Application of Box-Behnken Method for Optimization and Modeling of 1,5 – Benzodiazepine Production Reaction by $CuFe_2O_4$/Clinoptilolite Nanocatalyst

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ABSTRACT

In this study, the Box-Behnken design (BBD) was used in the response surface method (RSM) to investigate the modeling and optimization parameters in the synthesis of a 1,5-Benzodiazepine. This method was used to optimize the influencing factors in the synthesis process of this material, including the amount of nanocatalyst, temperature, and reaction time. The obtained mathematical model was analyzed by variance analysis. To determine the optimal conditions, graphs of graphic counters and response levels were used. The results showed that the amount of nanocatalyst has the greatest effect on the synthesis reaction of 1.5 Benzodiazepines. The maximum efficiency for the synthesis of the product was determined at a temperature of 283 K, the amount of $CuFe_2O_4$/Clinoptilolite = 6 g/lr and time = 60 minutes.

1 Introduction

Optimizing processes reduces costs and increases productivity. Recently, response surface method (RSM) is a mathematical and statistical technique used for modeling and optimization of various processes such as removal of organic and many dyes from different wastewater by different process [1-4]. The Box-Behnken Design (BBD) in RSM is an important design, implement used for optimization of processes. BBD prepares comprehensive results and detailed

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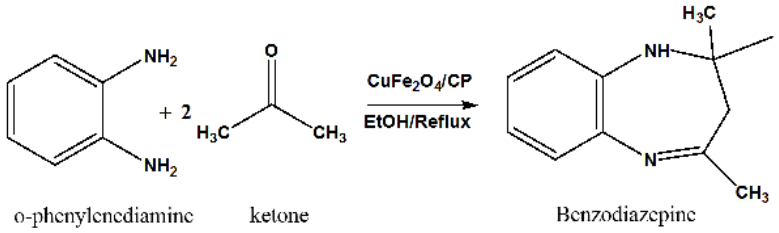
information even for a smaller number of experiments and positive influences of operating parameters on all responses [5]. The main goal of this study is to optimize the catalytic production of one 1,5 Benzodiazopin. In current research, a novel $CuFe_2O_4$ nancatalyst supported on Clinoptilolite was used for synthesis of 1,5 Benzodiazepin. A Box–Behnken design was selected to study the effects of operational parameter such as temperature, reaction time, and amount of nanocatalyst on the efficiency of the synthesis process.

2 Experimental Procedure

Procedure for the synthesis of Benzodiazepine

The reaction of o-phenylenediamine with ketone (Acetone) in the presence of $CuFe_2O_4$/CP as a new catalyst for the synthesis of a sample of Benzodiazepine (Schem 1) was optimized and modeled by Box-Behnken method.



Schem1: The reaction of o-phenylenediamine with ketone

Different amount of $CuFe_2O_4$/CP was added to a mixture of OPDA (0.1 mol), a ketone (0.2 mol), and 10 ml of ethanol (EtOH). This mixture was stirred at different temperature. Upon completion of the reaction, $CuFe_2O_4$/CP was easily separated from the mixture by an external magnetic field. The reaction products were recrystallized in EtOH. The amount of product determined by HPLC (High Performance Liquid Chromatography) analytical method.

Results of these experiments used for Box-Behnken experimental design. The reaction efficiency for Benzodiazepine production was calculated using the equation (1):

$$Y = \frac{Experimental\ value}{Theoretical\ value} \times 100 \qquad (1)$$

Where Y (%) is reaction efficiency, the experimental value was determined based on HPLC results and the theoretical value was determined based on the stoichiometry of the reaction.

3 Results and discussion

In this study, the aim at the optimization was to find conditions that gave the maximum yield. Box–Behnken a design was also identified the relationship between the controllable input parameters and the response variable. Three variables, including temperature (X_1), time (X_2), and nanocatalyst concentration (X_3) are responsible to change the reaction yield. A three factor, 3 levels in a Box–Behnken design was created and three levels were promised and encoded by (–1,

0, +1). The Box–Behnken is a high-quality design in the sense that it could be fitted in the Quadratic model.

In the current experiments,the effects of three independent variables on response performance a nd optimal conditions were investigated by engaging with BBD and RSM [6,7]. Among all RSM designs, Box–Behnken design requires fewer runs (for example 15 runs at three-parameter experimental design) and lets calculations of the response function at intermediate levels and provides estimation of the method efficiency at any experimental point within the range studied through careful analysis [8]. In this study, the optimization of experimental conditions for production of Benzodiazepine was studied using Box–Behnken method of RSM. In order to calculate the influence of operating parameters on this reaction, three main factors and three levels for each one was chosen: Temperature (°C) (X_1), Reaction time (min) (X_2), and nanocatalyst concentration (g/L) (X_3) as shown in Table 3. Each variable was studied at three levels the low (-1), medium (0) and high (+1). With statistical analysis of the obtained experimental data, a second-order polynomial equation (2) was achieved as an empirical model that describes the response surface. The behavior of the system is clarified by the following quadratic equation [9]:

$$Y = \beta_0 + \sum \beta_i X_i + \sum \beta_{ii} {X_i}^2 + \sum \beta_{ij} X_i X_j, \quad (2)$$

Where Y is the response (reaction efficiency), β_0 , β_i, β_{ii} and β_{ij} are coefficients of the intercept, linear, square and interaction effects, respectively. The optimum response and also the process parameters were also determined. Test of F in the ANOVA analysis is used for evaluating model variance in residual variance. The variance is almost identical, this ratio is almost one, which indicates that the probability that each of the factors has a significant effect on the response. The statistical significance of the model and the coefficient was analyzed by means of F-test and P-value, respectively [10]. In the present study, the Benzodiazepine synthesis process was investigated to treat with different operating conditions such as temperature (30–90°C), nanocatalyst amount (1.2–6g/L), reaction time (20–60 min), these effective variables in the synthesis process and their levels are given in Table 1. The number of experiments (n) needed for the development of BBD is defined as:

$$n = 2k\,(k\,-1) + C_0 \quad (3)$$

Where K is the number of factors and C_0 is the number of repeated central points. Three factors and three levels (for each factor) of BBD were occupied to optimize and check the effect of operation variables on the responses.

Table 1: Experimental variables and levels

Variables	Range and levels		
	Level 1(-1)	Level 2(0)	Level 3(+1)
Temperature (°C), (X_1)	30	60	90
Time (min), (X_2)	20	40	60
Amount of catalyst (g/L), (X_3)	1.2	3.6	6

A Box-Behnken design was selected to study the effects of three influencing variables on the response (reaction efficiency). The reward using of Box–Behnken designs to include the fact that they are all spherical designs and require factors to be run at only three levels. Some of these designs also provide orthogonal blocking and if separate runs, need into blocks the Box–Behnken design, designs are available that let blocks be used in such a way that the approximation of the regression parameters for the factor influences are not affected by the blocks [10]. In all 15 runs the experiments were conducted in triplicate and all results attained from the Box–Behnken design is summarized in Table 2. The observed values and predicted response value with residuals for the runs are shown in Table 4. It shows the experimental results of production of Benzodiazepine versus model results. The tip collections of the diagonal line demonstrate that the difference between the experimental and predicted values was less and good fit of the model is obtained.

Table 2: Coded factor levels for a Box-Behnken design of a three-variable system

		Actual values			Reaction efficiency (%)		
Observation Run	X_1	X_2	X_3		$Y_{Experimental}$	$Y_{Predicted}$	Residual
1	30	20	3.6		53.000	52.957	0.043
2	90	20	3.6		51.350	51.229	0.121
3	10	60	3.6		53.280	53.314	-0.034
4	90	60	3.6		51.280	51.587	-0.307
5	10	40	1.2		38.660	38.741	-0.081
6	90	40	1.2		39.000	37.014	-0.014
7	10	40	6		97.800	97.806	-0.006
8	90	40	6		96.200	96.079	0.121
9	60	20	1.2		38.480	38.559	-0.079
10	60	60	1.2		37.370	37.196	0.174
11	60	20	6		95.720	95.904	-0.184
12	60	60	6		98.050	97.981	0.069
13	60	40	3.6		52.540	52.272	0.268
14	60	40	3.6		52.170	52.272	-0.102
15	60	40	3.6		52.281	52.272	0.009

All 15 runs were performed and used to build a mathematical model to describe the process, and the design matrix along with the experimental results are presented in Table 2. It was found that the relationship between reaction yields and the three operating parameters (i.e., temperature, Amount of catalyst and Time) was fitted to a second order polynomial equation. The predicted values of the efficiency were obtained from quadratic model fitting techniques for the reaction efficiency (%) using the software minitab17. The response functions (with the determined coefficients) for reaction efficiency are presented by equation (4). The ANOVA analysis indicates a linear relationship between the main effects of the amount of nanocatalyst, temperature and time. The final mathematical equation in terms of the actual factors (confidence surface above 95%) as determined by Minitab software 17 is given below:

$$Y = 45.984 - 0.08637x_1 - 0.05556x_2 - 7.33x_3 + 2.6282{x_3}^2 + 0.01792x_2 \times x_3 \quad (4)$$

The model equation shows that the amount of nanocatalyst has a significant synergistic effect (p-value=0.0001) on the percentage of reaction efficiency.
The effect of three independent variables (X_1, X_2 and X_3) on the reaction efficiency was performed using analysis of variance (ANOVA). The final equation was modified to include only significant parameters (p-value <0.05). The model was analyzed using analysis of variance (Table 5). The adjusted R^2 calculates the amount of variation explained by the form after adjusting to the number of parameters in it. The high value of R^2-adjusted designates the high fitness of the model [11]. The ANOVA was also conducted for each answer and the results are presented in Table 3, demonstrating the fact that the predictability of the model is at 95% of confidence surface. Response functions predictions are consistent with experimental data (R^2 = 99.95).

Table 3: AVOVA results for response function

Source	SS	DF	MS	F-value	P-value	Remarks
Model	7842.11	5	1568.42	48586.56	0.0001	Significant
Linear	6883.57	3	2327.86	72112.38	0.0001	Significant
X_1	5.97	1	5.97	184.89	0.0001	Significant
X_2	0.26	1	0.26	7.92	0.02	Significant
X_3	6977.35	1	6977.35	216144.34	0.0001	Significant
Square	855.58	1	855.58	26504.02	0.0001	Significant
x_3^2	855.58	1	855.58	26504.02	0.0001	Significant
2-Way Interaction	2.96	1	2.96	91.65	0.0001	Significant
$X_2 \times X_3$	2.96	1	2.96	91.65	0.0001	Significant
Error	0.29	9	0.03			
Lack-of-Fit	0.22	7	0.03	0.8	0.632	
Pure Error	0.07	2	0.04			
Total	7842.4	14				

R^2=0.9995Adjusted R^2=0.9997 Predict R^2=0.9992

4 Accuracy of the Model

The analysis of variance tests is a usual statistical method of the different fields. The analysis of variance provides a statistical process that determines the means of several groups are equal or not. F-value, is used to test the significance of the model, individual variables and their interactions [12,13]. The P-value used to check the significance of the coefficient and P-value < 0.05 shows that the model is significant and higher than 5% model is not significant. The results were analyzed using the analysis of variance a regression model, the coefficient of determination (R^2), adjusted R-square, Statistical-diagnostic and response plots. The F-value (48586.56) indirectly suggests that the model is significant. In addition, the P-value of the model is less than 0.05, that it is a significant and eligible model. The large value of F indicates that most of the

variation in the response can be demonstrated by the regression equation in the equation (4). The analysis of variance in Table 3, Indicates that the second-order polynomial model in term equation (4) was statistically significant and adequate to represent the actual relationship between the efficiency and the significant variables, with a very small P-value (0.0001) and (R^2 =0.9995). The positive coefficient of the term, X1, indicates that the amount of catalyst is pertaining to a synergy influence on the oxidation efficiency (p-value < 0.0001). The ANOVA results also revealed the synergy effect of the amount of catalyst on the oxidation efficiency (p-value < 0.0001).

5 Diagnostics of Model Adequacy

The natural probability graph is a graphical material that Fig.1 (a) shows that the remainder of the response is normally distributed. As is evident in Fig.1 (a), the obtained point consistently appears on a linear relationship and has indicated that the random error was independently and normally distributed. The results demonstrated that the model applied to the data was significant and sufficient to represent the relationship between the response and the independent variables. Summary of the ANOVA results is shown in (Table 3). Histogram of Fig.1 (b) and fitted to value Fig.1(c) shows that the classification of data is normal.

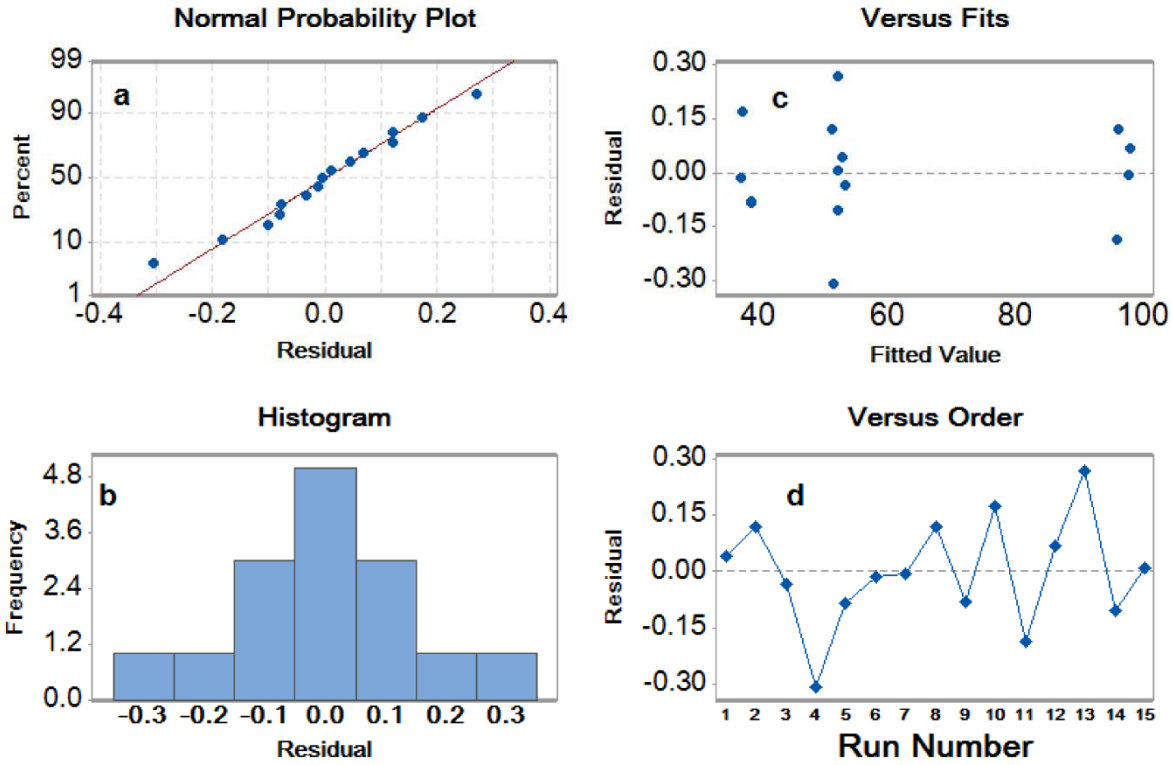


Fig. 1: Diagnostic plots for the Box–Behnken model adequacy (a) normal probability plot of residuals (b) Histogram (c) residual versus fitted values and (d) Residual versus run the numbers.

The residuals were analyzed to determine the accuracy of the model. To recognize the validity of the prediction, the predicted values of efficiency were compared with experimental and they are presented in Fig.2. These results show that the predicted and experimental values are in a good agreement as painted by all points arranged to the diagonal line. The coefficient of the regression model (R^2) was 0.9995, which indicated that the regression model was statistically significant. Moreover, the R^2-Adj value was 99.97%, indicating a high degree of correlation between the experimental and predicted efficiencies.

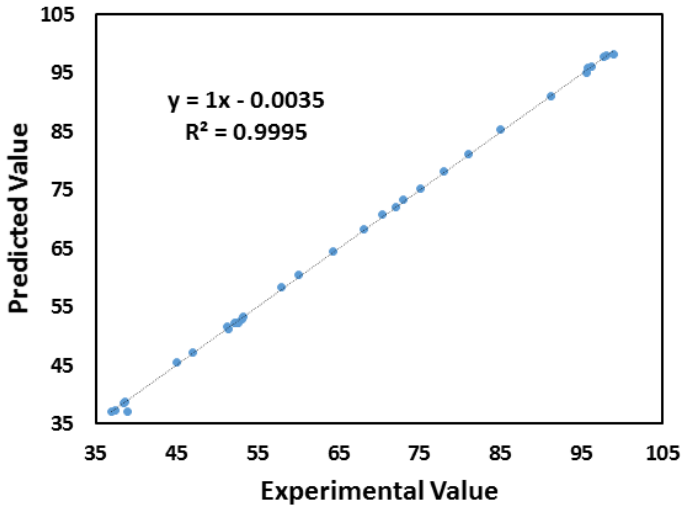


Fig. 2: Experimental and predicted plots using Box–Behnken design.

According to the resulted, the model in equation (4) showed that the time had no significant effect on the reaction product. These observations are not surprising, and in fact, matches the results at once at a time [14].

6 Three-Dimensional Response Surfaces and Contour Plots

Response surface plots and Contour plots and are useful for the model equation and recognizing the character of response surface. A simple examination of the effect of experimental variables on responses is 3D response levels and corresponding contrast components [15].
The resulted surface response 3D plots of efficiency as a function of two independent variables are shown in Fig.3. Fig.3 (a) and Fig.3 (b) depicts the interaction of each two variables by keeping the other at its central level for reaction product thus equation (4) is used to be drawing the plots. The common interaction between temperature and nanocatalyst amount on the reaction efficiency can be best understand from the response surface contour diagram (Fig. 2(a)), which indicates that reaction efficiency directly related to nanocatalyst amount.

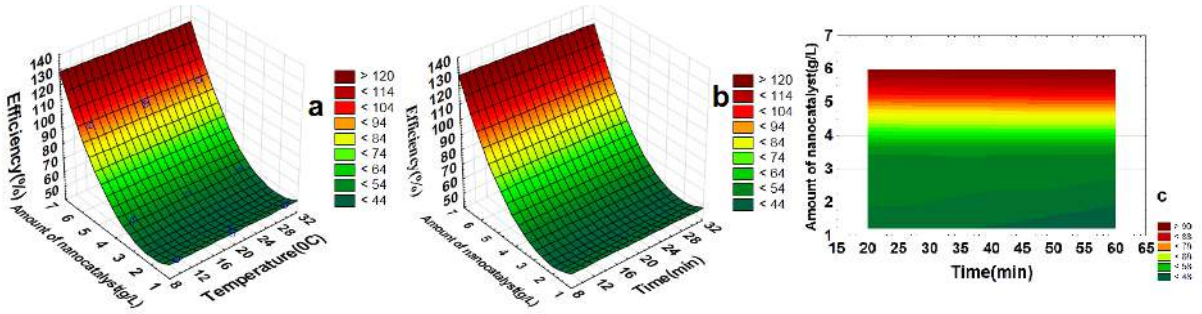


Fig. 3: Response surface plots for the Box–Behnken design: (a) 3D plot of efficiency vs. Amount of nanocatalyst and temperature, (b) 3D plot of efficiency vs. Amount of nanocatalyst and time, (c). 3D wafer plot of amount of nanocatalyst and time. As shown in Fig.3 (a) and Fig.3 (b) efficiency increases with increase in nanocatalyst amount and the temperature (or time) increase is not significant role in increasing the efficiency of reaction. As shown in 3D wafer plot Fig.3 (c), efficiency increases with increasing reaction time and the amount of nanocatalyst.

7 The Interaction Effects of Catalyst Concentration and Reaction Time

The BBD was effectively used to optimize and study the interactive effect of reactants in the surface of nanocatalyst. The contour plot of the influence of the operation parameters on the reaction efficiency is depicted in Fig.4. Contour plots efficiency (%) versus amount of nanocatalyst and contour plot efficiency (%) versus temperature are presented in Fig.4 (a) and 4 (b). It is important to note that Fig.4 (a) represents the evolution of influence amount of nanocatalyst versus time. It can be seen that with the increase in amount of nanocatalyst, the efficiency (%) increases. Fig.4 (b) shows the effect of temperature and time on reaction efficiency (%). It can be seen that with the decrease in Temperature, the reaction efficiency (%) increases, but in conditions the optimum value of 283K.

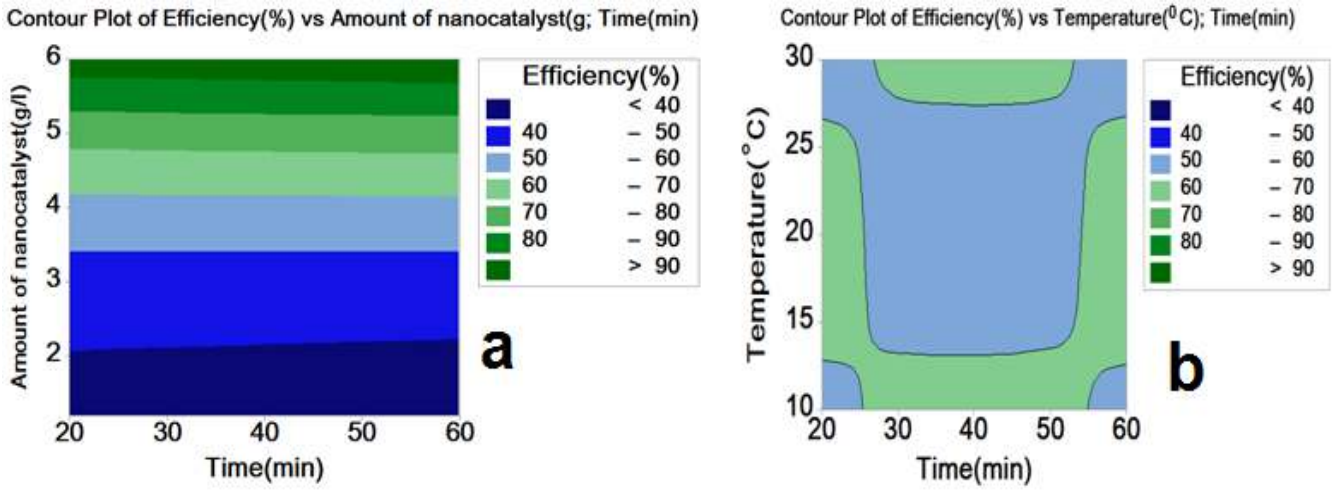


Fig. 4: Contour plot describing for reaction efficiency as a function of amount of nanocatalyst versus temperature.

8 Conclusions

In this research, production of Benzodiazepine was done using $CuFe_2O_4$/CP as nanocatalyst in the low temperature range of 10–30°C. The Box–Behnken design was used to investigate the effect of reaction time, temperature and amount of nanocatalyst on experiments. The synthesis of Benzodiazepine process was optimized with respect to three main parameters; temperature, time, and nanocatalyst amount, using BBD. A second polynomial quadratic was fitted with experimental values (R^2= 0.9995). According to the results, it can be concluded that the application of this reaction has great potential to be economically and industrially. The fitted model is in a good agreement with the experimental data, so a good correlation coefficient for the quadratic model was gained as 0.9995. The statistical design method predicts a maximum conversion to 99% for the optimum values of three process variables, reaction temperature 30°C, nanocatalyst amount 6g/l and reaction time 60 min.

Acknowledgments

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