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SYNTHESIS OF FATTY ETHANOLAMIDES FROM LAURIC AND PALMITIC ACID: OPTIMIZATION USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT

Response Surface Methodology is used for the prediction and optimization of the conversion of lauric and palmitic acid in the synthesis of fatty ethanolamide from monoethanolamine using zirconium (IV) chloride as a metal catalyst and n-hexane with isopropanol as a mixed solvent. By performing some experimental design by Central Composite Design, a suitable range of independent parameter of substrate molar ratio, catalyst concentration, and the solvent ratio was determined using a contour plot approach. Results show that the substrate molar ratio and catalyst concentration are the significant parameters on the lauric acid conversion, and the solvent ratio is the significant parameter on the palmitic acid conversion. The conversion is decrease by reducing catalyst concentration, and by increasing the substrate molar ratio amine to acid up to 10/1, the conversion increase but afterward gradually decreases.

Keywords: amidification, monoethanolamine, metal catalyst, response surface methodology.

INTRODUCTION

Fatty ethanolamides are versatile oleochemicals that usually used as non-ionic surfactants in personal care and household products [1]. Fatty ethanolamides can be produced by reacting fatty esters and fatty acids with monoethanolamine [2]. However, the reaction using fatty acids is preferred because the by-product of the reaction is in the form of water, where water is safer rather than methanol [3, 4]. Water separation is easier to do by dissolving the product mixture with acetone, while if the by-product is methanol the separation is done by evaporating methanol or working at near-vacuum pressure [5, 6].

In general, surfactants fatty ethanolamine used as thickener, foam stabilizer and defoaming agent [7]. Specifically, fatty ethanolamides from lauric acid are widely used in cosmetic products, namely as thickener, softener and moisturizer, as well as in medicinal products, because they have good antimicrobial properties [8, 9]. Fatty ethanolamide from palmitic acid itself has been known to function as mast cell degranulation inhibitors, reduce allergic reactions, and show anti-inflammatory activity and reduce pain sensations [5, 10].

Lauric acid and palmitic acid are medium and long-chain saturated fatty acids that are abundant, renewable, and readily available in nature [9]. The reaction results between lauric acid and palmitic acid with monoethanolamine will produce lauroyl and palmitoylethanolamide, respectively. The use of monoethanolamine as an amine source is very interesting to be developed because the presence of amine groups and alcohol in monoethanolamine is expected to show a unique ability of reaction for both groups [11].

The use of transition metal salts as a catalyst is an interesting research to observe [12]. One of a group of IV transition metals, whose availability is abundant in the earth's crust is zirconium (IV) chloride. Zirconium (IV) chloride is a catalyst with low toxicity, easy to handle, has high catalytic activity and strong coordination ability which allows it to produce very good reactions [13]. Zirconium (IV) chloride also has a high efficiency in the direct amidation of carboxylic acids with primary and secondary amines [10].

The success of this amidification process is characterized by the acquisition of high fatty acid conversions [14]. The highest conversion of fatty acids is influenced by input parameters. Due to the many types of independent variables involved, a new method is needed so that the control and optimization of amidification processes are not costly and time-consuming tasks.

One of the most widely used methods to solve this problem is Response Surface Methodology (RSM). The RSM technique is easy to estimate can observe the effect of interaction between two variables and can find the best compromise between the responses evaluated [15, 16, 17]. The model produced by RSM can also be useful for further investigation of search space by excluding observations on unexpected responses [18, 19, 20].

In this research, by controlling the input parameter of the substrate molar ratio, catalyst concentration, and solvent ratio, the optimal fatty acid was obtained from the experimental test. There are three factors with each of the five levels, and the value of each level has been confirmed in the previous study [3, 6]. Then by using Central Composite Design (CCD) and RSM, the effects of input parameters were investigated on fatty acid conversion. After that, the best value of input parameters was predicted for achieving higher conversion [21]. carboxylic acids with primary and secondary amines [1, 16].

MATERIALS AND METHODS

Materials

The sources of fatty acids (FA) used are lauric acid (LA) and palmitic acid (PA). Lauric acid ($C_{12}H_{24}O_2$), palmitic acid ($C_{16}H_{28}O_2$), monoethanolamine (C_2H_7NO) and zirconium (IV) chloride ($ZrCl_4$) were purchased from E Merck, Darmstadt Germany. All common chemicals and solvents were purchased from commercial sources and used as received.

Amidification of Monoethanolamine

The required amount of fatty acid (FA) was added to the three-neck flask. Added a mixture solvent of n-hexane and isopropyl alcohol (1/1, v/v) with a solvent ratio of 0.318 to 3.682 (v/wFA). Monoethanolamine (MEA) was then added with a variation of the substrate molar ratio of 6.636 to 13.336 (MEA/FA). After homogeneous, zirconium (IV) chloride catalyst was added with a concentration of 1.636 to 8.364 (w/wFA) to fatty acids. The raw material mixture is heated at a temperature of 65^{o}C, for 3 hours with a stirring speed of 250 rpm. Then, the product was mixed with 5 mL citric acid to precipitate the catalyst and the precipitate formed was separated by filtration. After removing the metal catalyst, the lauroyl or palmitoyl ethanolamide produced was separated from the mixed solvent in a rotary evaporator at 90^{o}C. Then the product was mixed with acetone to remove the remaining monoethanolamine.

Fatty ethanolamide products will be obtained as a lower layer, while excess monoethanolamine will dissolve with acetone as the top product. In order to make sure about the complete removal of the solvent, the residue was placed in a freeze dryer. The acid number of the solution is determined at the beginning and the end of the experiment.

Optimization of the process

The design in this study uses the CCD method with a total run of 20 runs and done in duplicate [8]. Furthermore, the research data obtained were analyzed using MINITAB 17 software (trial version) to form the relationship between variables that can be determined by regression analysis. The equations obtained, are then tested by Analysis of Variance (ANOVA). ANOVA is used to test individual parameter freedom and compare the components of total deviation [7, 21]. Variables and levels developed are included in Table-1.

Table-1. Variables and levels developed.

Variable	Code Levels of Variables				
	-1.682	**-1**	**0**	**1**	**1.682**
Substrate Molar Ratio (MEA/Fatty Acid)	6.636/1	8/1	10/1	12/1	13.364/1
Catalyst Concentration (w/wFatty Acid)	1.636	3	5	7	8.364
Solvent Ratio (v/wFatty Acid)	0.318/1	1/1	2/1	3/1	3.682/1

Table-2. The optimization results of the synthesis of lauroyl and palmitoyl ethanolamide.

Experiment No.	Substrate Molar Ratio (X_1)	Catalyst Concentration (X_2)	Solvent Ratio (X_3)	Lauric Acid Conversion (Y_{LA})	Palmitic Acid Conversion (Y_{PA})
1	-1	-1	-1	96.8254	74.6410
2	1	-1	-1	95.2381	73.5897
3	-1	1	-1	87.6191	78.4102
4	1	1	-1	91.7460	75.7179
5	-1	-1	1	94.2857	92.6496
6	1	-1	1	95.3824	93.4615
7	-1	1	1	89.4179	92.4359
8	1	1	1	96.2273	94.6154
9	-1.682	0	0	90.6878	90.6410
10	1.682	0	0	95.4497	91.6154
11	0	-1.682	0	95.5555	80.7692
12	0	1.682	0	94.4974	91.3589
13	0	0	-1.682	91.8519	71.2341
14	0	0	1.682	92.4868	91.2820
15	0	0	0	96.5080	91.2820
16	0	0	0	95.9790	90.2370
17	0	0	0	96.0840	88.9894
18	0	0	0	96.4023	90.8974
19	0	0	0	96.2184	91.6667
20	0	0	0	96.3824	91.0256

RESULTS AND DISCUSSIONS

The fatty ethanolamide in this study was obtained from the reaction between lauric acid or palmitic acid with monoethanolamine (MEA) as an amine source, using n-hexane with isopropyl alcohol as a solvent and zirconium (IV) chloride ($ZrCl_4$) as a catalyst. The main problem of this synthesis is the conversion of fatty acids that are not too high. For this purpose, optimization of fatty acid, the conversion was carried out on three dominant variables, namely substrate molar ratio, catalyst concentration, and solvent ratio. The optimization result, for the synthesis of lauroyl and palmitoylethanolamide in percent conversion values of fatty acid are shown in Table-2.

Model prediction and analysis of variance

The initial stage in RSM is predicting the regression model, then proceed with the analysis of variance and model verification test. The goal is that the model does not deviate from the actual situation. In Table 3 and Table 4, the results of predictions of regression coefficients are used to compile a response surface model for the synthesis of lauroyl- ethanolamide and palmitoyl-ethanolamide synthesis in sequence. Based on Table-3 and Table-4, the equation model, which can show the relationship of reaction variables and their interaction with the percent conversion of lauric acid (Y_{LA}) and palmitic acid (Y_{PA}) in fatty ethanolamide synthesis, was obtained as follows:

$$Y_{LA} = 96.2593 + 2.2728X_1 - 2.2786X_2 + 0.6101X_3 - 3.1379X_1^2 - 1.1802X_2^2 - 4.0373X_3^2 + 4.0408X_1X_2 + 1.8966X_1X_3 + 3.0680X_2X_3 \quad (1)$$

$$Y_{PA} = 90.7294 - 0.1092X_1 - 3.0352X_2 + 12.8713X_3 - 0.4113X_1^2 - 5.4755X_2^2 - 10.2815X_3^2 - 0.0967X_1X_2 + 2.3812X_1X_3 - 1.7526X_2X_3 \quad (2)$$

where X_1, X_2, X_3 is the substrate molar ratio, catalyst concentration, and solvent ratio.

The biggest and most significant positive effect on the synthesis of lauric acid is the substrate molar ratio and catalyst concentration. When at the synthesis of palmitic acid, the solvent ratio shows a positive value and gives the most significant effect on percent conversion compared to other variables.

Table-3. The Prediction of Regression Coefficient for the Synthesis of Lauroyl Ethanolamide.

Term	Coef	P
Constant (Y)	96.2593	0.000
Substrate Molar Ratio (X_1)	2.2728	0.001
Catalyst Concentration (X_2)	-2.2786	0.001
Solvent Ratio (X_3)	0.6101	0.230
(X_1)*(X_1)	-3.1379	0.002
(X_2)*(X_2)	-1.1802	0.162
(X_3)*(X_3)	-4.0373	0.000
(X_1)*(X_2)	4.0408	0.003
(X_1)*(X_3)	1.8966	0.101
(X_2)*(X_3)	3.0680	0.015
S = squared due to error, residual, deviance = 1.0497		
R-Sq = total squared = 91.88%		
R-Sq(adj) = squares due to treatment = 84.57%		

Table-4. The Prediction of Regression Coefficient for the Synthesis of Palmitoyl Ethanolamide.

Term	Coef	P
Constant (Y)	90.7294	0.000
Substrate Molar Ratio (X_1)	0.1092	0.923
Catalyst Concentration (X_2)	3.0352	0.020
Solvent Ratio (X_3)	12.8713	0.000
(X_1)*(X_1)	-0.4113	0.823
(X_2)*(X_2)	-5.4755	0.012
(X_3)*(X_3)	-10.2815	0.000
(X_1)*(X_2)	-0.0967	0.969
(X_1)*(X_3)	2.3812	0.346
(X_2)*(X_3)	-1.7526	0.0483
S = squared due to error, residual, deviance = 2.4055		
R-Sq = total squared = 94.92%		
R-Sq(adj) = squares due to treatment = 90.35%		

The influence of independent variables X_1, X_2, and X_3 on the dependent variable, Y, is indicated by the coefficient of determination (R^2). From the analysis of variance, R^2 values for lauroyl and palmitoylethanolamide synthesis were 91.88% and 94.92% respectively. So that for the two reactions, the selected independent variables greatly influence the dependent variable.

Interaction of substrate molar ratio and catalyst concentration

Analysis of the interaction effect of the variables aims to determine the relationship between the percent conversion of fatty acids (Y) with the substrate molar ratio (X_1), catalyst concentration (X_2) and the solvent ratio (X_3), and to optimize the response, the conversion of fatty acid. The interaction effect of substrate molar ratio and catalyst concentration on the percent conversion of fatty acid is indicated by the contour response in Figure-1 and Figure-2.

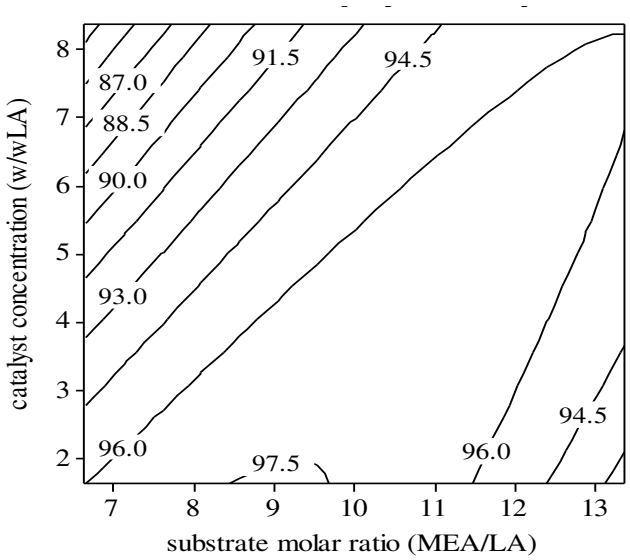

Figure-1. The interaction effect of substrate molar ratio and catalyst concentration for lauroyl ethanolamide

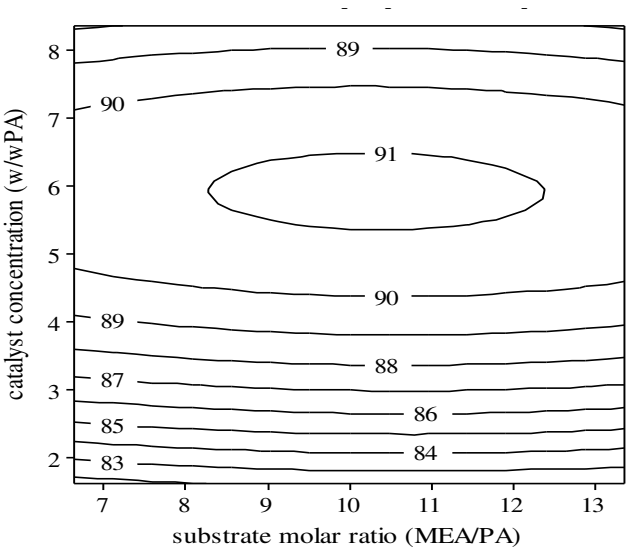

Figure-2. The interaction effect of substrate molar ratio and catalyst concentration for palmitoyl ethanolamide.

The observation for the synthesis of lauroyl ethanolamide in Figure-1 shows that if the concentration of $ZrCl_4$ is maintained at a certain amount and the substrate molar ratio is increased, the percent conversion will experience a slight but not significant decrease. Conversely, if the $ZrCl_4$ catalyst is increased and the substrate molar ratio is maintained at a certain amount, the percent of conversion increases.

Meanwhile, observations of the contour plot in Figure-2 show that the conversion of palmitic acid will increase along with the increase in the substrate molar ratio and catalyst concentration to certain limits. This contour plot also shows that the increase in palmitoyl ethanolamide conversion is sharper when the catalyst concentration increases compared to when the substrate ratio increases.

The substrate molar ratio between fatty acids and monoethanolamine is one of the important factors and affects the acquisition of fatty ethanolamide surfactants [6]. At the high substrate ratios, monoethanolamide results are generally high. The acquisition influenced by the number of amines [1]. However, a further increase in the substrate molar ratio resulted in a decrease in monoethanolamide yield due to the effect of thickening ethanolamine [3].

The maximum conversion of lauric acid obtained at lauroyl ethanolamide synthesis was obtained at substrate molar ratio of 10/1-11/1 (MEA/LA) with 2-5% catalyst concentration, while for palmitoylethanolamide synthesis obtained at substrate molar ratio of 10/1-11/1 (MEA/PA) and catalyst concentration of 5-7%.

Interaction of substrate molar ratio and solvent ratio

The fatty ethanolamide synthesis was carried out for 3 hours with a reaction temperature of 65^{o}C and a stirring speed of 250 rpm. Figure-3 shows the expression of the contour response to percent conversion in the synthesis of lauroyl ethanolamide. It was observed that in the low and high range of substrate ratio and solvent ratio, it would be possible to obtain the maximum conversion of lauric acid. Thus, if the solvent ratio is maintained at a certain amount and the ratio of the substrate is increased, there will be a reduction in the conversion of lauric acid. Likewise, if the solvent ratio is raised and the substrate ratio is maintained, the percent conversion also decreases. Observation of the effect of substrate molar ratio and solvent ratio on the conversion of palmitic acid is shown in Figure-4. It can be seen from the figure that the conversion of palmitic acid will increase along with the increase in solvent ratio and substrate molar ratio to certain limits.

From the contours in Figures 3 and 4, it can be seen that the solvent ratio has a greater effect than the substrate molar ratio in the formation of alkyl ethanolamide surfactants. This is because monoethanolamine turns out to be more soluble in polar alcohol solvents while fatty acids are more soluble in non-polar solvents such as n-hexane [9, 10].

Interaction of catalyst concentration and solvent ratio

Observation of the interaction effect between catalyst concentration and solvent ratio to the conversion of fatty acid are shown in Figures 5 and 6. The catalyst used is $ZrCl_4$, which is considered to work efficiently. In Fig 5, for synthesis lauroyl ethanolamide, it can be seen that if the solvent ratio is increased while the catalyst concentration is maintained at a certain amount there is a decrease in the percent conversion of lauric acid. In addition, if the solvent ratio maintained at a certain amount while the catalyst concentration is raised it does not provide a significant increase in the percent conversion.

The contour plot observations in Figure-6 show that the conversion of palmitoyl ethanolamide will increase along with an increase in catalyst concentration and solvent ratio to certain limits. The plot shows that the

increase in the conversion of palmitic acid is sharper when the solvent ratio increases compared to when the catalyst concentration increases. The optimum conditions were obtained at 5-7% catalyst concentration and solvent to palmitic acid ratio of 3/1, resulting in a conversion of 94.6164%.

These results are in line with Tinnis *et al* (2012), who reported that zirconium (IV) chloride is a highly efficient catalyst for carboxylic acid amidification with primary and secondary amines [10].

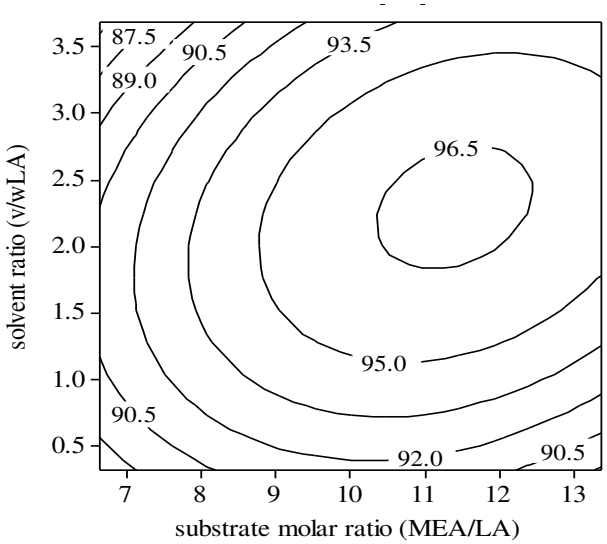

Figure-3. The interaction effect of substrate molar ratio and solvent ratio for lauroyl ethanolamide.

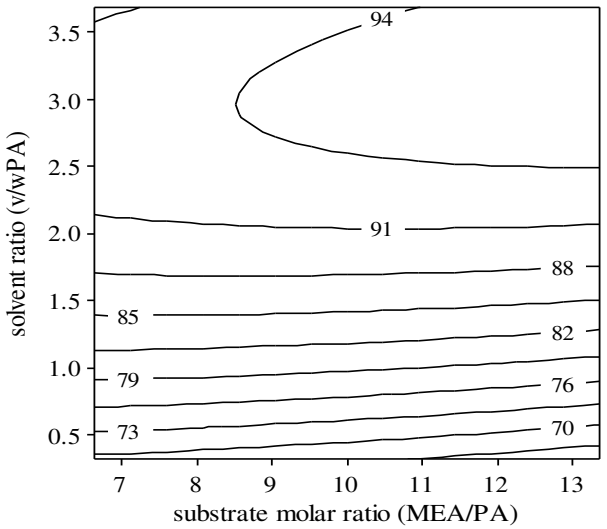

Figure-4. The interaction effect of substrate molar ratio and solvent ratio for palmitoyl ethanolamide.

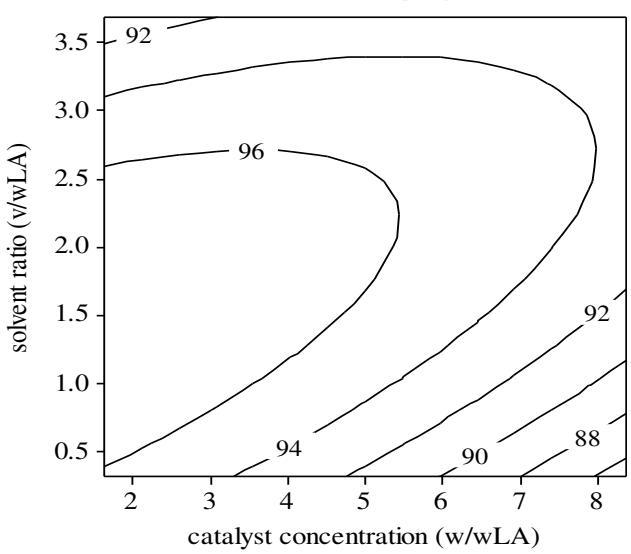

Figure-5. The interaction effect of catalyst concentration and solvent ratio for lauroyl ethanolamide.

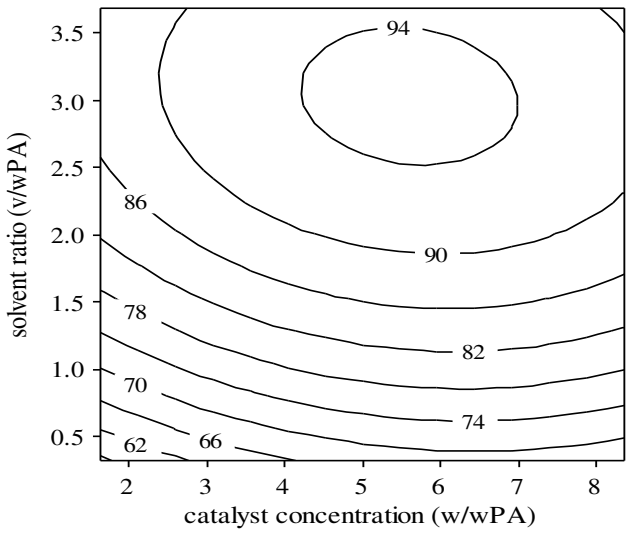

Figure-6. The interaction effect of catalyst concentration and solvent ratio for palmitoyl ethanolamide

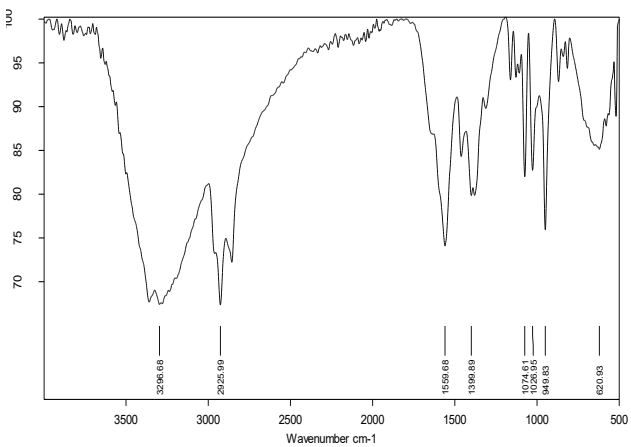

Figure-7. The FT-IR spectrum of lauroyl ethanolamide.

Lunberg *et al* (2012) also reported the application of $ZrCl_4$ in the amidification reaction of a carboxylic acid reacts with an amine and getting a yield of 99% [12]. The solvent ratio has a greater effect than the substrate molar ratio in the formation of lauroyl diethanolamide surfactant [5]. The total volume of the solvent affects the concentration of the product, reactant and catalyst [14]. Solvents in small quantities may not completely dissolve the reactants and products. Reduced product formation occurs because a low solvent volume causes the dissolution of the product and solution to become more turbid [4].

FT-IR spectrum analysis

FT-IR spectroscopy is often used to obtain non-destructive and cost effective measurements [22]. FT-IR was used to detect the functional groups of lauroyl and palmitoyl ethanolamide. As with esters, lauroyl ethanolamide surfactants also have carbonyl groups. Infiltration of the infrared spectrum carbonyl obtained (1630-1840 cm^{-1}), and only at the carbonyl position for lauroyl ethanolamide and esters have differences, the lauroyl ethanolamide leach is at 3300-3500 cm^{-1}, and ester absorption at 1740 cm^{-1}. The results of the lauroyl ethanolamide spectrum obtained, is shown in Figure-7.

It is seen that the presence of a C-N group for amide compounds is indicated by peak absorption obtained (1074.61 cm^{-1}). Then followed the absorption peak at wave number 620.93 cm^{-1}, which states the N-H group. The presence of an N-H group shows a sample containing an amide group. Infiltration peaks at 2925.99 cm^{-1} and 949.83 cm^{-1}, indicate the presence of C-H and C-O groups for aliphatic ester compounds.

CONCLUSIONS

The research variables that significantly influence the acquisition of fatty ethanolamide surfactant are the substrate molar ratio, catalyst concentration, and solvent ratio. The CCD method was used and solved by RSM for a number of twenty observations and the best optimization conditions obtained for the synthesis of lauroyl ethanolamide, were the optimum condition for maximum yield of lauroyl and palmitoyl ethanolamide were obtained at 10/1-11/1 (amine/acid) of substrate molar ratio and 2/1-3/1 (v/w acid) of solvent ratio. However, the optimum catalyst is different for both reactions wherein the synthesis of lauroyl ethanolamide is at a concentration of 2-2.5% (w/wLA) and for palmitoyl ethanolamide is at 5% (w/wPA). Prediction and analysis of variance in both reactions give an R2 value of more than 90%, which shows a significant validity for obtaining fatty acid conversion. Thus it can be concluded that RSM is one of the best methods and can be used to predict the output parameters and save the time and cost of additional experiments.

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