Original Article

Central Composite Design Aided Formulation Development and Optimization of Clarythromycin Extended-Release Tablets

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ABSTRACT

Objectives: The present work was designed to formulate extended-release tablets of clarithromycin by means of central composite design. To assess the systematic considerate of input and output variables and to construct design space, the central composited design was used. **Methods:** The concentrations of tamarind kernel powder (X_1), ethyl cellulose (X_2) and polyvinyl pyrrolidone (X_3) remained as independent variables and responses were drug release in 2 h, 8 h and t50%. Polynomial equations were employed to forecast the quantitative result of nondependent constraints at different levels on responses. The model stood nonlinear and the curvature outcome was significant. Henceforth the study employed central composite design for optimization. Wet granulation method was used to prepare the tablets and were evaluated for pharmacotechnical properties. **Results:** FTIR and DSC studies signposted that drug and excipients were compatible. Precompression constraints specified respectable flow properties. The *in vitro* drug release of entire formulations at the end of 12 h was found to be 96.14% - 98.23%. Increase in the concentration of tamarind kernel powder, ethyl cellulose decreased percentage drug release. Contour plots were utilized to assess the relationship between independent variables and dependent variables. **Conclusion:** The statistical model is scientifically effective as the investigational estimates and foreseen estimates proposed by the model were relatively close to each other. The outcomes confirmed the success of the anticipated design for development of clarithromycin extended-release tablets with optimized properties.

Key words: Tamarind kernel powder, Ethyl cellulose, Polyvinyl pyrrolidone, Clarithromycin, Central composite design, Extended release.

INTRODUCTION

Extended release (ER) formulations can permit for lessening in dose frequency, which may boost suitability and thereby progress adherence.[1] The ER preparations possibly will uphold therapeutic concentrations over extended periods. The practice of ER formulations circumvents the elevated blood concentrations and can possibly progress the patient consistence.[2] ER dosage form is the one that permits in any event a twofold decrease in dosage recurrence when contrasted with that medication introduced as an immediate-release.[3] The clarithromycin drug is semi-synthetic macrolide antibiotic used to treat a variety of bacterial infections and extensively engaged in usual abolition treatment of gastric *H. pylori* infection and upper respiratory tract infections by preventing the bacteria by reducing the protein synthesis.[4,5] The drug has short half-life of 3-4 h, which requires frequent administration with normal conventional dosage form causing large and undesirable fluctuations in plasma concentration and this shortens duration of action for providing adequate treatment. Henceforth

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this necessitates the formulation of ER of semi-synthetic macrolide antibiotic that can be administered once or twice daily that can maintain therapeutic range of the drug. Design of Experiments (DoE) is broadly used for the application of QbD in both research and industrial backgrounds. Central Composite design (CCD) can fit a full quadratic model. CCD's are a factorial or fractional factorial design with center points, amplified with a group of axial points that let to estimate curvature and are specifically suitable in successive experiments which permits to shape on earlier factorial experiments.[6] Optimization of a formulation or process is finding the finest probable composition or operating conditions. The persistence of optimization is to govern quantitatively the impact of the diverse factors collected on the response variables.[7] By considering the numeral of factors, levels and probable interactions, the experimental designs were selected. The prime objective of the existing investigation is to formulate the ER tablets of clarithromycin by central composite design and to investigate the consequence of factors on the responses. The concentrations of tamarind kernel powder (TKP), Ethyl cellulose (EC) and Polyvinyl pyrrolidone (PVP) remained as factors and responses selected were drug release in 2 h, 8 h and $t_{50\%}$.

MATERIALS AND METHODS

Clarythromycin was offered as a free sample from Finoso Pharma Pvt Ltd, Hyderabad, Telangana. Ethyl Cellulose was purchased from SD Fine Chemicals, Mumbai. Avicel, PVP, Talc, Magnesium stearate and other chemicals were purchased from Loba Chemicals, Mumbai. All the chemicals used were of investigative grade.

Preparation of tamarind kernel powder (TKP)

TKP was prepared in accordance with the method described by Manchandana *et al.* 2014[8]

FTIR studies

FT-IR spectroscopy (FT IR- 8400-S Shimadzu, Japan) was engaged to determine the compatibility of drug with the excipients.[9] Pure drug and excipients were mixed Potassium bromide and compressed into discs and were run over in the series of 4000 to 400 cm^{-1}.

DSC studies

DSC studies were performed using DSC instrument (Mettler, Toledo) to determine the compatibility between the dug and excipients. Precisely gauged 3 mg of drug alone and the blend containing excipients were transferred into aluminium crucible of the instrument and run over the temperature scope of 50 to 300°C by maintaining 10°C / min of heating rate.[10]

Optimization by the central composite design

In the current research, Sigma Tech software Version 3.1 was used for the design of experimentation of clarithromycin tablets employing 2^3 full factorial design with 4 replicates.[11] The curvature effect was significant and the model was found to be nonlinear which suggested to central composite design for optimization. According to this design, each of the three factors was evaluated at three levels. The concentration of TKP (X_1), EC (X_2) and PVP (X_3) were designated as nondependent factors and percentage drug release in 2h, 8h and $t_{50\%}$ were selected as responses were tabulated in Table 1 and the experimental trials were represented in Table 2.

Preparation of clarithromycin ER tablets

Clarithromycin ER tablets were developed by wet granulation scheme. The entire formulation requirements were weighed in accordance with the composition as tabulated in Table 2.1 & 2.2 and screened via sieve no 40. The required quantities of Clarithromycin, tamarind kernel powder, ethyl cellulose were triturated in a mortar with pestle. To the above mixture PVP was added as binding agent and mixed well to obtain the wet mass. The granules were prepared by allowing the wet mass via sieve #16 and then dried at 30°C for 1h.[12] These dehydrated granules were screened using sieve #22 and added with magnesium stearate and talc. Tablet compression machine (Rimek, India) was used to compress the granules into tablets.

Precompression parameters

Bulk density (BD)

The BD was assessed by transferring the correctly weighed mixture sample into the 100ml graduated cylinder by keeping it in a slanting position. The early volume and mass were recorded. Proportion of the mass to the volume it involved was calculated.[13]

Table 1: Coded variables with responses.

Factors	Actual values (%w/w)					Response
	-2	-1	0	+1	+2	
X_1 (TKP)	5	7.5	10	12.5	15	Y1= Drug release at 2h Y2= Drug release at 8h Y3= t_{50}%
X_2 (EC)	1.25	3.25	5.25	7.25	9.25	
X_3 (PVP)	2	2.75	3.5	4.25	5	

Table 2: Experimental design layout.					
	Formulation code	**Combinations**	**TKP (X_1) (%)**	**EC (X_2) (%)**	**PVP (X_3) (%)**
Factorial Design	F1	1	7.5	3.25	2.75
	F2	X_1	12.5	3.25	2.75
	F3	X_2	7.5	7.25	2.75
	F4	X_1X_2	12.5	7.25	2.75
	F5	X_3	7.5	3.25	4.25
	F6	X_1X_3	12.5	3.25	4.25
	F7	X_2X_3	7.5	7.25	4.25
	F8	$X_1X_2X_3$	12.5	7.25	4.25
Mid-point	F9	Mid-point	10.5	5.25	3.5
	F10	Mid-point	10.5	5.25	3.5
	F11	Mid-point	10.5	5.25	3.5
	F12	Mid-point	10.5	5.25	3.5
Central Composite Design	F13	X_1At-2L	5.0	5.25	3.5
	F14	X_1At+2L	15.0	5.25	3.5
	F15	X_2At-2L	10.0	1.25	3.5
	F16	X_2At+2L	10.0	9.25	3.5
	F17	X_3At-2L	10.0	5.25	2
	F18	X_3At+2L	10.0	5.25	5

Table 2.1: Composition of formulation batches F1 – F9.									
Ingredients (Quantity in mg/tab)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Clarithromycin	250	250	250	250	250	250	250	250	250
Tamarind kernal powder	37.5	62.5	37.5	62.5	37.5	62.5	37.5	62.5	50
Ethylcellulose	16.25	16.25	36.25	36.25	16.25	16.25	36.25	36.25	26.25
PVP	12.5	12.5	12.5	12.5	22.5	22.5	22.5	22.5	17.5
Avicel pH 101	173.7	148.7	153.7	128.7	163.7	138.7	143.7	118.75	146.25
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total weight of the tablet(mg)	500	500	500	500	500	500	500	500	500

Table 2.2: Composition of formulation batches F10 – F18.									
Ingredients (Quantity in mg/tab)	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Clarithromycin	250	250	250	250	250	250	250	250	250
Tamarind kernal powder	50	50	50	25	75	50	50	50	50
Ethylcellulose	26.25	26.25	26.25	26.25	26.25	6.25	46.25	26.25	26.25
PVP	17.5	17.5	17.5	17.5	17.5	17.5	17.5	7.5	27.5
Avicel pH 101	146.25	146.25	146.25	171.25	121.25	166.25	126.25	156.25	146.25
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total weight of the tablet(mg)	500	500	500	500	500	500	500	500	500

Tapped density (TD)

TD was examined by transferring the exactly weighed blend into 100ml measuring cylinder which was placed in tapped density apparatus (Electro lab). Cylinder having Initial volume (V_0) was recorded and was subjected to 100 times (tapping) measured the volume.[14]

Compressibility index (CI)

The CI is an indication of compressibility of a powder.[15] It was calculated by the formula as below.

$$CI = \frac{TDpre}{TD} \times app$$

Hausner ratio (HR)

HR is an ancillary guide of ease of powder flow.[16] It was determined by the accompanying equation

HR = TD / BD

Angle of repose (AR)

This is the modest technique for measuring the resistance to particle movement. AR is the extreme viewpoint probable amid the exterior of heap of powder and horizontal plane.[17]

$\text{Tan } \Theta = h/r$

$\Theta = \tan^{-1} h/r$

Post compression parameters

Weight variation

The test was performed as per IP. Twenty tablets were chosen haphazardly from every formulation and weighed separately, assessed the average weight and standard deviation was determined.[18]

Thickness

Five tablets were casually drawn from individual formulations and thickness was assessed by means of vernier callipers.[19]

Hardness

Hardness of randomly selected tablets was examined via Monsanto tablet hardness tester.[20] Five tablets from respective formulations were tested. It is expressed in kg/cm^2.

Friability

Tablets ten in number were weighed and positioned in the Roche friabilator apparatus and was run at 25 rpm for 4 min.[21] These tablets were de dusted and weighed again. The % friability was measured using

% Friability=(M1–M2)/M1×100

where, M1 is the tablets weight prior to run and M2 is the tablets weight later run.

Drug Content

Phosphate buffer of pH 6.8 was availed to find out the amount of drug present in one tablet. 10 tablets of respective formulations were crushed and fined. The Powder alike to 500 mg of clarithromycin was weighed and liquified in Phosphate buffer in a 100 ml volumetric flask.[22] The resulting solution was analysed at 264 nm using UV Spectrophotometer.

In vitro drug release (DR)

In vitro DR of clarithromycin extended release tablets was assessed by means of USP dissolution test apparatus II (Paddle type) availing 900 ml of 0.1 N HCl in 2 h, then shadowed by phosphate buffer of (pH 6.8) maintained at 37 ± 0.5°C with 100 RPM of paddle. The samples were collected at defined time intervals.[23] Aliquots from withdrawn were filtered and was analysed at 264 nm with UV spectrophotometer and DR was deliberated.

Statistical analysis and optimization

In order to generate the study design, the data gained from all the formulations were examined employing Sigma Tech software (version 3.1). As per the numerous statistical constraints comparison furnished by the Sigma Tech software, best-fit model was chosen. To identify noteworthy possessions of factors on response regression coefficients, ANOVA was used. Contour designs were applied to further explicate the connection amid the reliant and non-reliant constraints. To produce innovative formulations with the anticipated retorts a graphical optimization system with contour plots were engaged and were evaluated for drug release at 2h, 8 h and $t_{50\%}$ to verify the theoretical prediction. The relative errors (RE) (%) amongst the projected and investigational results for individual response were calculated.

RESULTS AND DISCUSSION

FT-IR spectroscopy showed that the major distinctive crests of unadulterated drug and blend were retained in the spectra which ensures that the compatibility of drug with the excipients used (Figure 1 and 2). In the spectra of clarythromycin wave numbers were recorded at 3467.77, 3475.47 and 1730.90 cm^{-1} which resembled to O-H stretching, N-H stretching and C=O stretching. DSC thermograms of pure drug and blend reveals that no key modification in the position of the melting peak of drug (Figure 3) which suggests the drug and polymers used in the study are compatible. The bulk density of the all formulations (F1-F18) were found to be in the range of 0.41±0.07 to 0.55±0.04. The TD

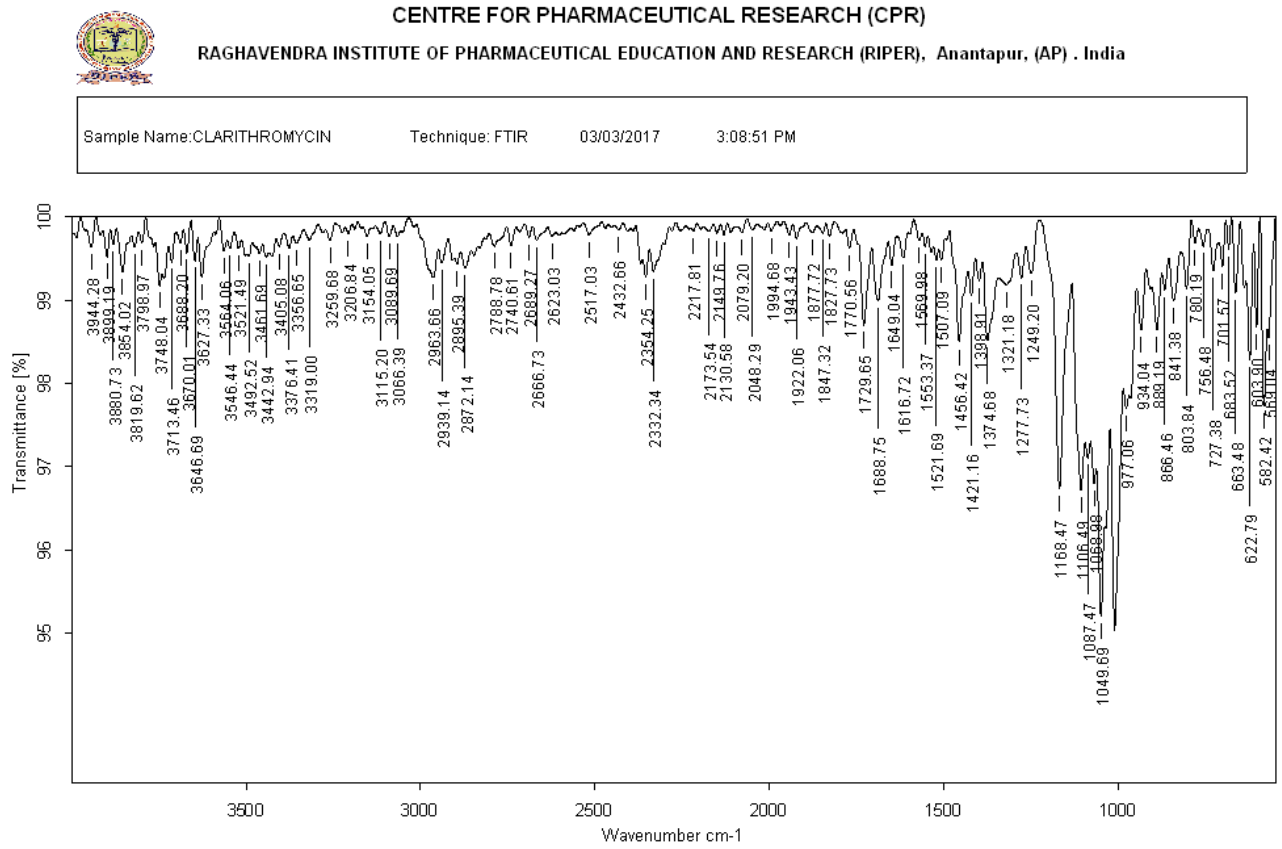

Figure 1: FT-IR spectra of clarithromycin.

of the all formulations (F1-F18) stood in the score of 0.47±0.04 to 0.62±0.07. The angle of repose was found in between 20.35° – 25.41°. The CI and HR was in the range of 10.63±0.02 % to 15.00±0.06 % and1.11±0.03 to 1.17±0.04 which ensures good flow properties and the values were shown in Table 3.

The average weight of the all formulations was found to be within ±5% deviation as per the IP specifications. The thickness and hardness of the all formulations were found to be 6.61±0.4 to 6.69±0.1 mm and 7.9 - 9.0 kg/cm^2. The friability of entire formulations was less than 0.5%, which ensures good mechanical strength of the tablets. The drug content of (F1-F18) was found to be 95.6±0.45 - 99.50±0.37 and was depicted in Table 4. The *in vitro* DR of all formulations at 2 h, 8 h and 12 h was found to be 20.14%- 37.36%, 66.24% - 85.57% and 96.14% – 98.23% (Figure 4).

In vitro drug release data at 2 h (Y1) was analysed and found that interaction of X1, X2, X3 was uppermost with SS ratio (35.9483%) and a positive sign of the coefficient (2.6) represented in Table 5.

Ultimate equation of coded factors

$Y1 = 27.0128 – 0.7006.X_1 – 0.669\ X_2 + 0.2169.X_3 + 2.1062\ X_1X_2 + 1.7287\ X_1X_3 + 1.5513\ X_2X_3 – 0.5885\ X_1^2 - 0.851\ X_2^2 – 0.7585\ X_3^2$

Ultimate equation of actual factors

Y1 = 27.0128 – 0.7006.TKP – 0.669 EC + 0.2169. PVP + 2.1062 TKP.EC+ 1.7287 TKP. PVP + 1.5513 EC.PVP – 0.5885 $(TKP)^2$- 0.851 $(EC)^2$– 0.7585 $(PVP)^2$

ANOVA was availed to recognize significant effect of the factors on the response. Obtained value of F is greater than critical *F*-value, the result was found to be significant at that level of probability ($p<0.05$) as shown in Table 6. The critical value of F is 4.95, obtained F value (i.e. 10.1) is larger than critical value and so it can be resolved that attained *F* value is expected to happen by chance with a $p<0.05$. Subsequently the association between Y_1 Vs $X_1X_2X_3$ is nonlinear as shown by Sigma Tech software, the CCD has been implemented. The results of the multiple linear regression analysis revealed that the increase in the amount of X_1, X_2, X_3 increased the DR at 2h.[24] All the three factors exhibited significant interactions.

In vitro drug release data at 8 h (Y_2) was ascertained and observed that interaction of X_2 was maximum with SS

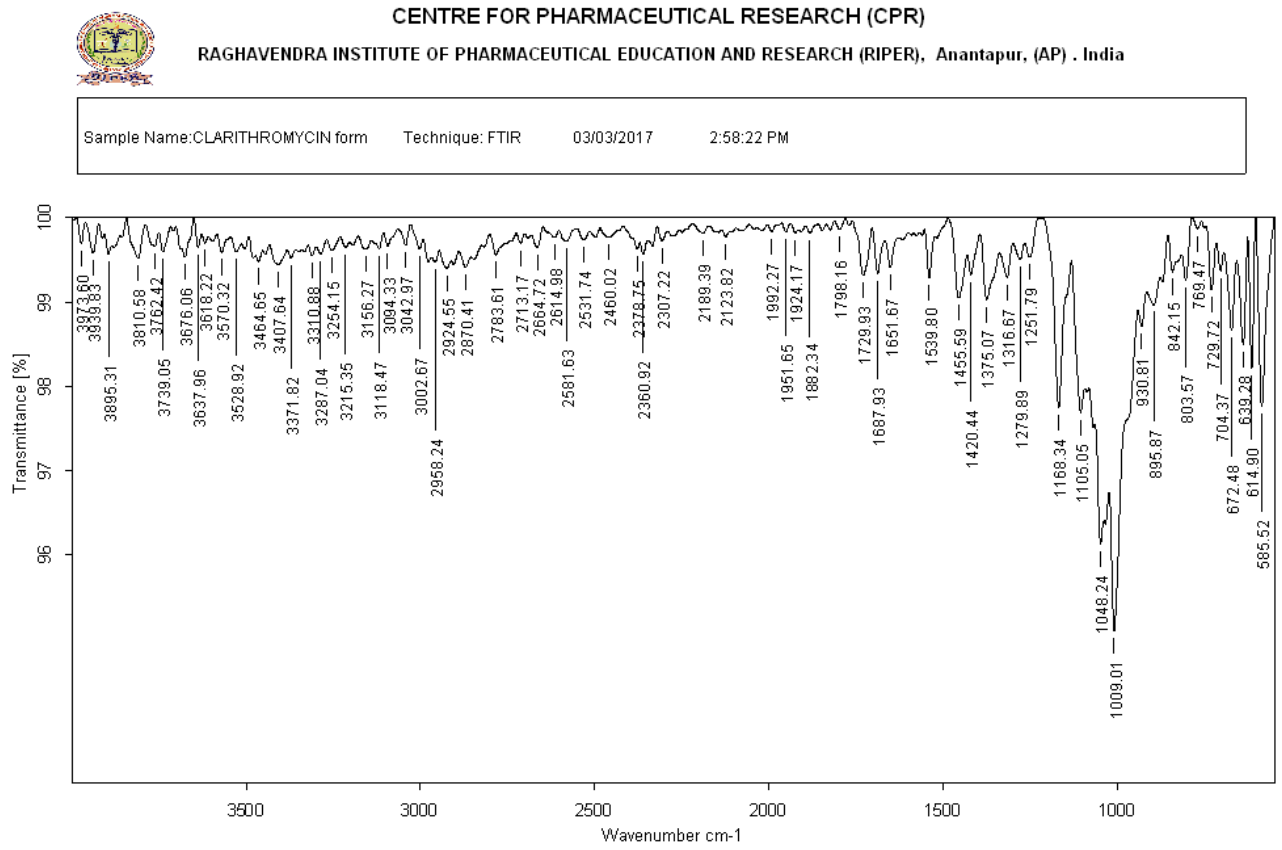

Figure 2: FT-IR spectra of clarythromycin with excipients

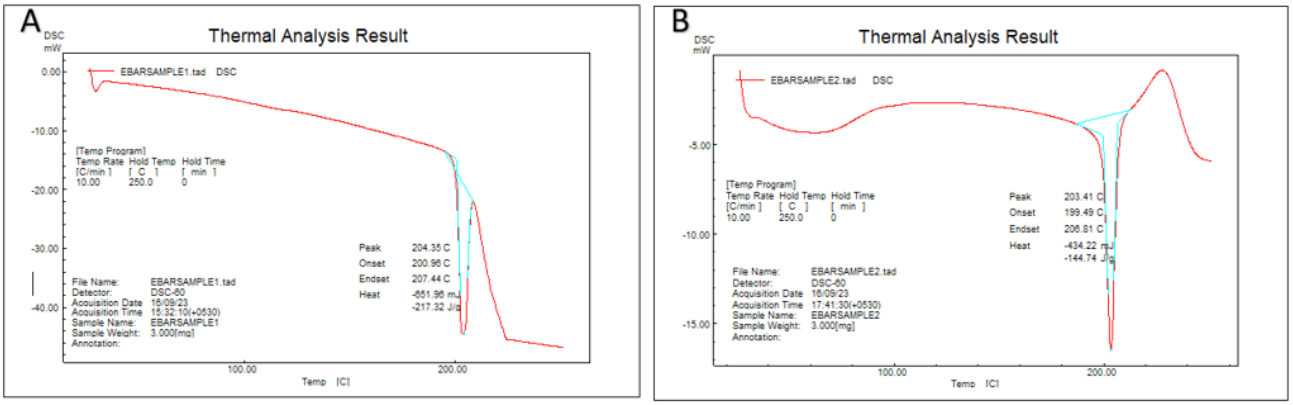

Figure 3: DSC thermograms A) clarythromycin B) clarythromycin with excipients.

ratio (44.8271%) and a negative sign of the coefficient (-2.6637). It specified that the rise in the quantity of X_2 decreased the DR and the data was tabulated in Table 7. ANOVA was availed to categorize significant effect and the results were shown in Table 8.

Final equation in terms of coded factors

$(Y_2) = 78.9451 - 0.3869\ X_1 - 1.6594\ X_2 - 1.5756\ X_3 - 0.3313\ X_1X_2 + 0.0813\ X_1X_3 + 1.2687\ X_2X_3 - 1.0016\ X_1^2 - 1.7629\ X_2^2 - 1.2279\ X_3^2$

Final equation in terms of actual factors

$Y2 = 78.9451 - 0.3869\ TKP - 1.6594\ EC - 1.5756\ PVP - 0.3313\ TKP.EC + 0.0813\ TKP.PVP + 1.2687\ EC.PVP - 1.0016(TKP)^2 - 1.7629\ (EC)^2 - 1.2279\ (PVP)^2$

The polynomial equations were engaged to furnish conclusions subsequently in view of the magnitude of the coefficient and the mathematical sign it possess (i.e., positive or negative). The outcomes of the multiple linear regression analysis exposed that DR decreased with an upsurge in the ethyl cellulose.[25]

Table 3: Precompression parameters of F1-F18 formulations.					
Formulations	**Angle of repose (⁰) ±SD***	**Bulk density gm/cm³±SD***	**Tapped density (gm/cm3) ±SD***	**Carr's index (%) ±SD***	**Hausner ratio ±SD***
F1	24.2±0.07	0.55±0.04	0.62±0.05	11.66±0.09	1.12±0.05
F2	25.41±0.06	0.54±0.03	0.61±0.07	11.47±0.08	1.12±0.05
F3	24.35±0.07	0.51±0.02	0.60±0.05	15.00±0.06	1.17±0.04
F4	21.28±0.04	0.53±0.05	0.62±0.07	14.51±0.04	1.16±0.04
F5	20.84±0.02	0.52±0.02	0.59±0.04	11.86±0.02	1.13±0.03
F6	25.21±0.02	0.47±0.03	0.55±0.01	14.54±0.01	1.17±0.03
F7	23.26±0.01	0.46±0.04	0.54±0.02	14.81±0.02	1.17±0.02
F8	22.51±0.01	0.48±0.06	0.55±0.04	14.58±0.02	1.14±0.02
F9	24.31±0.06	0.42±0.07	0.47±0.04	10.63±0.05	1.11±0.03
F10	20.35±0.04	0.42±0.07	0.48±0.04	12.45±0.05	1.14±0.03
F11	24.63±0.02	0.41±0.07	0.47±0.04	12.76±0.05	1.14±0.03
F12	20.39±0.08	0.42±0.07	0.49±0.04	14.28±0.05	1.16±0.03
F13	25.12±0.03	0.49±0.04	0.56±0.06	12.50±0.06	1.14±0.05
F14	21.64±0.01	0.48±0.02	0.54±0.07	11.11±0.02	1.12±0.06
F15	25.17±0.01	0.51±0.02	0.60±0.02	15.00±0.01	1.17±0.03
F16	21.25±0.03	0.47±0.07	0.55±0.06	14.54±0.06	1.17±0.04
F17	21.11±0.04	0.51±0.03	0.59±0.03	13.55±0.02	1.15±0.03
F18	24.89±0.04	0.51±0.02	0.58±0.02	12.06±0.04	1.13±0.02

All values are expressed as mean ±standard deviation (*n*=3)

Table 4: Post compression parameters of F1-F18 formulations.					
Formulations	**Average weight (mg) ±SD* (*n*=20)**	**Thickness (mm) ±SD* (*n*=6)**	**Hardness (kg/cm²) ±SD*(*n*=6)**	**Friability (%) ±SD* (*n*=10)**	**Drug content ±SD (n=10)**
F1	504.3±0.11	6.67±0.4	7.9±0.05	0.06±0.03	96.2±0.12
F2	505.2±0.66	6.69±0.5	8.5±0.09	0.07±0.05	97.3±0.23
F3	499.6±0.45	6.64±0.2	8.4±0.01	0.06±0.03	98.4±0.35
F4	498.4±0.45	6.64±0.8	8.1±0.08	0.05±0.03	97.4±0.44
F5	502.1±0.41	6.62±0.1	9.0±0.12	0.07±0.02	98.7±0.46
F6	501.4±0.03	6.61±0.4	8.9±0.08	0.05±0.03	97.5±0.37
F7	500.8±0.10	6.62±0.1	8.1±0.02	0.05±0.02	95.8±0.34
F8	499.6±0.18	6.64±0.7	8.5±0.02	0.06±0.02	98.7±0.74
F9	500.1±0.13	6.64±0.8	8.0±0.01	0.07±0.04	96.6±0.53
F10	500.1±0.13	6.63±0.8	8.0±0.01	0.07±0.04	95.9±0.84
F11	500.1±0.13	6.62±0.8	8.2±0.01	0.07±0.04	98.9±0.58
F12	500.1±0.13	6.64±0.9	8.3±0.01	0.07±0.04	99.5±0.37
F13	498.8±0.16	6.65±0.8	8.4±0.05	0.07±0.02	98.4±0.69
F14	500.2±0.13	6.68±0.6	8.9±0.07	0.08±0.05	96.8±0.34
F15	487.3±0.18	6.69±0.1	8.3±0.04	0.07±0.03	96.7±0.55
F16	497.4±0.08	6.68±0.4	8.8±0.07	0.06±0.02	95.6±0.45
F17	500±0.14	6.66±0.7	8.6±0.03	0.07±0.03	98.9±0.58
F18	500.2±0.12	6.62±0.9	8.9±0.05	0.05±0.02	99.4±0.45

All values are expressed as mean ±standard deviation (*n*=3)

Table 5: Statistical analysis of DOE experimental observations for response Y1 (2h).

S N0.	Combination	Coefficient	F-value	SS ratio
1	B0	27.4638	0.0	…
2	B1	-1.4462	17.22281	10.4004%
3	B2	-0.8538	6.0047	3.625%
4	B12	2.1062	36.541	22.0593%
5	B3	0.4787	1.8876	1.1395%
6	B13	1.7287	24.6162	14.8605%
7	B23	1.5513	19.8232	11.967%
8	B123	2.6	34.3543	35.9483%

F is Fisher's value, SS is Sum of squares

Table 7: Statistical analysis of DOE experimental observations for response Y2 (8h).

S NO	Combination	Coefficient	F-VALUE	SS Ratio
1	B0	79.29	0.0	…
2	B1	-1.0613	2.9814	7.1162%
3	B2	-2.6637	18.7806	44.8271%
4	B12	-0.3313	0.2905	0.6934%
5	B3	-2.2513	13.4154	32.021%
6	B13	0.0813	0.0175	0.041%
7	B23	1.2687	4.2605	10.1692%
8	B123	0.9012	2.1497	5.1311%

Table 6: Results of ANOVA for response Y1 (2 h).

S NO	Source of Variance	SS	DF	MS	F- value	F-std 0.1p	F-std 0.05p	F-std 0.01p
1	Model	103.0477	6	17.1746	1.4548	3.4	4.95	10.7
2	Error	57.835	5	11.567				
3	Total	160.8827	11					

Standard Deviation : 0.3485 F Standard Value at 0.05 p : 10.1
Curvature Effect : -5.7488 F Standard Value at 0.01 p : 34.1
95% Confident Level of Curvature Effect FROM: -6.4276 TO: -5.0699 (Non Linear)

DF is Degrees of freedom, MS is mean squares, P is probability

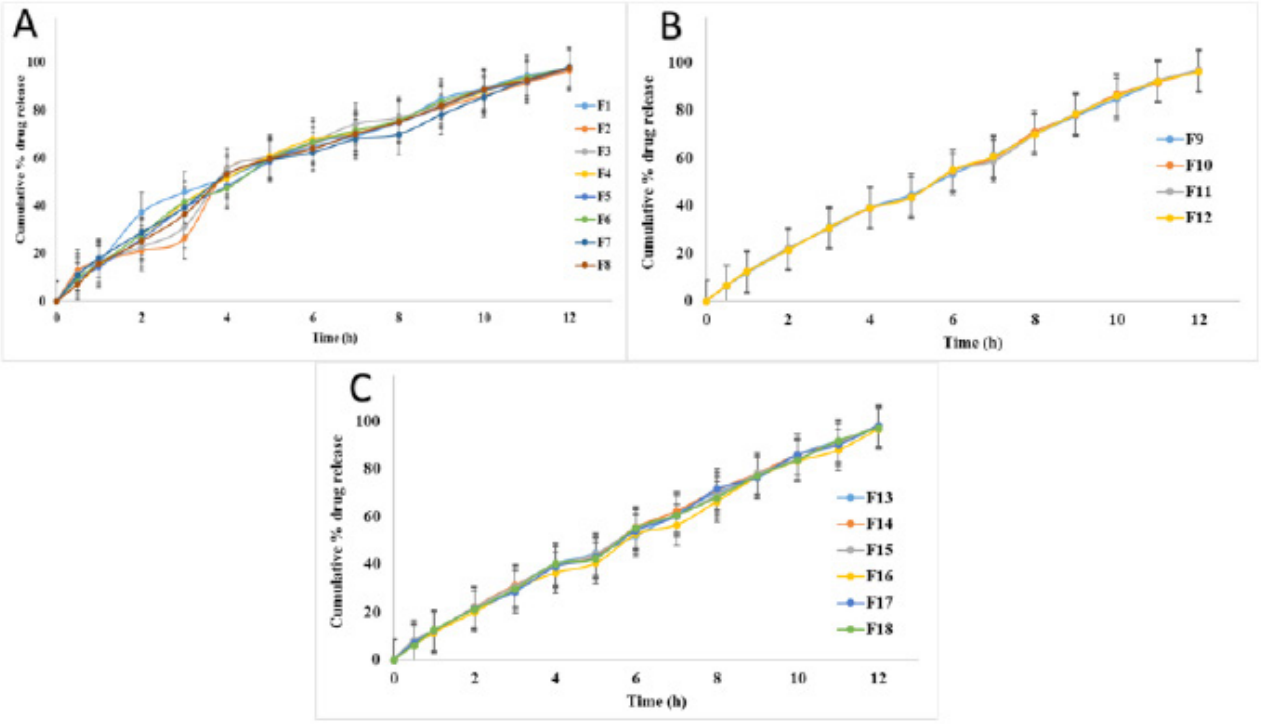

Figure 4: *In vitro* drug release profile of formulations A) F1-F8, B) F9 – F12 C) F13 – F18.

Time to dissolve 50 percent of the drug, t_{50} data (Y_3) was scrutinized and noticed that interaction of X2 X3 was peak with SS ratio (53.1915%) and a negative sign of the coefficient (-0.125). and the data was represented in Table 9.

Final equation in terms of coded factors

$(Y_3) = 4.1333 + 0.1\ X_1 + 0.0125\ X_2 + 0.0375\ X_3 + 0.05\ X_1X_2 + 0.0\ X_1X_3 - 0.125\ X_2X_3 + 0.0833\ X_1^2 + 0.2083\ X_2^2 + 0.1833\ X_3^2$

Final equation in terms of actual factors

$Y3 = 4.1333 + 0.1\ TKP + 0.0125\ EC + 0.0375\ PVP + 0.05\ TKP.EC + 0.0\ TKP.PVP - 0.125\ EC.PVP + 0.0833\ (TKP)^2 + 0.2083\ (EC)^2 + 0.1833\ (PVP)^2$

It was noticed that t_{50} time increased with rise in concentrations of EC and PVP[26] and the ANOVA was used to identify significant effect and data was shown in Table 10.

From contour plots it was found that suitable design space for drug release was found between the coded values as illustrated in Figure 5. The study lead to the design space from multidimensional combination of 2 h, 8 h and t_{50} that lead to the acceptable operating ranges for formulating extended release tablets. By considering the predicted values the formulation was prepared and examined for the responses. Contour plots allowed the configuration of TKP as 50 mg (0) and Ethyl cellulose 26.25 mg (0) and Polyvinyl pyrrolidone 13.75 mg(-1); and all other ingredients remained same for optimized formulation. The RE amongst the prophesied and investigational values for individual outcome were calculated and results was noticed to be 0.28%, 0.43%, 0.20% represented in Table 11. The investigational values were in promise with the prophesied values authorizing the expectedness and strength of the model.

Table 8: Results of ANOVA for response Y2 (8 h).

S NO	Source of Variance	SS	DF	MS	F-Value	F-std 0.1p	F-std 0.05p	F-std 0.01p
1	Model	120.1279	6	20.0213	15.4057	3.4	4.95	10.7
2	Error	6.498	5	1.2996				
3	Total	126.625	11					

Standard Deviation : 0.6146 F Standard value at 0.05 p : 10.1
Curvature Effect :-9.0383 F Standard value at 0.01 p : 34.1
95% Confident Level of curvature effect FROM : -10.2356 TO : -7.8409 (Non Linear)

Table 9: Statistical analysis of DOE experimental observations for response Y3 ($t_{50\%}$).

S NO	Combination	Coefficient	F-VALUE	SS Ratio
1	B0	3.875	0.0	…
2	B1	0.0	0.0	0.0%
3	B2	-0.075	2.25	19.1489%
4	B12	0.05	1.0	8.5106%
5	B3	0.075	2.25	19.1489%
6	B13	0.0	0.0	0.0%
7	B23	-0.125	6.25	53.1915%
8	B123	0.0	0.0	0.0%

Table 10: Results of ANOVA for response Y3 ($t_{50\%}$).

S NO	Source of Variance	SS	CF	MS	F-Value	F-std 0.1p	F-std 0.05p	F-std 0.01p
1	Model	0.235	6	0.0392	9.22337	3.4	4.95	10.7
2	Error	0.0	5	0.0				
3	Total	0.235	11					

Standard Deviation: 0.05 F Standard value at 0.05 p : 10.1
Curvature Effect: 1.7 F Standard value at 0.01 p : 34.1
95% Confident level of curvature effect FROM: 1.6026 TO 1.7974 (Non Linear)

Table 11: Comparison of experimental results with predicted responses of clarithromycin extended release tablets formulation.

Ingredient	Composition (%/tab)	Response	Predicted value	Experimental Value	Standard Error (%)
TKP	10	Y1 (2 hr) (%)	23.54	22.98	0.28
EC	5.25	Y2 (8 hr) (%)	70.88	70.02	0.43
PVP	2.75	Y3 (t_{50})	5.27	4.87	0.20

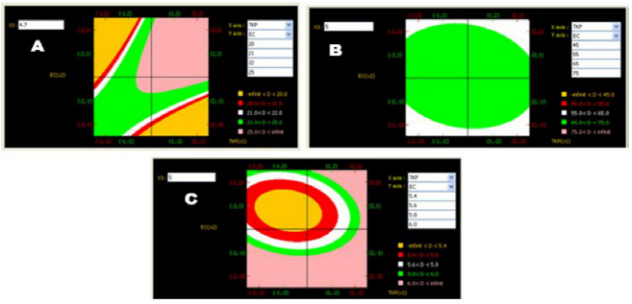

Figure 5: Contour plots A) Drug release at 2h B) Drug release at 8h C) t_{50}%.

CONCLUSION

Clarythromycin ER tablets were successfully prepared by wet granulation method to overcome the frequency of intake of tablets. The concentration of variables was observed to have a deep and conjunct outcome on the dissolution of 2h, 8 h, t_{50} as shown by the model obtained using central composite design. The data exhibited that investigational plan was efficaciously enforced to augment the concentration of polymers to formulate extended release tablets with necessary release of drug at 2 h, 8 h, t_{50}. and also clinched that the central CCD might be effectively useful meant for the buildout of clarithromycin extended release tablets with less trials and improved value characteristics.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

ER: Extended release; **DoE:** Design of Experiments; **CCD:** Central Composite design; **TKP:** Tamarind kernel powder; **EC:** Ethyl cellulose; **PVP:** Polyvinyl pyrrolidone; ***H. pylori:*** Helicobacter Pylori; **FTIR:** Fourier-transform infrared spectroscopy; **DSC:** Differential scanning calorimetry; **IP:** Indian Pharmacopoeia; UV::Ultraviolet; **HCl:** Hydrochloric acid; **RPM:** Revolutions per minute; **ANOVA:** Analysis of variance; **SS ratio:** Sum of squares ratio; **RE:** Relative error.

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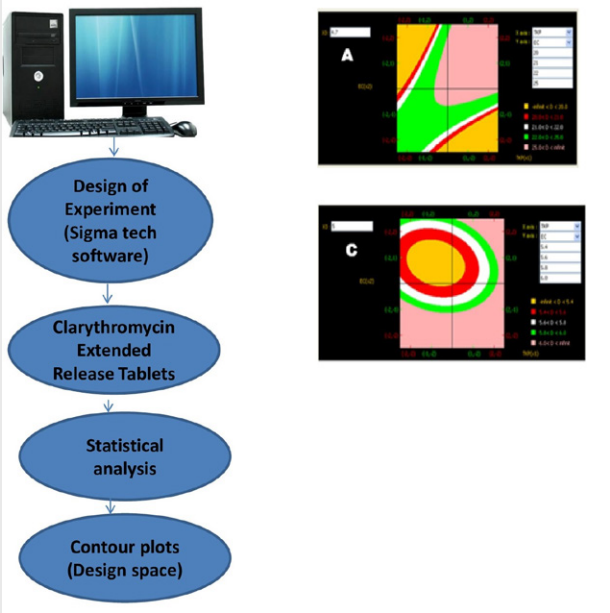
PICTORIAL ABSTRACT



Central composite design aided ER tablets

SUMMARY

- In the present study, clarythromycin extended release tablets were formulated and optimized by using CCD.
- The concentrations of tamarind kernel powder (X_1), ethyl cellulose (X_2) and polyvinyl pyrrolidone (X_3) stayed as non-dependent factors and responses selected were drug release in 2 h, 8 h and t_{50}%.
- From the results obtained it was inferred that the concentration of independent variables had shown profound effect on dissolution profile.
- Contour designs were utilized to further explicate the bond amid the non-dependent factors and responses. Suitable design space for drug release was found from the contour plots.

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