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Selection of a design for response surface

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Abstract: Box-Behnken, Central-Composite, D and I-optimal designs were compared using statistical tools. Experimental trials for all designs were generated. Random uniform responses were simulated for all models. R-square, Akaike and Bayesian Information Criterion for the fitted models were noted. One–way ANOVA and Tukey's multiple comparison test were performed on these parameters. These models were evaluated based on the number of experimental trials generated in addition to the results of the statistical analyses. D-optimal design generated 12 trials in its model, which was lesser in comparison to both Central Composite and Box-Behnken designs. The R-square values of the fitted models were found to possess a statistically significant difference ($P<0.0001$). D-optimal design not only had the highest mean R-square value (0.7231), but also possessed the lowest means for both Akaike and Bayesian Information Criterion. The D-optimal design was recommended for generation of response surfaces, based on the assessment of the above parameters.

1. Introduction

Response surface methodology is a term applied to multivariate techniques that can generate response surfaces and provide optimal solutions for a particular process. Optimizing a process refers to the selection of the parametric conditions such that the response is maximized or minimized. It is carried out by keeping one factor constant while varying the other factors. This process is called a one factor at a time method. It is, however, a very time-consuming process due to the large number of trials involved, along with increased usage of chemicals, thus making it economically expensive. Furthermore, the OFAT method does not consider the interaction effects of the variables influencing the process. Therefore this technique does not give complete information about the response.

As opposed to this method, RSM takes interaction effects into consideration. It consists of a series of mathematical and statistical tools that fit polynomial equations to the experimental data, thus explaining the behavior of the data set. The goal of RSM designs is to optimize many variables simultaneously to achieve optimal performance of the system.

RSM is to be carried out after careful selection of variables that have a major effect on the responses. This can be done using screening experiments such as factorial designs. These first order designs estimate the linear functions of the variables on the output. Curvature is not estimated by these designs. Second-order designs like Central Composite, Box-Behnken as well as Doelhert designs estimate the curvature- interaction of the variables and present it in the form of a quadratic equation [1-3]. Some examples of response surfaces are given in Fig. 1. Another set of designs gives the user an option to choose the equation-linear, quadratic or cubic. Such designs are called optimal designs. This paper discusses two classic response surface designs-Central Composite and Box-Behnken, and optimal designs like D-optimal and I-optimal ones.

In the laboratory, after models are generated using classical RSM designs, the models are fitted after carrying out the experimental trials and feeding the responses in the model. The fitted model may not be significant in the first instance. Thus the experimenter has to perform all the

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experimental trials again or re-design the model, followed by experimentation. Thus constructing a model, performing the trials and getting a good model fit may be a time consuming process.

The aim of the study is to search for a model which has the highest prospective of rendering a good fit, by assigning software- generated random values to the response variable, before fitting the model. The fitted models have then been assessed on various parameters using statistical tools. The response variable in this study is the viscosity of an emulsion. This study takes viscosity of formulated emulsion as an example to determine the best model. To the best of the authors' knowledge, this approach for selecting models for generating response surfaces has not been done previously.

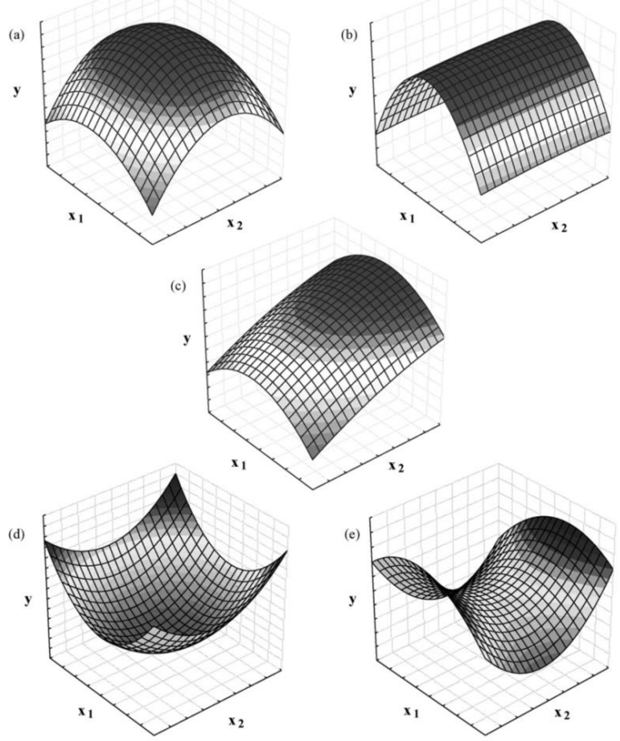

Figure 1. Response surface profiles generated after optimization of two variables using a quadratic model (a) maximum, (b) plateau, (c) maximum outside the experimental region, (d) minimum, and (e) saddle surfaces [3].

1.1 Central Composite Design

Box and Wilson presented the Central Composite Design in 1951. CCD consists of three types of designs-circumscribed, inscribed and face-centered (Fig. 2). CCC involves factorial points, center points as well as star points. Star points represent the extreme values of the variables. The distance between the center point and factorial point is ±1; between center point and star point is α. For CCD, α is greater than 1. For the CCI design type, the star points take the specified limit values of the variables. The factorial points lie within the variable limits. The star points and factorial points are located at a distance of ±1 from the center point for the FCC design and therefore, α is equal to 1.The number of experiments in CCD is calculated using the formula $N = k2 +2k+cp$ where k is the number of variables and cp is the number of replicates for the centre point. The α value is determined by using the equation $\alpha=2(k-p)/4$. The α value depends on the number of variables. It is 1.41, 1.68, and 2.00 for 2, 3 and 4 variables respectively. Another important aspect of CCD is that five factor levels are considered while constructing the design -α,-1,0,+1 and +α. Representations of two and three- factor optimizations carried out using central composite designs are shown in Fig. 3(a-b) [3,4]. CCD has been used for the optimization in the field of biology and analytical chemistry [5-9].

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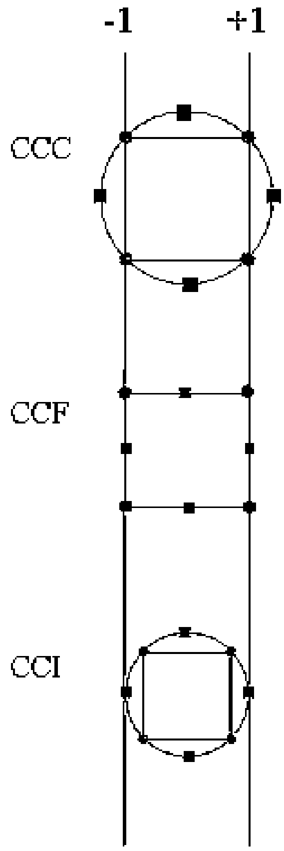

Figure 2. Types of central composite designs CCC- circumscribed, CCF- face-centered and CCI-inscribed [4]

1.2 Box-Behnken Design

George Box and Donald Behnken devised the Box and Behnken design in 1960. This design takes the midpoints of the edges of the process space and the centre point into consideration while constructing the design (Fig. 4). BB designs take three equally spaced levels *viz.*,-1, 0 and +1, of the factors into consideration. These designs are more economical as compared to other 3k designs due to the reduced number of experimental trials in the design. The number of experimental trials is computed using the formula; N= 2k (k−1) + cp where N is the number of trials, k is the number of factors and cp is the number of replicates for the centre points. All the experimental points are present in the form of a hypersphere and are placed equidistant from the central point. Fig.4 represents a three factor Box-Behnken design [3,4]. Such designs have been used in optimization studies involving enzyme assays, emulsion formation, etc. [10-14].

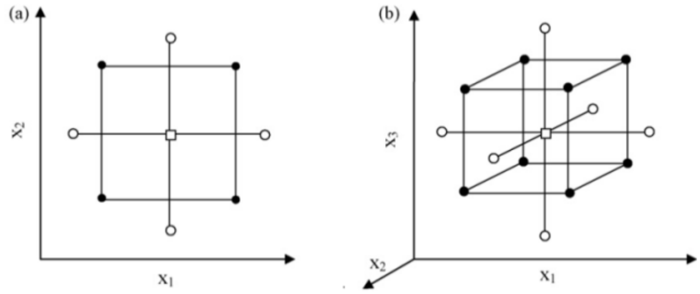

Figure 3. Representation of a (a) two and (b) three-factor optimizations using central composite designs (●) Points of factorial design, (○) axial points and (□) central point [3].

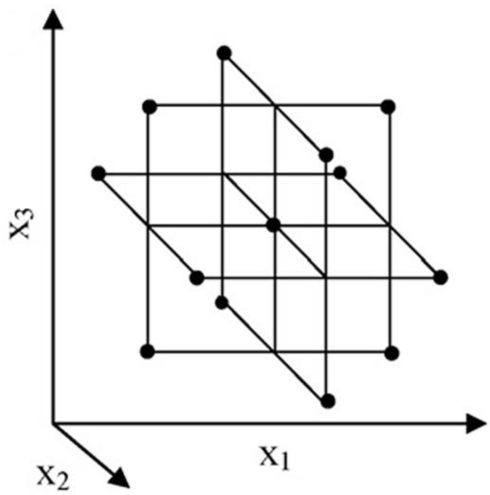

Figure 4. Three factor Box-Behnken design

1.3 Optimal Designs

Such designs like the D and I ones are generated based on computer algorithms and called computer-aided designs. They are not orthogonal like classic RSM types. The effects of the variables are correlated in these designs. The main advantage here is that it can be used to fit any type of model (first and second orders, quadratic, cubic) or for any particular research objective like screening or generating a response surface. Besides this, optimal designs afford lesser number of experimental trials than classic types and provide a constrained design space. The D and I in optimal designs stand for determinant and integrated respectively. D is an optimality criterion that maximizes the determinant of the information matrix XX of the design. I-optimality is a criterion that reduces the estimated variance over the design space. Optimal designs, particularly D-optimal ones have been mainly used in the field of pharmaceutical chemistry for the formulation of emulsions [15, 16].

2. Materials and methods

One of the latest statistical software-JMP 12 (SW), was chosen for generating response surfaces using Box-Behnken (BB), Central Composite and Optimal Designs-D and I. Randomized trials were generated for five variables, viz., amounts of grapeseed oil, surfactant and water, all in grams, HLB value of surfactant and viscosity of grape seed oil in cP. Grapeseed oil is a vegetable oil chosen for this study due diverse applications [17-19].

Grapeseed oil emulsions find applications in many fields. GSOE have been used in the as nutraceutical delivery systems as well as in the formulation of vaccines, to mention a few [20, 21]. GSO amount was kept constant at 2.5 g. The S variable was allotted discrete values, viz., 0.5, 1.0, 1.5, 2.0 and 2.5 g for optimal designs. It was taken as a continuous variable ranging from 0.5-2.5 g for CCD and BB designs due to the unavailability of the discrete numeric option for the variables, in case of these designs. W was provided continuous values varying from 95 to 97 g. The mixture of variables GSO, S and W totaled to 100 g. The factors, HS and VGSO were kept constant at 7 and 43.84 cP respectively. The required HLB value of grapeseed oil is 7. Therefore the HS variable was assigned a value of 7. The value of HS can be changed according the oil HLB requirement and surfactant used. The viscosity of grapeseed oil was measured using an Ostwald viscometer and found to be 43.83 cP. Hence, this value has been set for factor VGSO. The designs were generated for 3 center points and 3 replicates. Random responses for a specified range of values were generated using the random uniform function in JMP 12 (SW) software. The JMP 12 (SW) software uses the Mersenne-Twister technique for generation of pseudo random numbers. Responses of the resulting emulsion were generated for 5 different ranges of viscosity values, viz., 100-10,000 cP, 10,000-20,000 cP, 20,000-30,000 cP, 30,000-40,000 cP and 40,000-50,000 cP. The responses were labelled as VGSOE. Literature survey has revealed that the viscosities of marketed emulsion products range between 10,000-70,000 cP [22] (For this study, the viscosity range of the formulated emulsion was chosen to be between 100-50,000 cP. Thus the above-mentioned response ranges were selected). Numbers which do not possess a particular pattern are random. Hence they provide an equal probability for the test models to generate a favorable output. For every range of response, 3 designs were generated. Therefore 15 models and responses were generated for one particular type of design. Since 4 types of designs were evaluated, a total of 60 designs were generated. The models were fitted and the R-square values were noted down. The models were considered significant if the R-square value was more than 0.8. The mean of the R-square values was calculated. One-way ANOVA was carried out to check if the difference in R-square values of the fitted models was statistically significant. Furthermore, Tukey's multiple comparison test was carried for the R-square values of the four designs in order to determine the best design. The Akaike Information Criterion and Bayesian Information Criterion values for the fitted models were tabulated and compared using one-way ANOVA and Tukey's multiple comparison test. The choice for the final model was done on the basis of the number of experimental trials generated, R square values of the fitted models, the AICc and BIC values. One-way ANOVA and Tukey's multiple comparison test were carried out using GraphPad Prism Version 7 [23].

3. Results and discussion

The number of trials computed for each design was very dissimilar. Random responses for the generated models were then simulated. It was observed that the optimal designs generated the least number of trials. The mean responses for the D-optimal design are shown in Table 1. After fitting the models, the R-square values were calculated. The standard R-square value for a good model is 0.8 [24]. Only one design, the D-optimal design, with a response range of 20,000-30,000 cP showed an R-square value of 0.8104 (Table 2). All the other designs showed non-significant models. Though majority of the models were non-significant (R-square<0.8), from Table 2, it may be observed that the R-square values for optimal designs (especially D-optimal) are closer to 0.8 in comparison to other designs. One way ANOVA revealed that the R-square values for the fitted models are statistically different. This was substantiated by the fact that the P value was <0.0001 (Table 3). In addition, the D-optimal design displayed the highest mean R-square value in Tukey's multiple comparison test (Table 4).

Table 1. The mean viscosity responses for D-optimal design.

Design Type	**DO**				
Trail No.	Mean responses (cP) for particular viscosity ranges				
	100-10000	10000-20,000	20000-30000	30000-40000	40000-50000
1	3282.126312	12987.98328	24766.45952	31776.1191	45140.29904
2	7083.653559	12908.08582	23875.3863	35246.83638	46028.96651
3	5938.863041	14590.64768	25717.75413	33920.99056	45167.09226
4	2605.326007	15980.82628	25581.6616	34844.03287	45716.01144
5	5438.463239	16994.93662	25294.11439	34089.35363	45303.75468
6	4673.177566	17237.60035	23434.33608	33434.75653	46742.05936
7	6935.140976	15532.5647	26083.73339	34523.549	42121.3013
8	5044.298625	15950.4412	26579.76863	35994.47109	43969.69438
9	7761.132123	14892.17061	22819.46039	37233.62638	43530.41287
10	7155.370042	16739.96276	24744.64698	37735.7158	42815.23066
11	6954.958752	14280.6621	24445.49981	33419.53369	47248.46107
12	5189.018135	14008.6325	24011.30243	35747.58023	47037.58333

Table 2. Table showing the design type, experimental runs and R-square values.

Design Type	**Response range (cP)**	**Computed Experimental runs**	**R-square values**	**R-square (mean)**
BB	**100-10,000**	172	0.0279	0.026733
			0.0434	
			0.0089	
	10,000-20,000	172	0.0036	0.005733
			0.0102	
			0.0034	
	20,000-30,000	172	0.0272	0.022467
			0.0117	
			0.0285	
	30,000-40,000	172	0.0085	0.022227
			0.0183	
			0.03988	

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	40,000-50,000	172	0.016769	0.013997
			0.000792	
			0.02443	
CCD	**100-10,000**	116	0.048971	0.027562
			0.019169	
			0.014545	
	10,000-20,000	116	0.000242	0.004561
			0.004778	
			0.008663	
	20,000-30,000	116	0.016261	0.013268
			0.021135	
			0.002408	
	30,000-40,000	116	0.01682	0.021505
			0.00703	
			0.040664	
	40,000-50,000	116	0.00363	0.002471
			0.00311	
			0.000674	
DO	**100-10,000**	12	0.468749	0.731635
			0.96722	
			0.758937	
	10,000-20,000	12	0.630939	0.741755
			0.733158	
			0.861169	
	20,000-30,000	12	0.761871	0.8104
			0.722006	
			0.947323	
	30,000-40,000	12	0.874898	0.684409
			0.503749	
			0.674581	
	40,000-50,000	12	0.549792	0.647457
			0.543998	
			0.848581	
IO	**100-10,000**	12	0.555297	0.762567
			0.859693	
			0.872711	
	10,000-20,000	12	0.329794	0.521433
			0.735581	
			0.498925	
	20,000-30,000	12	0.811938	0.664764
			0.235847	
			0.946506	

	30,000-40,000	12	0.698037	0.169602
			0.579227	
			0.44805	
	40,000-50,000	12	0.621011	0.680405
			0.799664	
			0.620539	

Table 3. One-way ANOVA results for the R-square values of the fitted models.

ANOVA table	SS[a)]	DF[b)]	MS[c)]	F (DFn, DFd)	P value
Treatment (between columns)	2.022	3	0.6741	F(3,16)= 45.62	P<0.0001
Residual (within columns)	0.2364	16	0.01478		
Total	2.259	19			

a) SS-sum of squares

b) DF-degrees of freedom

c) MS-mean square value

Table 4. Multiple comparison of means of the R-square values of the fitted models.

Tukey's multiple comparison test	Mean 1	Mean 2	Mean Diff.	Significant or not	Adjusted P Value
BB vs. CCD	0.01823	0.01387	0.004358	No	>0.9999
BB vs. DO	0.01823	0.7231	-0.7049	Yes	<0.0001
BB vs. IO	0.01823	0.5598	-0.5415	Yes	<0.0001
CCD vs. DO	0.01387	0.7231	-0.7093	Yes	<0.0001
CCD vs. IO	0.01387	0.5598	-0.5459	Yes	<0.0001
DO vs. IO	0.7231	0.5598	0.1634	No	0.1873

The average AICc and BIC values for the fitted models for each of the response ranges have been displayed in Table 5. The AICc and BIC values for fitted models were used for comparison of different models. The AICc and BIC values represent models having a better likelihood of fit. The likelihood of fitted models is presented in terms of L(β). The higher the value of L(β), the better the fit of the model. The parameters in a model attempt to maximize the function of L(β). Instead, it is easier to assess the fit of the model using the negative natural logarithm of the likelihood function. Since, the AICc and BIC values depend on the negative natural logarithm of likelihood, the model displaying the least AICc and BIC values, is considered the best model [25-27]. They are calculated using the formulae:

$$AICc = -2LogLikelihood + 2k + 2k(k+1)/(n-k-1)$$
$$BIC = -2LogLikelihood + kln(n)$$

Where ‘k’ is the number of parameters for a given model and ‘n’ is the number of observations.

Table 5a. Average values for response ranges of fitted models (a) AICc

Response range	**AICc**			
	BB	CCD	DO	IO
100-10,000	3229.014	2181.823	398.2725	395.3405
10,000-20,000	3230.241	2180.886	356.8737	318.3962
20,000-30,000	3222.581	2183.633	308.3722	353.7673
30,000-40,000	3230.355	2180.279	359.7494	360.2296
40,000-50,000	3237.343	2189.195	321.5262	361.4628

Table 5 (b) Average values for response ranges of fitted models BIC

Response range	**BIC**			
	BB	CCD	DO	IO
100-10,000	3241.364	2192.477	226.2933	223.3612
10,000-20,000	3242.592	2191.54	228.0662	232.7604
20,000-30,000	3234.931	2194.287	222.7364	224.9597
30,000-40,000	3242.706	2190.933	230.9418	231.4221
40,000-50,000	3249.694	2199.849	235.8903	232.6553

Statistical analyses were performed using the average AICc and BIC values of the fitted models. One-way ANOVA results indicated that there was a statistically significant difference for

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both, the AICc and BIC values of the fitted models of the four designs. Further, Tukey's multiple comparison test for AICc and BIC values of the fitted models for the four designs revealed that the D-optimal design displayed the lowest mean for both values. The results of the one-way ANOVA Tukey's multiple comparison test have been tabulated in Tables 6-9.

4. Conclusion

Based the number of trials, the R-square values, the AICc and BIC values of the fitted models, the D-optimal design can be considered as the best design for generation of response surfaces. The D-optimal design is a CAD design which sequentially adds and deletes points from a design to select an optimal combination of treatments from a set of possible runs for the experiment. Since the D-optimality criterion reduces the number of trials and the AICc and BIC values depend on the number of trials in a model, the D-optimal design has lower AICc and BIC values compared to BB and CCD designs. Though the I–optimal design has generated the same number of trials as the D-optimal design, the two designs differ slightly in their likelihood function, which in turn depends on the probability density functions. The probability density functions are calculated based on the observed data.

Since the AICc and BIC values of D-optimal design are slightly lower than the I-optimal design, it is the preferred model for generating response surfaces.

Table 6. Tables showing One-way ANOVA results for AICc.

ANOVA table	**SS[a)]**	**DF[b)]**	**MS[c)]**	**F (DFn, DFd)**	**P value**
Treatment (between column)	30425622	3	10141874	F (3, 16) = 19861	P<0.0001
Residual (within column)	8170	16	510.6		
Total	30433792	19			

a) SS-sum of squares
b) DF-degrees of freedom
c) MS-mean square value

Table 7. Tables showing Tukey's test results for AICc.

Tukey's multiple comparison test	**Mean 1**	**Mean 2**	**Mean Diff.**	**Significant or not**	**Adjusted P Value**

BB vs. CCD	3230	2183	1047	Yes	<0.0 001
BB vs. DO	3230	349	2881	Yes	<0.0 001
BB vs. DI	3230	357. 8	2872	Yes	<0.0 001
CCD vs. DO	2183	349	1834	Yes	<0.0 001
CCD vs. DI	2183	357. 8	1825	Yes	<0.0 001
DO vs. DI	349	357. 8	- 8.88	No	0.92 37

Table 8. Tables showing One-way ANOVA result for BIC

ANOVA table	**SS[a)]**	**DF[b)]**	**MS[c)]**	**F (DFn, DFd)**	**P value**
Treatment (between column)	33726874	3	11242291	F (3, 16) = 526070	P<0.0001
Residual (within column)	341.9	16	21.37		
Total	33727216	19			

a) SS-sum of squares
b) DF-degrees of freedom
c) MS-mean square value

Table 9. Tables showing Tukey's test result for BIC

Tukey's multiple compariso	**Mean 1**	**Mean 2**	**Mean Diff.**	**Significant or not**	**Adjusted P Value**

n test					
BB vs. CCD	3242	2194	1048	Yes	<0.0001
BB vs. DO	3242	228.8	3013	Yes	<0.0001
BB vs. DI	3242	229	3013	Yes	<0.0001
CCD vs. DO	2194	228.8	1965	Yes	<0.0001
CCD vs. DI	2194	229	1965	Yes	<0.0001
DO vs. DI	228.8	229	-0.2461	No	0.9998

5. List of Abbreviations

AICc-Akaike Information Criterion
BB- Box-Bhenken
BIC- Bayesian Information Criterion
CAD-Computer-aided design
cP- centipoise
CCC- Central Composite-circumscribed
CCD- Central Composite Design
CCI- Central Composite-inscribed
CCF- Central Composite-face centered
DO- D-optimal design
GSO- Grapeseed oil
IO- I-optimal design
OFAT- One factor at a time
RSM- Response surface methodology
S- Surfactant
W- Water
HS- HLB value of surfactant
VGSO- Viscosity of grapeseed oil
VGSOE- Viscosity of grapeseed oil emulsion

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