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ORIGINAL ARTICLE / ÖZGÜN MAKALE

BOX-BEHNKEN DESIGN APPROACH (BBDA) IN DEVELOPMENT AND OPTIMIZATION OF METFORMIN EXTENDED RELEASE TABLETS (MERT)

METFORMİN UZATILMIŞ SALIMLI TABLETLERİN (MERT) GELİŞTİRİLMESI VE OPTİMİZASYONUNDA BOX-BEHNKEN TASARIM YAKLAŞIMI (BBDA)

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ABSTRACT

Objective: *The present research outlines the use of quality by design (QbD) method to formulate MERT using Box-Behnken Design approach (BBDA). Based on quality target product profile (QTPP) to achieve tablets hardness and % cumulative Drug Release (% CDR) (at 2 hour and 10 hour), Critical quality attribute (CQA)were identified and selected as independent variable. In this present work, HPMC K 100M, Eudragit RL 100, and excipients MCC are selected as independent variables at their high and low levels in development of MERT.*
Material and Method: *As per Design-Expert® prediction, total 19 formulations are prepared where each tablets of weight of 850 mg prepared by direct compression method. For each formulation, responses are determined and analyzed to find most optimized concentration.*
Result and Discussion: *HPMC K 100 M, Eudragit RL 100 and MCC have antagonistic effects on the % CDR after 2 hour and 10 hours. From diagnostic plot it has been observed normal distribution of all data points near to straight line for normal plot of residuals, and predicted vs. actual. The desirability cube and the contour graph showing maximum desirability for optimized values of 76.75 mg, 203 mg and 58 mg for HPMC K 100M, Eudragit RL 100 and MCC respectively which are selected as independent factors in formulation of MERT. Prepared optimized tablets of MERT releases drug for more than 10 hr.*
Keywords: *Box Behnken Design, extended release tablets, QbD, metformin*

ÖZ

Amaç: *Bu çalışma, tasarımla kalite (QbD) yaklaşımı kullanılarak MERT formülasyonunun geliştirilmesini ve Box-Behnken Tasarım (BBD) yöntemiyle optimize edilmesini ele almaktadır. Tabletlerin sertliği ve kümülatif etkin madde salım yüzdesi (% CDR) (2. ve 10. saatlerde) hedef ürün kalite profiline (QTPP) dayalı olarak belirlenmiştir. Kritik kalite özellikleri (CQA) tanımlanmış ve bağımsız değişkenler olarak seçilmiştir. Bu doğrultuda, MERT formülasyonunun geliştirilmesinde HPMC K 100M, Eudragit RL 100 ve yardımcı madde olarak MCC yüksek ve düşük seviyelerde bağımsız değişkenler olarak değerlendirilmiştir.*
Gereç ve Yöntem: *Design-Expert® programı tahminlerine göre toplam 19 farklı formülasyon hazırlanmıştır. Her biri 850 mg ağırlığında olan tabletler doğrudan basım yöntemiyle üretilmiştir. Her bir formülasyon için yanıtlar belirlenmiş ve en uygun konsantrasyonun belirlenmesi amacıyla analiz edilmiştir.*

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Sonuç ve Tartışma: *HPMC K 100M, Eudragit RL 100 ve MCC'nin, 2. ve 10. saatlerdeki % CDR üzerinde antagonist etkiler gösterdiği tespit edilmiştir. Tanısal grafiklerden elde edilen veriler, normal artıklar grafiği ve tahmin edilene karşı gerçek değerler doğrultusunda tüm veri noktalarının doğruya yakın bir dağılım sergilediğini göstermektedir. Optimizasyon çalışmaları sonucunda belirlenen istenen değerlere göre en yüksek uygunluğu sağlayan HPMC K 100M, Eudragit RL 100 ve MCC konsantrasyonları sırasıyla 76,75 mg, 203 mg ve 58 mg olarak belirlenmiştir. Optimum formülasyon ile hazırlanan tabletler, 10 saatten daha uzun süre boyunca etkin madde salımı gerçekleştirebilmiştir.*
Anahtar Kelimeler: *Box Behnken Tasarımı, QbD, metformin, uzatılmış salımlı tabletler*

INTRODUCTION

In 21st century the prime objective is to formulate quality pharmaceutical preparationsnot only involving minimum number of man-hours but also without wasting raw materials used in formulations, which can save time. Therefore, nowadays research uses statistical tools such as factorial design to achieve this objective [1].

Quality by Design (QbD) approach first introduced by Dr. Joseph M. Juran [2]. Out of different stastical design based on QbD analysis, Box-Behnken design Approach (BBDA) uses lesser experimental runs during optimization making it more cost-effective technique without affecting quality of products [3-9]. This approach generates contour plots where independent factors are shown in vertical and horizontal axis. In QbD quadratic or cubic model generated by software represents complete description of process behavior. The confirmation of quality end product can be determined by design Space which is the operating ranges of input variables [10].

Metformin used in type II diabetes treatment as it lowers blood glucose concentrations without causing hypoglycaemia. It is frequently referred to as a "insulin sensitizer", resulting in a decline in insulin resistance and a considerable fall in plasma fasting insulin levels with therapeutic significance. A further well recognized advantage of this medication is its ability to cause modest weight loss, making it a very useful option for obese individuals with type II diabetes [11-14].

Study of CQA of Formulations and Process

During formulations of Pharmaceutical products, if parameters like CQA and Critical Material attributes (CMA) are controlled, then it helps to prepare a quality product which is safety, efficacy and stable. CQAs are qualities (physical, chemical, biological, or microbiological) that should fall within acceptable ranges to ensure the product meets quality standards. Whereas CMAs are characteristics of raw materials that must remain within predetermined parameters in order to produce consistent, high-quality drug compounds, excipients, or intermediates. Critical Process Parameters (CPP) are production process variables that may affect finished product, for which it has to be monitored and controlled properly for obtaining quality product [15].

Initial Risk Assessment of Formulation Variables

The failure mode and effects analysis (FMEA) was used to determine the majority of risk factors and their levels in order to prepare pharmaceutical formulations development [16]. These factors are selected based on their CMAs and CPPs which have an impact on drug release. Various research works suggest in preparation of extended release tablets, polymers role is vital for extending drug release [17]. QbD principles help to study the risk levels of different polymers and excipients and helps in optimization and in formulation of MERT. In this present work Polymer levels (HPMC K 100 M, Eudragit RL) along with MCC levels, are selected significant variables that affects % CDR and tablet hardness which are selected as responses in formulation of MERT.

Design Space

Design space is generated from the chosen initial set point by considering appropriate limits different independent factors which is then used in formulating an optimized formulation of MERT.

MATERIAL AND METHOD

Materials

The pharmaceutical company Pfizer India Healthcare Limited supplied the metformin. All the polymers like HPMC K 110 M, Eudragit RL 100, microcrystalline cellulose (MCC) along with talc and magnesium stearate used in this research work purchased from Rolex Pharmaceuticals, Bhubaneswar, Odisha.

Methods

Box-Behnken Experimental Design Approach (BBDA) used in optimization of independent factors and in analysis of responses [18-19].

Preparation and Optimization of MERT

MERT were prepared by direct compression method. Based on initial risk assessment in formulation of extended release tablets of Metformin, parameters like HPMC K 100 M amount (A), Eudragit RL amount (B), MCC amount (C) have highest influence on the dissolution profiles. So based on the above outcomes a screening design was constructed taking the independent factors like HPMC K 100 M amount (A), Eudragit RL 100 (B), MCC (C) at their low and high levels to study on selected responses like hardness (Y1) and % cumulative drug release (CDR) at 2 hour (Y2) and at 10 hour (Y3). The powder mixture then compressed in 10 mm tablet press punching machine. The weight of tablets was 860 mg. Optimization done by using Design-Expert® software (version 13; Stat-Ease Inc., Minneapolis, MN, USA). QbD Approach in Selection of Independent Variables at their High and low Levels for formulation of MERT mentioned in Table 1. Similarly the selected dependent responses are shown in Table 2. Based on the results of responses are analyzed by ANOVA and diagnostic plots are plotted ho evaluate factors effect [20-21]. The model also predict quadratic equation, which is used to identify the effect of factors on responses. The positive and negative sign on the magnitude of regression coefficients represent synergistic and antagonistic effect respectively [22].

$Y=b0+b1A+b2B+b3C+b4AB+b5BC+b6AC + b7A^2+b8B^2+b9C^2$
Where Y=dependent variable or response;
A, B, and C= independent variable coded levels;
b0=intercept; b1 to b9=regression coefficients

Table 1. QbD approach in selection of independent variables at their high and low levels for formulation of MERT

Factor	Name	Units	Minimum	Maximum
A	HPMC K 100M	mg	65.00	100.00
B	EUDRAGIT RL 100	mg	200.00	215.00
C	MCC	mg	50.00	70.00

Table 2. Responses (dependent variables)

Response	Name	Units
Y1	HARDNESS	kg/cm2
Y2	% CDR (after 2hour)	%
Y3	% CDR(after10 hours)	%

Compatibility Study

Fourier Transform Infrared Spectroscopy (FTIR) Study

In FTIR study, 10 milligrams of the sample and four hundred milligrams of potassium bromide (KBr) were triturated in a mortar. Next, a tiny amount of the triturated mixture was put into a pellet maker and compacted with a hydraulic press at a pressure of 10 kg/cm². A Shimadzu FTIR Spectrophotometer was used to scan the resultant pellet from 4000 cm^{-1} to 400 cm^{-1} after it was placed on the sample holder.

DSC Study

The thermal behavior of a drug or a polymer can be measured by DSC (Schimadzu, DSC-60, Japan). Samples weighing 5mg were sealed in aluminum pans and heated to 300ºC at a rate of 40ºC per minute.

Characterization of Pre Compression Parameters of Tablets

Pre-compression parameters like bulk density, tapped density, angle of repose and Compressibility index and percentage porosity were calculated [23].

Bulk Density

In bulk density determination, volume occupied is determined by transferring 25 gm powder samples into 100 ml graduated cylinder and the ratio between weights of sample to volume gives bulk density value.

Tapped Density

In tapped density, 25 gm of powder samples transferred to a 100 ml graduated cylinder and tapped to get tapped volume reading and ratio between weigh to tapped volume gives tapped density.

Compressibility Index (CI)

It is determined by using following formula.

$CI= (\rho t - \rho 0)/(\rho t) x\ 100$

ρ_t =tapped density, ρ_0=bulk density

Percentage Porosity

It was determined by liquid displacement method by applying formula

% Porosity= (True Density-Bulk Density)/True Density X 100

Angle of Repose

Angle of repose was calculated by following funnel method using the equation.

$\theta = \tan -1h/r,$

Where “h” and “r” are the height of pile and radius of the pile.

Characterization of Post Compression Parameters of Tablets

Characterization of MERT

From experimental batches as suggested by software, different tablet batches are prepared and evaluated post compression parameters. Tablets parameters like thickness, hardness (measured with Pfizer hardness tester and units in Kg/cm²) and percentage friability were determined [24]. Roche Friabilator (Labindia) was used to determine friability, where 10 tablets were weighed initially by placing in the friabilator for 4 min giving 100 rpm and after that final tablet weight was measured.

The percent friability (PF) = (Initial Weight – Final Weight) / Initial Weight X 100.

Weight variation test is performed as per USP guidelines to calculate average weight which compared with % deviation.

Drug Content

To determine drug content of MERT, five tablets of each formulation were weighed and finely powdered. About 0.1 gm equivalents were accurately weighed completely dissolved in buffer and was filtered. About 1ml of the filtrate was further diluted to 100ml with buffer. The solution's absorbance was measured at 282 nm using a UV-visible spectrophotometer.

In Vitro Dissolution Studies

It was carried out by USP Type II paddle type dissolution apparatus (Disso 2000, Labindia) by taking 900 ml of 0.1 N HCl (pH 1.2) media by maintaining temperature at 37±0.5°C. MERT are immersed in medium by setting the paddle to rotate at 100 rpm [25]. At regular intervals 10 ml samples were removed and replaced with same media of the same volume. The samples were examined for drug concentration using a double beam UV-Visible spectrophotometer (Genesis-2, USA) at a wavelength of 282 nm, to calculate the percentage of cumulative drug release.

RESULT AND DISCUSSION

FTIR Study

The characteristic absorption of the Metformin shows peak at 3367.71 cm^{-1}, which is assigned to the stretching vibration of Primary amine group of Metformin HCl and another characteristics bands at 1623, 1560 and 1068.78 cm^{-1} assigned to C=N stretching band at is due to C=N symmetric vibration. FTIR spectrum of Eudragit RL 100 showed the peak at 3432.1 cm^{-1} due to the presence of tertiary amine, at 1731.4 cm^{-1} due to the presence of C = O (ester), and at 1450.2 cm^{-1} due to –CH3 bend. The FTIR of drug and drug with excipients shown in Figure 1 and 2 which showed that compatibilities occurred between the drug and polymers used.

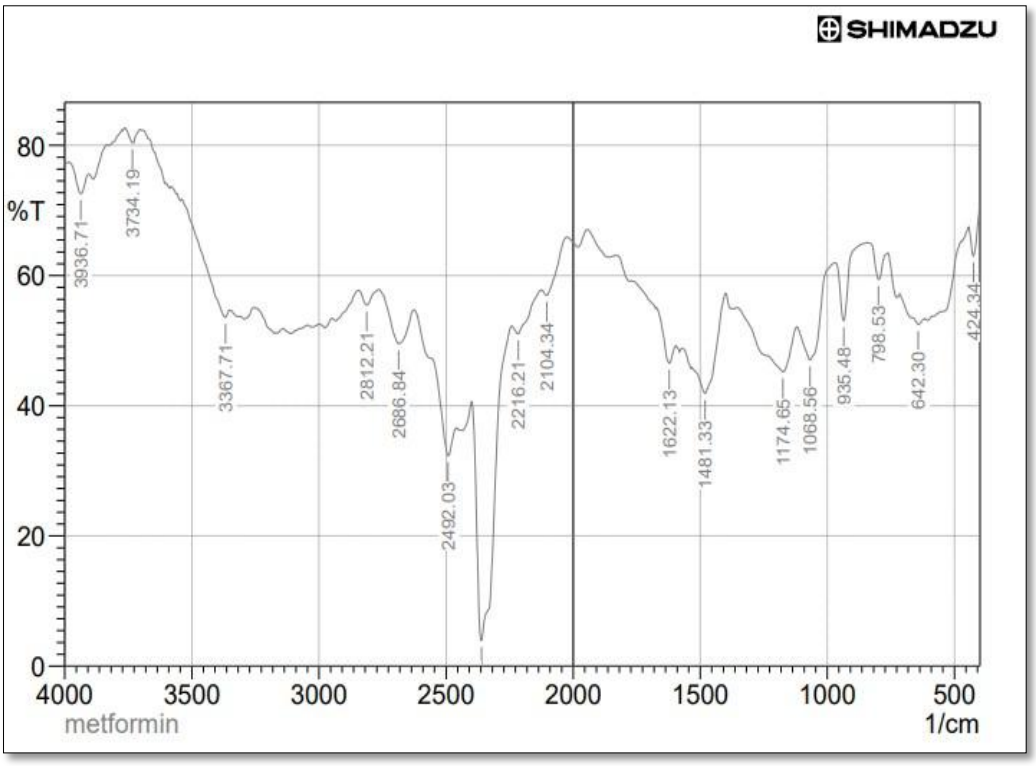

Figure 1. FTIR Spectrum of metformin

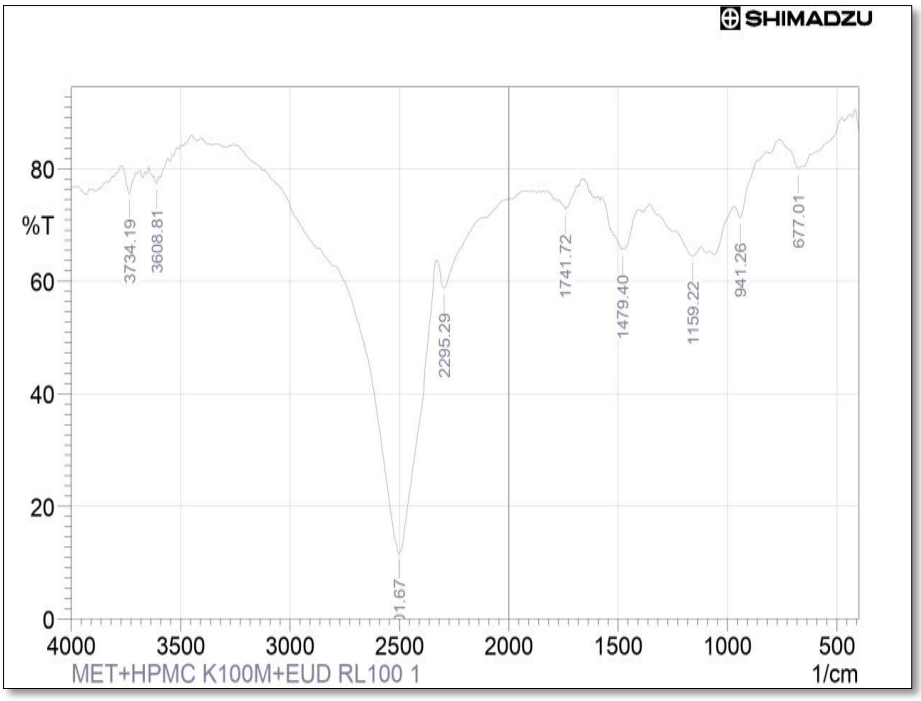

Figure 2. FTIR Spectrum of physical mixture of metformin, HPMC K 100 M and Eudragit RL 100

DSC Study

In DSC curve of Metformin showed a sharp endothermic peak at 251.61°C corresponding to its melting point. There was no significant change in the endothermic peak between drug and formulation which shows peak at 248.12°C and use of polymer HPMC K 100 M does not affect the stability of the drug confirming the formulation thermodynamically stable nature (Figure 3 and Figure 4).

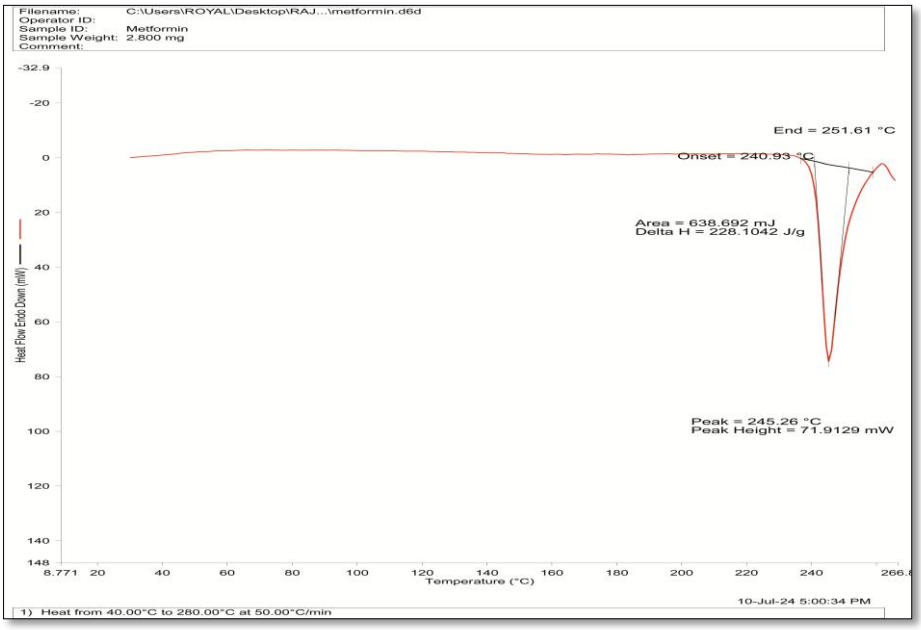

Figure 3. DSC thermogram of drug metformin

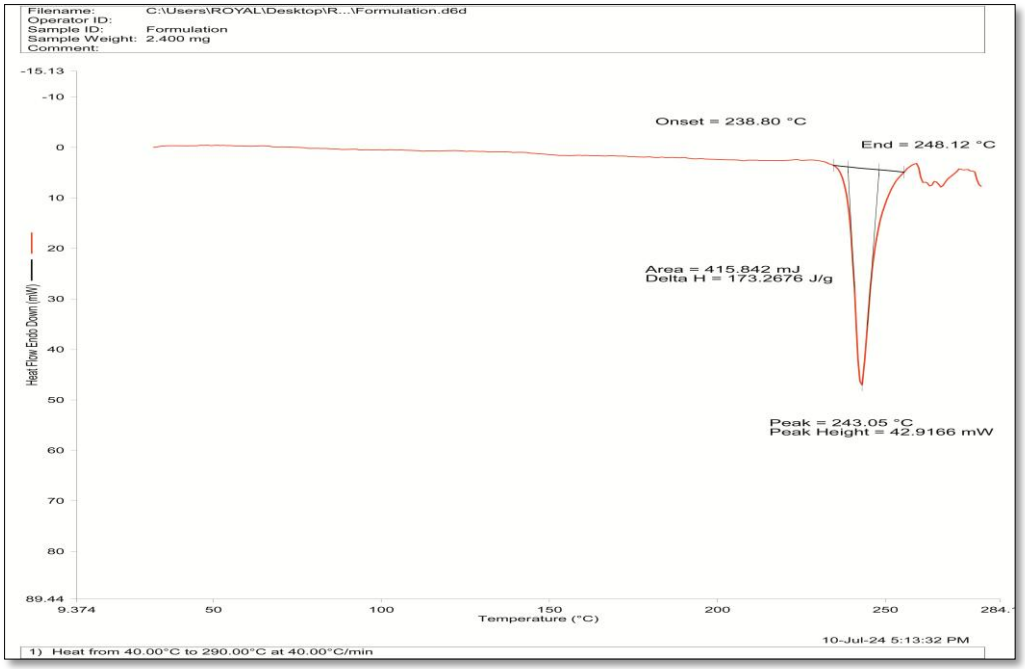

Figure 4. DSC thermogram of tablet

Results of Experimental Formulation of MERT

The total 19 formulations of MERT were prepared experimentally in triplicate and all dependent responses (Y1, Y2 and Y3) are calculated as per prescribe procedure. Results are shown in Table 3 for all experimental formulations. Data obtained for responses were analyzed by Design Expert software.

Table 3. Results of different responses at different level of independent variables

Run	Factor A (HPMC K M)	Factor B (EUDRAGIT RL 100)	Factor C (MCC)	HARDNESS kg/cm^2	% CDR (After 2 hours)	% CDR (After 10 hours)
1	65	200	60	5	55.052	99.98
2	100	200	60	6	33.09	95.65
3	65	215	60	6	57.272	99.12
4	100	215	60	7	33.09	92.73
5	65	207.5	50	5	57.272	99.12
6	100	207.5	50	6	42.102	91.75
7	65	207.5	70	6	51.052	96.87
8	100	207.5	70	7.5	33.09	92.36
9	82.5	200	50	5	55.052	98.65
10	82.5	215	50	7.5	57.272	97.16
11	82.5	200	70	7.5	55.052	98.36
12	82.5	215	70	7.5	39.82	95.98
13	82.5	207.5	60	6	57.272	98.36
14	82.5	207.5	60	7.5	37.32	94.12
15	82.5	207.5	60	7.5	42.102	96.09
16	82.5	207.5	60	7	33.09	94.36
17	82.5	207.5	60	7	47.272	97.65

Data Interpretation for Response Y1

The obtained data for response Y1 as shown in Table 4is analyzed by ANOVA by fitting to the appropriate models (linear, 2-FI, and quadratic) and results are shown in Table 4 to 9. The model is significant when $p<0.05$, and lack of fit is non significant if $p>0.05$ [26]. The quadratic equation generated by software helps to find out the effect of dependent variables (A, B, and C) on the responses Y1, Y2, Y3. Table 4 and 5 indicate summary of results on Hardness. As the results indicate P-values of less than 0.0500 indicate model terms are significant and factors A, B, C, BC, A^2 are more significant to affect response Y1. The Lack of Fit F-value of 0.05 ($p>0.05$) implies model is not significant relative to the pure error and Model F-value of 7.11 implies the model is significant for response Y1.

Table 4. Results of p value and lack of fit p value for different equation on effect of independent variables on hardness (ResponseY1)

Factors (Types of Equation)	p-value	Lack of fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0101	0.3507	0.4701	0.2646	
2FI	0.3777	0.3418	0.4873	0.0433	
Quadratic	***0.0026***	***0.9824***	***0.7746***	***0.7929***	***Suggested***
Cubic	0.9824		0.6202		**Aliased**

Table 5. Results of ANOVA for responses Y1

Source	Sum of squares	F-value	p-value	
Model	0.5292	7.11	0.0085	significant
A-HPMC K 100M	0.1040	12.58	0.0094	
B-EUDRAGIT RL 100	0.1040	12.58	0.0094	
C-MCC	0.1263	15.27	0.0058	
AB	0.0001	0.0089	0.9275	
AC	0.0014	0.1732	0.6897	
BC	0.0631	7.63	0.0280	
A^2	0.1238	14.97	0.0061	
B^2	0.0031	0.3695	0.5625	
C^2	0.0001	0.0071	0.9354	
Residual	0.0579			
Lack of Fit	0.0022	0.0516	0.9824	not significant
Pure Error	0.0557			
Cor Total	0.5871			

The model also predicts that there is very less difference of 0.2 between Predicted R^2 (value of 0.7929) and Adjusted R^2 (value of 0.7746) as shown in Table 5. Similarly the selected independent variables for response Y1 shows Adeq Precision of 7.704 (desirable value is greater than 4) which indicates an adequate signal and can be used to navigate the design space and results are shown in Table 7.

Quadratic equation:

$$Y_{1=} +2.64+0.1256\ A +0.1140\ B +0.1140C-0.0043\ AB +0.0189\ AC -0.1256\ BC -0.1715\ A^2-0.0269B^2-0.0037\ C^2$$

Above equation shows the impact of the independent factors that affect response Y1. So from equation it is concluded that higher polymers concentration increases hardness of MERT. The result is

similar to earlier reported study where It was observed that tablets containing HPMC K100M as the intra granular polymer increase hardness, this could be due to the higher binding capacity of HPMC K100M [27-28]. Eudragit concentration also affects drug release from tablets. Eudragit at higher levels causes reduction in the permeation of water inside the powder granules causing slower drug release [29]. Similar effect also derived for MCC, which explain synergistic effect on hardness of tablets.

Data Interpretation for Response Y2

In Table 6 and 7 which explain the effect of independent variables on response Y2, shows p value of 0.0028 indicating significant of model. The lack of fit F value of 0.3843 which indicates model is non significant (p>0.05), and is adequate for prediction of the response. The Model F-value of 6.16 also confirms the model is significant for response Y2.

Table 6. Results of p value and lack of fit p value for different equation on effect of independent variables on % CDR at 2 hours (Response Y2)

Factors (Types of Equation)	p-value	Lack of fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.4431	0.8967	0.4207	0.1431	
2FI	0.7178	0.8321	0.4189	0.1237	
Quadratic	***0.0028***	***0.8925***	***0.4916***	***0.3735***	***Suggested***
Cubic	0.8967		0.1139		**Aliased**

Table 7. Results of ANOVA for responses Y2

Source	Sum of squares	F-value	p-value	
Model	933.67	6.16	0.0078	significant
A-HPMC K 100M	785.59	15.54	0.0017	
B-EUDRAGIT RL 100	14.56	0.2880	0.6005	
C-MCC	133.53	2.64	0.1281	
Residual	657.04			
Lack of Fit	304.67	0.3843	0.8925	not significant
Pure Error	352.37			
Cor Total	1590.71			

Similarly as per results shown in Table 10, the Predicted $R^2$and adjusted value are 0.3735 and 0.4916 respectively andAdeq Precision of 8.117 indicates model can be used to predict the design space.

Coefficients in Terms of Coded Factors:

$Y2=+46.25-9.91\ A\ -1.35\ B\ -4.09C-0.097AB\ +0.0731\ AC\ -0.1256\ BC\ -4.1715\ A^2-2.0269B^2-0.1213\ C^2$

Data Interpretation for Response Y3

In Table 8 and 9 which explain the effect of independent variables on response Y3, shows p value of 0.0012 which demonstrates that the model is significant (p<0.05) . The lack of fit F value of 0.5376 and Model F-value 9.82 confirm that the proposed model is model is significant and adequate for prediction of the response.

Table 8. Results of p value and lack of fit p value for different equation on effect of independent variables on % CDR at 10 hours (Response Y3)

Factors (Types of Equation)	p-value	Lack of fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.1717	0.9968	0.6794	0.7569	
2FI	0.7665	0.6946	0.5607	0.1575	
Quadratic	***0.0012***	***0.7982***	***0.6231***	***0.4956***	***Suggested***
Cubic	0.9968		0.4456		**Aliased**

Table 9. Results of ANOVA for responses Y3

Source	Sum of Squares	F-value	p-value	
Model	72.37	9.82	0.0012	significant
A-HPMC K 100M	63.85	25.98	0.0002	
B-EUDRAGIT RL 100	7.32	2.98	0.1081	
C-MCC	1.21	0.4920	0.4954	
Residual	31.94			
Lack of Fit	17.49	0.5376	0.7982	not significant
Pure Error	14.46			
Cor Total	104.31			

Similarly as per results shown in Table 11, Adeq Precision of 9.9457 indicates model can be used to predict the design space.

$Y3= +96.37-2.83\ A -0.9563\ B -0.3888C-0.373\ AB -1.190\ AC -0.634\ BC -0.775\ A^2-0.3269B^2-1.037\ C^2$

So for response Y2 and, Y3 the equation indicates higher level of polymer concentration causes decrease in drug release in extended release tablets. Polymer HPMC K100Mat higher level prevents water uptake and form a thick and turbid gel that shows resistant to erosion by forming a protective gel layer causing the slower drug dissolution from the tablet surface [25]. As suggested by the polynomial equations, Eudragit RL 100 has negative or antagonistic effect on drug release. At higher levels Eudragit retards the release of drug and can be used in the sustained release tablet formulation due to its property of formation of a matrix system. Above results are in agreement with previous research report which shows Eudragit polymer along with HPMC can be used in formulation of extended release tablets [30]. Similarly at higher levels MCC retards the release of drug as presence of MCC causes less disentanglement or increased binding, resulting in a lower percentage of medication release during that time period.

Diagnostic Plots for Different Responses Predicted by BBDA

In order to study the effect of independent variables on selected response Y1, Y2 and Y3, diagnostic plots and contour plots are designed by software based on BBDA and are shown in Figure 5 to 8. From figure it has been observed for Normal plot of residuals, and Predicted vs. Actual, normal distribution of all data points near to straight line. Similarly in plots of Residuals *vs.* Predicted, and Residuals *vs.* Run between predicted and actual response, all data points are placed within the limits, which indicates the fit of the model.

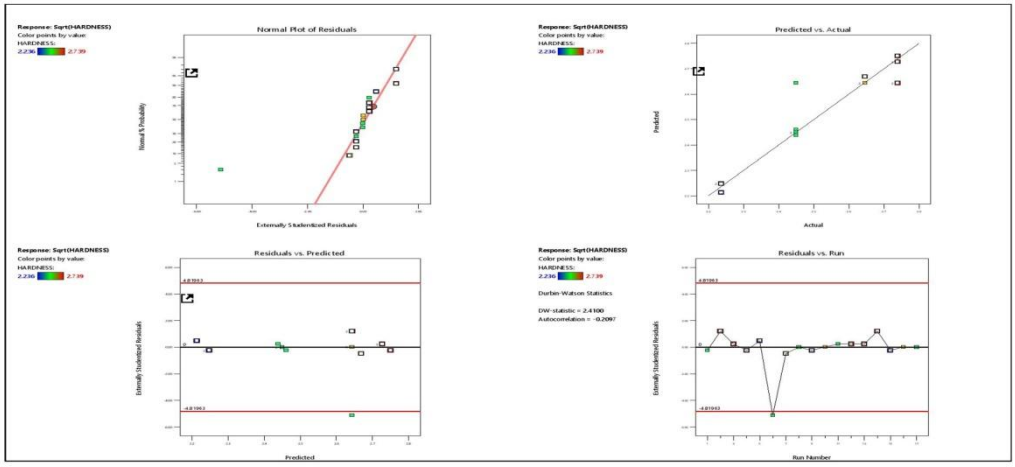

Figure 5. Diagnostic plots showing the effect of independent variables on hardness of tablets (Y1) for (a) Normal plot of residuals, (b) Predicted vs. Actual (c) Residuals *vs*. Predicted, (d) Residuals *vs*. Run between predicted and actual response

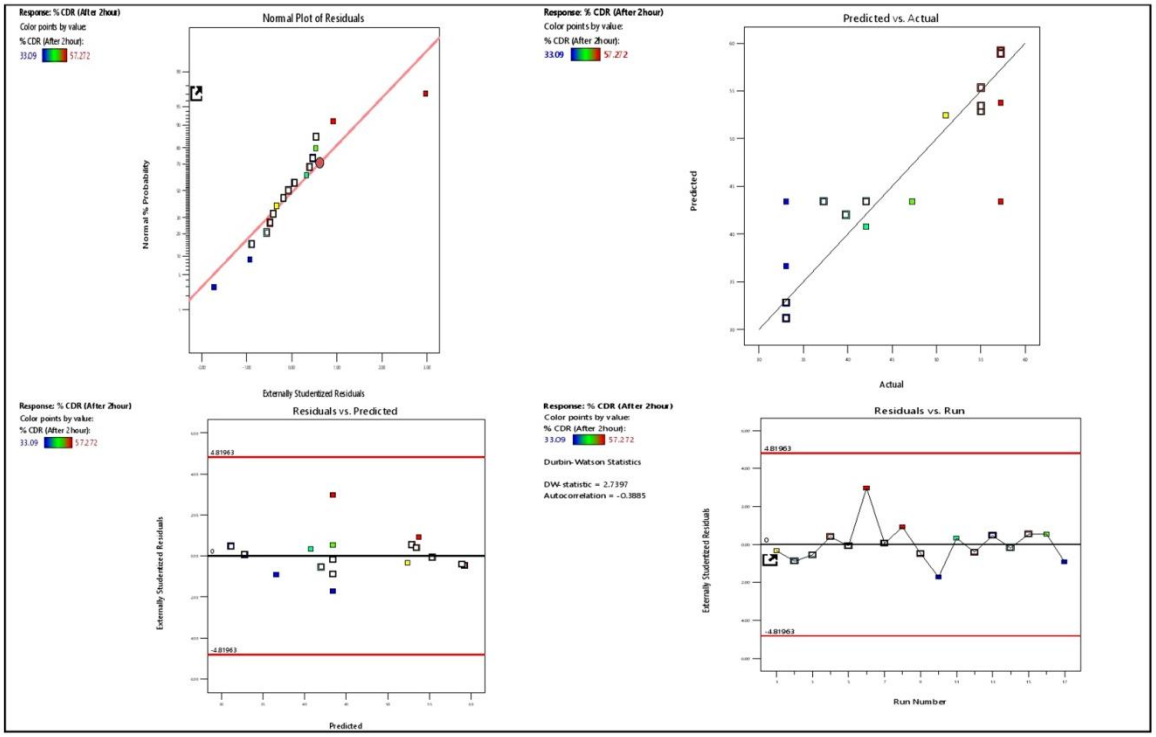

Figure 6. Diagnostic plots showing the effect of independent variables on % CDR at 2 hr (Y2) (a) Normal plot of residuals, (b) Predicted vs. Actual (c) Residuals *vs*. Predicted, (d) Residuals *vs*. Run between predicted and actual response

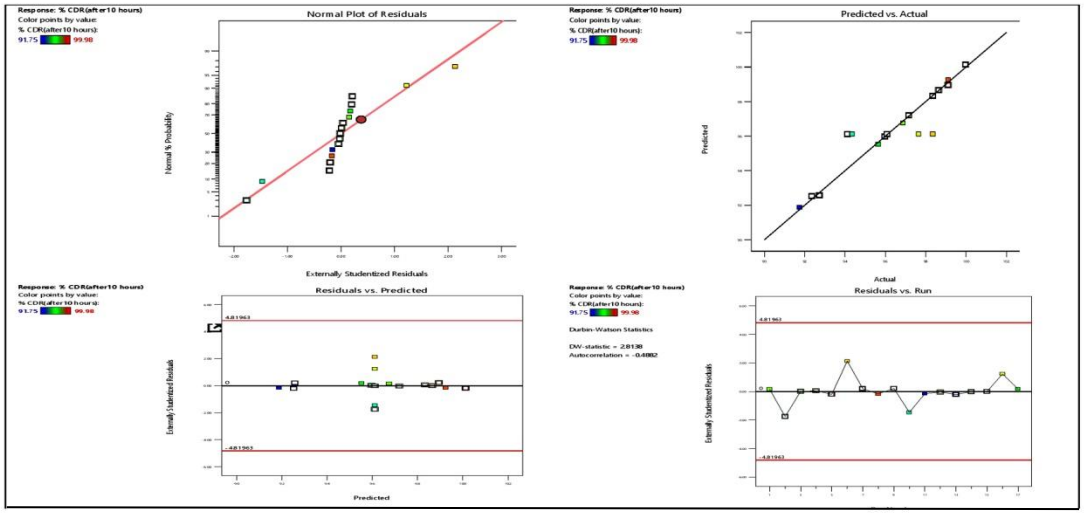

Figure 7. Diagnostic plots showing the effect of independent variables on % CDR at 10 hr (Y3) (a) Normal plot of residuals, (b) Predicted vs. Actual (c) Residuals *vs*. Predicted, (d) Residuals *vs*. Run between predicted and actual response

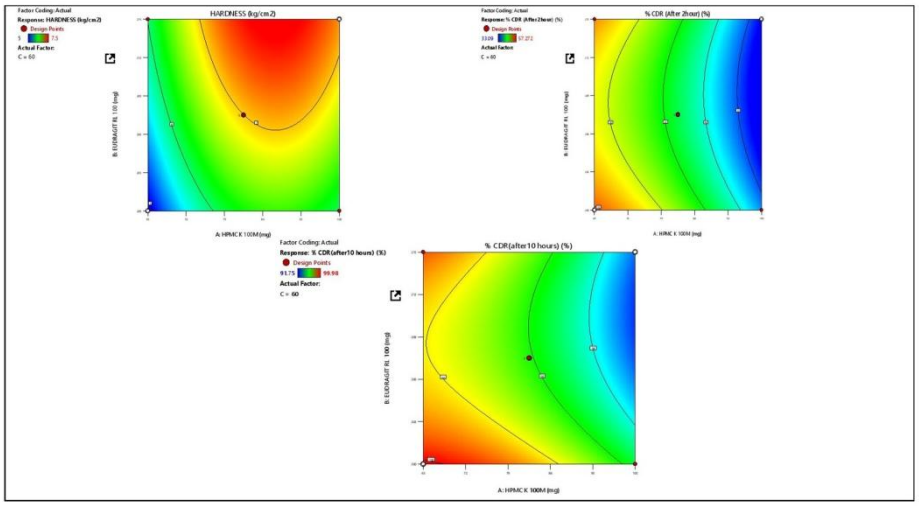

Figure 8. Contour Plots showing effect of independent variables on the hardness (Y1), drug release at 2 hour (Y2) and drug release at 10 hours (Y3)

Cook's Distance

It can be used to prioritize which runs to investigate first. It is a measure of how much the regression would change if the case is omitted from the analysis [31-32]. Relatively large values are associated with cases with high leverage and large studentized residuals. Large values should be investigated as they could be caused by recording errors or form an incorrect model, or a design point far from the remaining cases. In our cases all values are less than 1 indicating feasibility of responses and cook's plot for all variables against responses Y1, Y2, and Y3 are mentioned in Figure 9.

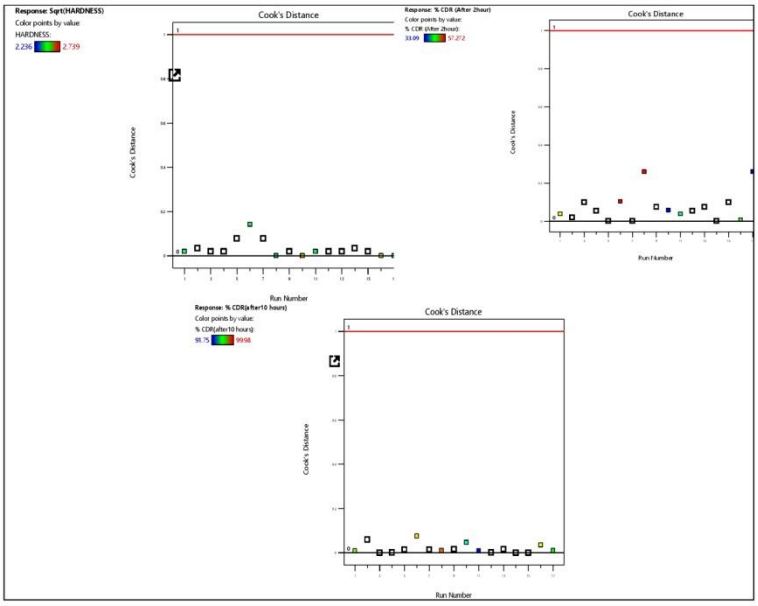

Figure 9. The diagnostic plots showing Cook's distance plot obtained by the Box-Behnken Design using Cook's distance versus run number by the different independent factors against responses

Optimization of Data in Defining Design Space

From prediction by design expert, the optimized values are76.75 mg, 203 mg and 58 mg for HPMC K 100M, Eudragit RL 100 and MCC respectively which are selected as independent factors in formulation of MERT and the values are shown in Figure 10 was designed for preparing MERT to generate space based on contour plots [24]. The desirability cube and the contour graph showing maximum desirability of 1 for optimized MERT is shown in Figure 11 and 12. For constructing a satisfying fit of the model for the optimized formulation, result analysis was carried out for predicted and observed response and results are shown in Table 10. The results are shown in cube plot and in contour graph showing how three factors combine to affect the different responses. This demonstrated the reliability method using BBDA in predicting the optimized formula for MERT.

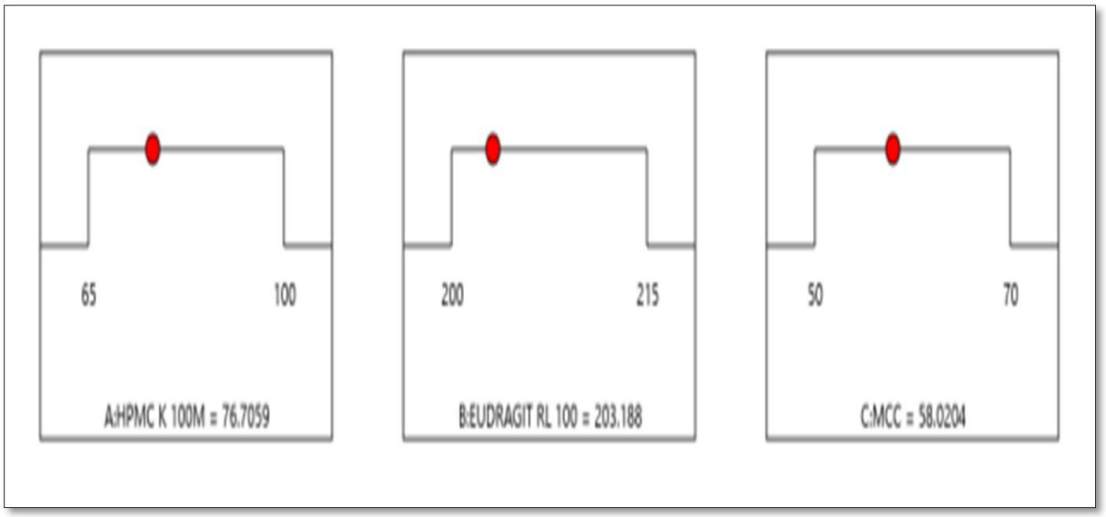

Figure 10. Optimized values of independent factors in formulation of MERT

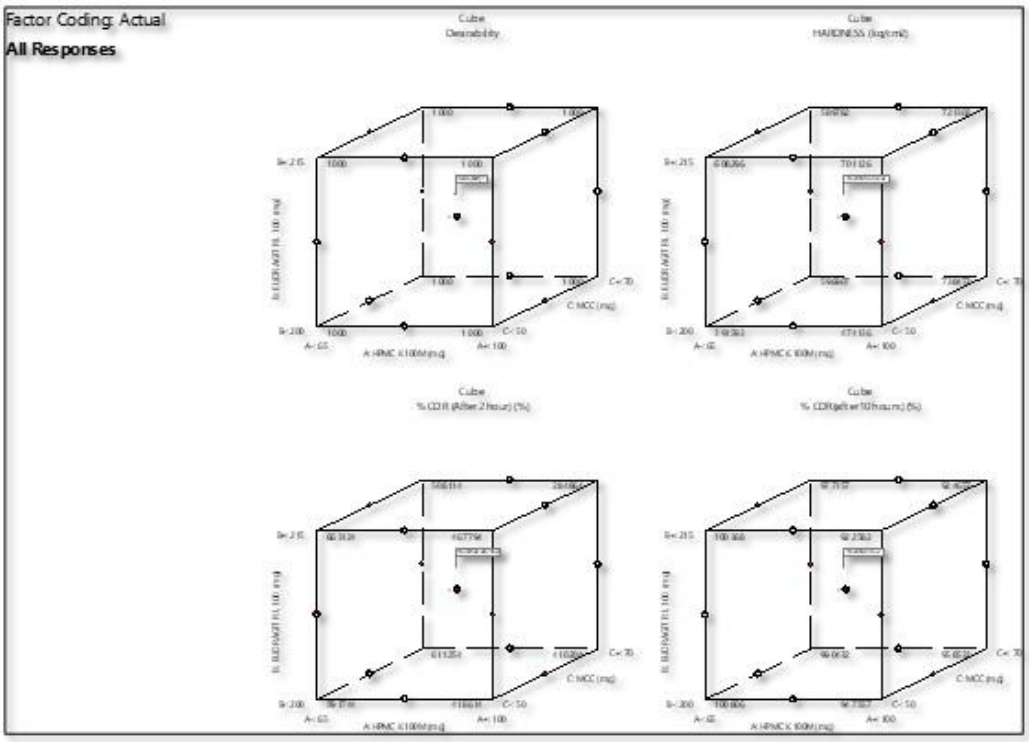

Figure 11. The optimized formulation with maximum desirability shown in cube

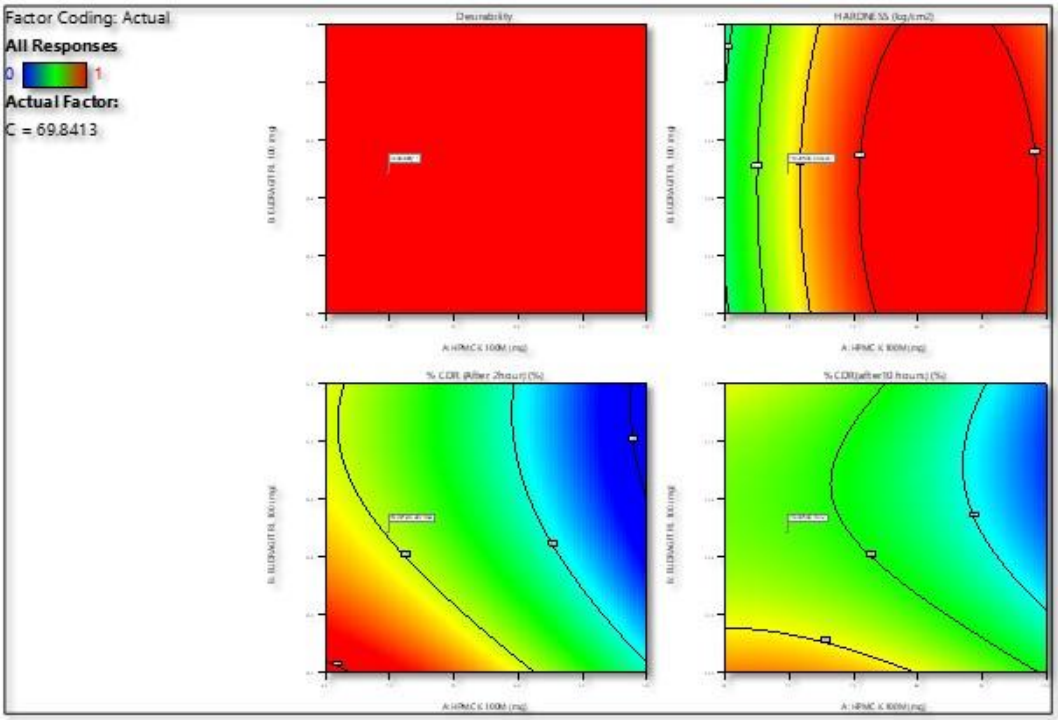

Figure 12. The optimized formulation with maximum desirability has shown in contour graph showing how independent factors combine to affect the different responses

Table 10. The result of predicted and observed response for the optimized formulation of MERT with maximum desirability

Analysis of Selected Responses	Predicted Mean	Predicted Median	Observed
HARDNESS	6.99712	6.98885	7
% CDR (After 2hour)	46.2513	46.2513	47.329
% CDR (after10 hours)	96.3712	96.3712	96.439

The desirability cube and the contour graph showing maximum desirability for optimized values of 76.75 mg, 203 mg and 58 mg for HPMC K 100M, Eudragit RL 100 and MCC respectively which are selected as independent factors in formulation of MERT. The prepared MERT are evaluated for different parameters like weight variation, tablet hardness, % Friability and Percentage of drug content along with drug release and the results are shown in Table 11. All the results are within the acceptable limit as per official compendia available. The results of drug release shows prepared MERT release drug which extended for more than 10 hr and dissolution profile is shown in Figure 13.

Table 11. Results of pre compression parameters and post compression parameters of tablets for optimized formula

Parameters	Results
Angle of repose(Ɵ)	25.3±0.76
Compressibility index (%)	16.02± 0.36
Hausners ratio	1.12± 0.02
Thickness (mm)± S.D	3.1 ± 0.2
Hardness(kg/cm^2) ±S.D	8.4±0.12
%Friability± S.D	0.11±0.01
Weight variation ±S.D	860±1.22
%Drug content± S.D	99.98±1.5

n= 6; SD-standard deviation

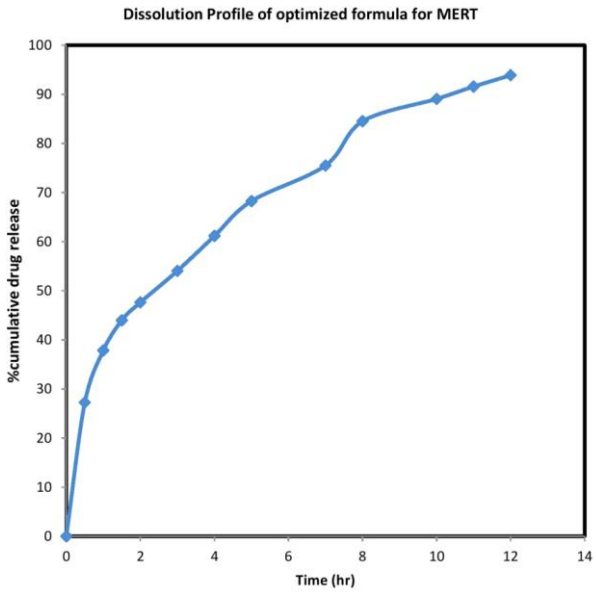

Figure 13. Dissolution profile of optimized formula for MERT

So QbD based BBDA represents a systematic and science-based strategy to optimize polymer concentration by a thorough understanding of formulation and process variables. In this research work QbD helps to formulate MERT by optimizing different Polymers and excipients levels to give hardness, drug release, as per QTTP. The desirability cube and the contour graph showing maximum desirability for optimized MERT. So the present experimental work prepared MERT, which shows extended drug release of more than 10hour thereby reducing the frequency of dosing and improved patient compliance.

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AUTHOR CONTRIBUTION RATE STATEMENT

Concept: A.P.; Design: A.P., S.K.S., G.B.; Control: A.P., S.K.S., G.B.; Sources: A.P., S.K.S., G.B.; Materials: A.P., S.K.S., G.B.; Data Collection and/or Processing: A.P., S.K.S., G.B.; Analysis and/or Interpretation: A.P., S.K.S., G.B.; Literature Review: A.P., S.K.S., G.B.; Manuscript Writing: A.P.; Critical Review: A.P., S.K.S., G.B.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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