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Chapter

Central Composite Design for Response Surface Methodology and Its Application in Pharmacy

Sankha Bhattacharya

Abstract

The central composite design is the most commonly used fractional factorial design used in the response surface model. In this design, the center points are augmented with a group of axial points called star points. With this design, quickly first-order and second-order terms can be estimated. In this book chapter, different types of central composite design and their significance in various experimental design were clearly explained. Nevertheless, a calculation based on alpha (α) determination and axial points were clearly described. This book chapter also amalgamates recently incepted central composite design models in various experimental conditions. Finally, one case study was also discussed to understand the actual inside of the central composite design.

Keywords: central composite design, response surface method, circumscribed design, the uncoded value value of alpha (α), two-factor central composite design

1. Introduction

Any optimization process is achieving by going through certain phases, i.e., Screening; where identification of significant and important factor is important [1]; Improvement; where factors need to be identified which is near to optimum, Response surface design [2]; where optimum or best product has been designing by response surface method (RSM) by quantifying the relationship between one or more measured responses and vital input factor [3]. It is always been a tedious tasks to choice a suitable experimental design, which can easily explain many response variables. Such variables often end as quadratic surface model. For such kind of interpretation central composite design can be an excellent choice. In the process of Optimization and finding the best possible product from the ongoing batches, an experimental design called the central composite design (CCD) concept has emerged [4]. The CCDmodel is an integral part of response surface mythology. The biggest advantage of this type of optimization model is, it is more accurate, and no need for a three-level factorial experiment for building a second-order quadratic model [5]. After excising the CCDmodel within the experiment, a linear regression model has been used to construct the model, and coadded values have been used [6]. The CCDmodel is otherwise called A Box-Wilson Central Composite Design. In this design, the center points are eventually augmented with the group of "star points" that allows estimation of curvature [7]. If the distance from the center of the

design space to a factorial point is ±1 unit for each factor, the distance from the center of the design space to a star point is ± α with ıα8] 1 < ı]. The precise value of α depends on certain specific properties required for the design. Since there are many factors available in the CCD model, therefore, the possibility of more than two or many star points within the model is more palpable. The star points represent lower and higher extreme values. The CCD model allows to extends 2 level factors, which have been widely used in response surface modeling and Optimization. As far as pharmaceutical research is a concerned, much scientific research has been carried out in recent times in this direction. As per Krishna Veni *et al* (2020), environment-sensitive Eudragit coated solid lipid nanoparticles can be prepared using a central composite design (CCD) model [9]. In another study, Ye, Qingzhuo, et al.(2020) prepared puerarin nanostructured lipid carriers by central composite design, where 5 levels 3 factors central composite design was used to utilized to anticipate response variables and to constrats 3D plots [10].

However, in this book chapter, an attempt was made to highlight the basics of the CCD model and to corelate the concepts of CCD with suitable case studies, which could increase the readers' inquisitiveness.

2. Essential steps in responses surface methodology

a. After necessary Screening, the various factors and subsequent interactions of the experiment were identified [11].

b. The priority was given to the established various level of characteristics

c. Upon Optimization, the best suitable model has been selected [12].

d. The appropriate model, which is ideal for experimental design, can also be chosen [13].

e. To performed experimental studies, it is necessary to incept tangible factors and values which are needed to analyze systematically [14]

f. The selected model can be validated

g. There is a provision where if the data are not satisfactory, then another model of the experimental equation and experimental design is preferred. While pursuing the study, the aforementioned point c,d, and f need to be repeated until a suitable model is obtained, which is an acceptable representation of the data [15].

h. If required, a graphical representation of the surface is generated.

2.1 Models of the model used in the optimization process

The first-order model for the Optimization can be depicted as:

$$Y = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \epsilon \quad (1)$$

For quadratic or second-order model, if nonlinearity was reported, then the following equation was incorporated:

$$Y = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} {X_1}^2 + \beta_{22} {X_2}^2 + \epsilon \quad (2)$$

The factor must be very at level three while activating to fit the second-order model [16]. It was observed that, during the dictation of center point and two-level design, the quadratic terms can be identified, but it cannot be adequately estimated [17]. In **Figure 1,** the condition at which the Optimization can occur was explained, i.e., Optimization can be confirmed when second order model can be optioned from statistical outcomes and which coincide with the optimum value. During the factorial design experiment, it is preferable to avoid three-level designs as chances of an increase in the number of runs would be more [16].

For CCDDesign and Box–Behnken Design, second-order models are widely used. The analyzing aspect of these two designs can be explained by the following equation:

$$Y = b_o + b_1 X_1 + \ldots . + b_k X_k + b12 X_1 X_2 + b_{13} X_1 X_3 + \ldots + b_{k-1}, k\, X_{k-1} X_k + b_{11} {X_1}^2 + \ldots + b_{kk} {X_k}^2 + \epsilon \quad (3)$$

The above equation represents the quadratic model, which is near to the Optimization.

In this equation, Y = Dependent variables or Outcome variables or estimated responses, X_1 = independent variables, b_0 = overall mean response or intercept constant, b_1 = regression model coefficients, K = number of independent variables, ϵ = error.

Put into words, a mathematical model to the observed values of the dependent variables y, that indicates:

1. Main effects for factor $X_1 \ldots \ldots . X_k$

2. Their interactions $(X_1X_2, X_1X_3 \ldots ., X_{k-1}, X_k)$

3. Their quadratic components $({X_1}^2, \ldots \ldots {X_k}^2)$. No assumptions are made concerning the levels of the factors, and you can analyze any set of continuous values for the factors.

Based on the outcomes and empirical models from various experimental design, the central composite design gives us a direction to logically think and exercised multivariable analysis [18]. Three design points are prerequisite to establishing a

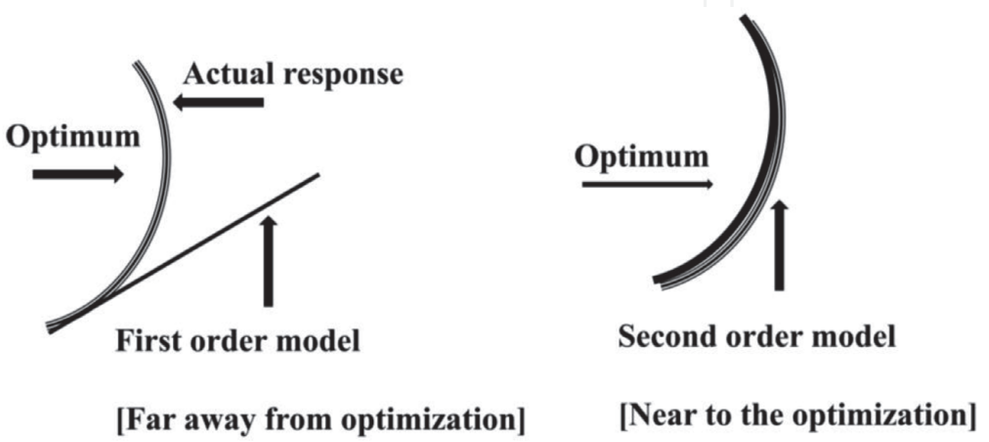


Figure 1.
Optimization condition.

second-order polynomial equation in CCDmodel [19]. When two levels of fractional factorial design need to be established, then 2^k should have possible +1 and − 1 levels of factors. In similar patterns, 2 k needs to be calculated, which can be otherwise called star points, and α forms the center to generate quadratic terms. The center point of the CCD., the model, provides an excellent independent estimation of experimental error.

$$N = k^2 + 2k + n, \tag{4}$$

Where N is the actual number of experiments, n is a number of repetition and k is the number of different factors which were incorporated within the study. Eventually, the CCD model can be best explained by the design of an expert (Version 11.0) software. The various steps involved in central composite design (CCD) was discussed in **Figure 2.**

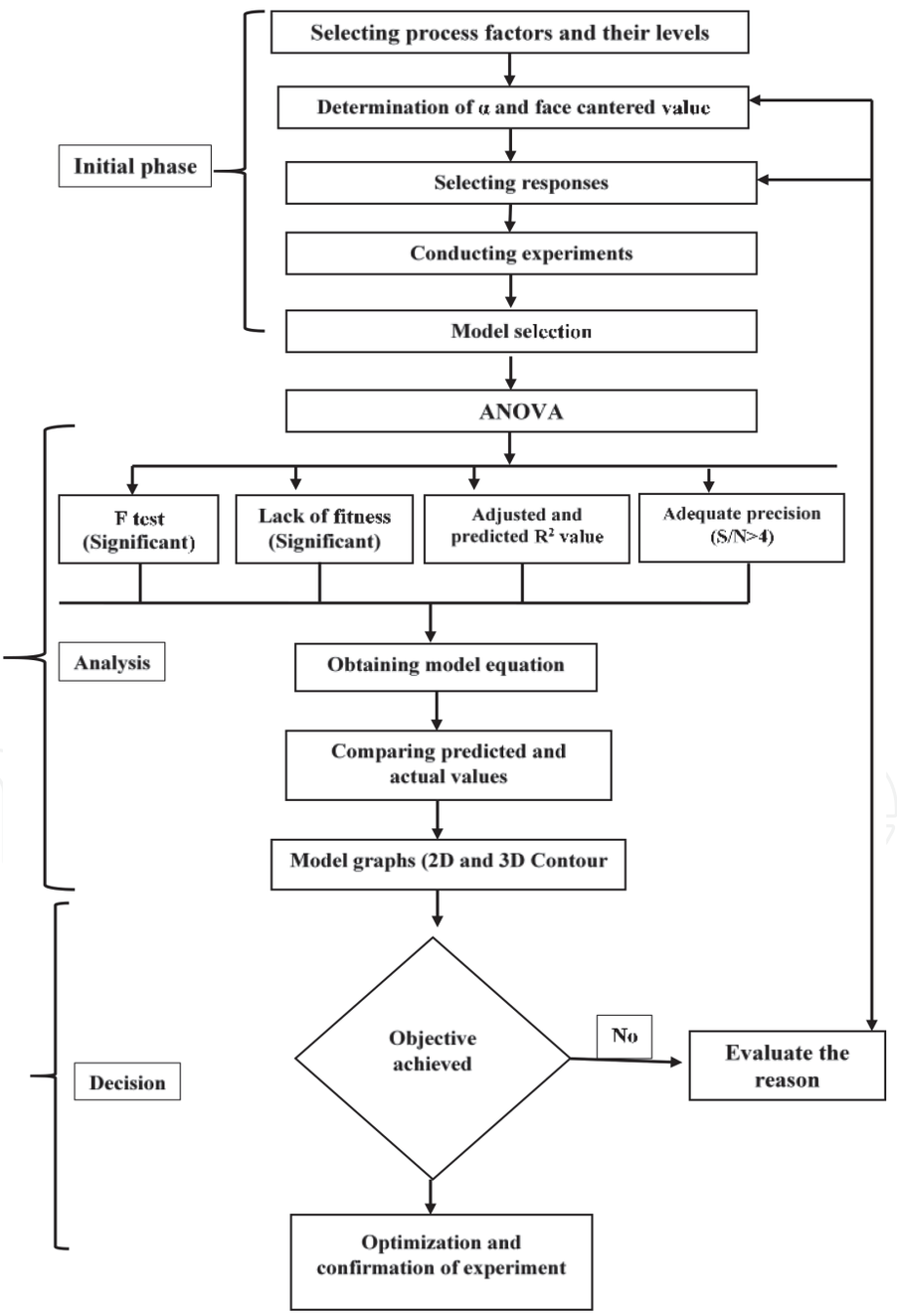


Figure 2.
Central composite design flow diagram.

To determine the local axial point, it is necessary to identify the alpha value in the CCD model. Depending on the alpha vale design can face cantered, rotatable, orthogonal. The alpha value can be calculated using the following equation:

$$\alpha = \left(2^{k}\right)^{0.25}.$$

If α value comes equals 1, the position of axial points stands within the factorial region. This is otherwise called a face-centered design, with three levels of factors that need to be kept in the design matrix. To calculate and analyze experimental results from response surface methodology, a polynomial equation needs to be implemented to study the correlation between dependent and independent variables.

$$Y = \beta_{+}\ \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} {X_1}^2 + \beta_{22} {X_2}^2 + E \qquad (5)$$

3. Types of central composite design

The Box and Wilson design or CCD model comprising of factorial[1], factorial[2,] and factorial[3] design [20]. The star point outside the domine and the center point, representing the experimental domine, helps determine the response surface plot [21]. By estimating the precision of surface responses, the value of α can be determined; where star design is ± α. There are three types of CCD; the α can be determined according to the calculation possibilities and the required precision, which can be obtained from surface responses. The α value's positioning determines the quality of the design or estimation. The rate by design is identified by determining the position of the points [22]. The precision of the estimation influence by the number of trials at the center of the domine. The quality by design approach is necessary to estimate the coefficients' variability and responses [23]. One key aspect is rotatability or iso-variance per-rotation, which means that the prediction error is identical from all the points to the center points from the same distance [24]. Eventually, the center composite design was classified into three types:

3.1 Circumscribed design (CCC)

In central composite design, the levels of the factors eventually stand on the edge.

The CCD model **(Figure 3)** is always magnate with corner points, which was represented in red dots. From the center point (blue), the extract points are constrained from the sides (green dots). In this CCD model, each factor would have 5 levels. The star points are establishing new extremes for the low and high settings for all factors. These designs having circular, spherical or hyperspherical symmetry and required 5 levels for each factor. Supplementing an already existing factor or factorial design with a start point can produce the design. The Circumscribed (CCC) was found to be a rotatable design [25].

3.2 Inscribed design (CCI)

When the limit is specified for factor settings, the CCI design utilized the factor setting as star points and created a factorial design within those limits [26, 27]. In other words, CCI design is a modified version of CCC design, where CCC design has been divided by α to generate the CCI model. Eventually, CCC and CCI were found to be a rotational model **(Figure 4)**.

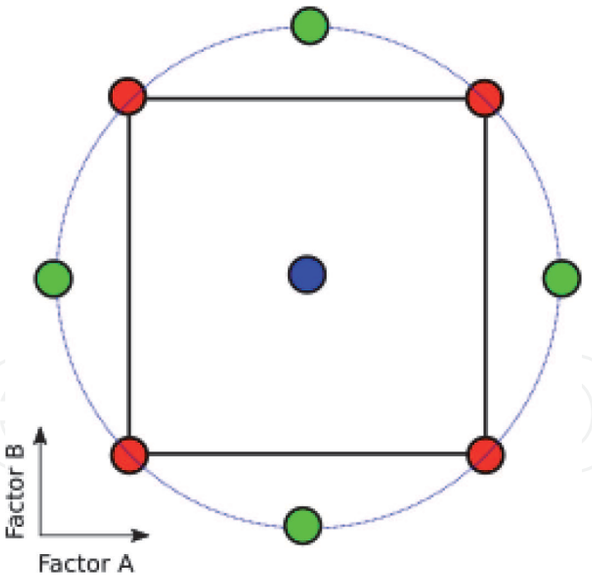


Figure 3.
CCDmodel.

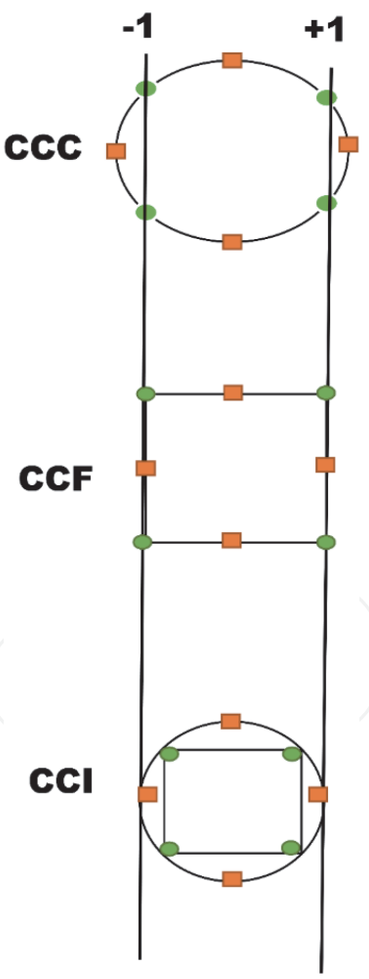


Figure 4.
Comparison of the three types of central composite designs.

3.3 Face cantered (CCF)

In this design, for each face of the factorial space, star points are the center point. Therefore. $\alpha = \pm 1$. This variable requires 3 levels of each factor [28]. The face cantered designs (CCF) are a non-rotatable design **(Figure 4)**.

In **Figure 4**, with two factors, three types of center composite design are used. From this design, one thing is clearly evidenced that; CCI explores the smallest process space, and CCC enjoys the largest process space. The CCC models looking like a sphere rotates around the factorial cube.

4. The parts of box and Wilson composite design

4.1 Determination of α value

Alpha (α) value can be defined as the calculated distance of each individual axial point (star point) from the center in the center composite design [29]. If Alpha (α) is less than 1, which indicates the axial point must be a cube, and if it is greater than 1, it indicates it is outside the cube. In central composite design, each factor has five levels, i.e., Extreme high or otherwise called a star point, higher point, center point, low point, and finally, extreme low star point. **Figures 5** and **6** describe how to select the total number of experimental runs for the CCD model as well as how to design two factors factorial design **(Table 1).** Coming to the Alpha (α) determination; which can be determined by the following equation:

α = (Number of factorial runs)$^{1/4}$.

= (2^k or 2^{k-r}) ¼.

If K (number of factors) =2.

Alpha (α) = $(2^2)^{1/4} = 2^{2/4} = 2^{1/2}$ = 1.414.

4.2 Uncoded value value of alpha (α)

To determine the uncoded value α value, the following equation can be used:

uncoded value value = (Coated value x L) + C; Where, L = Length expressed in real units between centre points and + 1 value of factor and C = Centre point value expressed in real units.

For temperature:

Uncoded value of – α = (Coded value × L) + C.

= (−1.414 × 30) + 60 = 17.58.

Uncoded vale of + α = (Coded value× L) + C = (1.414 × 30) + 60 = 102.42 **(Table 2).**

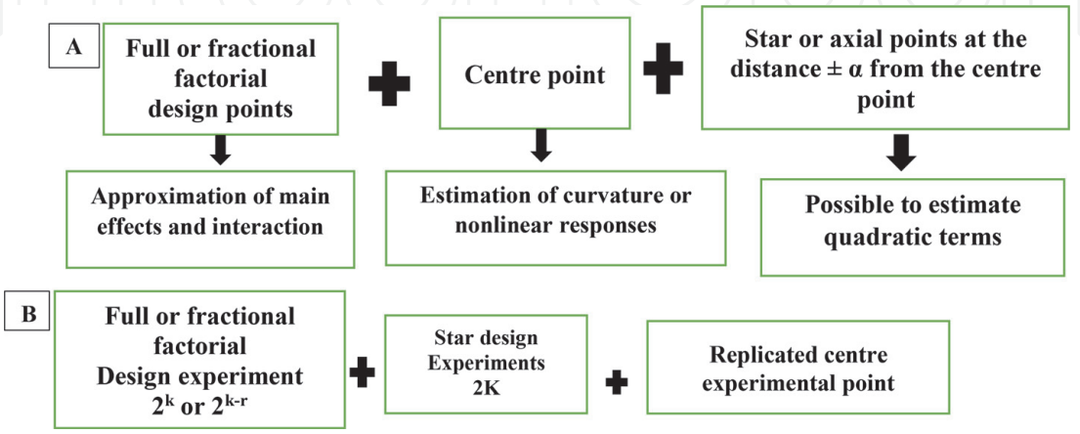


Figure 5.
(A) Parts of CCD (B) Total number of experimental runs required in the CCDmodel; where K = number of variables and r = fraction of full factorial. Thus, two-factor central composite design, the number of experimental runs is; $2^2 + 2(2) + 1 = 9$.

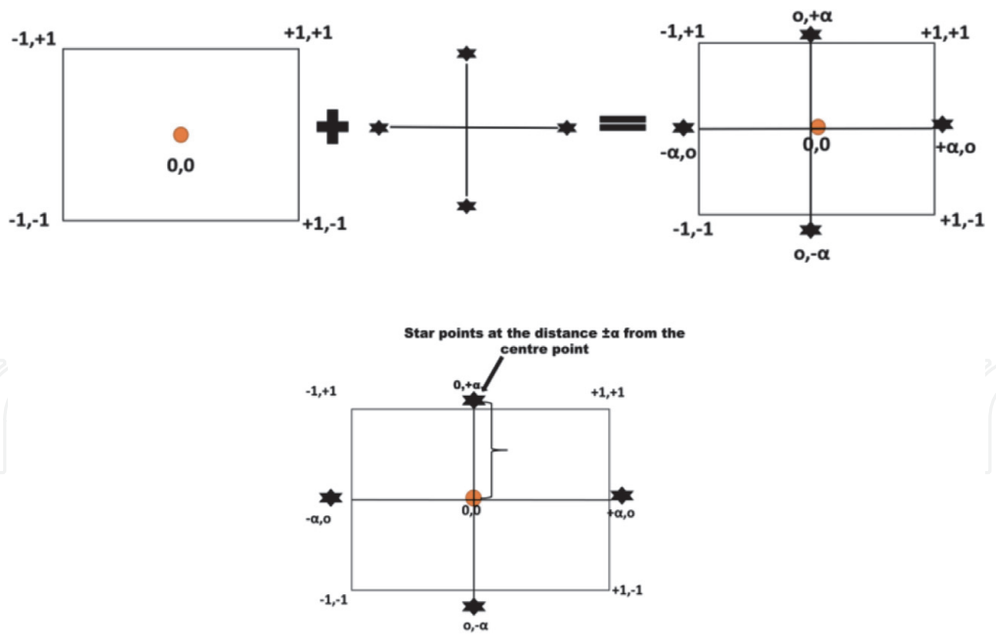


Figure 6.
Schematic presentation of two-factor central composite design.

Number of factors	α value related to ±1
2	±1.414
3	±1.682
4	±2
5	±2.378
6	±2.828

Table 1.
Number of factors and α value.

Level of factor	The temperature in ° C	Pressure in bar
-α (Lowest)	17.58	2.93
−1 (Lower)	30	5
0 (Centre point)	60	10
+1 (High)	90	15
+α (Highest)	102.42	17.07

Table 2.
α value of one experiment.

5. Advantages of center composite design

- It turns out to be the extension of 2 level factorial or fractional factorial design [21]
- To estimate nonlinearity of responses in the given data set
- Helps to estimate curvature in obtained continuous responses
- Maximum information in a minimum experimental trial

No.		Factor A	Factor B
1.	**Factorial runs 2^2 = 4**	−1	-1
2.		1	-1
3.		-1	1
4		1	1
5.	**Axial or star point runs 2(2) = 4**	−1.44	0
6.		1.414	0
7.		0	−1.414
8.		0	1.414
9.	**Centre point**	0	0

Table 3.
Design matrix for 2 factors central composite design [30].

No.		Factor A	Factor B	Factor C
1.	**Factorial runs 2^3 = 8**	−1	−1	−1
2.		1	−1	−1
3.		−1	1	−1
4.		1	1	−1
5.		−1	−1	1
6.		1	−1	1
7.		−1	1	1
8.		1	1	1
9.	**Axial or star point runs 2(3) = 6**	−1.682	0	0
10.		1.682	0	0
11.		0	−1.682	0
12.		0	1.682	0
13.		0	0	−1.682
14.		0	0	1.682
15.	**Centre point**	0	0	0

Table 4.
Design matrix for three factors central composite design [31].

- Reduction in the number of trials required to estimate the squared terms in the second-order model

- They have been widely used in response to surface modeling and Optimization (**Tables 3** and **4**)

6. Limitation of central composite design

- It was observed that the star points are outside the hypercube, so the number of levels that have to be adjusted for every factor is five instead of three, and sometimes it is not easy to achieve the adjusted values of factors [32].

- Depending upon the Design, the squared terms in the model will not be orthogonal to each other.

- Inability to estimate individual interaction terms, i.e., linear by quadratic or quadratic by quadratic.

Same examples of CCDoptimization in recent experimental conditions are mentioned in **Table 5.**

Title of the research	Author and Year	Model utilized	Variables taken	Findings	References
Development and optimization of baicalin-loaded solid lipid nanoparticles prepared by coacervation method using central composite design	Jifu Hao .et. a.l (2012)	central composite design	A two-factor five-level central composite design (CCD) was introduced.	The composition of optimal formulation was determined as 0.69% (w/v) lipid and 26.64% (w/w) drug/lipid ratio. The results showed that the optimal formulation of baicalin-loaded SLN had entrapment efficiency (EE) of 88.29%, particle size of 347.3 nm and polydispersity index (PDI) of 0.169.	[33]
Formulation, Development and Optimization of Propranolol Mucoadhesive Bilayer Tablets by Using Central Composite Design and its In Vitro Studies	Asif MASSUD		Angle of repose, compressibility index, bulk and tapped densities, Hausner's ratio for powders and granules were performed.	Mucoadhesive tablets with adequate mucoadhesion by adopting a new oral drug delivery concept Power was successfully developed to prevent liver degradation and propranololol enhancement Bioavailability Availability	[34]
Statistical Analysis of the Tensile Strength of Coal Fly Ash Concrete with Fibers Using Central Composite Design	Barbuta Marinela, et al. (2015)	CCD, Response Surface Method (RSM.)	Length, percentage, The total number of tests were statistically established taking into account the number of independent variables, the type of analyze that was done and	DOE is a structured, organized method that is used to determine the relationship between the different factors affecting a process and the output of that process. Analysis of	[35]

Title of the research	Author and Year	Model utilized	Variables taken	Findings	References
			the type of experimental plan that was chosen	variance (ANOVA) is a common method used to compare the relative strength of two related models	
Response surface modeling of lead (II) removal by graphene oxide-Fe3O4 nanocomposite using a central composite design	Khazaei Mohammad et al. (2016)	CCD, RSM (Response Surface Methodology)	4 independent variables: initial pH of Solution, nanocomposite dosage, contact time, initial lead ion concentration	Quadratic and reduced models were examined to correlate the variables with the removal efficiency of Magnetic Graphene Oxide. According to ANOVA, influential factors were pH and contact time.	[36]
Optimization of ferulic acid production from banana stem waste using central composite design	Sharif Nurul Shareena Aqmar Mohd (2017)	CCD, RSM (Response Surface Methodology)	Ratio of water to Banana stem waste (BSW), incubation time (hrs)	The RSM-CCD method optimize the hydrolysis conditions for maximum ferulic acid production. Hence, B.S.W. is proven useful and highly feasible for producing good quality natural products.	[37]
Central Composite Design Optimization of Zinc Removal from Contaminated Soil, Using Citric Acid as Biodegradable Chelant	Asadzadeh Farrokh et al. (2018)	CCD, RSM.	Citric acid concentration, pH, washing time	RSM based CCD is a promising tool for modeling and optimizing Zn removal from the contaminated soil using citric acid. It was found that pH and citric acid conc. Are the significant parameters in Zn removal process.	[38]
Removal of reactive red-198 dye using chitosan as an adsorbent: Optimization by Central composite design coupled with response surface methodology	Haffad Hassan et al. (2019)	C.C.D., Langmuir isotherm model, pseudo-second-order equation	pH, Concentration, temperature	Chitosan material based shrimp cells have countless opportunities in use of waste water treatment. The major effect is played by pH	[39]

Title of the research	Author and Year	Model utilized	Variables taken	Findings	References
Mixture optimization of high-strength blended concrete using central composite design	Hassan Wan Nur Firdaus Wan et al. (2020)	CCD, RSM.	Micro and Nano Palm Oil Fuel Ash (POFA.)	Mixture optimization of high-strength blended concrete using central composite Design, Run 1, containing 10% micro POFA and 2% nano POFA, showed the highest flexural strength	[40]

Table 5.
Examples of CC demployed for the optimization.

7. Case study-1

As per S. Bhattacharya., (2020) studies [41] varius independent variables viz., entrapment efficacy percentage, zeta potential, particle size, percentage of calmative drug release of a polymeric nanoparticle formulation was evaluated and optimized using central composite design (CCD); which was interpreted by Design Expert (Stat-Ease; version 11.0) software. Upon considering the alpha point at 1.68179, in this 21 baches experimental design, 4 factors, and 2 levels were considered **(Table 6)**. Based on the optimization surface plot batch with desired particle size, zeta potential, cumulative drug release (%) entrapment efficacy (%) were selected for further characterization studies. **Table 7** indicating critical quality attributes and necessary process attributes that affect the outcomes of the nanoparticles. By using polynomial equations and a 3-dimensional surface plot, the

S. No	Factors	Low Value	High Value
1	Homogenization speed (rpm)	10000	15000
2	**Homogenization Time (min)**	10	15
3	Surfactant Concentration (%)	1	1.25
4	Polymer concentration (mg/mL)	3	6

Table 6.
Critical process parameters that influence various critical quality attributes.

S. No	Critical Quality Attributes	Desired constrained
1	Particle Size (nm)	Finest
2	Zeta Potential (mV)	Finest
3	Cumulative drug release (%)	Moderately high
4	Entrapment efficacy (%)	Supreme

Table 7.
Desired construction of critical quality attributes.

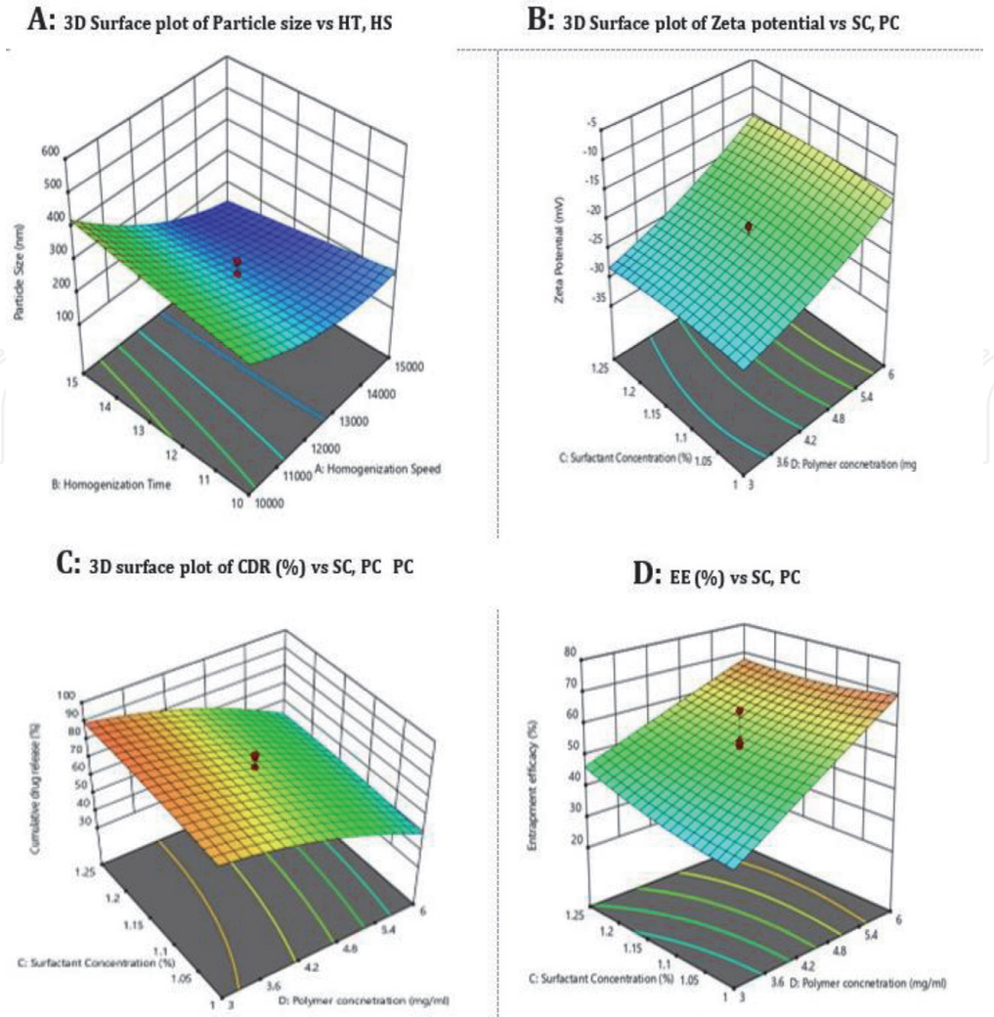


Figure 7.
(A-D) represents the surface plot identifying the effects of critical process parameters on essential attributes of quality.

effects of critical process parameters on essential attributes of quality were examined **Figure 7.**

From this CCDmodel, the following polynomial equations can be derived:

$$\begin{aligned}\textbf{Particle Size}\ (\textbf{nm}) = {} & 236.054 - 101.38A - 3.6663B - 8.85986C + 0.594604D \\ & - 40.7804AB - 24.375AC - 16.375AD + 2.625BC \\ & - 30.2549BD - 18.375CD + 45.2505\,A^2 + 1.23307B^2 \\ & + 11.1326C^2 + 0.879517D^2\end{aligned} \tag{6}$$

$$\begin{aligned}\textbf{Zeta Potential}\ (\textbf{mV}) = {} & -21.8583 + 1.11191A - 0.772985B - 0.19847C + 6.18685D \\ & - 1.42565AB + 0.77AC - 0.242985AD - 1.0125BC \\ & + 0.829409BD + 0.385CD - 0.644786A^2 - 1.44735\,B^2 \\ & - 0.805653C^2 + 1.23081D^2\end{aligned} \tag{7}$$

$$\begin{aligned}&\textbf{Cumulative drug release}\ (\%)\ \textbf{at}\ 80^{\textbf{th}}\ \textbf{hours} \\ &= 75.2947 + 2.52409A - 1.66192B + 2.1758C - 17.5081D + 2.73315AB \\ &\quad - 0.65625AC - 0.605667AD + 0.71625BC + 2.56284BD - 0.4687\,CD \\ &\quad + 0.534547A^2 - 1.0918\,B^2 - 1.11301C^2 - 5.01271\,D^2\end{aligned} \tag{8}$$

$$\textbf{Entrapment efficacy}\ (\%) = 53.323 + 0.184327A + 3.54978B + 2.29125C + 14.0832D + 5.83819AB + 1.2475AC + 1.6522AD + 3.1875BC - 4.10817BD - 3.25CD + 2.30194A^2 + 0.088697\ B^2 + 1.78045C^2 - 0.192378\ D^2 \quad (9)$$

By considering A as homogenization speed, B as homogenization time, C as surfacetant concentration (%) and D as polymeric concentration; respectively, the polynomial Eqs. 6,7,8, & 9 can be interpreted. From these polynomial equations, critical process parameters of qualifiable effects on essential attributes can be determined. It can easily predict from the polynomial Eq. 6, that particle size of the polymeric nanoparticles can be increased, when homogenization time & speed and surfactant concentration decrease. The elevated negative co-efficient in homogenization speed of polynomial Eq. 6, indicates it has a significant influence on particle size. Higher shearing stress during elevated homogenization time & speed could lead to mass transfer between the particles, ultimately resulting in nucleation and smaller particle size. From Eq. 7, it can be predict that homogenization time & surfactant concentration has antagonistic effects on zeta potential and homogenization speed has an agonistic effect on zeta potential. In a similar fashion equation, 8 shows homogenization speed & surfactant concentration has an agonistic effect on cumulative drug release (%) at 80th hours. From Eq. 9 it was clear that entrapment efficacy (%) increases with increases of homogenization speed, homogenization time & surfactant concentration.

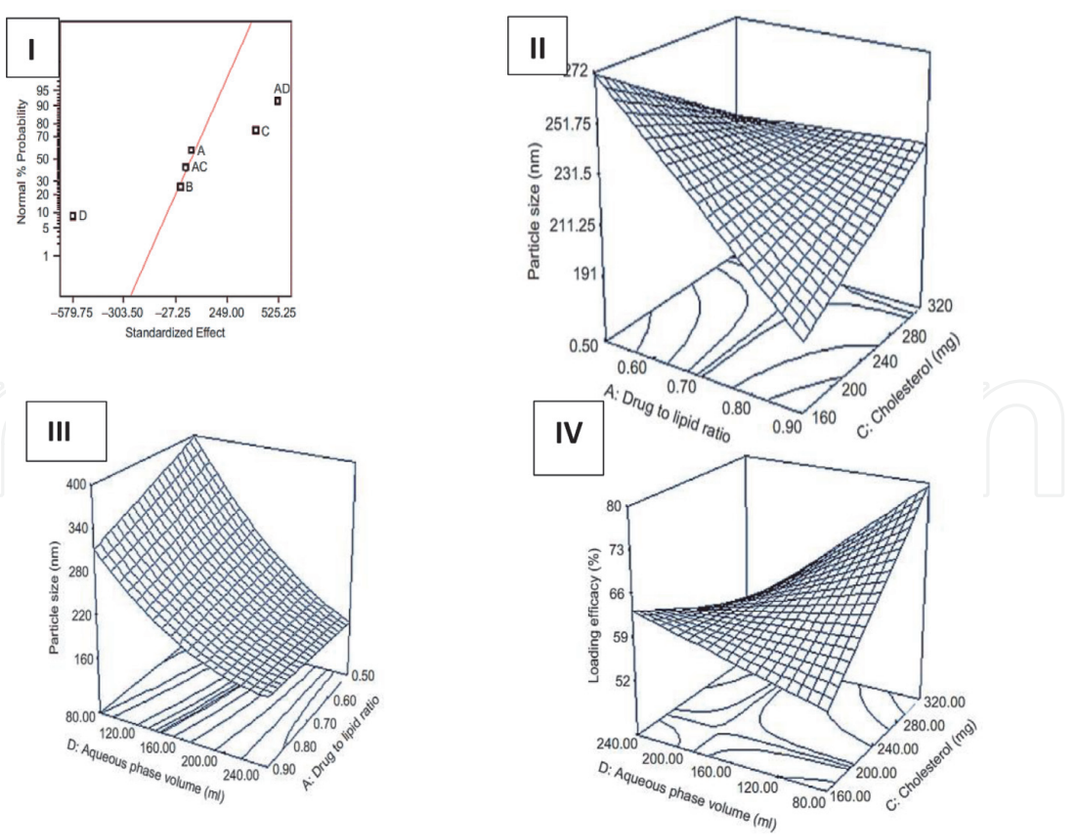


Figure 8.
(I) *Normal probability plot for broadcast, the most critical variables are influencing the particle size. The ratio of drug to lipid (a), surfactant type (B), amount of lipid phase (C), and volume of aqueous phase (D).* ***(II)*** *the effect of drug-to-lipid ratio (a) and amount of cholesterol (C) on particle size.* ***(III)*** *the effect of drug-to-lipid ratio (a) aqueous-phase volume (D) on particle size.* ***(IV)*** *the impact of aqueous-phase volume (D) and the amount of cholesterol (C) on loading efficacy(%).*

8. Case study 2

As per Jaleh Varshosaz *et al. (*2010) [42] research, amikacin solid lipid nanoparticles can be prepared by using a central composite design. In this research, central composite design (CCD) was utilized to identify a suitable formula with minimum particle size; where, three independent variables were considered, i.e., the ratio of drug to lipid (A), amount of lipid phase (B), the volume of aqueous phase (D). The alpha value of the experiment was found to be −1.682; the alpha value helps in determining rotatability and orthogonality within this design. In this experiment, a total of 20 experimental designs have been incepted, along with 8 factorial points and 6 axial points were considered. The best-fitted model can be assumed after quadratic model analysis by ANOVA and F-value determination. From the **Figure 8(II&III)** it was clarly evident that, decrease concentration of drug to lipid ratio, aquous phase valume whould certlay decrease particle size; which indicates agonistic effects on particle size, where else, from the **Figure 8(IV),** it was evident that, increase concentration of cholesterol would increases the drug loading capacity. Therfore, by resolving all the polynomial equation obtained from **Figure 8 graph**, it was identified that, at 0.5 drugs to lipid ratio, 314 mg cholesterol, 229 mL of aqueous phase an optimized formulation would possibly be constructed with lower particle size and higher drug loading efficacy (%). Therefore, At these levels of independent variables, predicted amikacin particle size and loading efficiency were calculated to be 153 nm and 86%.

9. Conclusion

This book chapter's main agenda was to enlighten the present approaches and recent optimization research activities based on the CCD model, as specially for pharmaceutical product development. The CCDmodel is useful for modeling and analyzing programs in which the response of interest influences several variables. The CCDmodel can be considered as a robust statistical tool for process optimization. The best part of CCDis, as compared to Plackett–Burman design, a limited number of experiments are required with less computational experience. The biggest challenge of the CCDmodel is finding the critical factor. Central composite designs are beneficial in sequential experiments because you can often build on previous factorial experiments by adding axial and center points.

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Conflict of interest

The author declares that the author has no competing interests.

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