predicted residual sum of square (PRESS). The quadratic models were selected as suitable statistical models for  $Q_2$  and  $Q_{12}$ , and linear model for  $Q_{24}$  to optimize the formulation because the smallest PRESS values were observed (Table 8).

**Table 8** Summary of results (lack of fit and  $R^2$  analysis).

Source	$Q_2$		$Q_{12}$		$Q_{24}$	
	SS	P>F	SS	P>F	SS	P>F
Lack of fit	1.62	-	13.21	-	61.88	-
	Quadratic		Quadratic		Linear	
	Adjusted $R^2$	PRESS	Adjusted $R^2$	PRESS	Adjusted $R^2$	PRESS
$R^2$ analysis	0.9840	16.85	0.9014	125.38	0.7746	123.58

### 3.2. Factorial equations

#### 3.2.1. Factorial equation for $Q_2$

Concerning  $Q_2$ , the results of multiple linear regression analysis showed that both the coefficients  $b_1$  and  $b_2$  bear a negative sign. It is possible that at higher polymers concentration, clarithromycin is trapped in smaller polymer cells and it is structured by its close proximity to the polymer molecules. Therefore, increasing the amount of the polymer in the formulations increased the time it took the drug to leave the formulation and retard release of drug into the medium.

$$Q_2 = 24.20 - 5.40A - 2.04B - 2.85A^2 - 1.32B^2$$

The  $Q_2$  for all the batches F1 to F9 varied from 13.05% to 27% (Table 5) showed good correlation coefficient as 0.9262 (Table 7). Results of the equation indicated that the release

pattern after 2 hr follows a quadratic or non-linear model and both the concentration of the A and B were responsible for the  $Q_2$  but A has more effect to control the release.

### 3.2.2. Factorial equation for $Q_{12}$

The results of multiple linear regression analysis for  $Q_{12}$  showed that both the coefficients  $b_1$  and  $b_2$  also bear a negative sign indicating that increasing the amount of the polymer in the formulations decreases the rate of drug release from the tablet matrices.

$$Q_{12} = 72.74 - 5.40A - 2.88B - 5.12A^2$$

The  $Q_{12}$  for all the batches F1 to F9 varied from 60.06% to 70.03% (Table 5) showed a correlation coefficient of 0.5842 (Table 7). Results of the equation indicated that both the concentration of the A and B were responsible for the  $Q_{12}$  but A has more effect to control the release.

### 3.2.3. Factorial equation for $Q_{24}$

$Q_{24}$  is also an important parameter to determine the release kinetics and predict the release pattern. The results of multiple linear regression analysis showed that the coefficient  $b_1$  bears a negative sign meaning that increasing the amount of this polymer in the formulations will delay the release of drug into the medium.

$$Q_{24} = 83.21 - 6.38A$$

The  $Q_{24}$  for all the batches F1 to F9 varied from 71.01% to 91.89% (Table 5) showed a correlation coefficient of 0.6499 (Table 7). The drug release pattern after 24 hr follows a linear model. Results of the equation indicated that only the concentration of A has the effect to control the release of drug from the tablet matrices.

### 3.3. Response surface analysis

Two dimensional (2-D) contour plot and three-dimensional (3-D) surface response plots were constructed to estimate the impacts of independent variables on the response. The contour and surface response plots for  $Q_2$  show the nonlinear pattern of drug release and also indicate that the Methocel<sup>®</sup> K100M CR has comparatively greater influence on response variable (Fig. 2).

Fig. 3 represents the influence of Methocel<sup>®</sup> K100M CR and Methocel<sup>®</sup> K15M CR on dependent variable at  $Q_{12}$ . Contour plot for drug release at 12 hr shows that the release pattern follows somewhat quadratic fashion. However, the effect of Methocel<sup>®</sup> K100M CR is more pronounced compared to Methocel<sup>®</sup> K15M CR in the selected range of concentration.

The influence of Methocel<sup>®</sup> K100M CR and Methocel<sup>®</sup> K15M CR on dependent variable at  $Q_{24}$  is depicted in Fig. 4. Contour plot for drug release at 24 hr predicts that the drug release follows linear fashion and significantly dependent on the Methocel<sup>®</sup> K100M CR in the selected range of concentration.

### 3.4. Optimized formulation

An overlay plot was constructed considering the drug release models at  $Q_2$ ,  $Q_{12}$  and  $Q_{24}$  to identify the area where both of the independent variables are at levels to satisfy the USP specified dissolution requirements (Fig. 5).

The theoretical optimized quantities for A and B were about 426.25 mg and 57.75 mg, respectively, with a maximum value of desirability of 1.00. The predicted responses of  $Q_2$ ,  $Q_{12}$  and  $Q_{24}$  for optimum formulations were 19.37, 68.04 and 80.96%, respectively (Fig. 6).

In this formulation, the percentages of Methocel<sup>®</sup> K100M CR and Methocel<sup>®</sup> K15M CR were 38.75 and 5.25%, respectively. (Table 9).

**Table 9** Composition of Clarithromycin sustained release optimized formulation.

Name of the ingredients	Amount (%)	Amount (mg)
Clarithromycin	45.45 <sup>a</sup>	500 <sup>a</sup>
Methocel <sup>®</sup> K100M CR	38.75	426.25
Methocel <sup>®</sup> K15M CR	5.25	57.75
Avicel PH 102	8.55	94
Aerosil 200	1	11
Magnesium stearate	1	11

<sup>a</sup> Based on 100% potency.

The physical properties of the compression blend (Bulk density, tapped density, Carr's index, Hausner ratio and angle of repose) and tablet matrix (hardness, friability and weight variation) were found to be satisfactory and are presented in Table 10.

**Table 10** Physical properties of compression blend and compressed tablet.

Compression blend		Compressed tablet	
Properties	Results	Properties	Results
Loose bulk density (gm/ml)	0.482±0.06	Average weight (mg)	1103.1±0.03
Tapped bulk density (gm/ml)	0.559±0.04	Caplet diameter (mm)	20
Carr's index	13.77±0.08	Caplet thickness (mm)	7.52±0.05
Hausner ratio	1.15±0.03	Hardness (kg/cm <sup>2</sup> )	12.8±0.03
Total porosity	13.77±0.07	Friability (%)	0.18
Angle of repose (°)	25.35±0.03		

The percent release of drug after 2, 12 and 24 hr were 19.26, 66.85 and 81.36%, respectively (Fig. 7) and the predicted error was calculated and found satisfactory (Table 11).

**Table 11** Predicted and observed responses of the optimized formulation.

Responses	Predicted	Observed	Predicted Error <sup>a</sup>	Remarks
Q <sub>2</sub>	19.37%	19.26%	-0.57%	Satisfactory
Q <sub>12</sub>	68.04%	66.85%	-1.78%	Satisfactory
Q <sub>24</sub>	80.96%	81.36%	0.49%	Satisfactory

<sup>a</sup> Predicted Error (%) = (observed value-predicted value)/observed value × 100%

Tolerance = ±2%

The best-fitted models for release kinetics of this formulation were Higuchi ( $R^2=0.978$ ), first order ( $R^2=0.974$ ), Korsmeyer-Peppas ( $R^2=0.969$ ) and Hixson-Crowell ( $R^2=0.945$ ). The  $T_{50\%}$  value was of 8.65 hr and the drug release mechanism followed anomalous/non-Fickian type release ( $n=0.65$ ).

#### 4. Conclusion

This study demonstrates the suitability of a combined mixture of the hydrophilic polymers, namely Methocel<sup>®</sup> K100M CR and Methocel<sup>®</sup> K15M CR in controlling the release of clarithromycin, which was found to follow Higuchi release kinetics and is both diffusion and erosion controlled. By using 426.25 mg of Methocel<sup>®</sup> K100M CR and 57.75 mg of Methocel<sup>®</sup> K15M CR in an 1100 mg tablet preparation, it is possible to maintain the release of clarithromycin up to 24 hr as per compendial requirement.

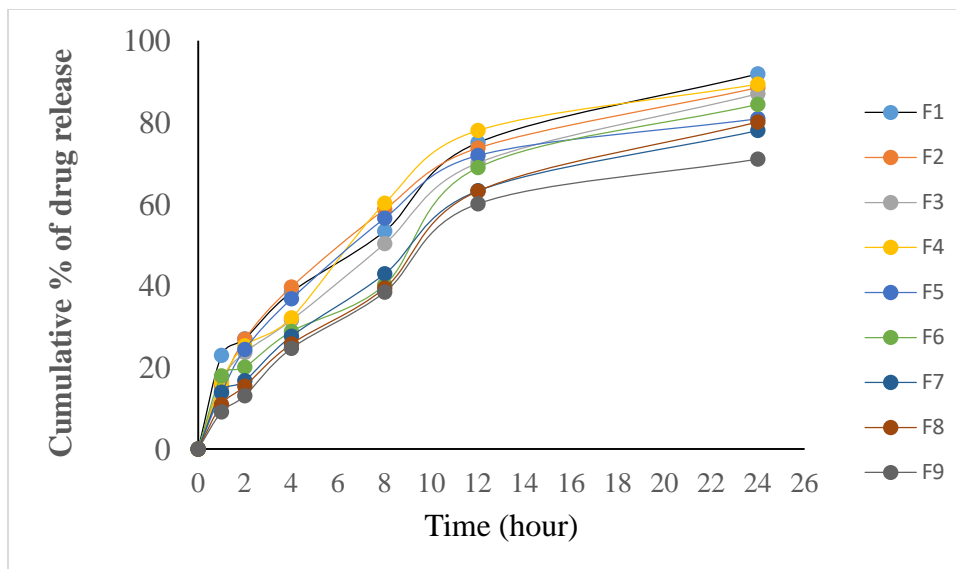
#### **COMPETING INTERESTS DISCLAIMER:**

**Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.**

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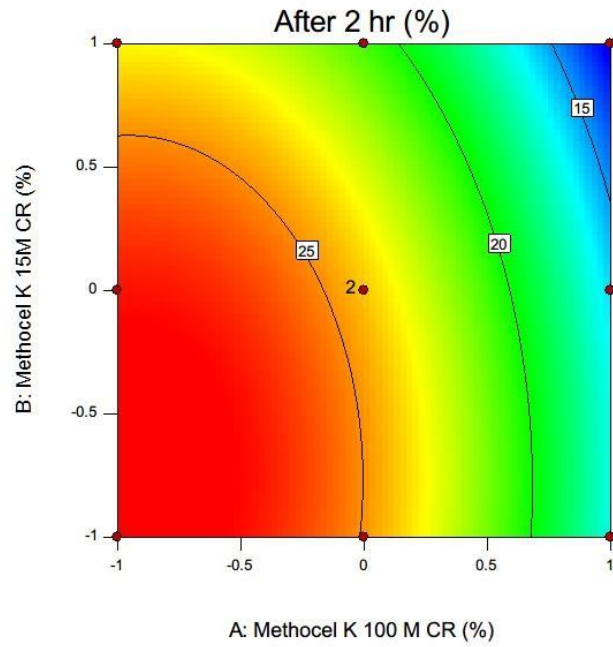
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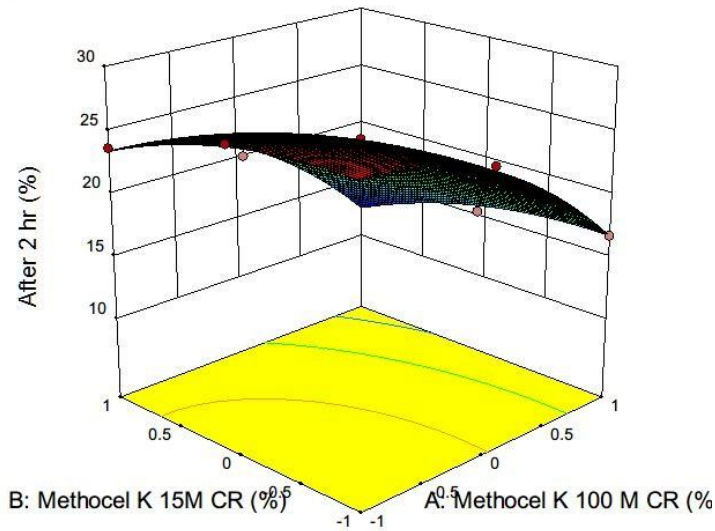
**Figure 1** Zero order release profile of nine formulations (F1 to F9) of clarithromycin matrix tablets

Design-Expert® Software  
 Factor Coding: Actual  
 After 2 hr (%)  
 ◆ Design Points  
 27  
 13.05  
 X1 = A: Methocel K 100 M CR  
 X2 = B: Methocel K 15M CR



(A)

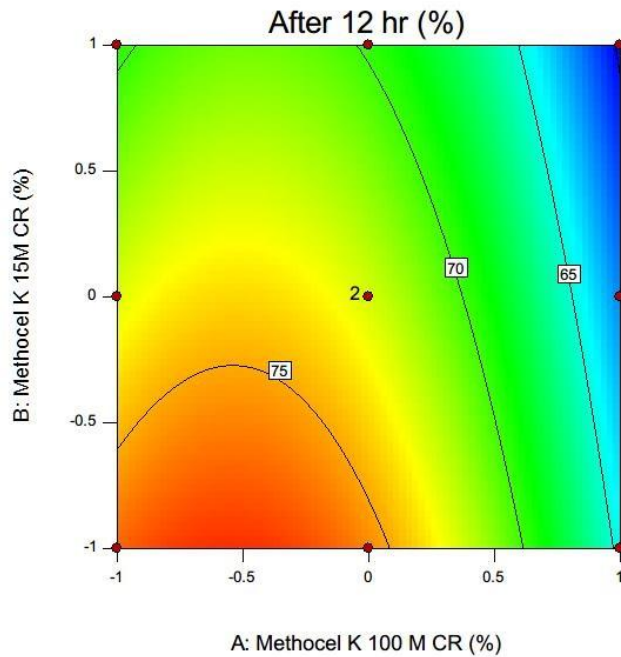
Design-Expert® Software  
 Factor Coding: Actual  
 After 2 hr (%)  
 ◆ Design points above predicted  
 ◆ Design points below predicted  
 27  
 13.05  
 X1 = A: Methocel K 100 M CR  
 X2 = B: Methocel K 15M CR



(B)

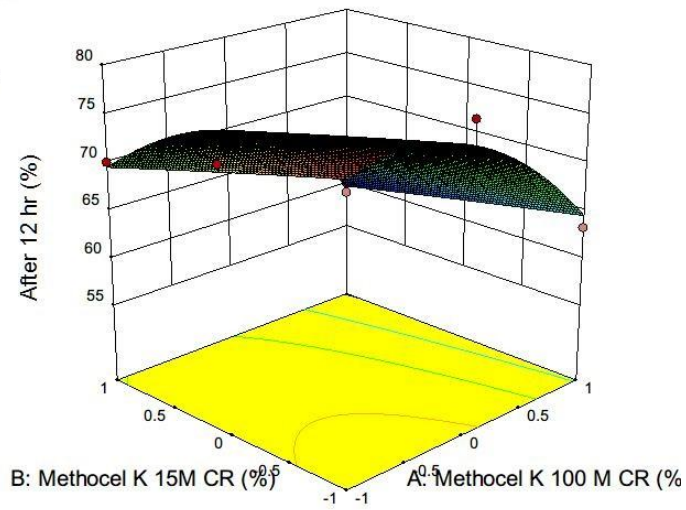
**Figure 2** (A) Two dimensional contour plot and (B) three-dimensional surface response plot for drug release after 2 hr.

Design-Expert® Software  
 Factor Coding: Actual  
 After 12 hr (%)  
 ◆ Design Points  
 78.03  
 60.06  
 X1 = A: Methocel K 100 M CR  
 X2 = B: Methocel K 15M CR



(A)

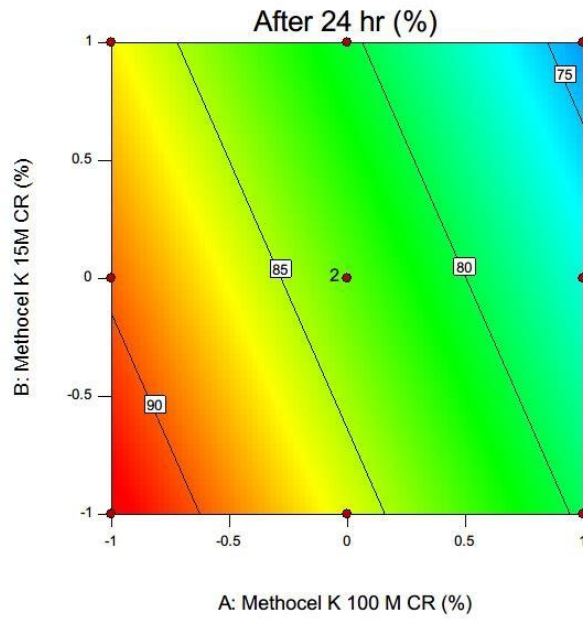
Design-Expert® Software  
 Factor Coding: Actual  
 After 12 hr (%)  
 ◆ Design points above predicted  
 ◆ Design points below predicted  
 78.03  
 60.06  
 X1 = A: Methocel K 100 M CR  
 X2 = B: Methocel K 15M CR



(B)

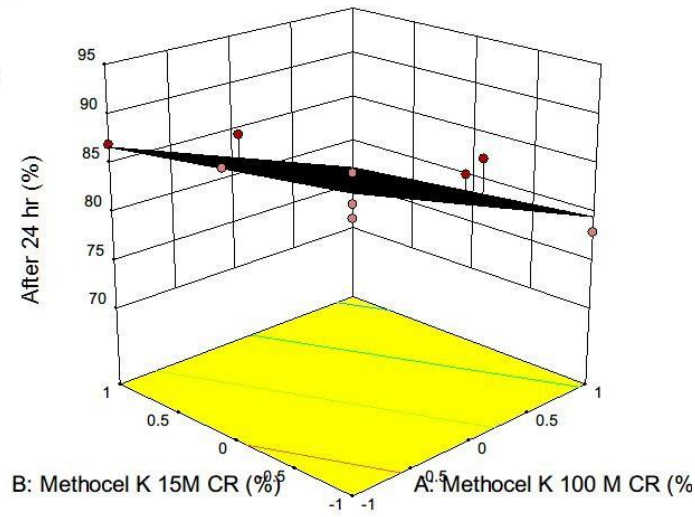
**Figure 3** (A) Two dimensional contour plot and (B) three-dimensional surface response plot for drug release after 12 hr.

Design-Expert® Software  
 Factor Coding: Actual  
 After 24 hr (%)  
 Design Points  
 91.89  
 71.01  
 X1 = A: Methocel K 100 M CR  
 X2 = B: Methocel K 15M CR



(A)

Design-Expert® Software  
 Factor Coding: Actual  
 After 24 hr (%)  
 Design points above predicted  
 Design points below predicted  
 91.89  
 71.01  
 X1 = A: Methocel K 100 M CR  
 X2 = B: Methocel K 15M CR



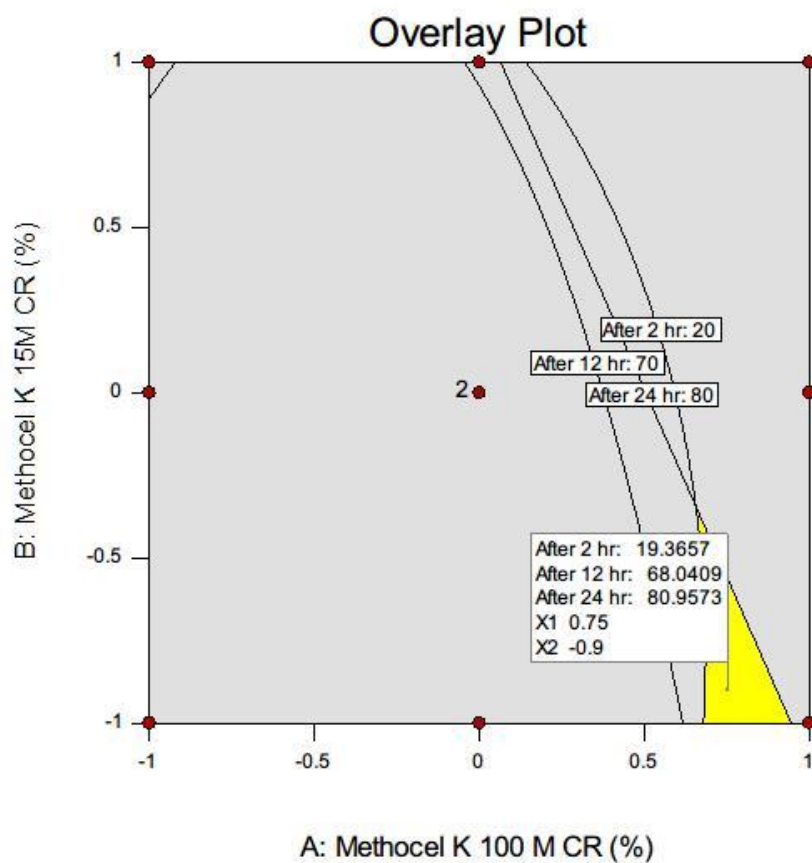
(B)

**Figure 4** (A) Two dimensional contour plot and (B) three-dimensional surface response plot for drug release after 24 hr.

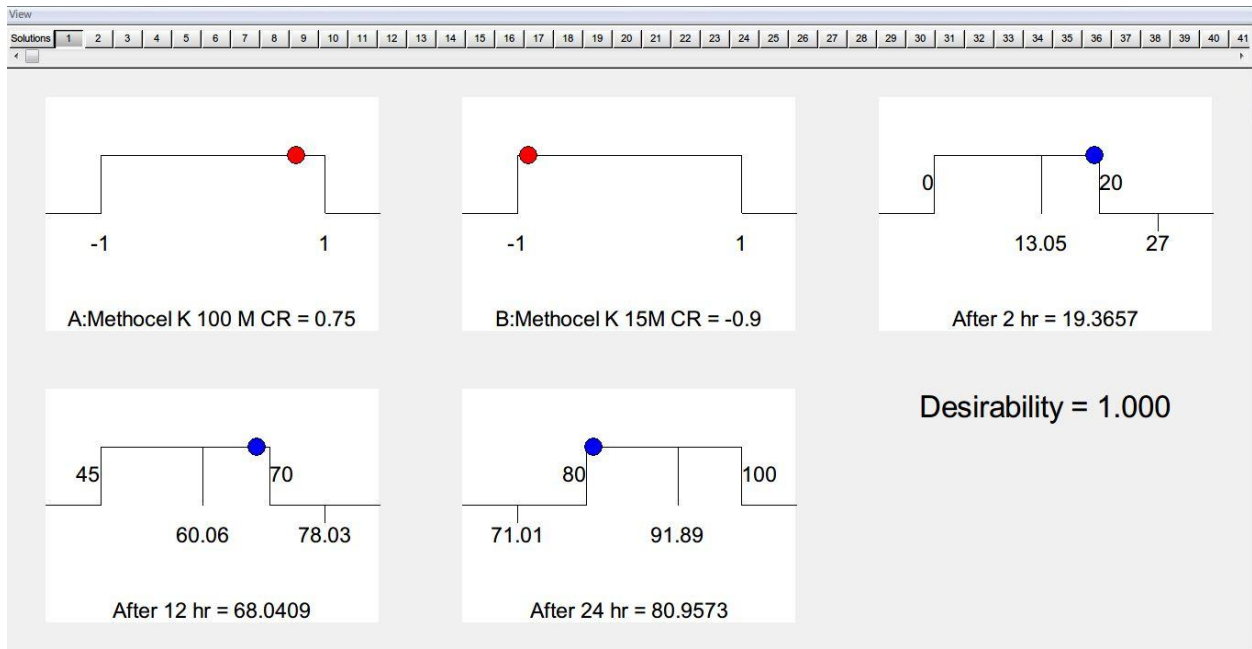
Design-Expert® Software  
Factor Coding: Actual  
Overlay Plot

After 2 hr  
After 12 hr  
After 24 hr  
◆ Design Points

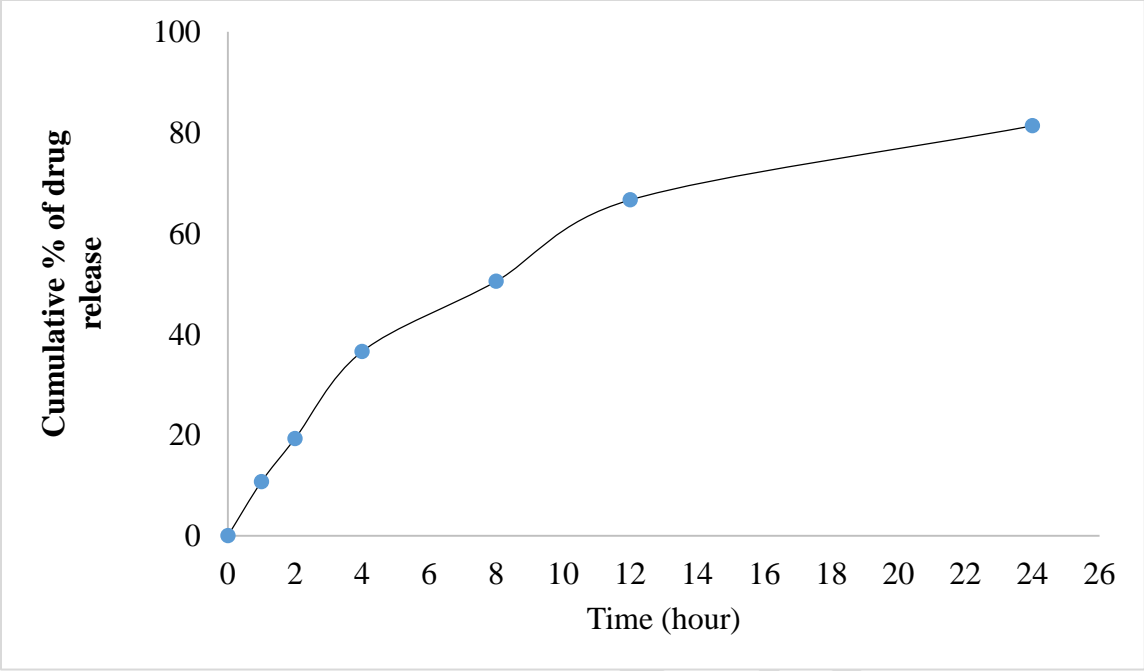
X1 = A: Methocel K 100 M CR  
X2 = B: Methocel K 15M CR



**Figure 5** The overlay plot of the optimization area.



**Figure 6** Levels of independent variables in theoretical optimized formulation with predicted response from overlay plot.



**Figure 7** Zero order release profile of optimized formulation.

UNDER PEER REVIEW