Chemistry and Technology of Fuels and Oils, Vol. 45, No. 5, 2009

APPLICATION OF PLACKETT-BURMAN EXPERIMENTAL DESIGN TO *tert*-METHYLCYCLOHEXYLATION OF *p*-CHLOROPHENOL

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Plackett–Burman experimental design was applied for screening significant variables influencing the yield of alkylation of p-chlorophenol with methylcyclohexanol in the presence of sulfuric acid. Analyses of the results revealed that temperature, molar ratio of p-chlorophenol to methylcyclohexanol, and amount of sulfuric acid were the main effective variables. The influence of individual effects of these variables and their interactions on experimental response were analyzed by applying fractional factorial design. Finally, a mathematical model was developed to predict the yield of alkylation of p-chlorophenol with methylcyclohexanol in the presence of sulfuric acid under any reaction condition. The experimental yields showed good agreement with the predicted yields calculated by the mathematical model.

Recently, experimental design has earned much attention from scientists because of its successful application in process development. Many research groups have reported the application of design of experiments (DoE) to optimize reactions [1-5]. This approach, which involves the systematic variation of variables over a series of experimental stages, aims to yield the maximum amount of information from the minimum number of experiments, in a rational, statistical fashion. Since a large number of factors are involved in any chemical process, a preliminary screening should be performed. Plackett–Burman design helps to identify the most significant variables for a certain system with only few experiments, but it cannot give the optimum value for each variable [6]. In order to obtain the optimum values for each variable involved in a certain system, a full factorial design is most widely used [7-9]. Recently we reported the development of a mathematical model for alkylation of *m*-cresol with cyclopentene in the presence of benzenesulfonic acid by means of experimental design [10]. Ludwik Synoradzki reported the optimization of alkylation of 2-phthalimidoethanol with ethyl chloroacetate leading to ethyl(2-phthalimidoethoxy)acetate with DoE. [11]

Alkylation of phenol and its derivatives is industrially important because alkylated phenols and their derivatives are effective antioxidants and multifunctional stabilizers in fuels, lubricating oils and polymeric

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Published in revised form in *Khimiya i Tekhnologiya Topliv i Masel*, No.5, pp. 23 – 26, September – October, 2009.

materials [12-15]. Moreover, they have also strong herbicidal, insecticidal and bactericidal activities [16-18].This study aimed at screening variables of tert-methylcyclohexylation of *p*-chlorophenol by Plackett-Burman design and to develop a mathematical model by fractional factorial design.

Alkylation was carried out in a three-necked round bottom flask fitted with a condenser, a thermometer, a dropping funnel and a magnetic stirrer. Methylcyclohexanol was added to a *p*-chlorophenol-sulfuric acid mixture gradually over a certain period of time (addition time t_a) at the desired temperature with constant stirring. The reaction mixture was then stirred at that temperature for an extended period of time (stirring time t_s) and then cooled to room temperature. The reaction mass was dissolved in toluene, neutralized, and washed with distilled water several times. Unconverted reactants and solvent were distilled off at atmospheric pressure. The product was finally distilled and analyzed by spectral means.

Six variables were selected to be examined by Plackett-Burman experimental dsign to investigate their influence on the yield of alkylation of *p*-chlorophenol with methylcyclohexanol. For each variable, a high (+1) and low (-1) level was tested. The variables and their levels are described in Table 1. The yield of 2-*tert*-methylcyclohexyl-4-chlorophenol was considered as the critical response. Since there were six factors, a 12-trial Plackett-Burman design was used. This design had a nominal capacity of 11 factors. Five unassigned factors (X_7 through X_{11}) were used in the computation to measure the experimental error. The stirring rate did not have any significant effect. Therefore, it was not included as a factor and was kept constant at a value of 300 rpm during the experiment. Each experiment was repeated twice and the mean was considered as the response. The main effect of each variable was determined according to the following equation:

$$\boldsymbol{E}_{x_i} = \left(\sum \boldsymbol{M}_{i^+} - \boldsymbol{M}_{i^-}\right)/\boldsymbol{N}$$

where $\boldsymbol{E}_{x_i}$ is the variable main effect, $\boldsymbol{M}_{i^+}$ and $\boldsymbol{M}_{i^-}$ are the response of trials in which the independent variable ($\boldsymbol{x_i}$) was present in high and low level, respectively, and N is the half number of trials.

The Plackett-Burman experimental design and the calculations are illustrated in Table 2. Each of the 12 trials of the design is listed in horizontal lines. The vertical columns X_1 through X_{11} indicate the level of the factor in each trial. In regard to the design, among the 12 trials each factor was at a high (+) level for six trials and at a low (–) level for six trials. The yield for each trial is indicated in the Y column on the right. The Sum+'s and Sum–'s were calculated. Summation of the Sum+'s and Sum–'was done to check the arithmetic. The difference

Table 1

Variable	Code designation	+ Level	–Level
Temperature, °C	X_1	140	80
PCP:MCH	X_2	10:1	3:1
Concentration of sulfuric acid, %	X_3	8	3
Amount of sulfuric acid, wt. % in PCP	X_4	94	80
Time of addition, t_a	X_5	2	1
Time of sterring, t_s	X_6	2	1
Unassigned factors to calculate standard deviation	$X_7 - X_{11}$		
Response: yield of TMCCP	Y		

Table 2

Trial	Mean	X_1	X_2	X_3	X_4	X_5	X_6	Unassigned factors to calculate standard deviation					Response: yield, %
								X_7	X_8	X_9	X_{10}	X_{11}	
1	+	+	+	+	–	+	+	–	–	–	+	–	93.5
2	+	+	–	+	+	+	–	–	–	+	–	+	57.2
3	+	–	+	+	+	–	–	–	+	–	+	+	59.7
4	+	+	+	–	+	–	–	+	–	+	+	–	81.0
5	+	+	+	–	–	–	+	–	+	+	–	+	80.7
6	+	+	–	–	–	+	–	+	+	–	+	+	30.5
7	+	–	–	+	–	–	+	+	–	+	+	+	31.2
8	+	–	–	–	+	+	+	–	+	+	+	–	29.0
9	+	–	+	+	–	+	–	+	+	+	–	–	56.7
10	+	+	–	+	+	–	+	+	+	–	–	–	56.6
11	+	–	+	–	+	+	+	+	–	–	–	+	53.0
12	+	–	–	–	–	–	–	–	–	–	–	–	19.6
ΣY_+	648.7	399.5	424.6	354.9	336.5	319.9	344.0	309.0	313.2	335.8	324.9	312.3	
ΣY_-	0	249.2	224.1	293.8	312.2	328.8	304.7	339.7	335.5	312.9	323.8	336.4	
$\Sigma Y_+ + \Sigma Y_-$	648.7	648.7	648.7	648.7	648.7	648.7	648.7	648.7	648.7	648.7	648.7	648.7	
$\Sigma Y_+ - \Sigma Y_-$	648.7	150.3	200.5	61.1	24.3	–8.9	39.3	–30.7	–22.3	22.9	1.1	–24.1	
E_{X_i}	54.06	25.05	33.4	10.18	4.05	–1.48	6.55	–5.12	–3.72	3.82	0.18	–4.02	

between the Sum+'s and the Sum–'s was also calculated. This represents the total difference in yield for the six trials when the factor was at the high level, and for the six trials where the factor was at the low level. The absolute values of the calculated factor effects relate to their relative importance. The analyses in Table 2 revealed that the molar ratio of *p*-chlorophenol to methylcyclohexanol, X_2, was the most significant variable.

Experimental error was considered in order to determine whether a factor effect was significant or not. The minimum value for the factor effect to be significant was computed using the five unassigned factor effects X_7 through X_{11}. Each unassigned factor effect was squared, totaled, and divided by 5, the number of unassigned factors. The square root of this number multiplied by a magic number gave the minimum significant factor effect MIN. The magic number used in this computation (2.57) came from a table of probability points of the t-distribution corresponding to five degrees of freedom (five unassigned factors) and 95% confidence level.

$$\Sigma(UFE)^2 = 70.47,\ 1/5\Sigma(UFE)^2 = 14.09,\ \sqrt{1/5\Sigma(UFE)^2} = S_{FE} = 3.75,\ [MIN]_{95} = 2.57 \times 3.75 = 9.64$$

It is evident from the Plackett-Burman experimental analysis that three variables, temperature (X_1), molar ratio of *p*-chlorophenol to methylcyclohexanol (X_2), and amount of sulfuric acid (X_4) were significant. The concentration of sulfuric acid, t_a and t_s, either had no effect or an effect so small that it was obscured by the experimental error and interaction effects. The most significant variables were further used to develop a mathematical model using fractional factorial design. The values of t_a, t_s and concentration of sulfuric acid were fixed at constant values of 2 h, 1 h, and 94%, respectively .

The experimental design used was the Yates pattern, 3-factor two-level factorial; that is, there were 2^3, i.e., eight trials, and each was run in duplicate. In order to check the lack of fit due to curvature, an additional trial was made at the midpoint level of each factor. The difference between the average center point value and the overall average of the design points indicated the severity of curvature.

The results of factorial design analyses are listed in Table 3. The average yield, $\overline{Y}$, the range and the variance are calculated for each trial. The variance, which is an estimate of dispersion of data, was calculated by the following formula:

Variance

$$S^2 = \frac{(Y_1 - \overline{Y})^2 + (Y_2 - \overline{Y})^2 + ... + (Y_n - \overline{Y})^2}{n - 1}$$

where Y = response value, $\overline{Y}$ = average or mean of response values, and n = number of observations.

The variances calculated for each trial are then used in the calculation of a weighted average of the individual variances for each trial.

Pooled variance

$$S^2_{pooled} = \frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2 + ... + (n_k - 1)S_k^2}{(n_1 - 1) + (n_2 - 1) + ... + (n_k - 1)} =$$

$$= \frac{0.32 + 0.72 + 0.98 + 1.62 + 0.72 + 0.98 + 1.28 + 2.42 + 3 \cdot 0.647}{1 + 1 + 1 + 1 + 1 + 1 + 1 + 3} = 0.998$$

The pooled standard deviation is the square root of the pooled variance:

Standard deviation

$$\sqrt{S^2_{pooled}} = \sqrt{0.998} = 0.999$$

The pooled standard deviation was used to calculate the minimum observed effect that was statistically significant.

The computation analysis for this experiment is shown in Table 3. The design matrix was supplemented with a computation matrix, which was used to detect any interaction effects. This computation matrix was generated by simple algebraic multiplication of the coded factor levels. The column at the far right of the table is the average yield for each trial. The sum of these two rows should equal the sum of all the average responses and is included as a check on the calculations. The difference row representes the difference between the responses in the four trials when the factor was at a high level and the responses in the four trials when the factor was at a low level. The effect was then calculated by dividing the difference by the number of plus signs in the column. In the second column of Table 3, labeled Mean, the effect row value is the mean or average of all data points. The average of the center point runs, Trial 9, was then subtracted from the mean effect to give a measure of curvature.

The statistical analysis and the significant influences of variables from the factorial design are summarized in Table 3. It was observed that the effects of temperature (X_1), molar ratio of *p*-chlorophenol to methylcyclohexanol (X_2), and amount of sulfuric acid (X_3) were significant. The effects were also significant in the interactions between temperature and *p*-chlorophenol to methylcyclohexanol (X_1X_2) and in the interactions among temperature, *p*-chlorophenol to methylcyclohexanol, and amount of sulfuric acid ($X_1X_2X_3$). There was no significant curvature effect. These results were expressed as a mathematical model using a first-order polynomial. The values for the coefficients are one-half the factor effects listed in the table since these are based upon coded levels +1 and –1.

Table 3

Trial	Mean	Design			Computation				Response, Y
		X_1	X_2	X_3	X_1X_2	X_1X_3	X_2X_3	$X_1X_2X_3$	
1	+	–	–	–	+	+	+	–	28.4
2	+	+	–	–	–	–	+	+	49.0
3	+	–	+	–	–	+	–	+	51.6
4	+	+	+	–	+	–	–	–	85.2
5	+	–	–	+	+	–	–	+	40.1
6	+	+	–	+	–	+	–	–	57.2
7	+	–	+	+	–	–	+	–	60.2
8	+	+	+	+	+	+	+	+	94.4
ΣY_+	466.1	285.8	291.4	251.9	248.1	231.6	232	235.1	
ΣY_-	0	180.3	174.7	214.2	218	234.5	234.1	231	
$\Sigma Y_+ + \Sigma Y_-$	466.1	466.1	466.1	466.1	466.1	466.1	466.1	466.1	
$\Sigma Y_+ - \Sigma Y_-$	466.1	105.5	116.7	37.7	30.1	–2.9	?2.1	4.1	
E_{X_i}	58.26	26.38	29.18	9.43	7.53	–0.73	?0.53	1.03	
Curvature = 58.26 – 57.4 = 0.86.									

$$Y = 58.26 + 13.19X_1 + 14.59X_2 + 4.715X_3 + 3.765X_1X_2 + X_1X_2X_3$$

Here the factors are expressed in coded units and these can be converted into real units as follows:

$$X_1 = \frac{T - \frac{140+80}{2}}{\frac{140-80}{2}} = \frac{T-110}{30}$$

where T is temperature (^{0}C),

$$X_2 = \frac{m - \frac{10+3}{2}}{\frac{10-3}{2}} = \frac{m-6.5}{3.5}$$

where m represents molar ratio of *p*-chlorophenol to methylcyclohexanol (m:1),

$$X_3 = \frac{y - \frac{8+3}{2}}{\frac{8-3}{2}} = \frac{y-5.5}{2.5}$$

where y is the amount of sulfuric acid.

These substitutions yield the following final expression:

The predicted and experimental yields of alkylation of *p*-chlorophenol with methylcyclohexanol under the experimental conditions of trial 1 are 28.9% and 28.4%, respectively. For other trials, the experimental yields showed a good agreement with the predicted yield. Thus, the adequacy of the mathematical model was tested.

In conclusion, initial screening of the variables was done by means of Plackett–Burman experimental design to understand the significance of their effect on alkylation of p-chlorophenol with tert-methylcyclohexanol. Among the experimental variables studied, the most significant variables were temperature, molar ratio of *p*-chlorophenol to *tert*-methylcyclohexanol, and amount of sulfuric acid which influenced the yield of 2-*tert*-methylcyclohexanol. A mathematical model was developed by 2^3 factorial design. The difference between the experimental and predicted yields was negligible. The highest experimental yield was 94.4% under the following conditions: temperature = 140^{0}C, molar ratio of *p*-chlorophenol to methylcyclohexanol = 10:1, concentration of sulfuric acid = 94%, amount of sulfuric acid = 8 wt. % p-chlorophenol, addition time 2 h and stirring time 1 h.

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