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FULL PAPER

Optimization of reaction parameters for 5,5'-methylenebis (salicylaldehyde) synthesis using sonochemical approach

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Maximizing the yield of synthesizing compounds is as a serious production concern. Therefore, developing a new and more effective synthesis method is necessary for practicable research. In this study, a novel approach was described to the synthesis of 5,5'-methylenebis (salicylaldehyde) (MBS) using a sonochemical technique. Response surface methodology (RSM) under Design of experiments (DOE) using central composite design (CCD) was developed to acquire a high yield through optimizing three practicable parameters. The quadratic model resulting from processing analysis of variance (ANOVA) showed a good agreement between the experimental and predicted responses, as (R^2 values of 0.9970 with adjusted and predicted R^2 values of 0.9944 and 0.9806, respectively) implying good conformity between predicted and experimental values. The highest yield (19.3%) approach was obtained after 8 hours at 80 °C with a S:F ratio = 1.4%. Furthermore, the characterization, such as FTIR, ^{1}H-NMR, ^{13}CNMR, and EI-Mass spectrometry results support the MBS structure achieved through the sonochemical method.

KEYWORDS

5,5'-Methylenebis (salicylaldehyde); design of experiments; response surface methodology; sonochemical method.

Introduction

5,5'-Methylenebis(salicylaldehyde) (MBS) is extensively used as a starting chemical for synthesis a new materials due to its aldehyde group, which reacts with acetophenones to produce chalcones [1] or with amines to produce a Schiff base on both sides [2,3], synthesis of copolymers [4], synthesis of coordination polymers [5,6], and catalytic reduction [7,8]. The position of the hydroxyl group in salicylaldehyde renders MBS a suitable ligand candidate for the coordination complex with several metal ions. This characteristic has resulted in practicable applications, including fluorescent sensors [9,10], hydrogen storage polymer [11], and biological activities such as anti-inflammatory, antifungals, antibacterial, and antiamoebic activity [1,2,12].

The reaction parameters used by Marvel and Tarköy [13], to synthesize MBS were a salicylaldehyde to formaldehyde ratio of 1.6: 1 mole at 90-95 °C for 22 hours, the calculated yield for pure product was 20.21%. The modification attempt was performed on the purification [4], yet there has been no effort either to predict another procedure or alter the reaction parameters.

Nevertheless, there are many published works on optimizing the reaction parameters process, exploiting the design of experiments (DOE) approach to improve the yield of the products. Response surface methodology (RSM) has been extensively utilized for optimization processes in the design of

experiments via combining statistical techniques and mathematical modeling [14,15].

In this study, 5,5'-methylenebis (salicylaldehyde) was synthesized for the first time utilizing the sonochemical method instead of the conventional reflux approach. The reaction parameters were optimized using the DOE approach and RSM experimental design to independently investigate the effect of variables and responses with only a minor number of experimental runs. We hypothesize that controlling reaction parameters such as reaction time, temperature, and formaldehyde ratio favor a stable product and increase the yield.

Experimental

Materials

2-hydroxybenzaldehyde (Merck),1,3,5-Trioxane (Sigma-Aldrich), glacial acetic acid (Merck), sulfuric acid (Merck), and solvents (Biosolve Chimie) were utilized without further purification.

Characterization

Nuclear magnetic resonance and carbon-13 (^{1}H-NMR and ^{13}C NMR) spectra of MBS were recorded on a BRUCKER-400MHz in DMSO-d_6 solution with tetramethylsilane (TMS) as a reference. The mass spectrum was recorded using a GCHS-QP 2010 Ultra (Shimadzu). The Infrared (IR) spectra were recorded in KBr, utilizing the FT-IR-8400S instrument (Shimadzu).

Sonochemical synthesis of 5,5'-methylenebis(salicylaldehyde)

In a 50 mL round-bottom flask equipped with a condenser under argon gas, 1,3,5 trioxane (1.4 g, 0.015 mol) was dissolved in glacial acetic acid (3 mL) before 2-hydroxybenzaldehyde (16 g, 0.131 mol) was slowly added. Then, a mixture of concentrated sulfuric acid (0.1 mL) and glacial acetic acid (0.5 mL) was slowly added to the previous mix. The reaction was processed in a sonicator 480 W, 60 Hz. The resultant solution was poured into ice-water and incubated overnight. The product was then filtered and smashed with petroleum ether three times before being dissolved in acetone, combined with charcoal, and filtered. The product color was off-white with an m.p of 142-143 °C. Three parameters (temperature, time, and formaldehyde ratio) were examined in this study to achieve the best results between laboratory experiments and statistical calculations.

Experimental design

The response surface methodology was used to estimate the association between the variable factors reaction temperature (A), reaction time (B), formaldehyde ratio (C), and the response yield. A central composite design (CCD) was exploited to categorize the most noticeable interaction between the appointed parameters toward acquiring a high yield. The RSM model with independent variables and their resembling levels is presented in Table 1. Analysis of variance (ANOVA) was used to evaluate the experimental data, and the adequacy and predictability of the model were determined using the lack-of-fit, determination R^2, and adequate precision according to the recommended polynomial characteristic criteria.

TABLE 1 Experiment factor levels and consistent independent variables

Independent Variables	Symbol	Coded levels				
		-α	-1	0	+1	+α
Reaction temperature (°C)	A	39.77	50	65	80	90.23
Reaction time (hour)	B	1.30	3	5.5	8	9.70
Ratio (%)	C	0.86	1	1.2	1.4	1.54

Results and discussion

The independent variable was examined via CCD-established RSM by applying the reaction parameters [temperature (A), reaction time (B), and formaldehyde ratio (C)] as independent factors, namely to exploit the MBS yield as a response factor and to create a systematic model that optimizes their practicable combination in a minimum number of the experimental runs.

According to CCD, 20 random experimental runs were implemented, comprising six central points, eight fractional factorial points, and six axial points. A quadratic model was used to design this experiment, and the results are summarized in Table 2. The lowest response (7.45) was found at the factorial point in run 19, while the highest response (24.3) was found at the axial point in run 17.

TABLE 2 Experimental design of three independent variables for MBS synthesis

Run	Space type	A: temp. Celsius	B: time Hour	[a]S:f ratio %	Weight g	Yield %
1	Axial	65	9.70448	1.2	1.951	11.60
2	Factorial	50	8	1.4	1.5140	9.00
3	Center	65	5.5	1.2	1.5643	9.30
4	Axial	65	5.5	0.86364	1.5138	9.00
5	Axial	39.7731	5.5	1.2	1.4701	8.74
6	Center	65	5.5	1.2	1.5980	9.50
7	Factorial	80	3	1.4	2.7921	16.60
8	Factorial	80	3	1	2.7753	16.50
9	Center	65	5.5	1.2	1.6484	9.80
10	Axial	65	5.5	1.53636	1.7830	10.60
11	Factorial	80	8	1.4	3.2176	19.13
12	Factorial	80	8	1	3.1970	19.00
13	Center	65	5.5	1.2	1.6484	9.80
14	Center	65	5.5	1.2	1.5811	9.40
15	Factorial	50	3	1.4	1.4297	8.50
16	Factorial	50	8	1	1.2615	7.50
17	Axial	90.2269	5.5	1.2	4.0872	24.30
18	Axial	65	1.29552	1.2	1.6181	9.62
19	Factorial	50	3	1	1.2531	7.45
20	Center	65	5.5	1.2	1.5980	9.50

[a]S:f ratio (salicylaldehyde: formaldehyde ratio)

The model fitness was justified by several parameters, as summarized in Table 3. The results revealed that the experimental data could be expressed suitably with a quadratic polynomial model, which was more favorable than a linear or cubic model.

TABLE 3 A fitting summary of the model justification

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001	< 0.0001	0.7148	0.6115	
2FI	0.9320	< 0.0001	0.6602	0.4521	
Quadratic	< 0.0001	0.0561	0.9944	0.9806	Suggested
Cubic	0.7797	0.0088	0.9927	0.6061	Aliased

The ANOVA results are shown in Table 4 for each term of the quadratic model. The F-value of 373.47 and P-values less than 0.0500 were considered as sufficient to indicate that the model was statistically significant. There is only a 0.01% chance that this large F-value could occur due to noise [16]. In this case, A, B, C, AB, AC, A^2, and B^2 are significant model terms. The lack of fit F-value of 4.75 reflects a 5.61% chance of this effect occurring due to the noise. Not-significance concerning the pure error value of the lack-of-fit is appropriate because it suggests the usability of the response predictor [17]. We used a second-order quadratic regression analysis method to determine the terms of the coded factors equation, presented in Equation (1), which is a statistical correlation to anticipate the response (yield) for the contributed level of each variable.

$$\text{Yield} = 9.53 + 4.76A + 0.6524B + 0.4006C + 0.5600AB - 0.2900AC + 0.0600BC + 2.57A^2 + 0.4766B^2 + 0.1902C^2 \quad (1)$$

Equation (1) indicates that the positive factors of A, B, C, AB, BC, A^2, B^2, and C^2 have the constructive effect of increasing the yield. In contrast, only the negative factor of AC destructively interfered in a reverse behavior.

The calculated correlation coefficient R^2 value indicates how much variation in the experimental values is described by the predicted values in a regression model. When R^2 is closer to one, it suggests good agreement between the experimental and predicted values. In this study, a high R^2 value of 0.9970 suggested a better correlation between the experimental and predicted responses, and the model was highly significant.

TABLE 4 ANOVA for Quadratic model results for each term

Source	Sum of Squares	Mean Square	F-value	P-value	
Model	415.81	46.20	373.47	< 0.0001	Significant
A-Temperature	308.88	308.88	2496.87	< 0.0001	
B-Time	5.81	5.81	46.99	< 0.0001	
C-F ratio	2.19	2.19	17.72	0.0018	
AB	2.51	2.51	20.28	0.0011	
AC	0.6728	0.6728	5.44	0.0419	
BC	0.0288	0.0288	0.2328	0.6398	
A^2	94.90	94.90	767.11	< 0.0001	
B^2	3.27	3.27	26.46	0.0004	
C^2	0.5215	0.5215	4.22	0.0672	
Residual	1.24	0.1237			
Lack of Fit	1.02	0.2044	4.75	0.0561	Not significant
Pure Error	0.2150	0.0430			
Cor. Total	417.05				
Std. Dev.	0.3517				
Mean	11.74				
C.V. %	3.00				
Adeq. Precision	70.3732				
R^2	0.9970				
Adjusted R^2	0.9944				
Predicted R^2	0.9806				

In addition, the R^2 coefficient value of 0.9970 revealed that the model could account for 99.70% of the variability in the data but could not clarify 0.30% of the overall dissimilarities, which was highly adequate. The adjusted and predicted R^2 values of 0.9944 and 0.9806, respectively, indicate that the proposed model has 98.61% flexibility in predicting response (yield) elsewhere the experimental variability of reaction conditions. Moreover, the adequate precision that the signal-to-noise ratio was 70.373 as an indicative of the adequate signal [18].

Figure 1(a) displays the good correlation between the predicted and actual experimental values, as indicated by the values arranged along the diagonal line. The low standard deviations of the models (SD = 0.3517) also support the significance of the fit.

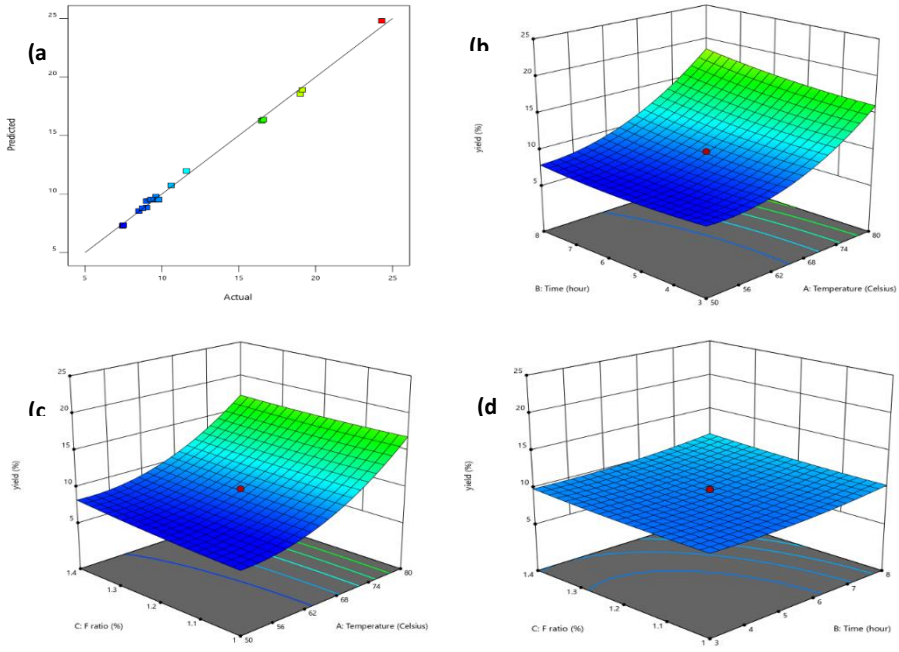


FIGURE 1 RSM analysis for MBS yield (a) Plots of predicted versus actual response, (b) 3D RSM plot between time and temperature, (c) 3D RSM plot between S:F ratio and temperature, and (d) 3D RSM plot between S:F ratio and time

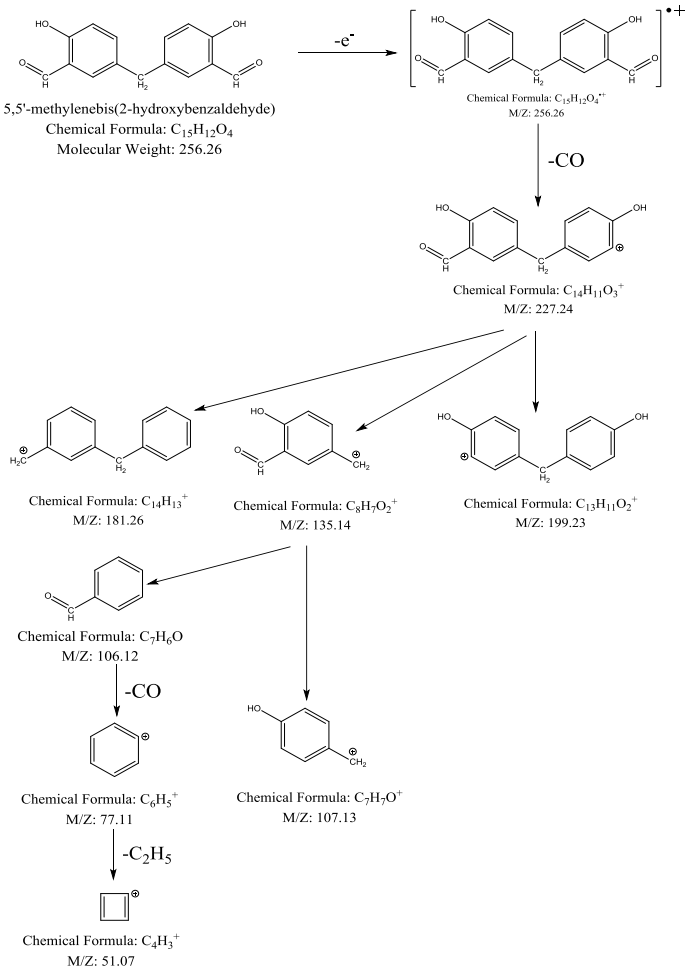
Figure 1 (b, c, d) illustrates the 3D quadratic response surfaces for different independent variables to better understand the connections between these variables, which leads to clarify the highest response results. From Figure 1 (b, c), the yield increased rapidly with the time and temperature, while an increase in S:F had no noticeable impact with an increase in time. Therefore, according to the DOE-based RSM analysis, the optimum condition to achieve a high yield (19.13%) was 80 °C for 8 hours at a S:F ratio = 1.4%.

After discovering the optimum parameter for synthesizing MBS utilizing the sonochemical method, the product was approved with several characterizations.

The infrared spectrum of MBS in supplementary data S1 exhibited a band at 3410 cm^{-1} attributed to *v* O-H, and a band appeared at 2746 cm^{-1} attributed to *v* C-H aldehyde. A very sharp band was observed in the IR spectrum of MBS at 1656 cm^{-1} assigned to the *v* C=O for the aldehyde. The asymmetric aliphatic C-H band for the methylene group was at 2914-2858 cm^{-1}, while the aromatic C-H group appeared at 3053 cm^{-1}. In addition, the C-O stretching band appeared at 1276 cm^{-1}.

The supplementary data S2 shows the ^{1}H-NMR signals and their chemical shifts. A sharp singlet peak at 10.928 ppm (2H) was attributed to the resonance of the phenolic hydroxyl group proton. Another sharp singlet peak, a chemical shift of 9.848 ppm (2H), was assigned to the resonance of aldehyde protons. The phenyl protons resonated as a multiplet at 6.962–7.368 ppm (6H), and the methylene group resonated as a singlet at 3.964 ppm (2H).

The supplementary data S3 shows the ^{13}C NMR spectrum for MBS. An aldehydic carbon signal existed at 196.4 ppm, and a C-OH signal appeared at 160.3 ppm. The aromatic carbon signals were found in the 137.9-118.0 ppm range. The carbon of the methylene group was shown at 39.4 ppm. The EI-mass spectrum of MBS is presented in the supplementary data S4, and the expected fragmentation pattern is in Scheme 1. The molecular ion peak $[M]^{\bullet+}$ exists at m/z = 256.1, confirming the stoichiometry of the compound. The molecular ion peak of the compound in the mass spectrum resembled related formula weights and exhibited the satisfactory agreement with the proposed molecular structures.



SCHEME 1 The expected fragmentation pattern of MBS

Conclusion

This study proposed a new approach to synthesizing 5,5'-methylenebis (salicylaldehyde) (MBS) using the sonochemical method. The DOE exploited CCD under the RSM method was applied for the compound process optimization of three practicable parameters to acquire a high yield of MBS. The ANOVA results of the quadratic model revealed a good agreement between experimental and predicted responses, as indicated by high R^2 values of 0.9970, highly suggestive of a correlation between experimental and predicted responses and the model. The optimized preparation conditions for MBS were 80 °C reaction temperature, 8 h reaction time, and 1.4% S:F ratio to achieve a 19.13% yield. Furthermore, to establish the MBS structure, characterization techniques which are FTIR, 1HNMR, 13CNMR, and EI-Mass spectrometry were exploited to characterize MBS synthesized using this new approach. The characterization results confirmed the MBS structure that it was synthesized using a sonochemical method.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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