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Application of central composite experimental design to optimise sustained release tablet formulations of muscle relaxant baclofen

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Abstract
The aim of this study was to apply and evaluate usefulness Central Composite design for the optimization of polymer concentration in sustained release tablets of muscle relaxant Baclofen. Drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs}) were taken as target responses, whereas the concentration of different polymers such as Polyox WSR 303 (hydrogel) and HPMC K4M (hydrophilic matrix system) were considered as impacting factors. A second-order polynomial equation was concluded using the multiple regression analysis for the experimental data. The design space was established targeting the successful operating ranges for drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs}) as 30.0-40.0% and 90.0-100.0% respectively. The design space illustrated that the available operation range is wide at the laboratory scale and thus ensuring the product quality. From the results of study it was concluded that successful application of central composite design of experiments is helpful to select grade and concentration of polymers cost effectively to reduce cost of goods which ultimately can improve profitability of pharmaceutical production unit.

Keywords: QbD, DOE, Optimization, central composite design, Analysis of Variance, Response Surface Design

Introduction

Baclofen

Baclofen is a central nervous system depressant. It is used as a skeletal muscle relaxant. The main use Baclofen is to treat spasticity. The other use is in topical pain creams as a muscle relaxant by compounding pharmacies. Baclofen available in the market brand name like Lioresal.

Baclofen is a GABA receptor agonist, precisely of the GABAB receptors [1, 2]. It is advantageous effects in spasticity result from actions at spinal and supraspinal sites. Baclofen is a derivative of γ-aminobutyric acid (GABA).

The tolerance to muscle-related therapeutic benefits does not seem to occur to a significant degree is the useful property of baclofen. After many years of continued use, Baclofen maintains its therapeutic anti-spasmodic effects [3]. However, tolerance may develop in some people receiving intrathecal baclofen treatment, as per some recent studies [4, 5, 6]. In the United States, as of 2015, the price for a usual course of cure is less than 25 USD [7].

Medical uses of Baclofen

The large usage of Baclofen is for the treatment of spastic movement disorders, particularly in instances of spinal cord injury, cerebral palsy, and multiple sclerosis [8]. Baclofen is not recommended to person with Parkinson's disease or stroke [8].

Mechanism of action

Baclofen's range of therapeutic properties is due to variation of the GABAB receptor. Baclofen activates the GABAB receptor and give its effects. This similarity is also observed in the drug phenibut, which activates the GABAB receptor and gives the some of its effects. Baclofen acts as an inhibitory neurotransmitter, postulated to block mono-and-polysynaptic

reflexes and to block the release of excitatory transmitters. Nevertheless, baclofen is known to 'no absue' potential and do not have any substantial connection for the GHB receptor [9].
Like phenibut (β-phenyl-GABA), Pregabalin (β-isobutyl-GABA) is also close analogues of baclofen. Baclofen (β-(4-chlorophenyl)-GABA) has been found to block α2δ subunit-containing voltage-gated calcium channels (VGCCs) [10]. But it is weaker relative to phenibut in this action (Ki = 23 and 39 μM for R- and S-phenibut and 156 μM for baclofen) [17]. Besides, as an agonist of the GABAB receptor, baclofen is in the range of 100-fold further potent by weight in assessment to phenibut, and in agreement, is used at very lower comparative dosages. As such, the actions of baclofen on α2δ subunit-containing VDCCs are likely not clinically-relevant [10].

Sustained release drug delivery systems

The mechanism used in the capsules or in pill tablets to dissolve a drug over time in order to be released stable and slower into the bloodstream is known as time release technology or sustained release (SR), extended release (ER, XR, XL), controlled release (CR) technology. Such time release technology is more beneficial and reduces the frequent interval of drug dosage than the immediate release (IR) formulations. For example, extended-release morphine allows for people with chronic pain to only need one or two tablets per day [11].
Now a days, most time-release drugs are formulated so that the active ingredient is set in a matrix of insoluble substance(s) (various: some acrylics, even chitin; these substances are often patented) such that the dissolving drug must find its way out through the holes in the matrix. In some SR formulations, the drug dissolves into the matrix, and the matrix physically swells to form a gel, permitting the drug to departure through the gel's external surface.

Baclofen sustained release drug delivery system

Currently, the most commonly used dose form for baclofen is the immediate release (IR) tablet (10-20 mg) to be administered three times a day. A serum concentration of 80 ng/mL or more is considered an effective concentration. Because higher doses often cause side effects such as drowsiness, dizziness, and muscle weakness, a dose of 10 mg is used in most patients as it provides enough symptomatic relief with minimal side effects. Also, the frequent administration of conventional baclofen IR tablets leads to fluctuations in plasma concentration, producing peaks and troughs. The peaks are associated with side effects, such as drowsiness, dizziness, and muscle weakness, and troughs are associated with inadequate control of muscle spasm. These side effects are considered as major deterrents to the prescribers for up-titration of the dosage for optimization of therapy. In addition, as baclofen IR has to be taken three times a day, medication noncompliances are not rare occurrences. The latter factor of noncompliance can be overcome by the prescription of medications that require a minimal number of doses. A once-a-day dosage formulation with the same therapeutic effectiveness as the baclofen IR tablet would vastly improve patients' compliance with treatment. This will increase the outcome of therapy, as more number of patients will adhere to treatment plan [12].

A Central composite design of experiments

A central composite design is the most commonly used response surface design experiment. Central composite designs are a factorial or fractional factorial design with center points, augmented with a group of axial points (also called star points) that help to estimate curvature.
A central composite design can be used to efficiently estimate first- and second-order terms.
Model a response variable with curvature by adding center and axial points to a previously-done factorial design.
Central composite designs are especially useful in sequential experiments because you can often build on previous factorial experiments by adding axial and center points.
For example, to determine the best conditions for injection-molding a plastic part. One will first run a factorial experiment and determine the significant factors: temperature (levels set at 190° and 210°) and pressure (levels set at 50MPa and 100MPa). If the factorial design detects curvature, one can use a response surface design experiment to determine the optimal settings for each factor. The design points for this experiment are below.

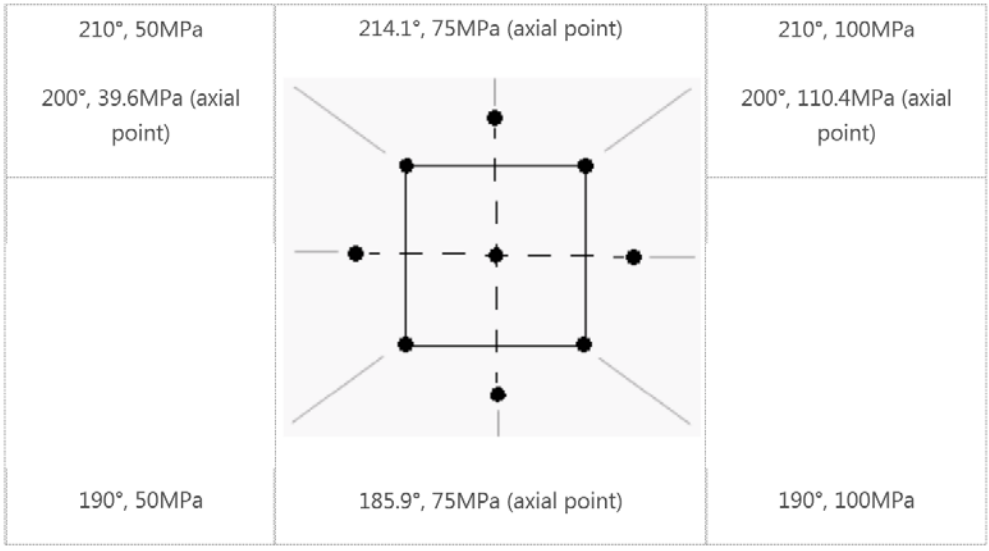

Fig 1: Points on the diagram represent the experimental runs that are done in central composite design of experiments

When possible, central composite designs have the desired properties of orthogonal blocks and rotatability.

Orthogonal blocks

Often, central composite designs are done in more than one block. Central composite designs can create orthogonal blocks, letting model terms and block effects be estimated independently and minimizing the variation in the regression coefficients.

Rotatability

Rotatable designs provide constant prediction variance at all points that are equidistant from the design center.

A face-centered central composite design

Face centered designs are a type of central composite design with an alpha of 1. In this design the axial points are at the center of each face of the factorial space, so levels = + 1. This variety of design requires 3 levels of each factor. Augmenting an existing factorial or resolution V design with appropriate axial points can also produce this design [13].

In the present study central composite design was applied for the optimization of polymer concentration in sustained release tablets of baclofen. Drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs}) were taken as target responses, the concentration of different polymers such as Polyox WSR 303 (hydrogel) and HPMC K4M (hydrophilic matrix system) were considered as impacting factors.

Materials & Methods

Raw material obtained as a gift sample from various renown pharmaceutical companies.

Preparation of baclofen sustained release tablets

Various batches of sustained release were prepared by direct compression method using different concentration of polymers (Table 1). Baclofen and Avicel PH 101 were first mixed by geometric dilution method and all other excipients except lubricant were blended with it. This blend was lubricated with magnesium stearate (1%) and compressed into tablets at 250 mg average weight (8 station rotary tablet compression machine, Cadmach, Ahmedabad, India).

Evaluation of tablets

The prepared tablets were evaluated for drug release parameter with the official method described in Indian pharmacopeia, 1996 [14]. The purpose of this study was to systematically investigate the impact of several formulation variables on drug release using central composite design (CCD). Drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs}) were taken as target responses, the concentration of different polymers such as Polyox WSR 303 (hydrogel) and HPMC K4M (hydrophilic matrix system) were considered as impacting factors.

Optimisation study a central composite design

In this study, Minitab software version 14 was used to give desirability and overlay information to get optimized formulation with the possible interactions of the selected independent variables on the dependent variables. Selected factor levels for the experimental design used in the formulation of sustained release are given in Table 1.

Table 1: Selected factor levels for the experimental design used in the formulation of sustained release baclofen tablets

Model factor	Actual values		Coded values	
	Low	High	Low	High
X_1: Polyox WSR 303 (%)	50	100	-1	+1
X_2: HPMC K4M (%)	75	125	-1	+1

The two independent formulation variables evaluated were:

X_1: Polyox WSR 303 (%); X_2: HPMC K4M (%)

The response variables evaluated were:
Drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs})
The statistical analysis of the experimental batch was performed by multiple regression analysis using Minitab software version 14. The coefficient of determination (r2) and adjusted coefficient of determination (adj. r2) were compared for best fitting of the model. The effect of formulation variables on the responses were statically evaluated by applying two-way analysis of variance (ANOVA) at 0.05 levels. The optimum levels of the selected variables were obtained by solving the regression equation and analyzing the desirability and overlay plot.

Establishment of the design space

Design space is defined by the ICH Q8 as ‘‘the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality’’ [15]. The design space makes QbD a reality and the wider the design space, the more robust and flexible the process is to accommodate variations. In this case study, response surface methodology in combination with optimization was applied to establish design space. Design space was determined from the common region of successful operating ranges for two responses Drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs}). The successful operating ranges for the Drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs}) determined were 30.0-40.0% and 90.0-100.0% respectively.

Results & Discussion

***In vitro* drug release studies**

A study of dissolution profile for all the formulations gave an insight into the effect of polymer concentration on release profile of the formulations. From the release profiles, it was observed that the variation in type of polymer and polymer concentration from F1 to F13 (Table 2) had a variable effect on drug release shown in the Table 3.

Table 2: Summary of experimental runs of the formulations in central composite design

Formulation	X_1 (%)	X_2 (%)
F1	75.000	100.000
F2	100.000	75.000
F3	110.355	100.000
F4	75.000	100.000
F5	100.000	125.000
F6	50.000	75.000
F7	75.000	64.645
F8	75.000	100.000
F9	50.000	125.000
F10	75.000	100.000
F11	75.000	135.355
F12	39.645	100.000
F13	75.000	100.000

Table 3: Summary of experimental responses of the formulations in central composite design

Formulation	R_{4hrs} (%)	R_{12hrs} (%)
F1	27.86	99.78
F2	40.39	87.56
F3	57.80	95.45
F4	28.93	87.58
F5	42.29	91.14
F6	51.14	98.07
F7	25.08	84.58
F8	35.34	94.59
F9	45.24	102.45
F10	48.14	87.54
F11	25.46	99.45
F12	35.45	100.23
F13	48.52	101.24

Optimisation study central composite design

Optimisation study to examine effects and interactions of significant factors on product quality attributes mainly drug release. The optimisation study typically can use one of the following experimental designs; factorial, fractional factorial, central composite, mixture design, D-optimal, or Box-Behnken design. Central composite design was specifically selected for this study [13].

Summary of results of statistical analysis and optimization of the formulations using central composite design is given in Table 4. After a regression analysis for each of the responses the polynomial model established as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where Y is the response, X_1–X_2 are the main effects of factors, X_1X_2 is the interaction effects of factors, X_1^2, X_2^2 are quadratic effects of factors, b_0 is the constant, and b_1-b_2 are the coefficients of the factors. The p values of the regression coefficients (b_1–b_2) were determined to evaluate the significance of the factors on the responses. ANOVA was also applied to determine the significance of the model.

Table 4: Summary of results of statistical analysis and optimization of the formulations using central composite design

Central Composite Design

Factors: 2 Replicates: 1
Base runs: 13 Total runs: 13
Base blocks: 1 Total blocks: 1

Two-level factorial: Full factorial

Cube points: 4
Center points in cube: 5
Axial points: 4
Center points in axial: 0

Alpha: 1.41421

Design Table (randomized)

Run	Blk	A	B
1	1	-1.00000	-1.00000
2	1	0.00000	1.41421
3	1	0.00000	0.00000
4	1	1.41421	0.00000
5	1	0.00000	0.00000
6	1	1.00000	-1.00000
7	1	0.00000	0.00000
8	1	1.00000	1.00000
9	1	0.00000	0.00000
10	1	0.00000	-1.41421
11	1	-1.41421	0.00000
12	1	0.00000	0.00000
13	1	-1.00000	1.00000

Response Surface Regression: Y1, Y2 versus X1, X2
Response Surface Regression: Y1 versus X1, X2

The analysis was done using coded units.

Estimated Regression Coefficients for Y1

Term	Coef	SE Coef	T	P
Constant	41.1720	4.376	9.408	0.000
X1	1.8759	3.460	0.542	0.605
X2	-0.7625	3.460	-0.220	0.832
X1*X1	-5.7423	3.710	-1.548	0.166
X2*X2	2.7928	3.710	0.753	0.476
X1*X2	-9.1150	4.893	-1.863	0.105

S = 9.786 R-Sq = 50.5% R-Sq(adj) = 15.1%

Analysis of Variance for Y1

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	5	683.29	683.29	136.66	1.43	0.322
Linear	2	32.80	32.80	16.40	0.17	0.846
Square	2	318.15	318.15	159.08	1.66	0.257
Interaction	1	332.33	332.33	332.33	3.47	0.105
Residual Error	7	670.34	670.34	95.76		
Lack-of-Fit	3	84.36	84.36	28.12	0.19	0.897
Pure Error	4	585.98	585.98	146.50		
Total	12	1353.63				

Estimated Regression Coefficients for Y1 using data in uncoded units

Term	Coef
Constant	-77.7819
X1	2.91158
X2	0.169619
X1*X1	-0.00918760
X2*X2	0.00446840
X1*X2	-0.0145840

Response Surface Regression: Y2 versus X1, X2

The analysis was done using coded units.

Estimated Regression Coefficients for Y2

Term	Coef	SE Coef	T	P
Constant	94.7700	3.117	30.402	0.000
X1	-3.1433	2.464	-1.276	0.243
X2	-0.2490	2.464	-0.101	0.922
X1*X1	1.3444	2.643	0.509	0.627
X2*X2	-1.6381	2.643	-0.620	0.555
X1*X2	-1.2350	3.485	-0.354	0.734

S = 6.970 R-Sq = 26.3% R-Sq(adj) = 0.0%

Analysis of Variance for Y2

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	5	121.488	121.488	24.298	0.50	0.769
Linear	2	79.541	79.541	39.770	0.82	0.479
Square	2	35.847	35.847	17.923	0.37	0.704
Interaction	1	6.101	6.101	6.101	0.13	0.734
Residual Error	7	340.095	340.095	48.585		
Lack-of-Fit	3	133.826	133.826	44.609	0.87	0.529
Pure Error	4	206.269	206.269	51.567		
Total	12	461.583				

Estimated Regression Coefficients for Y2 using data in uncoded units

Term	Coef
Constant	76.2653
X1	-0.250784
X2	0.662441
X1*X1	0.00215100
X2*X2	-0.00262100
X1*X2	-0.00197600

Summary of results of statistical analysis and optimization of the formulations using central composite design is given in Table 4, shows that the responses drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs}) are not impacted significantly due to change in grade or concentration of polymers.

No interaction effect of factors X_1 and X_2 is observed on the responses drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs}).

From the regression coefficient values given in table 4 and surface and contour plots shown in Figure 2a and 2b it can be inferred that factors X_1 has positive effect on response Y_1 while factor X_2 has negative impact on response Y_1. From the regression coefficient values given in table 4 and surface and contour plots shown in Figure 3a and 3b it can be inferred that factors X_1 and X_2 have negative effect on response Y_2.

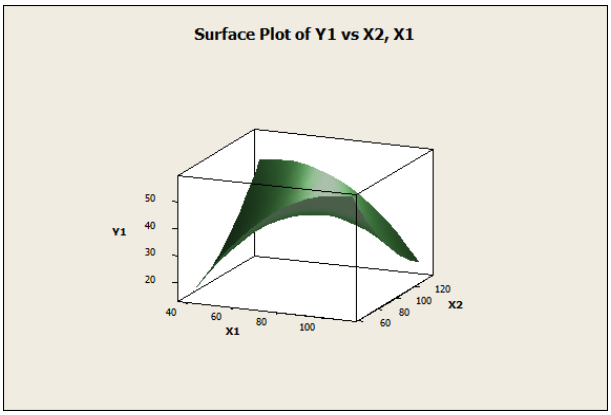

Fig 2a: Surface Plot of Y1 vs X2, X1

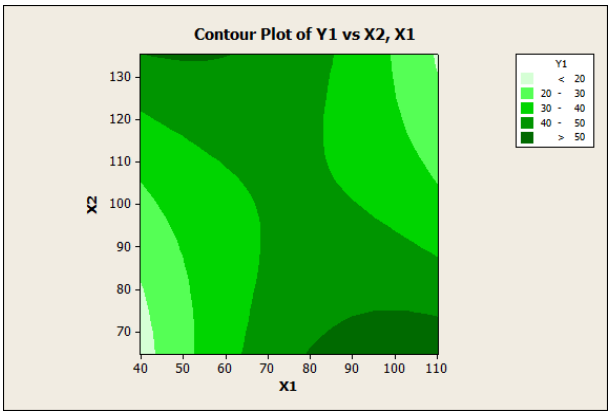

Fig 2b: Contour Plot of Y1 vs X2, X1

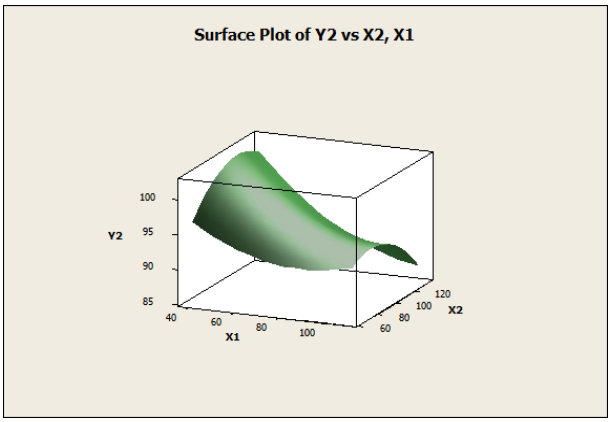

Fig 3a: Surface Plot of Y2 vs X2, X1

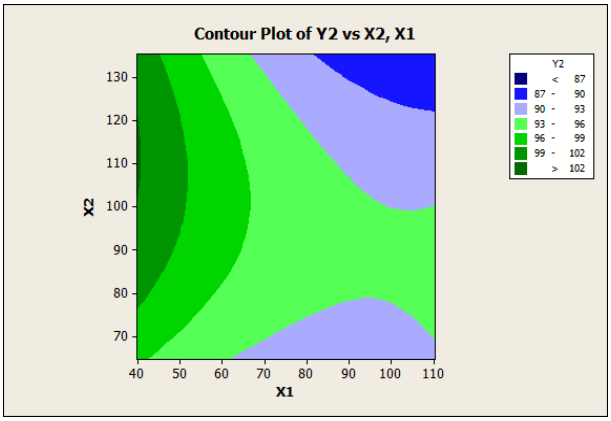

Fig 3b: Contour Plot of Y2 vs X2, X1

Evaluation of the design space

The design space for baclofen sustained release tablets was established targeting the successful operating ranges for the responses drug release at 4 hrs (R_{4hrs}) and 12 hrs (R_{12hrs}) as 30.0-40.0% and 90.0-100.0% respectively. The proposed design space (Figure 4) comprising of the overlap region of ranges for the two responses was obtained. The design space illustrated that the available operation range is wide at the laboratory scale and thus ensuring the product quality.

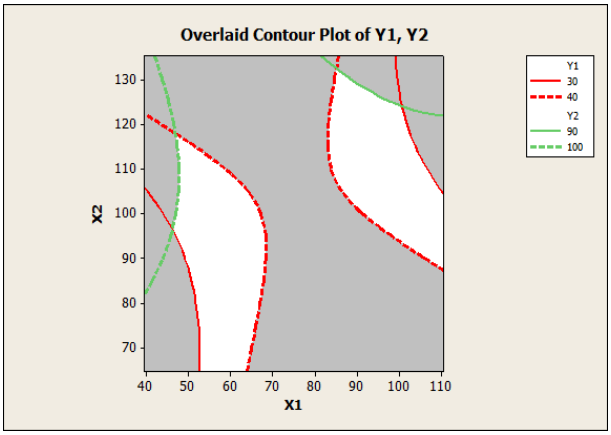

Fig 4: Overlaid Contour Plot of Y1, Y2

Conclusions

A central composite design was successfully applied for the optimisation of sustained release tablet formulation muscle relaxant baclofen. Optimisation study results revealed that polymer grade and its concentration do not have significant effect on drug release from the given tablet formulation. Using the design space plot obtained at the end of optimisation study one can select low cost grade of polymer with minimum concentration achieve target drug release. Thus it can be concluded that successful application of Central composite design of experiments is helpful to select grade and concentration of polymers cost effectively to reduce cost of goods which ultimately can improve profitability of pharmaceutical production unit.

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