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OPTIMUM DESIGN OF A PALMITOYL ARGININE SURFACTANT FROM ARGININE IN MIX SOLVENT HEXANE-ISOPROPANOL

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ABSTRACT

The added value of amino acids and palm oil derivatives as raw materials for amide surfactants has developed recently. Therefore, amide formation by the amino acid and arginine was investigated as a mix of solvent ratio, catalyst amount, and substrate ratio. Response Surface Methodology with Central Composite Design and twenty combination treatments synthesized this surfactant palmitoyl arginine. The results generally show that the highest conversion will be produced at the maximum selection of solvent ratio, catalyst amount, and substrate ratio variables. Only the interaction between the mixed solvent ratio and the substrate ratio has a significant effect on the interaction effect. However, the square of the interaction of the three variables has a very significant effect on the conversion of palmitic acid.

Keywords: central composite design, arginine, palmitic acid, mix solvent.

INTRODUCTION

Surfactants are widely used in the detergent, soap, cosmetic, lubricant, paint, and textile industries [1]. In addition, due to their surface tension-lowering properties, surfactants can be used as wetting agents, emulsifying agents, and solubilizing agents [2]. Based on the charge, the surfactants are divided into four essential parts: anionic, cationic surfactants, nonionic surfactants, and amphoteric surfactants [3].

Surfactants can be synthesized from petroleum derivatives. However, the waste generated from this synthesis can pollute the environment because it is difficult to degrade and is a non-renewable source of raw materials. For this reason, surfactant raw materials derived from vegetable oils are the right choice because surfactants from vegetable oils are biodegradable, so they do not pollute the environment [4].

Palmitic acid is a fatty acid formed from triglycerides obtained from vegetable and animal oils. Palmitic acid is an abundant ingredient with a content of 56.84% in palm oil [5]. Palmitic acid comprises 16 carbon atoms ($CH_3(CH_2)1_4COOH$). At room temperature, palmitic acid is solid and white. In industry, palmitic acid is widely used in cosmetics and coloring. From a nutritional point of view, palmitic acid is the most important source of calories but has low antioxidant power [6, 7].

The manufacture of protein-based surfactants is an excellent biodegradable and renewable candidate. Proteins are reacted with different fatty acids such as lauric acid, myristic acid, and palmitic acid to produce N-acyl products according to their characteristics [8]. Amino acid-based surfactants are a promising alternative to antimicrobial surfactants with high intrinsic toxicity. Amino acid-based surfactants have several different structural features as indicated by the chemical formula of the derivative N-acyl arginine. The unique property exhibited by this type of compound is due to the strong hydrogen bonding of the amide bond, which lies between the hydrophilic part (amino acid residue) and the hydrophobic part of this molecule [9]. The choice of raw material for arginine in synthesizing surfactant N-acyl arginine is because arginine is part of the hydrophilic head group bound to the hydrophobic tail of fatty acids, fatty alcohols, or fatty amines as a synthesis for amphiphilic structures [10, 11].

In this study, the surfactant Palmitoyl arginine was synthesized by the amidation reaction between palmitic acid and arginine with the help of a catalyst and mixed solvent. This time, the use of a catalyst in the amidation process serves to speed up the reaction time so that the reaction can take place more quickly [12]. The catalyst used is a chemical catalyst, namely sodium methoxide, because it is more economical than biochemical catalysts and provides a shorter reaction time [13]. In addition, the water problem can be avoided if the sodium methoxide solution can be treated water-free.

Although methoxide cannot avoid soap formation if the raw material contains free fatty acids, which is also true for using KOH or NaOH, very little saponification of esters or triglycerides will occur because the methoxide behaves as a weak Lewis base [14]. The amount of sodium methoxide catalyst significantly affects the density value obtained. It can be seen that the use of a 5% catalyst produced a surfactant with a greater density than the use of a 10% catalyst in the synthesis of cationic surfactants from methyl ester olein [15].

Then in this study, a mixed solvent will be used. The mixed solvent used was hexane and isopropyl alcohol with a 1:1 (v/v) ratio. The use of mixed solvents is based on research by Wang et al. in 2016, which reported that the amidation reaction without solvent is not recommended because it can cause precipitation, with the resulting yield value of 57.6%. Using solvents such as hexane, ethanol, hexane: alcohol (1:1) (v/v), and acetone, the yield values are 64.1%, 74.9%, 90.1%, and 23.8%. So, from these results, a mixture of alcohol and hexane is suggested to be the best solvent for the intermediate reaction because the mixture can dissolve all the required components and produce more product. [12].

Furthermore, the use of Response Surface Methodology (RSM) in this study has the advantage of optimizing the design through analysis and modeling of the relationship between the percentage of palmitic acid converted to three important research variables, namely substrate ratio, catalyst concentration, and solvent ratio. Therefore, RSM is expected to improve and optimize the process using palmitic acid conversion response. In addition, it can also be obtained a model of the relationship between the independent variables and the response and obtain the process conditions that produce the best palmitic acid conversion response [16].

The synthesis of surfactants made from vegetable oil has been carried out by several previous studies. Wang et al., 2016, using hexane: alcohol (1:1) (v/v) solvent, 1.5% catalyst concentration, and 30 minutes reaction time, the resulting vegetable oil surfactant is more than 90%. These results were obtained at a solvent ratio of hexane to ethanol 1:1 (v/v) and a catalyst concentration of 1 to 1.5%. The study conducted by Masyithah *et al*. (2021) in the range of 5-9% (w/w) amount of biocatalyst, the molar ratio of diethanolamine substrate to oleic acid 1/1 to 3/1, reaction temperature 60-65^{o}C, obtained the conversion of oleic acid the maximum reaches up to 78% [17]. Based on the rationale that has been described, it is necessary to study the effect of the ratio of raw materials, catalyst concentration, and solvent ratio on the level of amide content and surfactant characteristics obtained from the amidation reaction between palmitic acid and arginine, as well as to obtain important information related to the ratio of raw materials, catalyst concentration, and the ratio of solvent to surfactant produced in the amidation process so that this method can later be developed for industrial scale.

EXPERIMENTAL DESIGN

The experimental design was carried out using the principles of the response surface (Response Surface Methodology). The variables and levels in this study used the response variable for fatty acid conversion. The independent variables were the substrate ratio and the ratio of the solvent to the substrate.
The independent variables are in the following ranges:

- Substrate (A/PA), denoted (A), ranges between 2:1 to 4:1.
- Solvent (S/MS), denoted (B), ranges from 1:1 to 1:3.
- Weight of catalyst (%), denoted (C), ranges from 3 to 7.

The experimental design used a three-factor design with two levels consisting of the first eight runs (runs 1-8) with a coded variable (± l) for each factor (factorial point). The following six runs are called star points with a coded level (±α) as a significant curvature effect (runs 9-14), while six additional runs (runs 15-20) contain the center point as an estimate of the curve area with a code of 0. for each of the factors. The distance from the start to the center point is = 2n/4 (for three factors, = 1.682), so the total observations are 20 runs. The factor level corresponding to the center point can be calculated using the following formula [16, 18, 19]:

$$X_i = \frac{x_i - [x_{max} + x_{min}]/2}{[x_{max} - x_{min}]/2} \quad (1)$$

where: Xi = dimensionless code value of variable xi. xi = true value of substrate, catalyst weight, and solvent variables. xmax = maximum value of substrate, catalyst weight, and solvent variables. xmin = minimum value of substrate, catalyst weight, and solvent variables.

Synthesis Materials and Procedures

The materials used in this study were arginine ($C_6H_{14}N_4O_2$), Palmitic Acid ($C_{16}H_{32}O_2$), Sodium Methoxide (CH_3NaO), hexane, isopropanol, citric acid, acetone, potassium hydroxide (KOH), Phenolphthalein, tert-Amyl alcohol ($C_5H_{12}O$), and hydrochloric acid (HCl), obtained from E Merck.

The synthesis was started by introducing 5 g of palmitic acid into a three-neck flask. At the solvent ratio (S/MS) 2, a three-neck flask was added to a mixed solvent of hexane and isopropanol. After the palmitic acid was completely dissolved in the mixed solvent, arginine was added with an arginine ratio to Palmitic Acid 3 (A/PA). Then, sodium methoxide (CH_3NaO) was added with a weight percent of 5%. The mixture of raw materials and catalyst is heated with variations in heating temperature of 45, 55, and 65^{o}C. The mixture was stirred with a magnetic stirrer at speeds of 200, 300, and 400 rpm and reacted for 2, 3, and 4 hours. The observations were repeated according to the design in table 1. Subsequently, purification and FTIR analysis were carried out.

RESULTS AND DISCUSSIONS

Prediction Model and ANOVA

Arginine-based surfactants are amphiphilic compounds that possess excellent self-assembling properties, low toxicity profile, high biodegradability, and broad antimicrobial activity, making them candidates of choice as preservatives and antiseptics in pharmaceutical, food, and dermatological formulations [4,9].

Arginine is a type of amino acid biochemically grouped with histidine and lysine. Arginine is a semi-essential amino acid, which means the body can produce this amino acid in small amounts, so external intake is still needed. Arginine is abundant in seafood, watermelon juice, nuts, seeds, algae, meat, protein concentrates, and soy protein isolate but is low in milk of mammalian origin [3]. Sodium methoxide (CH_3ONa) is a catalyst obtained by dissolving NaOH with methanol. Sodium methoxide can react smoothly under low temperatures and atmospheric pressure [18].

The long-chain N-acyl amino acids are an exciting class of substances because of their limited tendency to lower or change the pH of the top layer and thereby reduce the swelling of the top layer. N-acyl amino

acids contain peptides that form a hydrophilic moiety and long chains that form a hydrophobic moiety. The N-acyl amino acid can be considered an anionic surfactant with applications in cosmetics. Since N-acyl amino acid is derived from protein, N-acyl amino acid can be an excellent growth medium for bacteria if not adequately protected. Arginine-based cationic surfactants, particularly methyl and ethyl ester derivatives, have been found to have high surface activity and interesting polymorphic phase behaviour [10].

The experimental design of the CCD is shown in Table-1, as well as the resulting responses in terms of percent palmitic acid conversion. The best results were found at A=3; B=7; and C=4, 90.93% palmitic acid will be converted to palmitoyl arginine. This shows that, in general, the highest conversion will be found in the full selection of variables A, B, and C. It is proven that palmitic acid will convert less than 80% on selecting the minimum value for the three.

The statistical summary model analysis results in Table-2 show that the recommended model is quadratic. The sequential p-value is more minor than 0.0001, and the R square is 93.6 percent. Therefore, the cubic model is not recommended, and the quadratic model is also chosen because the adjusted R square has the highest value of 0.8785 for the quadratic model. Next, an analysis of variance was performed on the selected quadratic model. The results of the ANOVA for the response surface quadratic model are shown in Table-3. The model's F-value is 16.26 which indicates that the model is significant. Because there is only a 0.01% chance that this large F-value could occur due to noise.

Table-1. CCD experimental design and palmitic acid conversion.

Run	A-Solvent (S/MS)	B-Catalyst (w/S)	C-Substrate (A/PA)	R1-PA Conversion (%)
1	2	5	3	75.00
2	2	5	1.318	81.64
3	0.318	5	3	82.30
4	1	7	4	84.73
5	1	7	2	84.70
6	2	5	3	74.34
7	2	5	4.682	85.62
8	2	5	3	75.00
9	3	3	4	88.50
10	3	3	2	80.09
11	3	7	2	87.17
12	2	5	3	75.00
13	2	5	3	76.11
14	2	8.364	3	84.96
15	1	3	2	83.63
16	2	1.636	3	82.30
17	2	5	3	79.87
18	1	3	4	83.41
19	3.682	5	3	86.28
20	3	7	4	90.93

Table-2. Model summary statistics of ANOVA.

Source	Sequential p-value	Standard Deviation	R- Square	Adjusted R- Square	Predicted R- Square
Linear	0.4619	4.94	0.1447	-0.0157	-0.1801
2 FI	0.8021	5.28	0.2056	-0.1611	-1.2799
Quadratic	<0.0001	1.71	0.9360	0.8785	0.7826
Cubic	0.8636	2.01	0.9469	0.8318	-0.8022

Table-3. ANOVA for response surface quadratic model.

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob>F
Model	427.80	9	47.53	16.26	<0.0001
A-Solvent	20.95	1	20.95	7.16	0.0232
B-Catalyst	19.63	1	19.63	6.71	0.0269
C-Substrate	25.53	1	25.53	8.73	0.0144
AB	6.34	1	6.34	2.17	0.1717
AC	19.10	1	19.10	6.53	0.0286
BC	2.42	1	2.42	0.83	0.0343
A^2	147.12	1	147.12	50.32	<0.0001
B^2	126.42	1	126.42	43.24	<0.0001
C^2	126.42	1	126.42	43.24	<0.0001
Residual	29.24	10	2.92		
Lack of Fit	8.57	5	1.71	0.41	0.8220
Pure Error	20.67	5	4.13		
Cor Total	457.03	19			

Parameters A, B, and C all significantly affect the number of fatty acids converted. It is indicated by the p-value of the three, which is smaller than 0.05. For the interaction effect, only the AC interaction has a significant effect of 0.0286. Interestingly, the squares of A, B, and C have a very significant effect on the conversion of palmitic acid.

The Prediction R-squared of 0.7826 reasonably agrees with the Adjusted R-squared of 0.8785 because the difference is only 0.2. Model precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The ratio obtained is 12.248 indicating an adequate signal. This model can be used to navigate the design space [16]. The final equation in terms of essential factors is as follows:

PA Conversion = + 133.81871 - 18.40202*Solvent - 6.86998 * Catalyst - 18.11833 * Substrate + 0.44500 * Solvent * Catalyst + 1.54500 * Solvent * Substrate - 0.27500 * Catalyst * Substrate + 3.19512 * $Solvent^2$ + 0.74044 * $Catalyst^2$ + 2.96178 * $Substrate^2$ (2)

The equation in terms of essential factors can be used to make predictions about the response forgiven levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor, and the intercept is not at the center of the design space.

Palmitic Acid Conversion and Interaction Variables

Palmitic acid conversion is a measure of the success of the amidation reaction between palmitic acid and arginine to palmitoyl arginine. Furthermore, the success of the amidation reaction is mainly influenced by three variables, namely the solvent ratio, the amount of catalyst, and the substrate ratio. Therefore, to obtain information on the success of palmitoyl arginine formation, which is characterized by high conversion of palmitic acid, the effect of solvent, catalyst, and substrate interactions, in increasing the conversion of fatty acids, in this case, palmitic acid [17].

Observations started on the interaction between solvent and catalyst in Figures 1 to 3. Figure 1 is a contour at a constant substrate ratio = 2. The single effect of catalyst shows that increasing the amount of catalyst on the substrate and solvent is constant, which will increase the conversion of palmitic acid.

When the single effect of increasing the amount of solvent, under other conditions constant explains that, conversion of less than 78% is only found in solvents 1.5 to 2.5, while at values below and above the solvent, palmitic acid conversion reaches 84%.

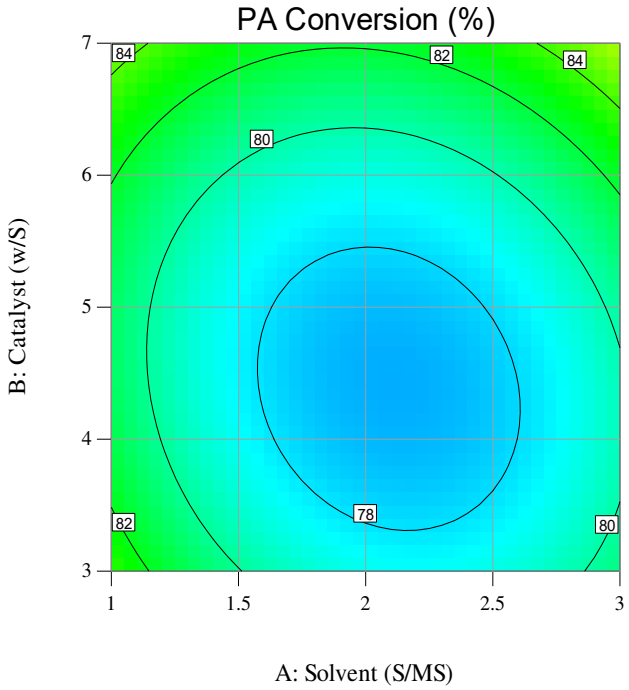

Figure-1. Palmitic acid conversion (%) and solvent-catalyst interaction at a substrate ratio of 2.

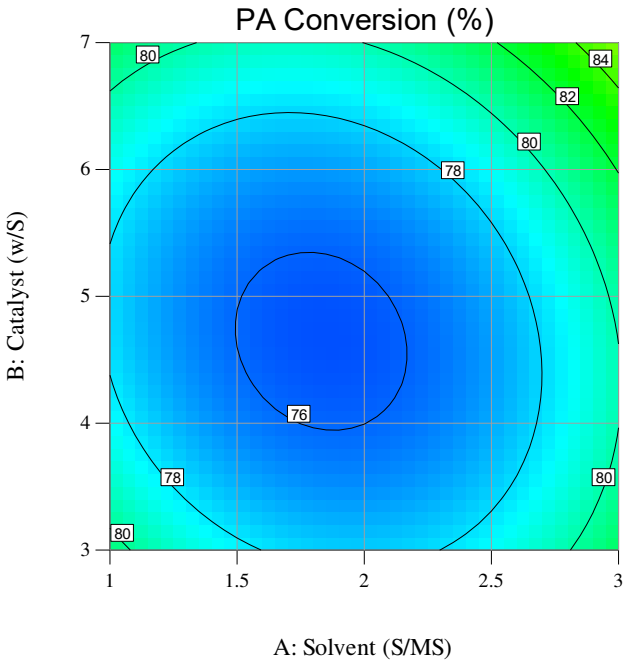

Figure-2. Palmitic acid conversion (%) and solvent-catalyst interaction at substrate ratio 3.

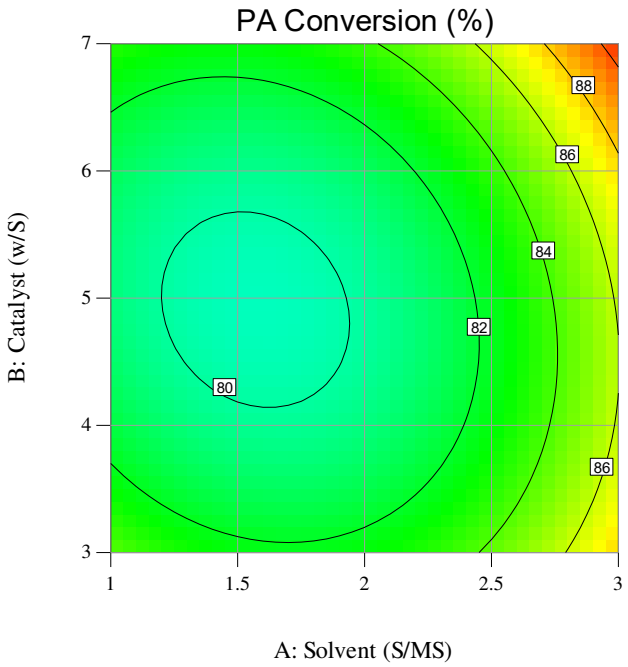

Figure-3. Palmitic acid conversion (%) and solvent-catalyst interaction at substrate ratio.

If the substrate ratio is increased to 3, then for the same interaction as Figure-1, the resulting contour is shown in Figure-2. It can be seen that increasing the substrate ratio, which means increasing the amount of arginine, will expand the contour with palmitic acid (PA) conversion by more than 78%. Previously, using a 6% catalyst would result in 80% PA conversion, but increasing the substrate ratio would reduce PA conversion to less than 78%. Therefore, the contours of Figures 1 and 2 have in common the full selection of A and B, both of which will result in a conversion of up to 84%.

In observing the interaction between the solvent and the catalyst, an attractive contour is found in Figure-3. It can be seen that, at a low solvent and catalyst zone, increasing the ratio of arginine/palmitic acid will increase the conversion of palmitic acid to palmitoyl arginine [18]. Also, palmitic acid conversion can reach 88% when using a combination of these variables, namely the substrate ratio 4 (A/PA), solvent ratio 3 (S/MS), and the amount of catalyst 7 (w/S).

Efforts to increase palmitic acid conversion were observed in the interaction between the solvent and the substrate. The contours obtained are given in Figures 4, 5, and 6. Figure-4 shows the lowest amount of catalyst, kept constant at B=3, on changes in the amount of solvent and substrate. If a small amount of catalyst is used, then in a low solvent and substrate ratio range, a minimum palmitic acid conversion will also be found, which is less than 78% [2]. Palmitic acid conversion will increase if solvent ratio > 2.5 (S/MS) and substrate ratio > 3 (A/PA) are used. In this condition, PA conversion can reach 80%.

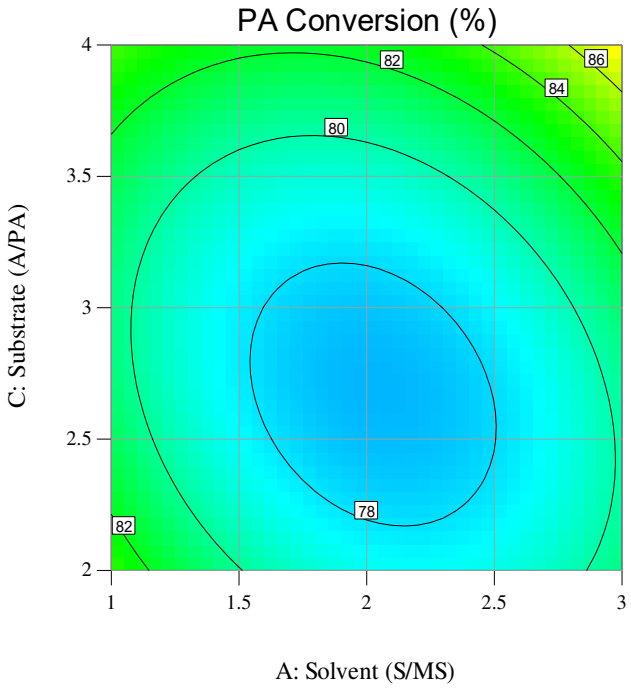

Figure-4. Palmitic acid conversion (%) and the interaction of solvent to substrate ratio on the amount of catalyst 3.

If the amount of catalyst is increased to 5, and the value is constant for all solvent and substrate changes, the contour obtained is shown in Figure-5. It can be seen that the contour with PA conversion < 78% increases in area, which means that increasing the amount of catalyst from 3 to 5 does not increase the amount of converted palmitic acid at constant amounts of A and C [12]. The highest gain was found insolvent 3 (S/MS) and the substrate 4 (A/PA).

In observing the effect of solvent and substrate interactions on a fixed amount of catalyst, B = 7, it was found that using a solvent of 1.5-2 S/MS will make palmitic acid conversion <80%. This contour is observed in Figure-6. Figure-6 shows that more than 80% conversion will be obtained over the entire solvent and substrate use range if the maximum amount of catalyst is used.

The overall palmitic acid conversion was over 78% over the entire range of the selected variables. This is observed in Figures 7, 8, and 9. Wherein Figure-7 observes the interaction effect of the amount of catalyst (B, w/S) and the mole ratio of the substrate (C, A/PA) on the converted palmitic acid. The center point values B=5 and C=3 are also expected to produce the highest conversion but produce the lowest conversion (<78%) of all the reactions carried out.

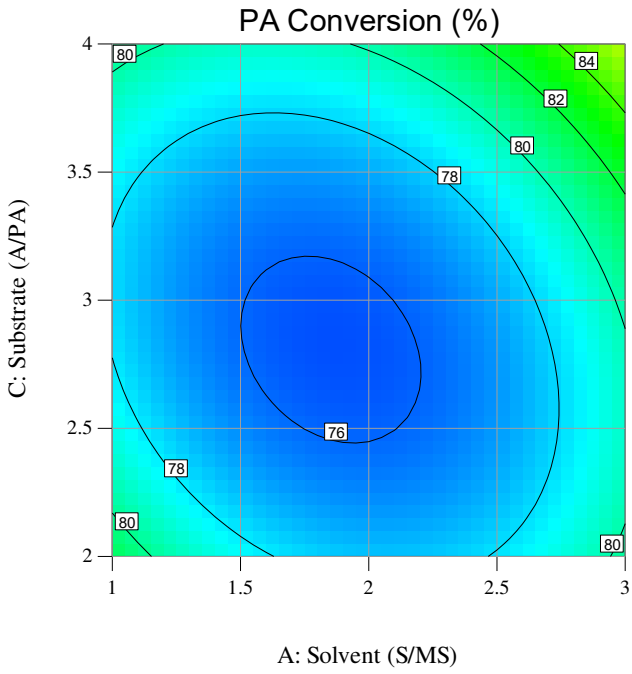

Figure-5. Palmitic acid conversion (%) and the interaction of solvent to substrate ratio on the amount of catalyst 5.

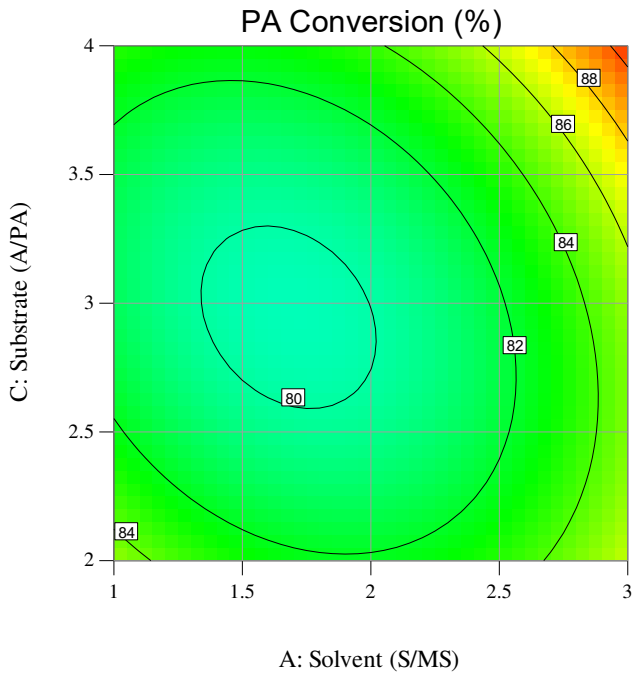

Figure-6. Palmitic acid conversion (%) and interaction of solvent to substrate ratio on the amount of catalyst 7.

Figure-8 is a palmitic acid conversion contour, observing the interaction between the catalyst and the substrate, with the solvent ratio kept constant = 2. Increasing the solvent ratio did not increase the PA conversion in the obtained contour. At this solvent ratio = 2, the use of a catalyst reaches 7, only increasing palmitic acid conversion by 82%, likewise with the increase in the substrate ratio. In the maximum range substrate ratio (3.5 - 4 A/PA), palmitic acid conversion was only 82%.

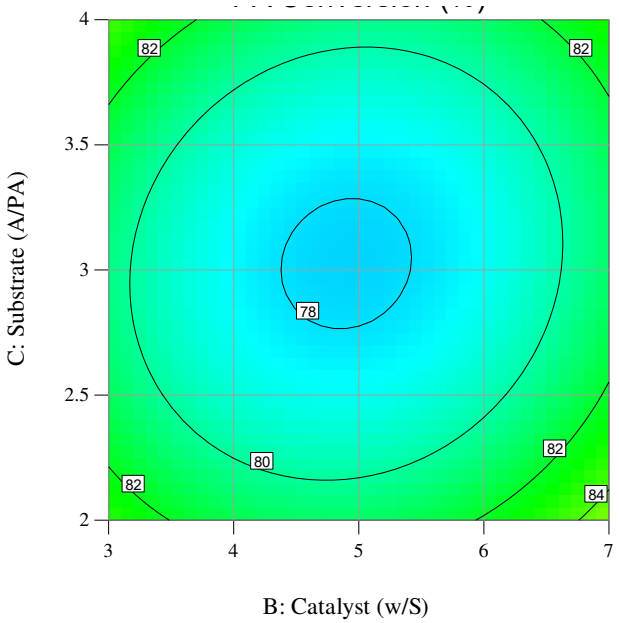

Figure-7. Palmitic acid conversion (%) and catalyst to substrate interaction solvent ratio 1.

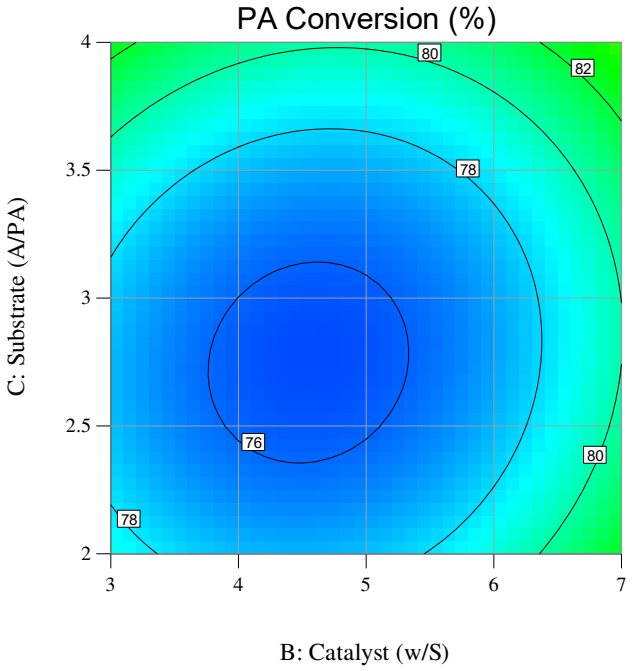

Figure-8. Palmitic acid conversion (%) and interaction of catalyst to substrate solvent ratio 2.

If the solvent ratio is kept constant = 3, the contour of the catalyst and substrate interaction, as shown in Figure-8, is given in Figure-9. As the top trend expected, the interaction of the catalyst with the substrate will also result in a maximum palmitic acid conversion, reaching 88%, if the highest solvent ratio is used, which is 3. The more solvent, the higher the substrate and catalyst, and the more mass transfer and reaction occur optimally [13].

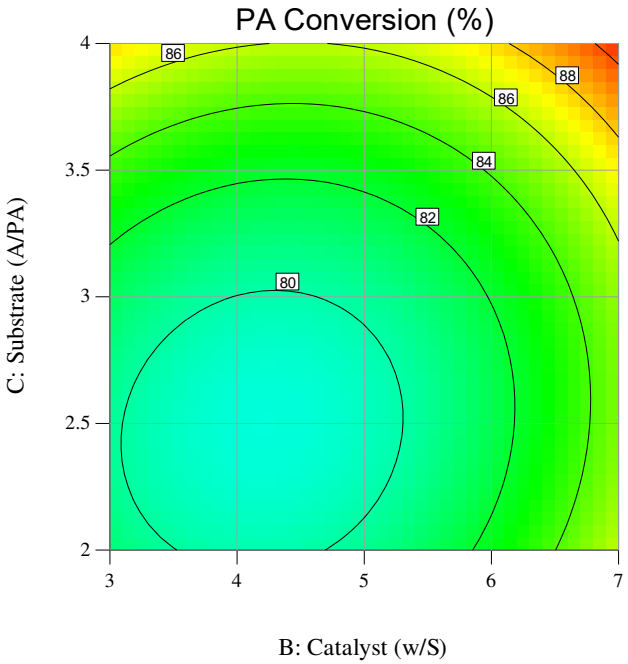

Figure-9. Palmitic acid conversion (%) and interaction of catalyst to substrate solvent ratio 3.

It is just that a large amount of solvent requires a longer solvent purification step and a higher energy requirement. So, the best compromise between the amount of solvent, substrate ratio, and the amount of catalyst is needed to optimize the amidation reaction between arginine and palmitic acid to palmitoyl arginine.

Effect of Reaction Time and Temperature

Based on the theory, the longer the reaction time, the greater the possibility of contact between substances to produce a large conversion. Increasing the reaction time will not be beneficial if the reaction has reached equilibrium because it will not increase the yield.

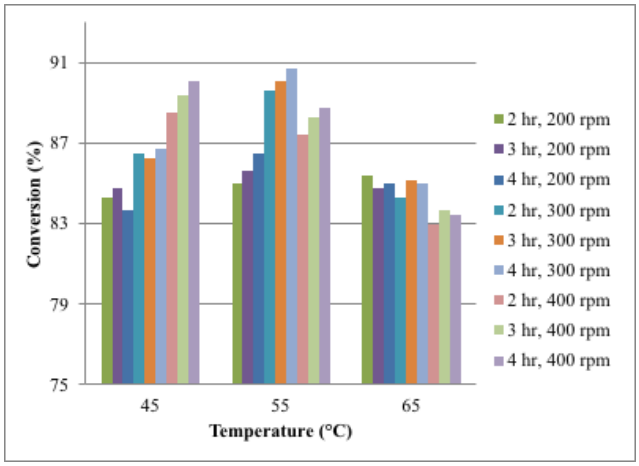

Figure-10. Palmitic acid conversion (%) on changes in reaction time and temperature.

From the study conducted, it is shown in Figure-10 that, from 1 hour to 2 hours, the conversion yield of

palmitic acid will continue to increase, but at a reaction time of 3 hours, the conversion reaction will decrease.

This is because the reaction equilibrium has been reached in less than 2 hours, so a time longer than 2 hours will not be profitable because the conversion of the reaction does not increase and instead increases the amount of water formed. The reaction temperature affects the degree of amidation because the higher the temperature will increase the reaction rate [20]. The study to study the effect of reaction temperature was carried out by changing the reaction temperature for each experiment (60, 70, and 80^{o}C), while the other variables were kept constant.

HLB Analysis

Hydrophilic-lipophilic balance (HLB) is one of the most widely used suitability indicators to determine the tendency of intermediate surfactants to oil or water [21]. As an illustration of the hydrophilic-lipophilic balance of surface-active ingredients, the hydrophile-lipophile balance scale, often called the HLB, was discovered by Griffin in 1949. With the help of this equilibrium value, we can optimally form the HLB range of each surfactant. The more significant the HLB value of a material, the more hydrophilic the material is. The formula is described as follows:

$$HLB = 20\ (1 - S/A\ ) \quad (3)$$

S is the saponification number, and A is the acid number [22,23].

HLB shows the balance scale of hydrophobic and hydrophilic groups of a surfactant. HLB will determine the function of the surfactant. Surfactants with a more dominant hydrophobic group have a low scale, and conversely, surfactants that hydrophilic groups dominate and have a large scale. Surfactants with HLB values above 9 are water-soluble surfactants used as solubilizing agents. In comparison, the surfactants used as detergents have HLB values on a scale of 15-18 and 13-15. Surfactants with an HLB value scale of 8-16 can also be used as oil-in-water (O/W) emulsifiers. HLB values in the range up to a scale of 6 were applied to anti-foaming. These surfactants are called oil solution surfactants [21].

CONCLUSIONS

The overall solvent ratio, catalyst amount, and substrate ratio parameters significantly affect the amount of palmitic acid converted. Therefore, the converted palmitic acid will also be less than 80% in combination with the minimum value for the three variables. The results of the analysis of variance used show that the recommended model to describe this synthesis is a quadratic model, with a sequential p-value of less than 0.0001 and an R square of 93.6%. Palmitoyl arginine surfactants are of great interest in novel surfactant research because of their biodegradable character.

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