International Journal of Farmacia (IJF)

IJF |Vol.10 | Issue 3 | Jul - Sept -2024

www.ijfjournal.com

DOI : https://doi.org/10.61096/ijf.v10.iss3.2024.51-60

ISSN: 2231-3656

Research

Optimization Of Repaglinide Chronomodulated Delivery System Using Box-Behnken Experimental Design

S. Vasanth Kumar[1], K. Senthilkumaran*[2]

[1]Assistant Professor, Department of Pharmaceutics, K.K. College of Pharmacy, Chennai, Tamilnadu, India.
[2]Professor and Head, Department of Pharmaceutics, K.K. College of Pharmacy, Chennai, Tamilnadu, India.

*Author for Correspondence: K. Senthilkumaran
Email: drkskumaran67@gmail.com

Published on: 4 Jul 2024

Published by:
DrSriram Publications

Abstract

Diabetes mellitus is a disease which shows circadian rhythm in the pattern of peak in the early morning between 4 and 8 a.m. The behaviour, physiology, and biochemistry of organisms changes rhythmically over 24 h. We have prepared chronomodulated release tablet to control plasma sugar level at early morning. Tablet of REP was prepared using CCS and lactose and coated with Eudragit to produce pulsatile release of the drug. Tablet was optimized using Box-Behnken design model. The ideal formulation variables for a formulation were found that 16.14 mg of CCS, 28.91 mg of Lactose, and 4.37 mg of Eudragit and response of tablet was 94.45 % Drug released and 5.99 hrs of lag time (T) with the desirability of around 1. In vitro release data revealed no release was observed in 0.1 N HCl (pH 1.2) and complete release of drug at pH 6.8 conditions.

Keywords: Repaglinide, Chrinomodulated delivery, Diabetus mellitus, Box-Behnken design.

INTRODUCTION

Pulsatile Drug Delivery System (PDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. PDDS are promising for various disorders. Such a novel drug delivery has been attempted for Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology.

Response surfaces methodology (RSM) a extensively trained advance into the growth as well as optimizations of drugs delivery campaign. Base taking place the principle of designs of trials, the method encompass the employ of a range of type of new designs, generations of polynomials equation as well as map of the response in excess of the new area to decide the best preparations. The method requires least testing in addition to moment in time, therefore prove to be faraway additional effectual plus cost efficient than the conventional technique of formulate the dosage form.

For present research work, various computation in favor of the current optimizations studies was perform by means of Design Expert® softwares (Design Expert trial versions 9; State-Ease Inc., Minneapolise, MN, USA) where a Three factors two levels complete factorial designs were used for systematic learning of effect of extent Crosscarmellose Sodium and Lactose and extend of Eudragit S100 weight gain were selected as the independent variables i.e. factor. The level of this factor was chosen taking place the base of beginning trial batch results and observations. The entire the additional formulations aspect in addition to process variable was reserved constant all the way through the studies. Polynomial model counting interactions in addition to linear term was generating in favor of the complete responses variable by means of multiples linear regressions analysis (MLRA) approaches.

Methods

Preparation of Repaglinide pulsatile release tablets

The granules were prepared by wet granulation method. The drug Repaglinide, Croscarmellose Sodium and lactose were passed through sieve 40# separately and blended thoroughly. After proper mixing then slowly added the binding solution containing PVP K-30 in IPA till fine uniform granules were obtained. The damp mass were conceded throughout sieve 16# as well as desiccated on 50°C for 30 min to get Moisture content less than one. Then lubricate the dried granules with magnesium stearate which were already passed through sieve 40#. Then lubricated granule was packed together taking place cadmach tablets punches machine for all formulations.

Coating of Eudragit S100 over the tablets

Eudragit S100 coating dispersion requires addition of polyethylene glycol as plasticizer and stirred the solution for few minutes with a magnetic stirrer. This solution was sprayed over the above processed tablets up to different weight gains.

Statistical optimization of formulation using Box-Behnken design (BBD)

According to the results obtained from the dissolution profiles of the preliminary experimental batch, the batch that showed desirable lag time was chosen in favor of factorial study to optimize effect of variable lying taking place formulation. A BB designs were applied during these studies. Into this designs three factors were evaluated, all on three level as well as experimental trial was perform on every 17 probable combination. Complete factorial designs was passed out using 3 factors namely extent of Eudragit S 100 (% w/w) coating weight gain and the extent of Cross carmellose Sodium and Lactose (% w/w). The dependent variable was the lag time of 5h (time period during which no or not more than 5% drug should be released in dissolution medium at pH 1.2, 7.4 and 6.8 respectively) and more than 90% of drug releases at pH 6.8 within 90 min. after lag time. Table below summarizes dependent and independent variables and the resulted formulations was shown in Table 01.

Table 1: Experimental Box-Behnken design: factor along with response

Factor (independent variable)	Level used			Response (dependent variable)
	-1	0	1	
X1=(A) Crosscarmellose Sodium	5	12.5	20	Y1= 90 % drug released
X1=(B) Lactose	20	32.5	45	
X3= (C) Eudragit S 100 coating weight gain (%)	2	4	6	Y2= lag time (hrs)

Statistical analysis of data

The common forms of the MLRA models are represent within the following equation:

$$Y = b_0+b_1X_1+b_2X_2+b_2X_{3+}b_{12}X_1X_2X_3+b_{11}X_1^2+b_{22}X_2^{2+}b_{23}X_2^3 \quad (1)$$

Into above equation 1, Y be the dependent variables; b_0 is the mathematics standard of every the quantitative outcome of nine run. b_1, b_2, b_{12}, b_{11}, b_{22} be present estimated coefficient compute as of the experiential experimental responses standards of Y along with X_1 with X_2 are the coded level of the independent variable. The interaction terms ($X_1X_2X_3$) shows how responses standards change while two factor are concurrently distorted. The polynomial term (X_1^2, $X_2^2X^3$) were incorporated to examine non linearity.

The polynomial equation could be used to illustrate conclusions following allowing for the magnitudes coefficients along with the mathematical signs so as to the coefficients carry. A elevated optimistic otherwise un constructive worth within the equations correspond to that by creation a small changes within the setting of that factor one may obtain a significant change in the dependent variables. Statistical validity of the polynomial are recognized happening the foundation of analysis of variance (ANOVA) stipulation within the software. Levels of implication be measured on $p < 0.05$. The most excellent appropriate numerical models were chosen base taking place the assessment of numerous arithmetical parameter, counting the coefficient of variations (CV), the several correlation coefficients(R^2), the attuned numerous correlation coefficients (adjusted R^2) along with the predicted

remaining sum of square (PRESS) provide as a result of the softwares. PRESS indicate how fine the models fit the information plus in favor of the selected models, it be supposed to be little relation to the additional model beneath reflections. The 3D responses surface graph along with the 3D contour plot was as well generated through the softwares. This plot is extremely helpful toward observe interface effect of the factor taking place responses. The fixed equation connecting the responses were *Y*1 as well as *Y*2 to the distorted factors final equation within terms of coded factors and actual factors.

***In vitro* drug release study of Repaglinide Pulsatile release formulations**

The test was carried out in a rotating basket method specified in the USP XXIII dissolution tester (Electrolab, TDT-08L, India) by the side of a rotation speeds of 100 rpm during 900 ml dissolution mediums on 37 ± 0.5 °C during medium among 0.1 N HCl pH 1.2, pH 7.4 (phosphate buffer) for 2 h, 3 h, and till the end of the test, respectively. 5 ml aliquots of the dissolution fluids be impassive on particular instance interval along with replaced with new dissolution media with assay in favor of the quantity of rapaglinide through spectrophotometers (JASCO V630, Japan) through wavelengths 245 nm. The dissolution data's were analyze to estimate % drug releasing at different time intervals.

RESULTS AND DISCUSSION

From the above results of the experimental trial batches, formulation F5 showed burst release with desirable lag time and hence it was selected for factorial studies to optimize effect of variables on formulation. There after further studies with BB experimental design was carried out using extent of Crosscarmellose sodium, lactose and Eudragit S 100 coating weight gain as variable factors.

A BB design was constructed to study the effect of the extent crosscarmelose sodium (A) lactose (B) and Eudragit L30D coating weight gain (C) on the drug release from the tablets. The layout of the two dependent variables chosen were selected i.e. % cumulative drug released (Y1) and lag time (Y2). The experimental runs and observed results were compiled and are shown in Table 2.

Table 2: Experimental runs for REP chronomodulated formulations using BB design

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	**Run**	**A:CCS**	**B:Lactose**	**C:Eudragit**	**90 % Drug Released**	**Lag Time**
		%	%	%	%	Hrs
4	1	20	45	4	92	4.5
10	2	12.5	45	2	65	3.8
8	3	20	32.5	6	82	7
2	4	20	20	4	90.8	5
11	5	12.5	20	6	84.6	7
3	6	5	45	4	69.8	5
6	7	20	32.5	2	92.5	5
17	8	12.5	32.5	4	94.6	6
1	9	5	20	4	75.2	5
13	10	12.5	32.5	4	92.58	5
12	11	12.5	45	6	86.8	7.5
9	12	12.5	20	2	95.38	3.5
5	13	5	32.5	2	64.8	2.5
7	14	5	32.5	6	59.5	8
14	15	12.5	32.5	4	90.24	6
15	16	12.5	32.5	4	90.24	6
16	17	12.5	32.5	4	90.24	6

ANOVA for Quadratic model
Response 1: 90 % Drug Released

Table 3: Analysis of Variance for response 90% drug release after lag time

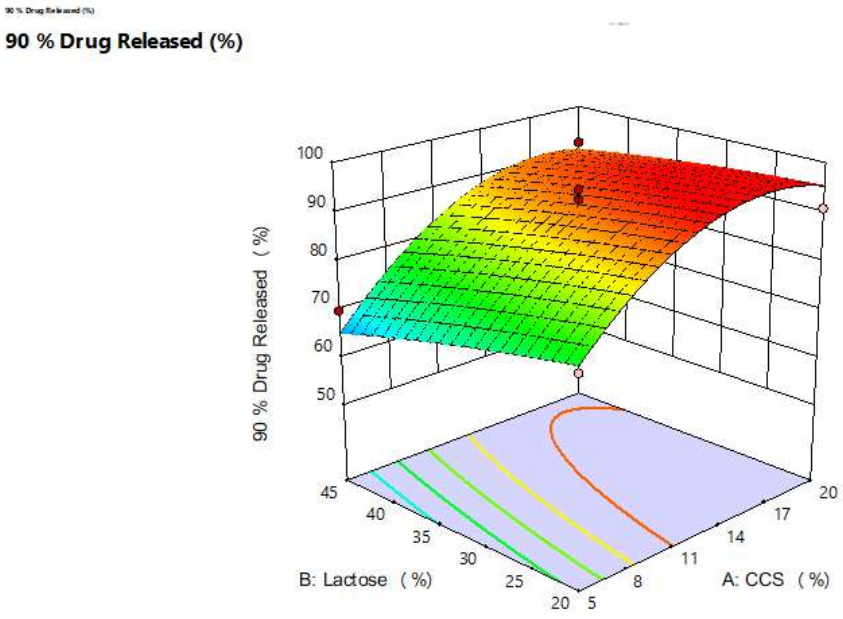
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2031.35	9	225.71	8.04	0.0059	Significant
A-CCS	968.00	1	968.00	34.48	0.0006	
B-Lactose	131.06	1	131.06	4.67	0.0675	

C-Eudragit	2.86	1	2.86	0.1017	0.7591	
AB	10.89	1	10.89	0.3879	0.5531	
AC	6.76	1	6.76	0.2408	0.6386	
BC	265.36	1	265.36	9.45	0.0180	
A^2	336.33	1	336.33	11.98	0.0105	
B^2	2.02	1	2.02	0.0719	0.7963	
C^2	265.61	1	265.61	9.46	0.0179	
Residual	196.52	7	28.07			
Lack of Fit	181.01	3	60.34	15.56	0.0114	Significant
Pure Error	15.51	4	3.88			
Cor Total	2227.87	16				

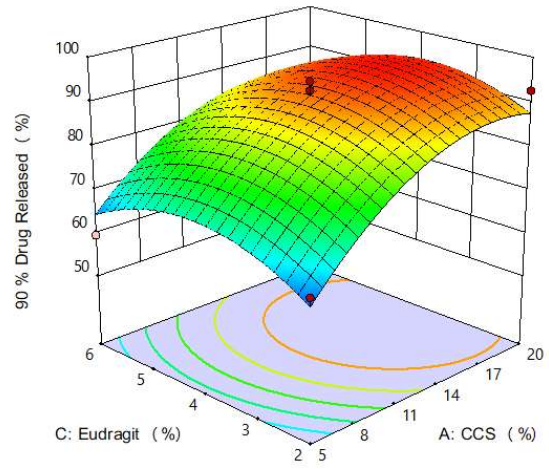
The **Model F-value** of 8.04 implies the model is significant. There is only a 0.59% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant. In this case A, BC, A^2, C^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The **Lack of Fit F-value** of 15.56 implies the Lack of Fit is significant. There is only a 1.14% chance that a Lack of Fit F-value this large could occur due to noise. Significant lack of fit is bad -- we want the model to fit.

Final Equation in Terms of Coded Factors

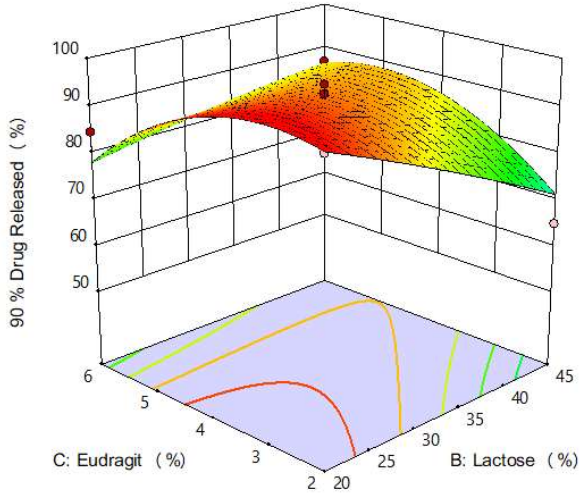
90 % Drug Released	=
+91.58	
+11.00	A
-4.05	B
-0.5975	C
+1.65	AB
-1.30	AC
+8.14	BC
-8.94	A^2
-0.6925	B^2
-7.94	C^2



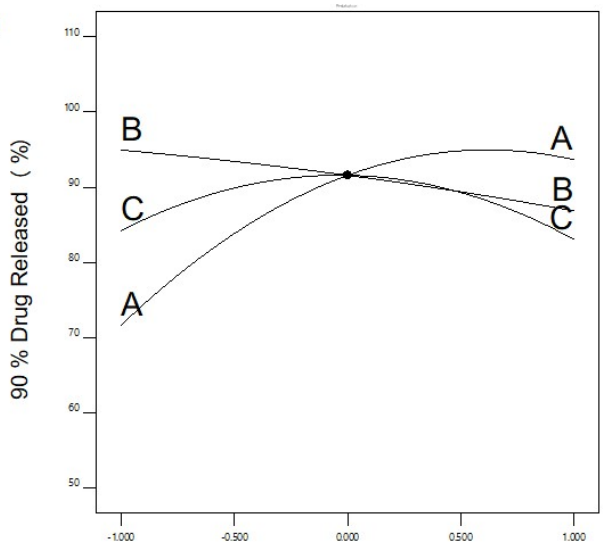
90 % Drug Released (%)



90 % Drug Released (%)



90 % Drug Released (%)



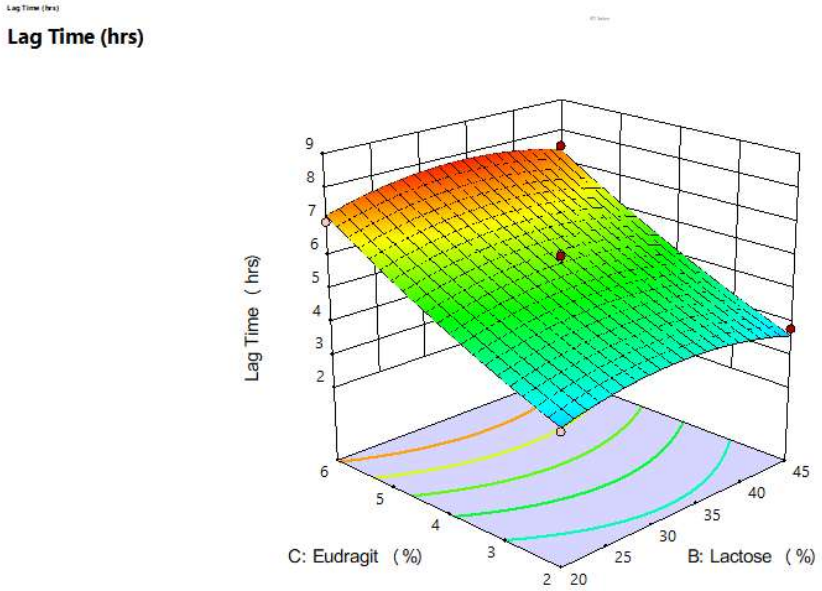
ANOVA for Quadratic model
Response 2: Lag Time

Table 4: Analysis of Variance for lag time

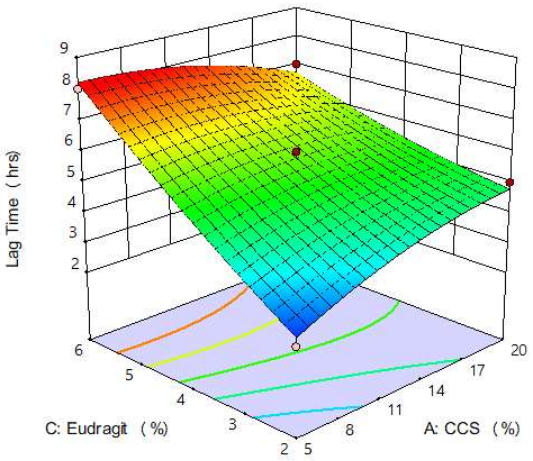
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	32.34	9	3.59	16.52	0.0006	significant
A-CCS	0.1250	1	0.1250	0.5747	0.4731	
B-Lactose	0.0112	1	0.0112	0.0517	0.8266	
C-Eudragit	27.01	1	27.01	124.19	< 0.0001	
AB	0.0625	1	0.0625	0.2874	0.6085	
AC	3.06	1	3.06	14.08	0.0071	
BC	0.0100	1	0.0100	0.0460	0.8363	
A^2	0.5921	1	0.5921	2.72	0.1429	
B^2	1.27	1	1.27	5.86	0.0461	
C^2	0.1684	1	0.1684	0.7743	0.4081	
Residual	1.52	7	0.2175			
Lack of Fit	0.7225	3	0.2408	1.20	0.4154	not significant
Pure Error	0.8000	4	0.2000			
Cor Total	33.86	16				

Final Equation in Terms of Coded Factors

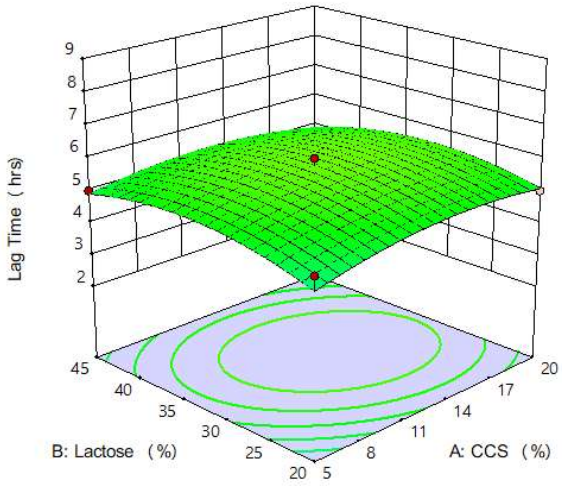
Lag Time	=
+5.80	
+0.1250	A
+0.0375	B
+1.84	C
-0.1250	AB
-0.8750	AC
+0.0500	BC
-0.3750	A^2
-0.5500	B^2
+0.2000	C^2



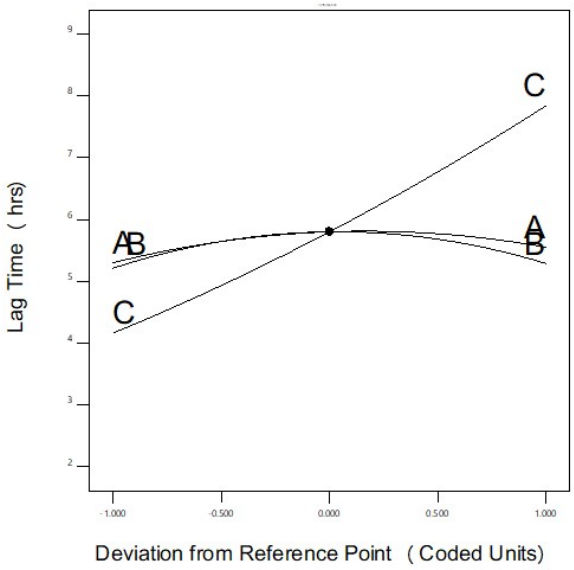
Lag Time (hrs)



Lag Time (hrs)



Lag Time (hrs)

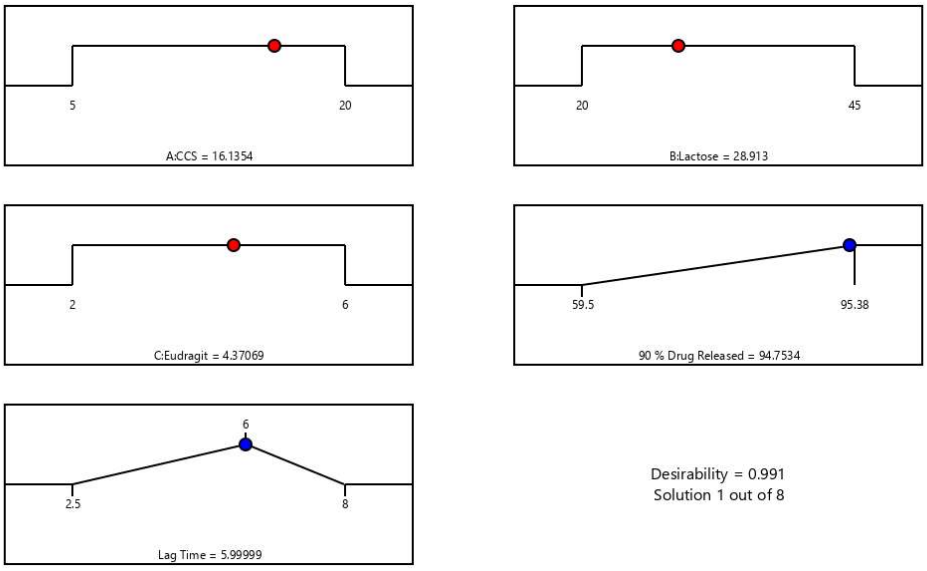


The Model F-value of 6.82 implied model was significant. There was only a 0.02% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A and B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve the model.

The 3D response curves were drawn to estimate the effects of the independent variables on each response. Figure 13 shows the effect of two formulation factors on lag time of 5h. This figure indicates that increase in coating weight gain of Eudragit S 100 rises lag time significantly. Figure 14 shows the effect of two formulation factors on percent of drug release within 90 min. after lag time of 5h at pH 6.8. This figure confirms that increasing coating weight gain of Crosscarbemellose , Sodium -AC-Di-So creats more pressure over outer Eudragit S 100 coat due to swelling and thus helps in releasing of drug by rupturing or disintegrating the outer membrane.

From the 2D contour plots the best area for formulation to obtain desired responses was found (Figure 15 - 18). The best conditions to optimize drug release corresponded to 15.29 mg Crosscarbemellose , Sodium -AC-Di-So and 25.39% Eudragit S 100 weight gain. In order to check the validity of the optimization procedure, a new batch with the predicted levels was prepared.

Validation of optimum formulations



Factors

Factor	Name	Level	Low Level	High Level	Std. Dev.	Coding
A	CCS	16.14	5.00	20.00	0.0000	Actual
B	Lactose	28.91	20.00	45.00	0.0000	Actual
C	Eudragit	4.37	2.00	6.00	0.0000	Actual

Point Prediction

Upper Bound, Confidence = 95% , Population = 99%

Solution 1 of 8 Response	Predicted Mean	Predicted Median	Observed	Std Dev	SE Mean	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
90 % Drug Released	94.7534	94.7534		5.29853	2.34237		99.1912		118.293
Lag Time	5.99999	5.99999		0.466369	0.206172		6.3906		8.07187

CCS	Lactose	Eudragit
16.1354	28.913	4.37069

90% Drug Released Lag Time

A numerical optimization technique by the desirability approach was used to generate the optimum selection of the formulation. The process was optimized for the dependent variables 90% drug release after lag time and lag time. The optimum formulation was selected based on the criteria of attaining the maximum value of % drug release and lag time minimum 5 hr. The predicted and actual values of the optimization batches given by the Design expert software are shown in Table 16. To justify the validity of the equations, values of $X1$ and $X2$ were substituted in equation 2 and 4 to obtain the predicted values of $Y1$ and $Y2$. The predicted and observed values were found to be in good agreement. The linear correlation plots drawn between the predicted and actual values for all the batches of optimization shown in Figure 19 and 20, which demonstrated high values of R^2 0.989 and 0.993 for 90% drug release after lag time and lag time respectively. Thus the low magnitudes of error as well as the values of R^2 in the present investigation prove the high prognostic ability of the optimization technique by factorial design.

Eight checkpoint formulations were found by software and the best conditions to optimize drug release and because of it's high desirability checkpoint formulation with 16.14 mg of CCS, 28.91 mg of Lactose, and 4.37 mg of Eudragit and response of tablet was 94.45 % Drug released and 5.99 hrs of lag time (T) was selected as optimum formulation with desirability of around 1, to ensure the validity of the optimization procedure, checkpoint formulation with the predicted levels was prepared and evaluated. The final optimized formulation was also subjected for the drug release profile. The tablet prepared according to optimum formulation released no repaglinide for 2h and 3h respectively. But drug release was in immediate manner as formulation come in contact at pH 7.4 medium.

CONCLUSION

Diabetes mellitus is a disease which shows circadian rhythm in the pattern of peak in the early morning between 4 and 8 a.m. The behaviour, physiology, and biochemistry of organisms changes rhythmically over 24 h. We have prepared chronomodulated release tablet to control plasma sugar level at early morning. Tablet of REP was prepared using CCS and lactose and coated with Eudragit to produce pulsatile release of the drug. Tablet was optimized using Box-Behnken design model. The ideal formulation variables for a formulation were found that 16.14 mg of CCS, 28.91 mg of Lactose, and 4.37 mg of Eudragit and response of tablet was 94.45 % Drug released and 5.99 hrs of lag time (T). No release was observed in 0.1 N HCl (pH 1.2).

Acknowledgment

This published work is a part of my Ph.D. thesis at the Tamil Nadu Dr. M. G. R. Medical University, Chennai. We thank our management and principal for providing the facilities for successful completion of the work.

REFERENCES

1. M Swetha, B Rama, V Sandhiya, G Rathnam, U Ubaidulla, PS Roy, Chronopharmacotherapeutic release of HMG-COA reductase inhibitor: using novel coating technique, World Journal of Pharmaceutical Research. 2016; (5):784-97.
2. B Rama, V Sandhiya, M Swetha, G Rathnam, U Ubaidulla., Pulsatile drug delivery: A comprehensive review., IJPDT. 2015; 5(2):125-130
3. U Ubaidulla, B Senthilkumar, RK Khar, FJ Ahmad., Studies on suspension of nimesulide solid dispersion: Development, characterization and in vivo evaluation, Indian journal of pharmaceutical sciences. 2005; 67(4): 422-426.
4. DS Karuna, AK Rasheedhabanu, U Ubaidulla, G Rathnam, Development of artemether and lumefantrine fixed dose combination tablets: Preparation, characterization and in-vitro evaluation, Int J Pharm. 2016; 4(4): 166.
5. DS Karuna, AK Rasheedhabanu, UR Ubaidulla., Development of Artemether Lumefantrine FDC tablet preparation; Characterization and in vitro evaluation., Pharm and BioAllied Sci Jl. 2014;1(2):1-4.
6. U Uthumansha, K Prabahar, DB Gajapathy, M El-Sherbiny, N Elsherbiny, Optimization and In Vitro Characterization of Telmisartan Loaded Sodium Alginate Beads and Its In Vivo Efficacy Investigation in Hypertensive Induced Animal Model, Pharmaceutics. 2023;15(2):709.
7. G Mani, H Pushparaj, MM Peng, P Muthiahpillai, U Udhumansha, Synthesis and characterization of pharmaceutical surfactant templated mesoporous silica: Its application to controlled delivery of duloxetine, Materials Research Bulletin. 2014;51: 228-235.
8. S Pandey, S Mattha Vijayendra Swamy, U Mansha Ubaid Ulla, A Gupta, Cell line and augument cellular uptake study of statistically optimized sustained release capecitabine loaded Eudragit S100/PLGA (poly (lacticco-glycolic acid)) nanoparticles, Current Drug Delivery. 2017;14(6):887-99.

9. NEMQ Kousalya Prabahar, Ubaidulla Udhumansha., Microneedle mediated transdermal delivery of β-sitosterol loaded nanostructured lipid nanoparticles for androgenic alopecia, Drug Delivery. 2022; 29(1):3022-34.
10. DS Karuna, G Rathnam, U Ubaidulla, M Ganesh, HT Jang., Chitosan phthalate: A novel polymer for the multiparticulate drug delivery system for diclofenac sodium., Advances in Polymer Technology. 2018; 37(6):2013-20.
11. V Loganathan, B Senthilkumar, MVS Reddy, N Sreekanth, U Ubaidulla., Compatibility studies between sparfloxacin and tablet excipients through differential scanning calorimetry, Indian Drugs-Bomba. 2003;40(11):661-64.
12. UU V.Loganathan, B. Senthil kumar, M.V.S. Reddy, N. Sreekanth, Compatibility studies between Pefloxacin and Tablet Excipients through Differential Scanning Calorimetry (DSC), Indian Drugs. 2003; 40(4): 219-22.
13. Udayakumar. T, Chordia Mayor Ashok, Udhumansha Ubaidulla. Design and development of bioadhesive gastro retentive drug delivery system of metoprolol succinate. International Journal of Research and Development in Pharmacy and Life Sciences. February-March, 2013; 2(2):355-62. Available online at http//www.ijrdpl.com