International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.2, No.1, pp 172-179, Jan-Mar 2010

Optimization of Microwave Assisted synthesis of some Schiff's bases

Rakesh Somani[*1], Ranjana Dandekar[1], Prabhakar Shirodkar[2], Paraag Gide[3], Pal Tanushree[1], Vilasrao Kadam[1]

[1]Bharati Vidyapeeth's College of Pharmacy, Sector 8, C.B.D. Belapur, Navi Mumbai 400614, Maharashtra, India.

[2]Rahul Dharkar College of Pharmacy, Karjat, Dist: Raigad, Maharashtra, India.

[3]MET College of Pharmacy, BKC, Nashik, Maharashtra, India.

[*]Corresp. author: rakeshrsomani@gmail.com

ABSTRACT: The purpose of the present study was to develop an optimized formula for microwave assisted synthesis of Schiff's bases by using specific optimization techniques. A 2^3 factorial design was employed in microwave synthesis of Schiff's base with power (X_1), time (X_2) and molar ratio (X_3) as independent variables and yield (Y) as dependent variable. The main effect and interaction of effects were qualitatively and quantitatively evaluated using a mathematical model. The result indicate that X_1 and X_3 significantly affected the yield of reaction which was calculated in percentage, but effect of time on yield of reaction was non-significant. From result obtained of Yates analysis and contour plot, we determined predicted values of $X_{1,}$ X_2 and X_3 and Y. These predicted values were validated by actual experimental set up.

KEYWORDS: Schiff's bases, Plackett-Burman Design, 2^3 factorial design, N'-(chlorobenzylidene) nicotinohydrazide.

INTRODUCTION

Schiff's bases of various heterocyclic scaffolds exhibit variety of biological activities like anti-HIV[1-2], anti-ancer[3], antibacterial[4], fungicidal[5] and anti-inflammatory[6]. Earlier reports reveal that hydrazones of substituted aroylhydrazine exhibit bacteriostatic, antiparasite[7], psychotropic[8] and antifungal activities[9]. It has been shown that the biological activities[10-16] associated with these hydrazones were attributed to presence of –CONHN=C- moiety in the molecule. Optimization techniques are generally performed to reduce the number of experiments required to be performed and to achieve optimum results for a set of experiments.

The main objective of the present study was to develop an optimized reaction formula for microwave assisted synthesis of Schiff's base. To achieve this objective, independent variables such as microwave power, time and molar ratio were examined. The dependent variable include yield of reaction in percentage can be obtained by Yates analysis and contour plot .We could determine the predicted values of microwave power (X_1) ,time (X_2) and molar ratio (X_3) and yield of reaction (Y). These predicted values were validated by using actual experimental set up.

MATERIALS AND METHODS

MATERIALS

All the chemicals viz. nicotinic acid, hydrazine hydrate, various aromatic aldehydes, and solvents were purchased from s.d. Fine Chem. India Ltd. Mumbai. Solvents were used only after distillation for the synthesis. Microwave assisted synthesis was carried out using Catalyst Microwave type oven, ranging from power levels 1-9 at 140-700 watt.

METHODS

Experimental design:

Factorial designs are the designs of choice for simultaneous determination of the effects of several factors and their interaction. The general notation for factorial design is $N = n^k$ where N is the number of experiments, n is the number of levels and k is the number of the factors[17-20]. Factorial designs are said to be orthogonal and all estimated effects and interactions are independent of effects of other factors. Plackett-Burman Design (PBD) is a special two level fractional factorial design with k = m*4 experiments, where m=1, 2….25 for the screening of (K-1) variables. The advantage of orthogonal design is that the effect can be estimated independently and the estimated effects have good statistical properties.

For experimental design of optimization of microwave assisted reaction, both quantitative and qualitatively optimization techniques were used. Once the experimental design is applied and the observations are obtained then the analysis of the data obtained is carried out by one of the methods mentioned below:

1. Yates algorithm: This method was devised by Yates for systematically analyzing data from 2^n factorial experiments (n factors at 2 levels). It can be used for 2^k and 3^k factorial design and also for 2^{k-p} fractional factorial design. The data is added first in pairs, followed by taking differences in pairs. The addition and subtraction is repeated sequentially on the n^{th} column (here n is the number of factors). Then the average effect is calculated by dividing n^{th} column by 2^{n-1}. The mean squares for the Analysis of Variance (ANOVA) are obtained by dividing the square of column (n) by 2^n. Then the F-test is applied to determine the significant factors. For this purpose the F- value, i.e. the ratio between mean squares and the residual squares (also known as error mean square) is calculated. If the calculated F-value is greater than the tabulated F-value then the factor is significant[21-25].

2. Regression: Regression is the most widely used method for estimation of quantitative factors. It cannot be used for identifying qualitative factors, because interpolation between the discrete factor values is meaningless. The first step in regression analysis is to transform the real values i.e. to obtain the coded values[26-29]. The regression equation is carried out using transformed values and equation is given by:

$$Y= \beta_0 + \beta_1 X_1 + \beta_2 X_2 +\beta_3 X_3 + \beta_{12}X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{123} X_1 X_2 X_3.$$

Where β_0, β_1, etc are the coefficients of the various terms in the equation and X_1, X_2 and X_3 are the transformed values for the respective factors.

OPTIMIZATION STUDIES:

OPTIMIZATION STUDIES FOR MICROWAVE ASSISTED SYNTHESIS OF N'-(2-CHLOROBENZYLIDENE) NICOTINOHYDRAZIDE:

Qualitative optimization and evaluation of N'-(2-chlorobenzylidene) nicotinohydrazide: Plackett–Burman design was used for qualitative optimization. In this different factors of reaction condition were studied for the yield of reaction in percentage. Four factors were chosen for the present study of effect viz. microwave power, time, molar ratio and type of solvent. The factors and there respective levels were chosen as shown in the **Table 1.**

In Plackett–Burman design each factor was studied at 2 levels and numbers of experiments were performed in the multiple of four. Experimental domain was set up and it was constructed as per the **Table 2**, the first row mentioned in the table was given in the literature and the remaining rows were obtained by permutation except last line which entirely consists of minus sign.

Each row in the design described an experimental run and each column described one of the four variables, corresponding to a factor tested at two levels viz. (+ and -). $\mathbf{X_1}$, $\mathbf{X_2}$, $\mathbf{X_3}$, and $\mathbf{X_4}$ were considered as the real factors where as X_5, X_6, and X_7 were considered as the dummy factors. To choose the influential variables, Plackett–Burman design was applied and the experimentation was performed as discussed in the experimental. Eight reactions were performed and evaluated for yield of reaction (Y). The results obtained are tabulated in **Table 3**

It was observed that even if we increase the power level we need to increase the time of reaction. So it was not clear from Plackett–Burman that which power level needed to be selected. So it was thought to use another experimental design for further and more realistic optimization of the reaction. The reaction containing DMF as solvent resulted good yield of reaction as compared to ethanol, so DMF was used for further study. According to reaction condition, time required for microwave assisted reaction can be varied so time for microwave reactions couldn't be fixed by using Plackett–Burman design. Time for microwave assisted reaction can be varied from 30 min to 90 min. It was same with molar ratio, so it was also varied according to reaction condition.

Quantitative optimization and evaluation N'-(2-chlorobenzylidene) nicotinohydrazide:

Quantitative Optimization was performed to study the effect of different levels of the independent variables X_1, X_2 and X_3 on the dependent variable Y. A 2^3 factorial design was used to study the effects of three factors at two levels on the yield of reaction in percentage. In 2^3 factorial design three independent variables viz. microwave power (X_1), time (X_2), and molar ratio (X_3) were studied at two levels viz. high level and low level and their effect on yield of reaction (Y) was evaluated.

Procedure: All the chemicals were weighed accurately according to each reaction condition and were placed in microwave oven at power range 490-560 watt. Accordingly, eight experiments were carried out and evaluated for yield of reaction in percentage. The summary of quantities of each reaction is explained in Table 4 and Table 5.

Calculations of 2^3 factorial designs:

Step 1: It included transformation of the values i.e. to code the levels of the factors so that the high level of each factor was +1 and the low level was -1.

Table 6 showed transformed values and these "transformed values" for the interactions were represented by +1 and -1. The interaction values were obtained by multiplying the appropriate columns. The 'Total' column contains only the value +1 and was used to calculate the intercept, β_0.

Step 2: In this step the coefficients for the polynomial equation were calculated. The coefficients (β_1) for the polynomial equation were calculated as:

$$\beta_1 = \frac{\sum X_1 Y_1}{2^n}$$

Where, X_1 is the value of the column X_1 and Y is yield of microwave assisted reaction in percentage. All other coefficients were calculated in the similar manner and the equation obtained was,

$$Y = 65.095 + 6.42\,X_1 + 30.92\,X_2 + 42.62\,X_3 - 18.14\,X_1X_2 - 8.56\,X_1X_3 - 7.5\,X_2X_3 - 22.28\,X_1X_2X_3 \quad \ldots\ldots\ldots\ldots\ldots \text{Eq.1}$$

Step 3: This step involves determination of significant factors which are responsible for high yield of reaction. The test for significance for the factors X_1, X_2, X_3 with respect to responses Y were assessed by Yates Treatment. Yates analysis was used as shown in Table 7.

In any factorial form of 2^n each effect and interaction has one degree of freedom.

$$F = \frac{\text{Mean Square}}{\text{Average of least mean squares}}$$

Assuming that factor b and interaction bc does not exist, since they have low mean squares compared to other their values were averaged for error estimation.

$$\text{Average of least mean squares} = \frac{(0.42 + 0.42)}{2} = 0.42$$

The **Table 7** was constructed by the following steps explained below:

Experimental data was first tabulated in standard order. Then the first two numbers relating to experiment (1) and (a) were added and the results were put into first row of the column headed 'A'. The next two were added (b and ab) and the results were put in second row of column A. The same steps were repeated for next two pairs (c and ac, ab and abc).Then the difference between the adjacent pairs was calculated (a-1, ab-b, ac-c, abc-bc) and were placed into fifth to eighth row of column **A** respectively. The same treatment was given to column **A** to get column **B** and to column **B** to get column **C**. Numerator has 1 degree of freedom and denominator has 2 degree of freedom. The effect and the mean squares were calculated as per the method discussed earlier and the **F** value was calculated as the ratio between mean squares and the residual squares (also known as error mean square). The predicted F-values were compared with the tabulated F- values from the F-distribution Table at numerator degree of freedom at 1 and denominator at 2. The predicted F-value was required to exceed the tabulated F-value i.e. 98.49 for $p<0.01$.

The values of a, ab, ac and abc were found above 98.49 which indicated that the power and in combination of all three parameter has a significant effect on yield of microwave assisted reaction. Hence the use of these factors for determination of yield of microwave assisted reaction in percentage in the optimization design was justified.

Step 4: It was found that the level of power and in combination of all three parameter has significant effect on yield of microwave assisted reaction. Observations suggested (from the equation 1) that level of power and molar ratio that X_1 and X_3 had a positive effect i.e. if these were decreased then there would be increase in the (%) yield of microwave assisted reaction. To obtain optimum molar ratio contour plots were plotted for the factors X_2 and X_3, as X_1 has no significant effect microwave assisted reaction thus it was considered as 0, and molar ratio showed linear effect on the yield of microwave assisted reaction. Thus by substituting $X_1 = 0$ in equation 1 new equation was obtained (Eq 2.)

$$Y = 65.95 + 30.92\ X_2 + 42.62\ X_3 - 7.5\ X_2 X_3 \text{..........Eq.2}$$

Equation 3 was rearranged as:

$$X_3 = \frac{Y_1 - 65.95 - 30.92\,X_2}{42.62 - 7.5\,X_2} \text{ ....Eq.3}$$

Y (% yield) values were assumed to be 70,80,90.100 %, thus the values for X3 at various levels of X2 such as X2= -1, -0.75, -0.5, -0.25, 0, 0.25, 0.5, 0.75, and 1 were calculated and placed in the Table 8, based on which the contour plot was plotted.

Result obtain from Yates analysis and contour plot, we can interpreted the optimize formula as shown in following Table 9.

RESULT AND DISCUSSION

The optimization of any organic reaction with regard to one or more attributes has always been subject of importance and attention for those engaged in synthetic research. The pharmaceutical chemist has the responsibility to choose and combine ingredients that will result in a synthesis whose attributes conform to certain prerequisite requirements. The objective of using optimization technique is to produce a mathematical model that describes the responses. Optimization techniques are the analytical tools, which are used to obtain the best results. Reports on use of optimization technique for Microwave assisted organic synthesis, so far have not been reported. This prompted us to develop the optimized reaction condition for microwave assisted organic reaction using various optimization techniques.

1. Plackett–Burman design is the best screening method used for qualitative optimization.
2. After qualitatively choosing the influential variables viz. power, time, molar ratio further factorial design is applied for quantitative optimization.
3. Factorial design is one of the simplest optimization technique used for optimization of synthetic reactions.
4. Data was further analyzed using Yates analysis treatment, so as to check the statistical significance of the results obtained.
5. Multiple regression analysis was carried out, to obtain the polynomial equation and further contour plots were constructed to obtain the experimental condition.

The optimized formula was evaluated for yield of reaction in percentage and it was observed that there was no significant difference in the predicted response and experimental responses .It can be conclude that statistical optimization allows the chemist to study wide range of independent and dependent variables.

This optimization was carried out in two steps viz. Qualitative optimization and Quantitative optimization. For qualitative optimization, Plackett-Burman design was applied where the effects of the four independent variables viz. grades of power, time, molar ratio and type of solvents were studied at two different levels viz. high level and low level on the yield of reaction. The levels were chosen as per shown in Table 1.

Eight experiments were performed and power, time, molar ratio and type of solvent were considered for quantitative optimization. The microwave assisted reaction further was optimized by varying the quantities of the independent variables. The three independent variables viz. power, time and molar ratio were varied at high and low level respectively. The experimental design was set up and experiments were conducted as per the design and then the response (yield of reaction in percentage) was obtained. The value of the response was further used for calculation of polynomial equation for both the responses and the response surface plots were plotted so that the optimum formulation was obtained.

From Yates analysis and contour plot, we can interpret the optimized formula as shown in Table 9.

CONCLUSION

Optimization techniques are thus representative analytical tools, which are used to obtain the best results. Optimization of the variables of microwave used for the synthesis of the Schiff's bases was done using Plackett - Burman methodology for qualitative and factorial design for the quantitative optimization. Experiments performed using the optimum values for the various parameters of microwave reduced the time required for the reaction to 30-40 minutes as compared to 6-8 hours required by conventional techniques and also maximized the percentage yield of the product.

Table 1: Factors and their respective levels.

Factors	High level(+)	Low level(-)
Power (watts)	560	490
Time (mins)	90	45
Molar ratio (mole)	1:2	1:1
Solvent	DMF	Ethanol

Table 2: Plackett–Burman Design for 8 experiments

Microwave Assisted Reaction No.	X_1	X_2	X_3	X_4	X_5	X_6	X_7
R-1	+	+	+	-	+	-	-
R-2	-	+	+	+	-	+	-
R-3	-	-	+	+	+	-	+
R4	+	-	-	+	+	+	-
R5	-	+	-	-	+	+	+
R-6	+	-	+	-	-	+	+
R-7	+	+	-	+	-	-	+
R-8	-	-	-	-	-	-	-

Table 3: Results of qualitative optimization of microwave synthesis of N'-(2-chlorobenzylidene) nicotinohydrazide.

Reaction No.	Yield of reaction (%)
R-1	67.45
R-2	80.45
R-3	76.14
R4	69.55
R5	53.04
R-6	61.15
R-7	85.40

Table 4: Factorial Design for 8 experiments.

Reaction No.	Factors			Response
	X_1	X_2	X_3	Y (%)
R-1	-	-	-	61.11
R-2	+	-	-	63.82
R-3	-	+	-	69.82
R-4	+	+	-	74.46
R-5	-	-	+	70.21
R-6	+	-	+	79.78
R-7	-	+	+	86.17

Table 5: Chosen factors and levels of the microwave assisted reaction variables.

Reaction No.	Y (%)	A	B	C	Effect	Mean Square	DF	F
1 (R-1)	61.11	124.93	269.07	600.67	150.16	-	-	-
a (R-2)	63.82	144.14	331.6	-89.14	-21.53	2818.12	1	**6709.8**
b (R-3)	69.82	149.9	7.49	7.41	1.85	0.42	1	1
ab (R-4)	74.46	161.7	-96.63	-113.7	-28.42	100.96	1	**240.38**
c (R-5)	70.21	2.71	19.21	62.53	15.63	30.53	1	72.69
ac (R-6)	79.78	4.78	11.8	104.12	26.03	84.69	1	**201.64**
bc (R-7)	86.17	9.57	2.07	7.41	1.85	.042	1	1
abc (R-8)	75.53	-106.2	115.7	-117.84	29.46	108.48	1	**258.28**

Table 6: Transformed values for 2^3 factorial designs along with the responses

Reaction No.	Factors			Response
	X_1	X_2	X_3	Y (%)
R-1	8	45	1	61.11
R-2	9	45	1	63.82
R-3	8	90	1	69.82
R-4	9	90	1	74.46
R-5	8	45	2.5	70.21
R-6	9	45	2.5	79.78
R-7	8	90	2.5	86.17

Table 7: Yates analysis for determination of significant factor for high yield of Microwave Assisted reaction.

React-ion. No.	X1	X2	X3	X1X2	X1X3	X2X3	X1X2X3	TOTAL	Y (%)
R-1	-1	-1	-1	+1	+1	+1	-1	+1	61.11
R-2	+1	-1	-1	-1	-1	+1	+1	+1	63.82
R-3	-1	+1	-1	-1	+1	-1	+1	+1	69.82
R-4	+1	+1	-1	+1	-1	-1	-1	+1	74.46
R-5	-1	-1	+1	+1	-1	-1	+1	+1	70.21
R-6	+1	-1	+1	-1	+1	-1	-1	+1	79.78
R-7	-1	+1	+1	-1	-1	+1	-1	+1	86.17
R-8	+1	+1	+1	+1	+1	+1	+1	+1	75.53

Y= yield of microwave assisted reaction in percentage.
Where C is the column “C” and n=3 i.e. number of factors.
Where n=3 i.e. number of factors.
DF= degrees of freedom.

Table 8: Transformed values for contour plot of microwave assisted reaction for N' (2-chlorobenzylidene) nicotinohydrazide.

For X1= 0	Y1	Y1	Y1	Y1	
	70	80	90	100	X1
X2	X3	X3	X3	X3	0
-1	0.202713	1.798883	3.395052	4.991221	0
-0.75	0.049876	1.708938	3.368001	5.027063	0
-0.5	-0.1155	1.611615	3.338731	5.065846	0
-0.25	-0.29502	1.505966	3.306956	5.107947	0
0	-0.49059	1.390875	3.272342	5.15381	0
0.25	-0.70446	1.265017	3.23449	5.203964	0
0.5	-0.93931	1.126808	3.192924	5.259039	0
0.75	-1.1984	0.974335	3.147067	5.319799	0
1	-1.48568	0.805269	3.09622	5.387171	0

Table 9: Optimized formula with the comparison of predicted and experimental results of N' (2-chlorobenzylidene) nicotinohydrazide.

Experiment No.	**X1 (watt)**	**X2 (min)**	**X3 (mole)**	**Y (%)**	
				Predicted Values	**Experimental Values (Average)**
1	525	35.75	1.7	90	88

REFERENCES

1. Venkal N. K., J. Med. Chem. 1998, 8, 11.

2. Bhardwaj S. D., Asian J. Chem. 2002, 14, 767.

3. Bhardwaj S. D., Phatak P. and Jolly V. S., Orient. J. Chem. 1995, 2, 181.[Chem.Abstr., 1995,120, 81209]

4. Desai R. M. and Desai J. M., Ind. J. Heterocycl. Chem. 1999, 8 (4), 329.

5. Dash B. and Patnaik J. M., Ind. Chem. Soc. 1984, 61, 1061.

6. Garg H. G. and Kaur M.J., J. Med. Chem. 1992, 15, 554.

7. Bahadue S., Goel A. K. and Verma R. S., J. Ind. Chem. Soc.1975, 52, 834.

8. Sasajima K., Katayama. S. and Inaba S., Chem. Abstr. 1976, 84, 161631. [Chem.Abstr., 1976,84, 1647755]

9. Giammanco L., Ann. Chem. 1961, 51,173.

10. Schiff's H., J. Am. Chem.1984, 131, 118.

11. Tipson S. R. and Clapp M. A., J. Org. Chem. 1946, 11, 292.

12. Hayes K., Gerver G. and Orchutt J., J. Am. Chem. Soc. 1950, 72, 1205.

13. Giovambattista N. and Rabassa R., Assoc. Bioguim. Argentina. 1953, 18, 220-222.

14. Chand S, M. and Singh-Jathar M. K. Ind. J. Chem. 1998, 37B, 352-357.

15. Xiao Wen Sun., Xin Ping Hui. and Li Yi Zang., Ind.J.Chem. 2000, 39B, 779-782.

16. Man Lin Li., You-Mins Zhang., Tai-Bao Wei., Ind.J.Chem. 2007, 46B, 544-549.

17. Jain N.K., Progress in Control Release Drug Delivery System..CBS publication, New Delhi. 2004.

18. Schwartz J. B., Optimization techniques in pharmaceutical formulation and processing in Banker.

4th Ed, Modern Pharmaceutics, Marcel Dekker, New York, 2000, 803-828.
19. Doornbas D. A., Dehaan P., Optimization techniques in formulation and processing, Encyclopedia of Pharmaceutical Technology, Marcel Dekker, New York, 1995, 77-160, Vo.11.
20. Bolton S. and Bon C., Pharm. Statistics–Practical and Clinical 4th Ed, Applications, Marcel Dekker, New York, 2004, 506-539.
21. Franze R. and Cooper C., Experimental Design, Modeling and Optimization strategies for product and process development in Lieberman. Pharmaceutical DosageForm: Disperse System, 2nd Ed, Marcel Dekker, New York, 2004, 506-539.
22. Kellner R., Mermet M. and Otto M., Anal. Chem: A Modern Approach Anal. Sci., 2nd Ed, 1987.
23. Lewis G. and Mathei D., Pharm. Expt. Design, Marcel Dekker, New York, 1999.
24. Kellner R., Mermet M., Otto, M. Analytical chemistry: A modern Approach Anal. Sci. 2nd Ed, 1985.
25. Shiromani P., Pharma. Bioingredient. 2004. 125-126. [Chem.Abstr., 2004,140, 233840y]
26. Sokoll K., Pharma. Bioingredients. 2006. 890-895. [Chem.Abstr.,2006,151, 460072a]
27. Fonner D. E., Buck J. R. and Banker G. S., J. Pharm. Sci. 1970, 59, 1587- 1596.
28. Schwartz J. B. and Flamholz J. R., J. Pharm. Sci. 1973, 62, 7, 1165-1170.
29. Malinowski H. J. and Smith W. E., J. Pharm. Sci. 1975, 64, 10, 1688-1692

*****