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(RESEARCH ARTICLE)

QbD: A novel approach for formulation and optimization of colon targeted drug delivery system containing mebeverine HCl

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Abstract

The aim of the work is to study the programmed release of model antispasmodic drug Mebeverine HCl based on pulsatile principle to target colon proximity. Compression coated tablets included core tablet consisting of Croscarmellose as super disintegrant and pulsatile layer comprising impermeable Ethocel cup and mixture of Keltone, Eudragit S100, Ethocel as swellable and rupturable layer. The prepared core tablet was evaluated for weight variation, hardness, thickness, friability, drug content, disintegration time and *in vitro* dissolution studies. For optimization Box-Behnken design was employed to study the effect of independent variables viz., weight ratio of Keltone (X_1), Eudragit S100 (X_2), Ethocel (X_3) on dependent variables viz., t_{10} (Y_1), t_{50} (Y_2) and Q_{12} (Y_3). Results revealed positive influence of independent factors on responses. The data were statistically analyzed using ANOVA and were found to be statistically significant ($P < 0.05$). Mathematical modeling for kinetic studies revealed that the release profile after lag time followed first order kinetics. The results concluding that a successful pulsatile drug delivery system of Mebeverine HCl was developed.

Keywords: Mebeverine HCl; Eudragit S100; Croscarmellose; Box Behnken Design; Optimization

1. Introduction

Irritable bowel syndrome (IBS) is a complex and widely encountered syndrome. It is a condition characterized by abdominal pain associated with disordered defecation in the absence of any demonstrable abnormality. Despite recent advances in the treatment of IBS[1-3] the exact pathophysiology of IBS is still incompletely understood. Alteration in neurohumoral mechanisms and psychological factors, bacterial overgrowth, genetic factors, gut motility, visceral hypersensitivity, and immune system factors are currently believed to influence the pathogenesis of IBS[4,5]. Mebeverine HCl is a musculotropic agent has antispasmodic activity and regulatory effects on the bowel function have been successfully used in the management of IBS for many years[6]. During oral administration it shows no typical anticholinergic side effects, such as dry mouth, blurred vision, and impaired micturition. Several clinical trials justify the utility of Mebeverine HCl in patients with IBS exist. In the present work, we systematically studied the formulation and optimization of colon targeted compression coated tablets loaded with Mebeverine HCl core tablets by QBD approach using Design of Experiment (DoE).

2. Material and methods

2.1. Materials

Mebeverine HCl (MEB) obtained from Magnus Pharma Pvt.Ltd, Nepal. Croscarmellose sodium (CCM), Eudragit S100 (ES100), obtained from Yarrow Chem Products, Mumbai. Galen IQ720 (GQ720) procured from Beneo-Palatinite,

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Germany. Keltone, Ethocel purchased from SD Fine Chem limited, Mumbai. All other reagents used were of analytical grade.

2.2. Methods

2.2.1. Formulation of core tablet (CT)

The core tablets containing MEB (130 mg per tablet), CCM (12% w/w), GIQ (q.s), Magnesium stearate (1% w/w) and Talc (1% w/w) were prepared by direct compression technique. Initially the powder blends of the core tablet ingredients were mixed in the mini double cone blender for 10 min. The core tablets (diameter 8 mm, flat, average tablet weight, 180 mg) were compressed using the 10 station rotary tablet compression machine.

Preparation of compression coated tablets: The T-1 to T-15 batches as per Box-Behnken design (BBD) (Table 1) of compression coated tablets were prepared by one step dry coating technique[7] using MEB-CT[8]. In each case impermeable ethocel was applied under the bottom of the die cavity and core tablet was placed carefully at the centre of die. MEB-CT was slightly pressed to fix, above it the mixture of pH dependent (ES100), rupturable and swelling polymers (Keltone, Ethocel) were filled and manually lowered the lower punch slowly and compressed by using 13 mm flat faced punch.

2.2.2. Drug-excipient compatibility study

The compatibility study of the drugs and excipients was checked out using the FTIR spectrophotometer. The FTIR spectra for MEB, MEB-CT and optimized tablet were recorded using BRUKER-FTIR spectrophotometer in the wave number region from 4000 cm^{-1} to 500 cm^{-1}. Samples were prepared by physically mixing drug and different excipients separately in ratio of 1:1 and were kept for a month at 40 °C/75% RH. Then the mixture was mixed thoroughly with dry KBr (IR grade) in ratio of 1:5 and triturated in a small size mortar pestle. Then pellet of mixture was prepared by compressing the powder in a hydraulic press. Pure KBr powder was used as background, and for baseline correction.

2.2.3. In vitro dissolution studies

- **For core tablets:** *In vitro* dissolution study core tablets were conducted by using USP Type II Paddle apparatus. Place the stated volume about 900 ml of the dissolution medium viz., phosphate buffer pH 7.4, free from dissolved air, into the vessel of the apparatus. Assemble the apparatus and warm the dissolution medium to 37 °C. Place one core tablet in the apparatus, allow the tablet to sink to the bottom of the vessel prior to the rotation of the paddle. Operate the apparatus immediately at the 50 rpm. At specified time interval withdraw the 5 ml sample and add a volume of fresh dissolution medium equal to the volume of the samples withdrawn to maintain sink condition. Filter the sample solution through Whatman filter 44, and measure at 263 nm for MEB content using a double beam UV spectrophotometer. The study was conducted in triplicate and data were computed by using dissolution software PCP Disso V3.0.
- **For compression coated tablet:** *In vitro* drug dissolution studies were carried out for compression coated tablets using USP Type II Paddle apparatus. The drug release was studied in three different medium to simulate GIT proximity. Initially the dissolution was carried out in 0.1N HCl for first 2 h to mimic the simulation of gastric fluid. After replace the 0.1N HCl with phosphate buffer pH 7.4 and continue the dissolution for 6 h. Replace the phosphate buffer pH 7.4 with phosphate buffer pH 6.8 and continue the dissolution for 12 h to mimic small intestine and colon pH. In each case at different intervals of time 5 ml was withdrawn and same 5 ml was replaced with fresh dissolution medium to maintain the sink conditions. Filter the sample solution through Whatman filter 44, and measure at 263 nm for MEB content using a double beam UV spectrophotometer. The study was conducted in triplicate and data were computed by using appropriate method.

2.2.4. Optimization by using BBD

Traditionally pharmaceutical formulations developed by changing one variable at a time by trial and error method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established tools such as per BBD. In addition to the art of formulation, the technique of BBD is an effective method of indicating the relative significance of a number of variables and their interactions. Design Expert® (Trial Version 13, Stat-Ease Inc., Minneapolis, U.S.A.) was used to generate BBD and the regression analysis was used to optimize the concentration of Keltone (X_1), ES-100 (X_2) and Ethocel (X_3). In this design, 3 factors were evaluated each at 2 levels, 3 centre points and experimental trials were performed at all 15 possible combinations. Y_1 (t_{10}), Y_2 (t_{50}), and Y_3 (Q12) were selected as dependent variables. Three independent factors were set at two levels viz., Low and High and were coded as - 1 and +1, respectively shown in table 1. The data obtained were treated using software (equation 1) and analyzed statically using

analysis of variance (ANOVA). The data were subjected to 3-D and 2-D response surface methodology to study the interaction of Keltone (X_1), ES-100 (X_2) and Ethocel (X_3). The actual formulation design of MEB compression coated tablets according to BBD layout was shown in table 2.

$$Y=\beta_0 + \beta_1 A + \beta_2 B + \beta_3 AB + \beta_4 A^2 + \beta_5 B^2 \text{ --- } 1$$

Where, Y is the dependent variable, β_0 is the arithmetic mean response of the 15 runs, β_1, β_2, β_3, β_4 and β_5 are the estimated constant regression co-efficient of the factors X_1, X_2 and X_3. All the formulations were evaluated for responses viz., Y_1 (t_{10}), Y_2 (t_{50}), and Y_3 (Q12)

Table 1 Variables and their levels in Box-Behnken design

Independent variables	Levels	
	Low (-1)	High (+1)
Keltone-X_1	70	90
ES 100-X_2	170	200
Ethocel-X_3	250	270
Dependent variables		
t_{10} (Y_1); t_{50} (Y_2) ;Q_{12} (Y_3)		

2.2.5. Accelerated stability studies

The accelerated stability study of the optimized formulation was carried out. The sample of tablets were wrapped in the laminated aluminum foil and placed in the stability chamber at 40 ± 2 °C/75 ± 5% RH for a period of one month. Sampling was done at a predetermined time intervals of 0, 15 and 30 days. The tablets were evaluated for different physicochemical parameters.

3. Results and discussion

3.1. Drug excipient compatibility studies

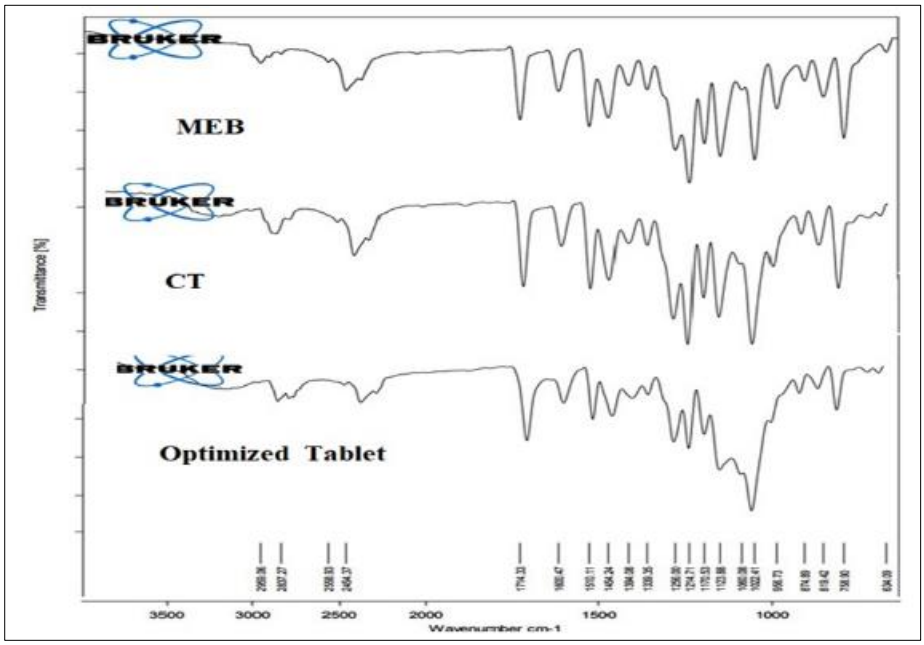

Figure 1 FTIR spectra of pure MEB, MEB-CT and Optimized tablet

The FTIR spectra of MEB shows characteristic absorption bands appeared at 2959.06 cm-1 for Ar-CH=CH-, 2837.27cm-1 for -CH2-,1714.33 cm-1 for C=O, 1510.11 cm-1 for Ar-CH=CH- and 1339.31 cm-1 for -C-N-. MEB, MEB-CT and compression coated tablets shows all the characteristic bands of MEB which clearly indicate that there is no interaction between the MEB and polymers (figure 1).

3.2. Tablet characterization

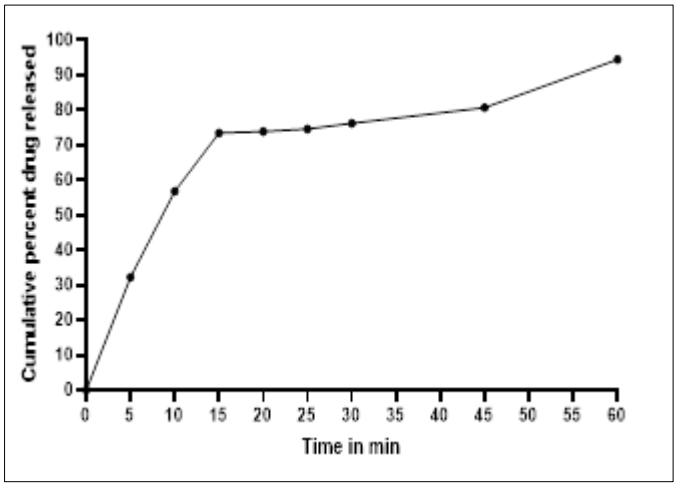

Figure 2 *In vitro* dissolution profile of MEB-CT tablet

MEB-CT of was characterized for pre and postcompression parameters. The results of precompression was found to be 0.336±0.011g/cm^3; tapped density 0.537±0.040g/cm^3; compressibility index value 37.64±6.201 and Hauser's value 1.603±1.557 for F-3 formulations indicates a powder with good compressibility and flowability, suitable for direct compression. The angle of repose was found to be 41.81±0.715 for F-3 formulation showing that the blends of powder were good flowing. The postcompression data of MEB-CT was found to be viz., 181 ± 2.321 mg weight variation; 3.837 ± 0.086 thickness; 8.064 ± 0.080 diameter; 3.10 ± 0.264 hardness; 0.750 ± 0.020 friability. The results suggest the MEB-CT has desired mechanical strength, tablet integrity and uniform weight throughout the batch prepared. Further the MEB-CT contains CCM at 12% had ability to disintegrate rapidly (22.12 ±1.02) which fulfilled the requirements for the burst release. The *in vitro* drug release profile of MEB-CT was shown in figure 2 and results indicate 94.473±0.71 drug release after 60 min which ideal for designing pulsatile pattern. The compression coated tablets viz., T1 to T15 (Trails as per BBD) characterized for content uniformity and other post compression parameters. The results were found to be in the of average of 718.75 ± 1.89 to 728.75±1.50 weight variation; 4.77 ± 0.05 to 5 ± 0.141 thickness; 12.98 ± 0.005 to 13.05 ± 0.0057 diameter. The data indicates compression coated tablets have desired, tablet integrity and uniform weight throughout the batches prepared.

3.3. Experimental design characterization

A BBD was applied to study the relationship between independent variables and dependent variables using software Design Expert Trail 13. Figure 3 shows the release profiles of the 15 experimental runs performed in accordance with Table 1. Results shown in Table 2 demonstrated responses of all the 15 design batches: response Y_1 (t_{10}), response Y_2 (t_{50}) and response Y_3 (Q_{12}). The data indicated that X_1 (Keltone), X_2 (ES 100) and X_3 (Ethocel) influences the selected responses viz., Y_1, Y_2 and Y_3. Table 4 exhibited the results of analysis of variance (ANOVA). P value of the applied quadratic model was below 0.05, thus suggested that the applied model was significant and hence further reduced model was not generated[9,10]. The individual parameters were evaluated and mathematical relationship was generated between dependent variables and independent factors using multiple linear regression analysis, for determining the optimum levels to yield desired response. The fitted polynomial equation (Eq.1, 2 and 3) relating the responses viz., Y_1, Y_2 and Y_3 to the transformed factors and the associated p-values, ANOVA and model suggested with regression coefficient data were presented in Table 4 and 3.

$$t_{10} = -3.63750 + 0.161000*\text{Keltone} - 0.061833*\text{ES100} + 0.069167*\text{Ethocel} - 0.000100*\text{Keltone}*\text{ES100} - 0.000050*\text{Keltone}*\text{Ethocel} - 0.000233*\text{ES100}*\text{Ethocel} - .000800*\text{Keltone}^2 + 0.000267*\text{ES100}^2 - 0.000050*\text{Ethocel}^2 \quad \text{……Eq-1}$$

$$t_{50} = -32.07550 - 0.007125*\text{Keltone} + 0.005333*\text{ES100} + 0.141375*\text{Ethocel}\ldots\ldots \quad \textbf{Eq-2}$$

Q_{12} = -46.36200 + 0.010000*Keltone + 0.054667*ES100 + 0.489000*Ethocel…….. **Eq-3**

Results depicted that significant factors affecting the response Y_1 (t_{10}) were synergistic with linear contribution of main effects of X_1 and X_3 whereas X_2 affected by antagonistic effect of linear contribution without producing any interaction. The response Y_2 (t_{50}) was significantly affected by antagonistic effect of linear contribution of X_1 and synergistic effect of linear contribution of X_2 and X_3, respectively without producing any interaction. The response Y_3 (Q_{12}) was significantly affected by synergistic effect of linear contribution of X_1, X_2 and X_3 respectively without producing any interaction. These results are justified through relationship between the dependent and independent variables by constructing contour plots, 3D surface plots, predicted vs actual and interaction plots based on BBD shown in figures 4, 5 and 6.

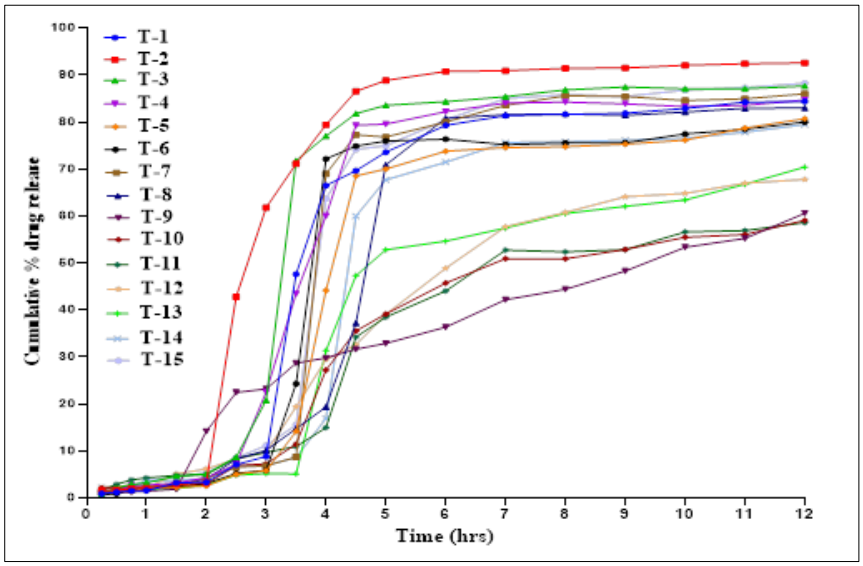

Figure 3 Comparative *in vitro* dissolution profiles of trials as per BBD

Table 2 Trial formula for MEB Compression coated tablets as per BBD

Trial Runs	Keltone X_1	ES100 X_2	Ethocel X_3	t_{10} Y_1	t_{50} Y_2	Q_{12} Y_3
T1	70	170	260	3.08	5.12	93.01
T2	90	170	260	3.12	5.06	92.17
T3	80	170	270	3.21	6.11	94.11
T4	70	185	250	2.58	3.55	84.34
T5	80	185	260	2.67	4.07	91.03
T6	70	185	270	2.54	6.54	95.01
T7	80	185	260	2.71	4.72	90.21
T8	80	200	270	2.13	6.39	96.34
T9	90	185	250	2.64	3.78	87.64
T10	90	185	270	2.58	7.24	97.25
T11	80	185	260	2.63	5.98	94.31
T12	80	170	250	3.25	3.69	85.22
T13	70	200	260	2.21	5.86	96.12
T14	90	200	260	2.19	4.42	92.22
T15	80	200	250	2.31	3.95	86.39

Table 3 Regression analysis for responses

Response	Significant Model suggested	R^2	Adjusted R^2	Adequate precision
Y_1	Linear	0.9696	0.9613	26.0383
	Quadratic	0.9938	0.9825	
Y_2	Linear	0.8116	0.7602	9.9306
Y_3	Linear	0.8159	0.7657	11.0070

Table 4 ANOVA data for all responses

t_{10}-Y_1					
Model	**Sum of squares**	**Df**	**Mean square**	**F-value**	**p-value**
Significant	1.88	9	0.2094	88.35	<0.0001
A-Keltone	0.0018	1	0.0018	0.7595	0.4234
B-ES100	1.82	1	1.82	769.64	<0.0001
C-Ethocel	0.0128	1	0.0128	5.40	0.0677
AB	0.0009	1	0.0009	0.3797	0.5647
AC	0.0001	1	0.0001	0.0422	0.8454
BC	0.0049	1	0.0049	2.07	0.2100
A^2	0.0236	1	0.0236	9.97	0.0252
B^2	0.0133	1	0.0133	5.61	0.0641
C^2	0.0001	1	0.0001	0.0389	0.8513
Residual	0.0119	5	0.0024		
NS-Lack of Fit	0.0087	3	0.0029	1.80	0.3763
t_{50}-Y_2					
Significant	16.08	3	5.36	15.79	0.0003
A-Keltone	0.0406	1	0.0406	0.1197	0.7359
B- ES100	0.0512	1	0.0512	0.1509	0.7051
C-Ethocel	15.99	1	15.99	47.11	<0.0001
Residual	3.73	11	0.3394		
NS-Lack of Fit	1.85	9	0.205	0.2176	0.9578
Q_{12}-Y_3					
Significant	196.76	3	65.59	16.25	0.0002
A-Keltone	0.0800	1	0.0800	0.0198	0.8906
B- ES100	5.38	1	5.38	1.33	0.2728
C-Ethocel	191.30	1	191.30	47.39	<0.0001
Residual	44.40	11	4.04		
NS-Lack of Fit	34.99	9	3.89	0.8260	0.6577

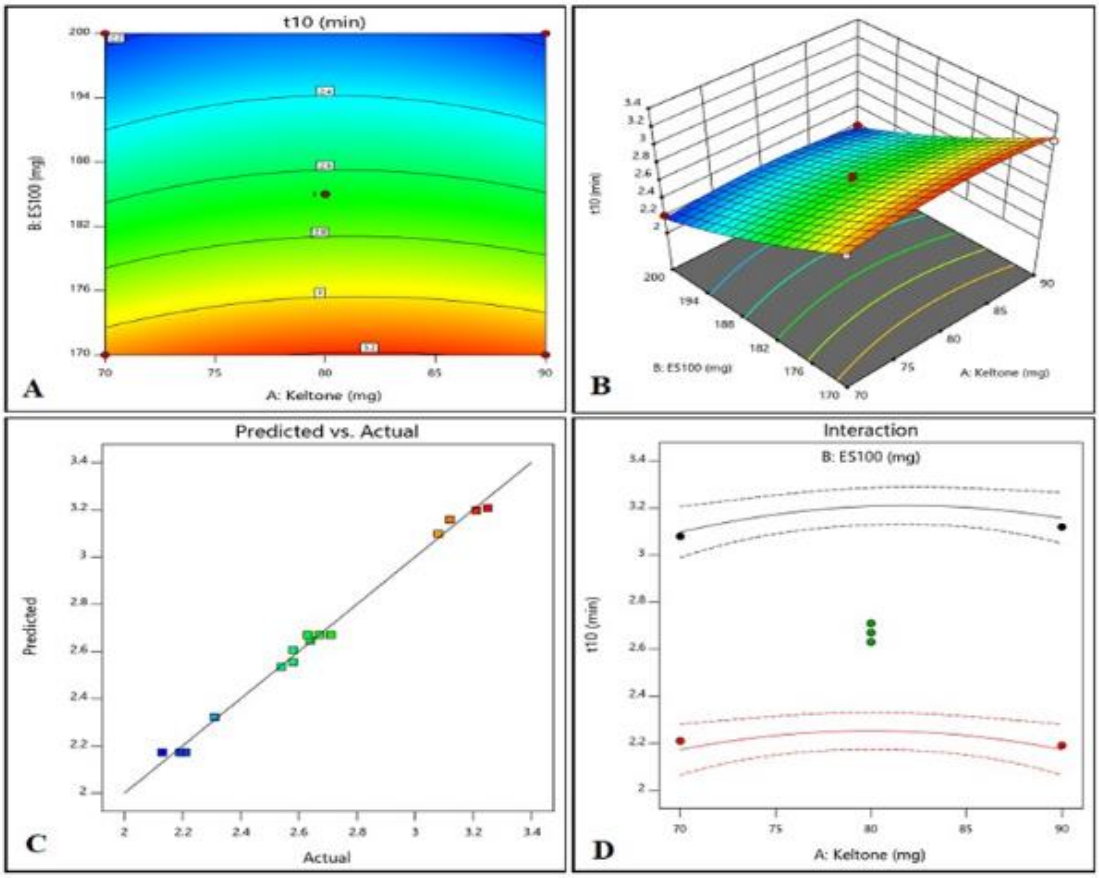

Figure 4 2D contour (A), 3D-Repsonse surface response (B), Predicted vs Actual (C) and Interaction (D) plots showing the influence of X_1 (Keltone), X_2 (ES 100) on Y_1 (t_{10})

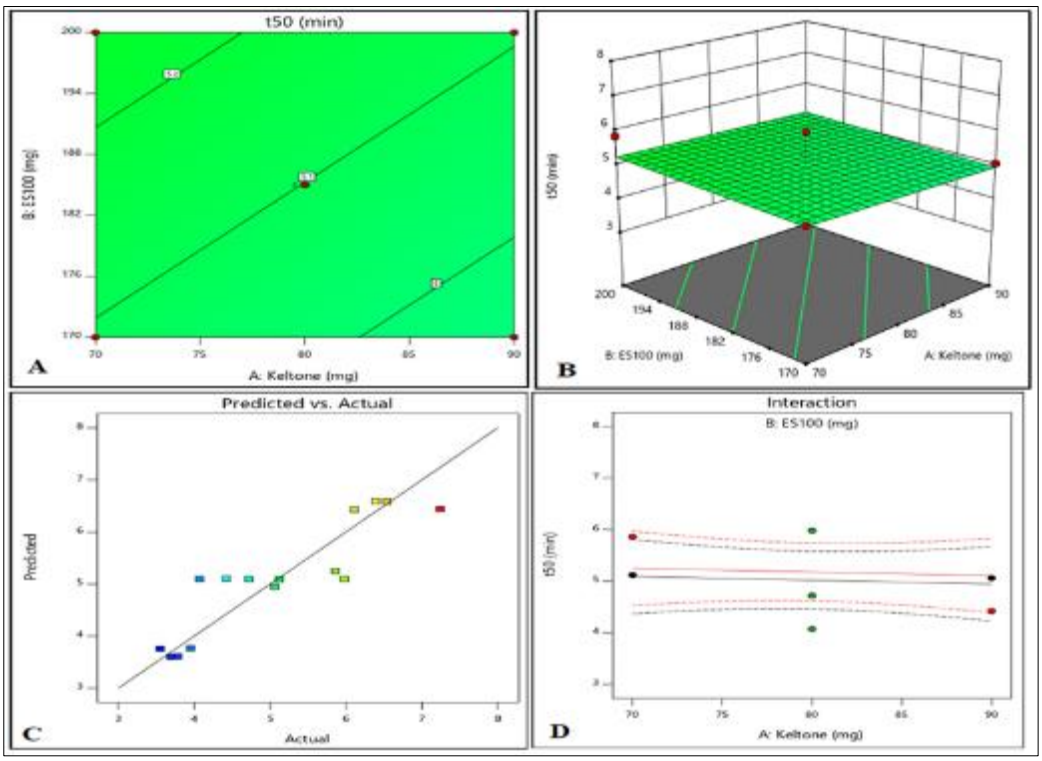

Figure 5 2D contour (A), 3D-Repsonse surface response (B), Predicted vs Actual (C) and Interaction (D) plots showing the influence of X_1 (Keltone), X_2 (ES 100) on Y_2 (t_{50})

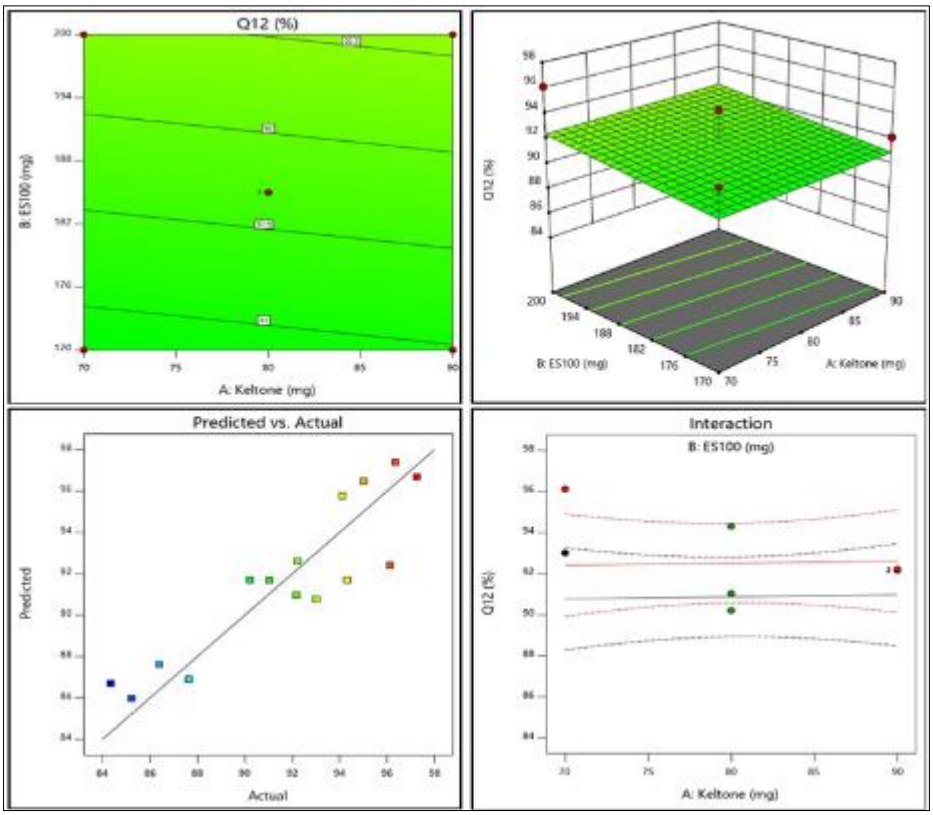

Figure 6 2D contour (A), 3D-Repsonse surface response (B), Predicted vs Actual (C) and Interaction (D) plots showing the influence of X_1 (Keltone), X_2 (ES 100) on Y_3 (Q_{12})

3.4. Development of optimized formulation by point prediction method

A numerical optimization technique using the desirability approach was employed to develop an optimized formulation with the desired responses. Constraints were set viz., linear range for independent variables viz., X_1 (Keltone), X_2 (ES100) and X_3 (Ethocel) concentrations; linear range is set for dependent variables viz., Y_1 (t_{10}), Y_2 (t_{50}) and Y3 (Q_{12}). Optimize the constraints by using Deign Expert software to generate the possible solution with high degree of desirability and generate the possible overlay plot to explain the details of the optimized batch.

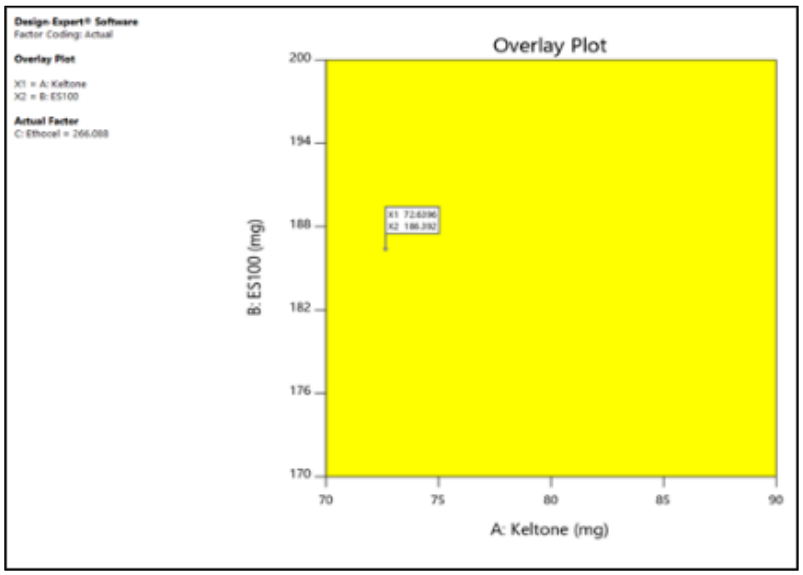

Figure 7 Overlay plot showing optimized region of compression coated MEB tablet

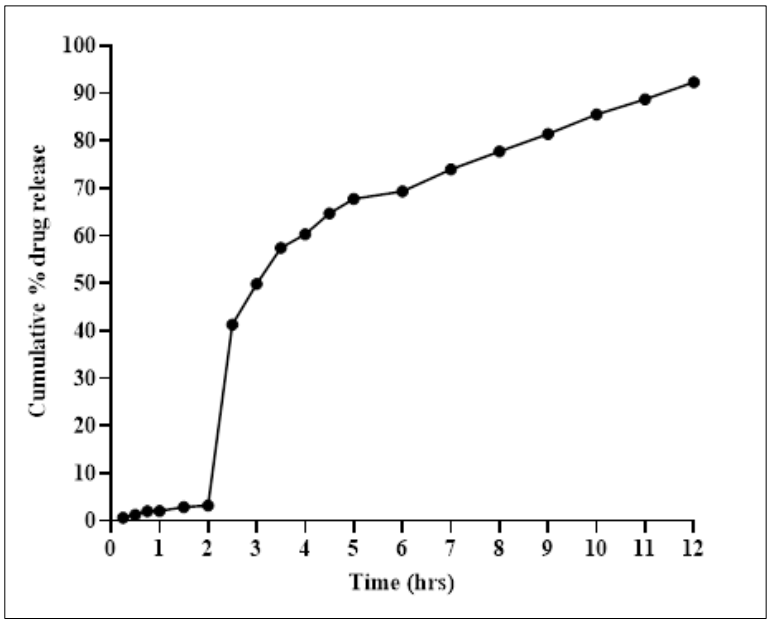

Figure 8 *In vitro* dissolution profile of experimental optimized compression coated tablet

The point prediction method confirms the ratio of X_1 (Keltone), X_2 (ES100) and X_3 (Ethocel) concentrations as shown in the table 5 and confirmed by predicted response mean with standard deviation (as per Two sided. Confidence interval = 95%) as shown in table 6**.** The desirability of constraints factors shown in over lay plot figure 7 gives the details of the optimized batch giving the optimum results of the optimized batch. The MEB-CT compression coated tablet as per BBD were identified by numerical optimization and desirability function by "trading off" of various response variables for attaining the desired goals, minimization of response variables. The optimum tablet formulation comprising Keltone, Eudragit S100 and Ethocel as per BBD was prepared and validated for the predicted response. The optimal formulae as per BBD were given in table 5. Validation of the predicted values of responses was performed experimentally and comparing the data, which indicated high degree closeness between the predicted and observed values of the responses as shown in table and confirmed excellent prognostic ability of the employed mathematical model. The experimental optimized formulation was further evaluated for precompression, post compression parameters and *in vitro* drug release studies. The corresponding profile was shown in figure 8.

Table 5 Formulae of optimal MEB-CT loaded compression coated tablet as per BBD

Ingredients	**OT-1**
Core tablet (MEB-CT)	180
Factors with levels as per BBD	
Keltone	79.60
Eudragit S 100	198.092
Ethocel	102.308
Impermeable cup polymer	
Ethyl cellulose	170
Total weight	730

The results of precompression data indicate good compressibility and flowability and can be used for direct compression. The angle of repose was found to be within the range indicating the blends of compression coat powder were free flowing. The Thickness and diameter was within the permissible range. The postcompression data suggest that the fabricated optimized compression coated tablet have desired mechanical strength and weight distribution within the tablets. The optimal MEB-CT loaded compression coated tablet was subjected for *in vitro* drug release studied

under standard conditions. The lag time is maintained for 2 hr with 3.237±0.13 drug release, after lag time the initial burst drug release was found to be 69.370±0.54 at the end of 6 hr; 92.321±0.31 at the end of 12 hr. In time controlled compression coated tablets, drug containing core compressed with the outer barrier layer, it prevents the rapid drug release from core tablets. The drug will not be released unless the coat is broken. When the dissolution medium reaches the core after eroding or rupturing the outer barrier layer rapid drug release was observed. The release profile of compression coated tablet exhibited lag time followed by burst release, in which the outer shell breaks into two halves. The best fit model was found to be peppas with exponential 'n' values was 1.1645 greater than 0.5 indicated the mechanism drug release was super case II transport.

Table 6 Comparison of experimental value of optimized-check point batch with theoretical value

Response	Predicted	Experimental	% Relative error
Y_1 (t_{10})	2.55	2.47	3.137
Y_2 (t_{50})	6.019	5.85	2.807
Y_3 (Q_{12})	94.67	92.32	2.482

Optimized batch was investigated for one month stability studies in accelerated conditions at 40 ± 2 °C/75 ± 5% RH. Results revealed no significant difference in physicochemical parameters like hardness, drug release lag time, drug content and % drug release.

4. Conclusion

The present study demonstrates the successful preparation of MEB loaded compression coated tablet with an aim of targeting colon proximity. The release profile clearly concludes maximum drug concentration at colonic pH. This will provide ideal therapeutic regiment with enhanced patient compliance. Experimental design applied to the manipulation of formulation parameters provided optimum levels of independent variables to formulate an optimal batch. The optimized formulation exhibited release profile closed to the predicted profile. Thus, the developed formulation can be considered as one of the promising preparation for treating IBS.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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