



# CATALYTIC AMIDE FORMATION OF N-STEAROYL LYSINE FROM CARBOXYLIC ACID IN MIX SOLVENT: ANALYSIS OF THE RESPONSE SURFACE

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## ABSTRACT

N-stearoyl lysine is a non-ionic surfactant. N-stearoyl lysine was synthesized by reacting stearic acid (SA) and lysine (L). In the synthesis of N-stearoyl lysine, the interaction effect between the substrate ratio, solvent ratio, and catalyst concentration was observed to obtain the optimal percentage of stearic acid conversion. The catalytic oxidation process is carried out by reacting lysine with stearic acid at a substrate ratio of 2-4 (L/SA), with the addition of mixed solvent hexane and 2-propanol with a ratio of 1-3 (v/wSA) and calcium oxide catalyst at 3-7% (w/wSA). The reaction was carried out at a temperature of 65 °C and a time of 3 hours. The optimal conditions using the response surface analysis were obtained at a substrate ratio of 4 (L/SA), a solvent ratio of 3 (v/wSA), and a catalyst concentration of 5%, and the resulting conversion of stearic acid was 85.2%.

**Keywords:** stearic acid, lysine, calcium oxide, mix-solvent, response surface analysis.

## INTRODUCTION

Surfactants are organic compounds that have a role in forming a homogeneous solution from nonpolar and polar phases by reducing the surface tension of a solution [1, 2]. Surfactants are characterized by the presence of hydrophilic (polar) and hydrophobic (nonpolar) groups on the same molecule [3]. The hydrophobic part dissolves in the oil phase or air phase, while the hydrophilic part is soluble in the water phase. The hydrophilic groups that form polar head groups are based on functional groups such as carboxy, sulfonates, ammonium, hydroxyl, and amides. Hydrophobic groups are nonpolar tails, like hydrocarbon chains with eight or more carbon atoms, and can be linear or branched [4].

Surfactants are often used to treat water contaminated with waste oil [5], and it can also absorb heavy metals such as Cu (II), Zn (II), Cr (III), and Ag (I) [6]. The increasing number of industrial applications that produce various surfactant products can affect the environment, so that surfactant products need to use natural raw materials that are biodegradable and non-toxic [7]. Petroleum-based surfactants are not biodegradable. In contrast, surfactants from renewable natural resources are mostly biodegradable and environmentally friendly [8, 9].

N-acyl amino acid surfactant is a type of surfactant of amino acids with a polar head group and a hydrophobic tail connected by amide bonds. This surfactant has good application prospects in the cosmetic field [10] because the surfactant n-acyl amino acid has good antimicrobial properties for the skin [11]. N-acyl amino acids and N-acyl laureates are nonionic surfactants [12], wherein nonionic surfactants have a better ability than other surfactants [13, 14].

Stearic acid is a mixture of solid organic acids obtained from fatty acids, mostly from octadecanoic acid (C<sub>18</sub>H<sub>36</sub>O<sub>2</sub>) and hexadecanoic (C<sub>16</sub>H<sub>32</sub>O<sub>2</sub>) hard, white, or yellow solid substance, slightly smelly, similar to waxy

fat. Stearic acid has the ability as a compatibilizer and has properties as a dispersant and lubricant. Stearic acid has been widely used in surfactant synthesis because stearic acid can be obtained in large quantities from vegetable oil derivatives such as palm oil. Besides, vegetable oil is the most common and inexpensive ingredient [15].

Lysine is one of the essential amino acids and one of the amino acids that are deficient in protein feed raw materials, primarily from vegetable ingredients. Lysine is antibacterial, which is both used in the pharmaceutical and biomedical fields [16, 17].

The response surface method consists of methods to determine the optimal operating conditions from experimental methods [18]. Typically, this involves several trials and using one of the experiment results to provide direction on what to do next [19]. Subsequent actions usually focus on experimenting around different conditions or gathering more current experimental data to fit higher-order models [20, 21].

Based on the theory that has been described, it is necessary to research to obtain a better n-stearoyl lysine surfactant with a better percentage conversion. For this reason, efforts can be made, among others, by observing the effect of the reaction variables (substrate mole ratio, solvent ratio, and catalyst concentration) and observing the effect of interactions and the optimum conditions of the reaction variables so that the problem is observing the influence of the three dominant research variables affecting the acquisition of N-stearoyl lysine surfactant and optimizing the effect of these three variables to obtain surfactants with the maximum stearic acid conversion.

## MATERIALS AND METHODS

### Chemicals

This study used the main ingredients of stearic acid (C<sub>18</sub>H<sub>36</sub>O<sub>2</sub>) and Lysine (C<sub>6</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>), then calcium



oxide (CaO) as a catalyst, and hexane (C<sub>6</sub>H<sub>14</sub>) and 2-propanol (C<sub>3</sub>H<sub>8</sub>O) as a mixed solvent. As a purification material in the form of citric acid and acetone, and as an analysis material in potassium hydroxide (KOH), phenolphthalein, 2-propanol, and hydrochloric acid (HCl).

### Amidation Process

The oxidation process is carried out in a three-neck flask equipped with a hot plate and reflux condenser. 5 g of stearic acid (SA) is put in a three-neck flask. Mixed solvent hexane/2-propanol 1/1 (w/w) with a solvent: substrate ratio (v/w) 1 to 3 is put into a beaker glass, and lysine is added with variations in the ratio of lysine: stearic acid 2 to 4 (L/SA). Furthermore, calcium oxide (CaO) catalyst is added to the beaker with a weight percent ratio of 3 to 7 to stearic acid. The mixture in a beaker glass is put into a three-neck flask. Heated to a temperature of 65°C, and the mixture was stirred with a magnetic stirrer at 250 rpm for 3 hours. The mixture is separated from the catalyst by filtering, and the solvent is evaporated.

The mixture was added 5 ml of 10% citric acid to precipitate the catalyst. The product mixed with the solvent is separated by evaporating the solvent at 90°C. The product containing excess lysine is then washed with acetone twice the product mix volume that will dissolve the lysine and filtered. The product will be obtained as a bottom layer, while excess lysine will dissolve with acetone as the top product. Excess acetone in the bottom product is evaporated until it is removed-calculated product mass and conversions.

### Optimization Procedures

To obtain N-stearoyl lysine surfactant, the oxidation method of stearic acid and lysine is used and uses a mixture of organic solvents (S) and calcium oxide

as a catalyst. There are three variations of the variables chosen in this study: substrate ratio, solvent ratio, and catalyst weight.

A second-order research design was used Box-Behnken Design (BBD), which combines the 2k factorial plus the observation points at the center point [18]. The maximum stearic acid conversion yield involved three factors and three levels and required 15 trials for data acquisition and response surface modeling [19]. Existing independent variables are coded ( $\pm 1$ ; 0) to simplify calculations.

BBD was chosen as a form of experimental design because it is considered to provide a systematic design to obtain the interaction between variables so that the best interaction is obtained, which results in the maximum conversion of stearic acid. The interaction of the three variables used was the substrate mole ratio (X<sub>1</sub>), solvent ratio (X<sub>2</sub>), and catalyst weight (X<sub>3</sub>). The variables and coded levels are listed in Table-1, and the yields of stearic acid converted into products at each level of the combination are given in Table-2.

**Table-1.** Variables and coded levels of N-stearoyl-lysine synthesis.

Variable	Variable Code	Level		
		-1	0	+1
Substrate (L/SA)	X <sub>1</sub>	2	3	4
Solvent (v/wSA)	X <sub>2</sub>	1	2	3
Catalyst (w/wSA)	X <sub>3</sub>	3	5	7

**Table-2.** Acquisition of stearic acid converted into products at each combination level.

Experiment No.	Substrate (X <sub>1</sub> , mol L/SA)		Solvent (X <sub>2</sub> , v/wSA)		Catalyst (X <sub>3</sub> , w/wSA)		Conversion (%)
	Code	Actual	Code	Actual	Code	Actual	
1	-1	2	-1	1	0	5	79.81
2	1	4	-1	1	0	5	80.96
3	-1	2	1	3	0	5	83.88
4	1	4	-1	3	0	5	85.20
5	-1	2	0	2	-1	3	79.55
6	1	4	0	2	-1	3	80.37
7	-1	2	0	2	1	7	82.00
8	1	4	0	2	1	7	83.97
9	0	3	-1	1	-1	3	79.23
10	0	3	1	3	-1	3	83.34
11	0	3	-1	1	1	7	82.67
12	0	3	1	3	1	7	84.57
13	0	3	0	2	0	5	80.41
14	0	3	0	2	0	5	79.97
15	0	3	0	2	0	5	80.00

## RESULTS AND DISCUSSIONS

This synthesis's response variable was the percent conversion of stearic acid, and the predictor variables were the substrate molar ratio, solvent ratio, and catalyst weight. The relationship between response variables and predictor variables will be determined by linear regression analysis, and for the regression equation obtained, analysis of variance (ANOVA) is then performed. ANOVA aims to mathematically test the regression model between the response variable and the predictor variable. The confidence level used is 95%, so that the value  $\alpha = 0.05$  is obtained, meaning that the maximum error tolerance is 5% [18, 20].

This model's prediction is made by looking at the regression value ( $R^2$ ) of the model obtained. This  $R^2$  value will be displayed in the form of a percent to make it easier to see the size of the independent variable's influence on the measured parameter. Besides seeing the  $R^2$  value of a model, it is also necessary to look at the model's p-value, where the p-value is not more than the  $\alpha$  value. Using the Minitab application, you can also get an equation model, where the equation model can be used to get the conversion value from the model. The conversion value of the model will later be useful compared to the actual conversion value [14, 21].

The results of the prediction of the regression coefficients for constructing the welcome surface model

are listed in Table-3. From Table-3, the p-value for substrate ratio, solvent ratio, and catalyst weight are 0.001, respectively; 0.000; and 0.000. The p-value of the three variables is smaller than  $\alpha$  (5%). So that all factors are significant because the value of all factors is less than 5%. In addition to the  $R^2$  and p-values, Table 3 also shows an equation model that connects the three variables and their interaction with the percent conversion. The resulting model is as follows.

$$\begin{aligned}
 \text{Conversion (\%)} = & 87.78 - 4.21 \text{ Substrate (L/SA)} \\
 & - 3.59 \text{ Solvent (v/wSA)} - 0.879 \text{ Catalyst (w/wSA)} \\
 & + 0.678 \text{ Substrate (L/SA)*Substrate (L/SA)} \\
 & + 1.658 \text{ Solvent (v/wSA)*Solvent (v/wSA)} \\
 & + 0.1670 \text{ Catalyst (w/wSA)*Catalyst (w/wSA)} \\
 & + 0.043 \text{ Substrate (L/SA)*Solvent (v/wSA)} \\
 & + 0.144 \text{ Substrate (L/SA)*Catalyst (w/wSA)} \\
 & - 0.276 \text{ Solvent (v/wSA)*Catalyst (w/wSA)}
 \end{aligned} \quad (1)$$

The negative sign in the equation shows the inversely proportional relationship with the % conversion [15]. The value of  $X_2$  gave the most significant influence, namely 1.9212, on the % conversion. The positive value of the coefficient  $X_2$  shows an enormous influence on the % conversion compared to other experimental variables.

**Table-3.** The value of the equation model that connects the three variables with the percent conversion.

Term	Effect	Coefficient	SE Coef	T-Value	P-Value	VIF
Constant		80.127	0.262	305.34	0.000	
Substrate (L/SA)	1.315	0.658	0.161	4.09	0.009	1.00
Solvent (v/wSA)	3.580	1.790	0.161	11.14	0.000	1.00
Catalyst (w/wSA)	2.680	1.340	0.161	8.34	0.000	1.00
Substrate (L/SA)* Substrate (L/SA)	1.356	0.678	0.237	2.87	0.035	1.01
Solvent (v/wSA)* Solvent (v/wSA)	3.316	1.658	0.237	7.01	0.001	1.01
Catalyst (w/wSA)* Catalyst (w/wSA)	1.336	0.668	0.237	2.82	0.037	1.01
Substrate (L/SA)* Solvent (v/wSA)	0.085	0.043	0.227	0.19	0.859	1.00
Substrate (L/SA)* Solvent (v/wSA)	0.575	0.287	0.227	1.27	0.262	1.00
Solvent (v/wSA)* Solvent (v/wSA)	-1.105	-0.553	0.227	-2.43	0.059	1.00

### Effect of Substrate Ratio and Solvent Ratio

The observations in Figure-1 show a contour plot of the effect of the substrate ratio and the solvent ratio on the conversion of stearic acid on the best prediction of the amount of catalyst, namely 5% (w/wSA). The contour in Figure-1 shows that the conversion of n-stearoyl lysine will increase gradually with increasing substrate ratio and solvent ratio. The optimization result of the stearic acid conversion on these two variables' interaction is at a ratio of 4 (L/SA) for the substrate ratio and 3 (v/wSA) for the solvent ratio, and the best conversion is 85.20%. When viewed from the contour plot, the ratio is in the area with more than 84% conversion.

A slightly different result is shown in Figure-2, namely, at the 3% hold value of the catalyst, which is the minimum catalyst concentration value in this study. It was found that at a constant solvent ratio and a minimum catalyst concentration, increasing the substrate ratio did not succeed in increasing the stearic acid, which was converted to an amide. The conversion will keep increasing gradually if the solvent ratio increases, and the substrate ratio is constant.

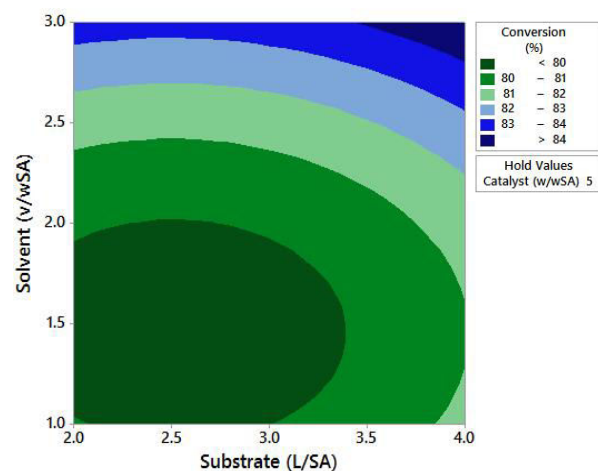
The use of a catalyst at a maximum value of 7% seems to increase the converted stearic acid, on the observation of the interaction between the substrate ratio and the solvent ratio in Figure-3. The best amide recovery is obtained from the combination of substrate ratio 4 (L / SA) and solvent ratio 3 (v/wSA). In this optimal condition, it will get a stearic acid conversion of > 86%. This result is in line with previous studies where product yields will also be maximum [15].

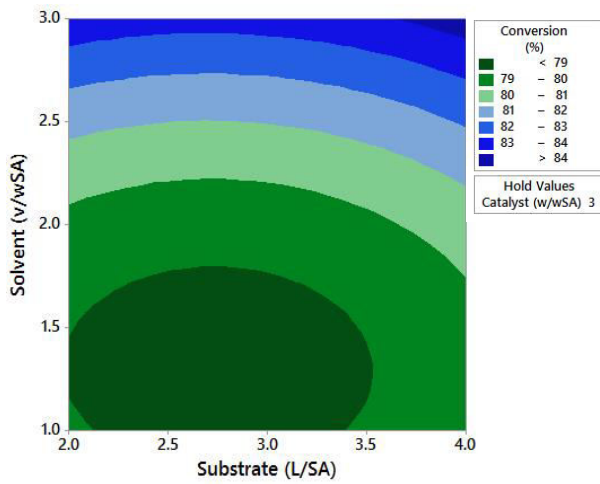
### Effect of Substrate Ratio and Weight of Catalyst

The observations in Figure-4 show a contour plot of the effect of the substrate ratio and the catalyst's weight on the conversion of stearic acid. Figure-4 shows that when the maximum substrate and catalyst ratio is maximum, a high lauric acid conversion will be obtained. When the substrate ratio is close to 3.5 (L/SA), but the catalyst concentration is still less than 4% (w/wSA), the converted stearic acid is still less than 80%. So, it appears

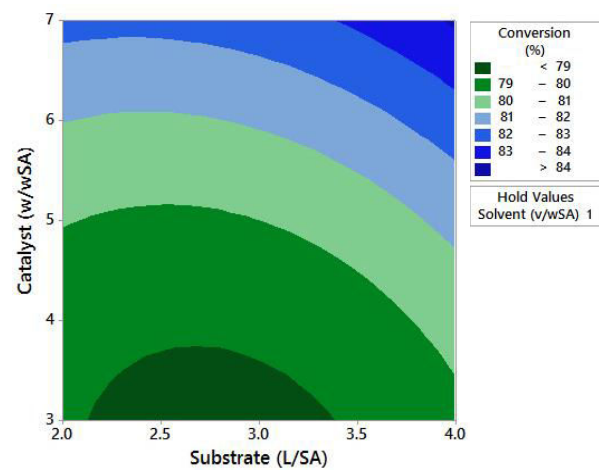
that the catalyst plays a more critical role in increasing the amount of stearic acid that is converted. This calculation is in line with the developed model, where the catalyst concentration coefficient is greater than the substrate ratio so that the effect of catalyst concentration is more dominant in increasing the conversion of stearic acid [7, 9].

Figure-5 shows the effect of the interaction between the substrate and catalyst ratios on using a minimum solvent ratio of 1 (v/wSA). The contour plot obtained shows that the maximum conversion of stearic acid is obtained in the linear increase of both substrate and catalyst concentrations. However, the maximum conversion seen from the contour plot is still not as good as using a solvent ratio of 2 (v/wSA). It is estimated that the amount of solvent is still not optimal to dissolve the entire substrate used [12].

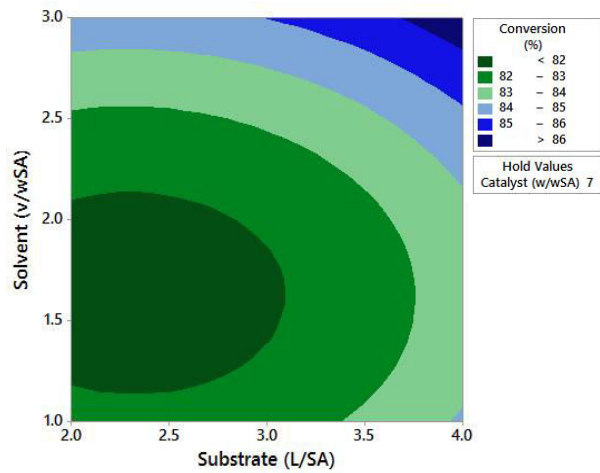
**Figure-1.** Plot contour of the substrate ratio and solvent ratio at hold value 1 w/wSA.



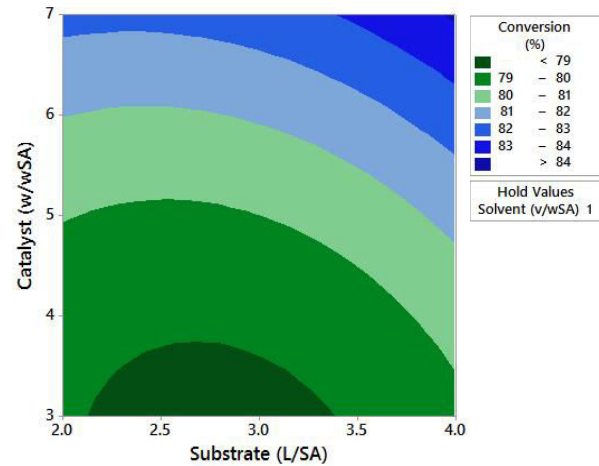
**Figure-2.** Plot contour of the substrate ratio and solvent ratio at hold value 3 w/wSA.



**Figure-4.** Plot contour of substrate ratio and catalyst weight at hold value 2 v/wSA.

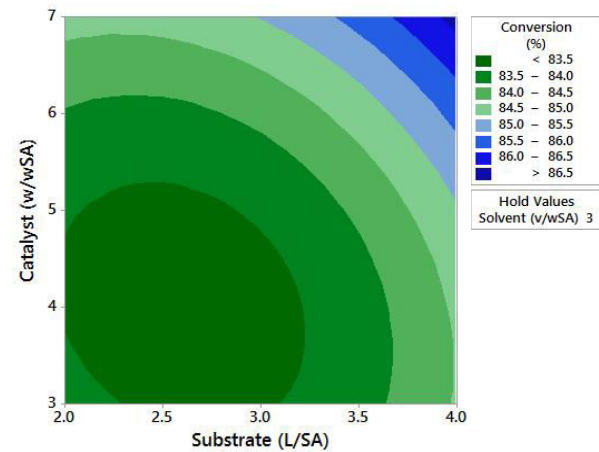


**Figure-3.** Plot contour of the substrate ratio and solvent ratio at hold value 7 w/wSA.



**Figure-5.** Plot contour of substrate ratio and catalyst weight at hold value 1 v/wSA.

At hold value for solvent ratio 3 (v/wSA), the interaction between the substrate and catalyst ratio is shown in Figure-6. The contour plot obtained shows that in the range of solvent ratio 2-3 (v/wSA) and the amount of catalyst 3-5% (w/wSA), the converted stearic acid will decrease significantly, although it is still in the 80% range.



**Figure-6.** Plot contour of substrate ratio and catalyst weight at hold value 3 v/wSA.

The best results appear to be obtained when using a substrate ratio of 4 (L/SA) and a catalyst of 7% (w/wSA), wherein the stearic acid converted reached more



than 86.5%. From the plots above, it can be seen that the CaO catalyst used is correct and optimal in the synthesis. CaO is a catalyst with high activity, can be used in moderate conditions and has a long life. However, these catalysts melt quickly and have a low surface area [4, 10].

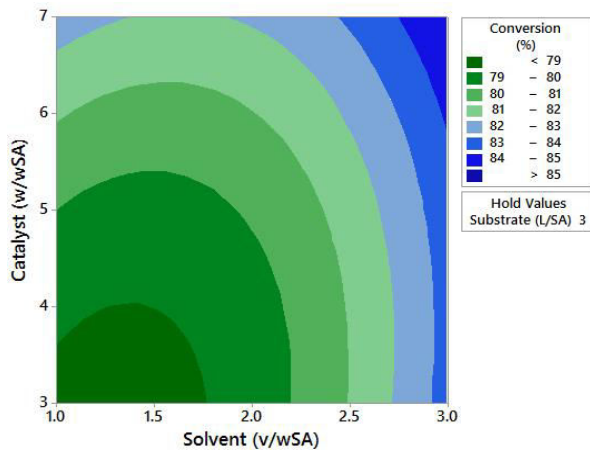


Figure-7. Plot contour of catalyst weight and solvent at hold value 3 L/SA.

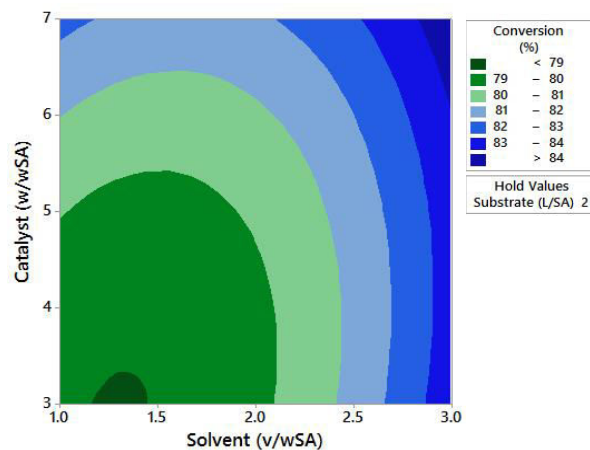


Figure-8. Plot contour of catalyst weight and solvent at hold value 2 L/SA.

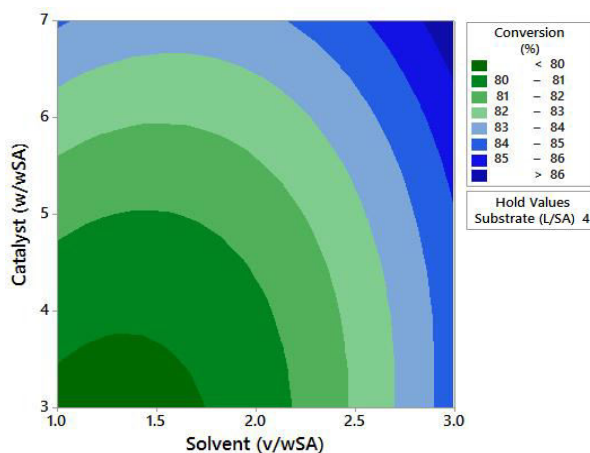


Figure-9. Plot contour of catalyst weight and solvent at hold value 4 L/SA.

### Effect of Solvent Ratio and Catalyst Weight

The observations in Figure-7 show a contour plot of the effect of the ratio of solvent and catalyst weight on stearic acid conversion to produce n-stearoyl lysine. This contour plot shows that at a solvent ratio of less than 2 (v/wSA), the conversion of stearic acid will increase linearly as the catalyst increases. However, at the maximum solvent ratio of 3 (v/wSA), using either a low or high-grade catalyst, all of which resulted in the maximum yield of stearic acid conversion, which was more than 85%. So it is concluded that the variable solvent ratio plays a more significant role in increasing the conversion than the variable catalyst concentration [13].

The contour plot in Figure-8 shows the effect of the interaction between the solvent and catalyst ratio on the minimum hold value of the substrate ratio. The same pattern as Figure-7 is also found here. At a low solvent ratio, increased use of a catalyst will increase the linear conversion of stearic acid, and the solvent ratio is more significant in increasing the yield of the product than the amount of catalyst.

The use of catalyst and solvent that is more than the median value shows the maximum results, as shown in Figure-9. Where the hold value for the substrate ratio is 4 (L/SA) and uses a solvent ratio of 3 (v/wSA) and a catalyst of 7% (w/wSA), then the stearic acid that is depleted and turned into products is more than 86%.

So it is concluded that the solvent ratio has a more substantial effect in increasing the conversion than the catalyst concentration. However, from the results of the regression model predictions, the three variables have a significant effect on the converted stearic acid, but the solvent ratio coefficient is greater than the catalyst concentration and the substrate ratio.

### Identification of N-Stearoyl Lysine

The N-stearoyl lysine functional group was detected using FT-IR spectroscopy. Figure-10 shows the results of the FT-IR spectrum analysis of the stearic acid raw material. The OH stretching absorption of stearic acid is found at  $2904.80\text{ cm}^{-1}$  and  $2657.91\text{ cm}^{-1}$ , a typical absorption of the C-H  $\text{sp}^3$  stretching vibration supported by the C-H  $\text{sp}^3$  bending vibration in the wavenumber area  $1431.18\text{ cm}^{-1}$ . At a wavelength of  $1700\text{-}1725\text{ cm}^{-1}$ , carbonyl absorption will be found, which in Figure 10 is found at  $1708.93\text{ cm}^{-1}$  with a strong enough intensity. The area of the stearic acid fingerprint showed a C-O stretch at  $1292.31\text{ cm}^{-1}$ .

Figure-11 shows the infrared spectrum of the lysine raw material used. Lysine showed C-C absorption at  $933.55\text{ cm}^{-1}$ . NH bending was found at  $1566.2\text{ cm}^{-1}$ , and OH bending at  $1369.46\text{ cm}^{-1}$ . Meanwhile, the NH stretch band was found at  $3336.85\text{ cm}^{-1}$ .

Figure-12 shows the results of FT-IR spectrum analysis on the best run of surfactant n-stearoyl lysine, namely the ratio of lysine to stearic acid 4 (L/SA), catalyst concentration of 5% (w/wSA), and solvent to substrate ratio of 3 (v/wSA). The result of this amidation reaction was purified by a purification procedure and then analyzed by FT-IR. The C-N stretch also expresses the vibration for



the C-N bond at  $1222.87\text{ cm}^{-1}$ . The peak of the absorption can be seen in the area of wave number  $3429.43\text{ cm}^{-1}$  which indicates the presence of an OH group. The vibration of the C = O (carbonyl) group appears in the region of wave number  $1651.07\text{ cm}^{-1}$  and C-N at  $1388.75\text{ cm}^{-1}$  which is a typical group of N-C = O amide.

## CONCLUSIONS

The best optimization conditions were obtained with the variable substrate ratio 4 (L/SA), solvent ratio 3 (v/wSA), and 5% catalyst weight (w/wSA), which resulted in a stearic acid conversion of 85.20%.

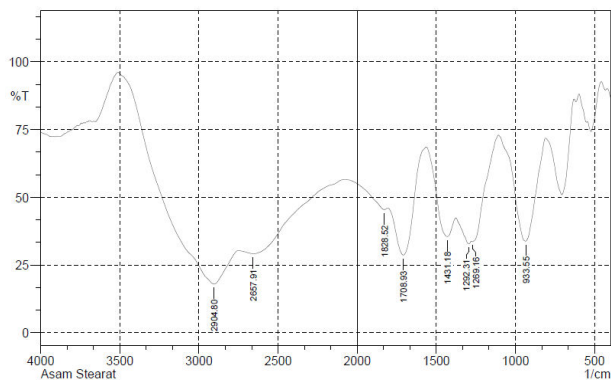


Figure-10. Results of the stearic acid spectrum.

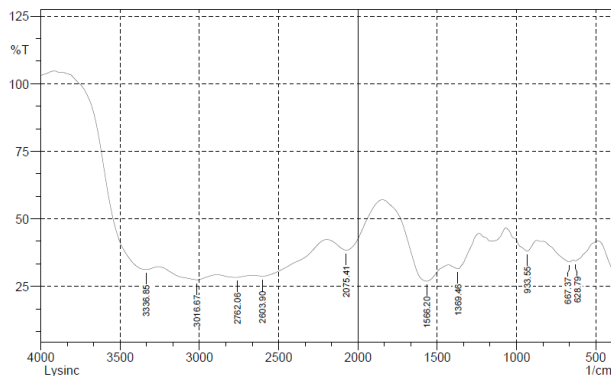


Figure-11. Results of the lysine spectrum.

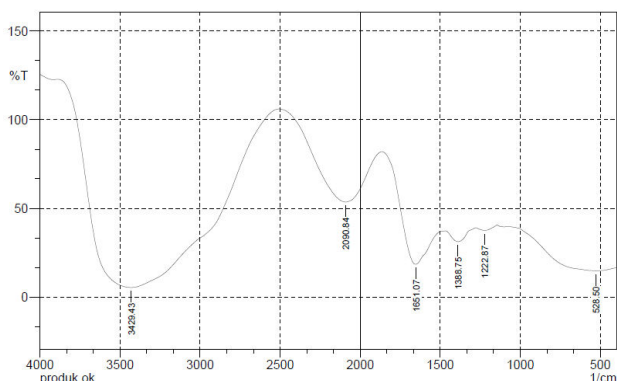


Figure-12. Results of the n-stearoyl lysine spectrum from the optimal result.

The prediction model that was carried out gave an  $R^2$  value of 93.11%. Analysis of variance shows that the model is linear and the model is quadratic with value ( $P = 0.000$ ); ( $P = 0.000$ ), has a significant effect on the model, but the interaction model between factors with value ( $P = 0.001$ ), does not have a significant effect. The interaction relationship between the substrate ratio and the solvent ratio with the conversion of n-stearoyl lysine shows a more significant effect than the catalyst's weight.

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