

Chemometric Approach to Assess Response Correlation and its Classification in simplex centroid design for Pre- Optimization stage of Catechin- SNEDDS

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RESEARCH ARTICLE

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Chemometric Approach to Assess Response Correlation and its Classification in simplex centroid design for Pre-Optimization stage of Catechin-SNEDDS

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ABSTRACT:

Catechins are isolated from tea leaves and shown to have pharmacological activities. However, the permeability and absorption capacity of the digestive tract is low, thus affecting the value of bioavailability. Self-nano emulsifying drug delivery system (SNEDDS) is formulated as a breakthrough in nano delivery to increase the value of bioavailability and stability in a model of natural compounds, namely catechins. This study applies chemometrics to the simplex centroid design (SCD) to analyze the catechin-SNEDDS pre-optimization design. The factors defined include oleic acid, croduret 50-SS, and propylene glycol. Evaluation parameters include emulsification time, percent transmittance (%T), freeze-thaw, and endurance test. The results showed a formula that met the requirements at the time of emulsification, stability, and %T. There were four clusters of results from the principal component analysis - cluster analysis (PCA-CA) in the SCD formula. The evaluation between responses in the SCD optimization design is indicated to have a positive correlation. Analysis using multivariate chemometric can describe the characteristics of each formula and the response based on the parameters used, which refers to the similarity, grouping, and correlation of each formula and response. The PCA-CA technique can group formulas from SCD in similar clusters and provide important information regarding response patterns or correlations.

KEYWORDS: SNEDDS, nanoemulsion, catechin, simplex centroid design, chemometric, PCA-CA.

INTRODUCTION:

Catechins are the main ingredients of tea leaves (*Camellia sinensis* L.) and are complex compounds of the polyphenol group with a flavonoid structure. Based on scientific data, catechins have antioxidant activities¹, antiobesity^{2,3}, antidiabetic⁴, and reduce cardiometabolic risk⁵. However, these active polyphenol compounds show less than 5% oral bioavailability, low membrane permeability, and poor absorption in the digestive tract (GIT)⁶. Therefore, catechins are formulated in the self-nano emulsifying drug delivery system (SNEDDS).

SNEDDS is formulated to increase bioavailability and deliver active substances to its target without affecting the surrounding environment by increasing the surface area of the gastrointestinal tract^{7,8,9}. Oil, surfactants, and co-surfactants are essential components in the SNEDDS formulation. The interaction of the three components is determined by the type and concentration of each constituent material^{9,10}. Therefore, in developing the SNEDDS formulation, an optimization stage is needed. Currently, many optimization studies use a mathematical-statistical modeling approach, known as the design of the experiment.

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The design of experiment (DoE) approach to optimization aims to make it easier to design, evaluate, model, predict, and interpretation data mathematically and statistically^{11,12,13}. Simplex centroid design (SCD) is

a DoE optimization approach included in the mixture design (MD). This DoE approach can reduce trial and error, be more effective and efficient because it uses not too many test points (run/formula). The use of SCD makes it possible to get designs with the right number of trials (formulas) and choose the best conditions for a given response through a variety of certain factors¹⁴.

There has been no combination of the SCD approach with chemometrics to design an optimization procedure. Chemometrics is a mathematical approach that can process, evaluate, and interpretation of large amounts of data^{15,16}. Chemometrics is used to facilitate visual interpretation of overlapping data^{17,18}. Chemometrics is widely used in the evaluation of authentication, adulteration, halal products, and quality assay^{4,17}. However, optimization design evaluation has not been found. The evaluation of catechin carrier SNEDDS can be carried out with test parameters, including emulsification time, transmittance, pH measurement, stability, an endurance test. Therefore, it is exciting to combine the SCD analysis with a chemometric approach to evaluate designs, classify the runs by character, and clarify the correlation between responses. The results of this study can provide information about a more comprehensive evaluation of the pre-optimization stage

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in the development of lipid-based drug delivery system formulations. In the future, the catechin active ingredients in the SNEDDS formulation have better bioavailability and reliable stability.

MATERIAL AND METHODS:

Chemicals and Reagents:

Materials needed in this study include catechins obtained from Sigma-Aldrich (Singapore), oleic acid from Bratachem (Jakarta, Indonesia), croduret purchased from Croda (United Kingdom), propylene glycol from Dow Chemical (Indonesia). Other materials such as aquadest, aqua pro injection are purchased from local distributors in Palembang, Indonesia.

Catechin-SNEDDS Formulation Design:

The number of SNEDDS formulated and evaluated using a chemometric approach based on the SCD. The SCD design in this study used two levels (upper level and lower level) in a certain proportion. Concentration ranges for oleic acid (20-60%), croduret 50-SS (20-60%), and propylene glycol (10-30%). The complete design at 9 results for the SNEDDS formula are presented in Table 1.

Table 1: Number of Runs and Components of Catechin-SNEDDS Using SCD

| Run | Factors | | | Responses (n=3) | | | | | | |
|-----|----------------|--------------|----------------------|-----------------------|-----------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| | Oleic acid (%) | Croduret (%) | Propylene glycol (%) | R ₁ (min.) | R ₂ (min.) | R ₃ (%) | R ₄ (%) | R ₅ (%) | R ₆ (%) | R ₇ (%) |
| 1 | 52.51 | 20.00 | 27.49 | 0.22±0.12 | 0.14±0.02 | 80.39±0.70 | 18.58±1.38 | 17.72±1.14 | 09.18±1.59 | 61.65±0.60 |
| 2 | 49.91 | 30.05 | 20.03 | 0.21±0.01 | 0.22±0.02 | 84.27±1.03 | 40.16±0.71 | 25.67±1.78 | 11.17±0.30 | 57.20±0.59 |
| 3 | 30.68 | 49.25 | 20.06 | 1.70±1.01 | 1.99±0.50 | 91.81±0.99 | 87.14±0.97 | 49.61±1.71 | 34.16±1.84 | 81.79±0.85 |
| 4 | 25.31 | 44.69 | 30.00 | 0.52±0.06 | 1.18±0.11 | 93.71±0.99 | 51.93±0.38 | 62.47±0.78 | 69.23±1.06 | 87.69±1.96 |
| 5 | 42.62 | 27.38 | 30.00 | 0.32±0.00 | 0.22±0.01 | 81.17±1.91 | 38.33±1.39 | 23.89±1.00 | 08.28±0.63 | 59.82±0.77 |
| 6 | 60.00 | 27.50 | 12.50 | 0.22±0.03 | 0.21±0.01 | 64.92±0.24 | 80.26±0.53 | 18.96±1.00 | 04.44±0.62 | 56.34±1.23 |
| 7 | 50.43 | 39.57 | 10.00 | 0.25±0.01 | 0.22±0.03 | 86.86±1.46 | 60.58±1.12 | 33.05±0.18 | 03.48±1.42 | 46.82±0.27 |
| 8 | 34.12 | 35.88 | 30.00 | 0.64±0.33 | 0.89±0.30 | 90.27±1.29 | 82.56±0.99 | 54.56±1.19 | 15.40±0.45 | 66.58±1.37 |
| 9 | 40.73 | 39.34 | 19.94 | 0.28±0.04 | 0.25±0.03 | 90.37±0.55 | 76.08±1.84 | 55.99±0.21 | 15.31±0.74 | 53.76±0.77 |
| 10 | 20.00 | 60.00 | 20.00 | 0.39±0.09 | 0.30±0.11 | 94.54±0.78 | 69.45±1.11 | 55.73±0.26 | 77.88±1.83 | 96.40±2.00 |
| 11 | 40.73 | 39.34 | 19.94 | 0.28±0.02 | 0.24±0.01 | 89.33±1.03 | 79.85±0.93 | 54.58±0.37 | 08.00±0.71 | 41.93±1.29 |
| 12 | 36.33 | 53.67 | 10.00 | 0.42±0.08 | 0.39±0.05 | 89.40±1.59 | 77.35±0.81 | 59.66±2.06 | 31.90±0.88 | 76.71±0.51 |

Note: (R₁) Emulsification time before a freeze-thaw assay, (R₂) Emulsification time after the freeze-thaw assay, (R₃) %T of SNEDDS, (R₄) %T of nanoemulsion after a freeze-thaw assay at 100x dilution, (R₅) %T of nanoemulsion after the freeze-thaw assay at 500x dilution, (R₆) %T of nanoemulsion before the freeze-thaw assay at 100x dilution, (R₇) %T of nanoemulsion before the freeze-thaw assay at 500x dilution.

Chemometrics:

The SCD design was evaluated using a multivariate statistical approach, known as chemometric analysis. In general, SCD is used to study the relationship between the proportion of variables and different responses. It defines a continuous variable surface model, estimates each element in the mixture and its interactions, and can optimize the component elements according to the target^{4,16,18}. Chemometrics is used to provide an understanding of data in experimental designs. The

chemometric approach uses the principal component analysis (PCA) and cluster analysis (CA) approaches.

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Catechin-SNEDDS Preparation:

Oil, surfactants, and co-surfactants are components of the SNEDDS formulation, which can rapidly form nanoemulsions in the dispersing medium. SNEDDS is prepared by dissolving catechins in 20 mg for a theoretical volume of 5 mL. Catechins were mixed with oil using a vortex and then sonicated for 15 minutes. Then the surfactant was added, homogenized using

vortex and sonication for 15 minutes. Co-surfactants were added and stirred with vortex and sonicated for 15 minutes¹⁹.

Emulsification Time:

The SNEDDS formula is subjected to an emulsification time test to determine how fast the formula forms an emulsion. The test was carried out by adding 20 μ L of catechin-SNEDDS in 5 mL of aquadest and maintaining the temperature at 37 °C using a magnetic stirrer with a speed of 120 rpm. Observations were also carried out on the nanoemulsion formed against settling.

Transmittance Measurement:

Nanoemulsion from SNEDDS was taken 1 mL and then diluted 100 times using aquadest. The percentage of transmittance was measured with a UV-Vis spectrophotometer Genesys 10S (Thermo Scientific, USA) at 638 nm with aquadest as a blank²⁰.

pH Measurement:

The catechin-SNEDDS formula is measured pH using a universal pH indicator. A total of 10 μ L catechin-SNEDDS is evenly dripped on the pH universal indicator surface. The color tones formed are matched with the pH standard colors available on the pH indicator box. The uniform color tone shows the pH of the catechins-SNEDDS.

Freeze Thawing Assay:

Freezing and thawing were carried out in 3 cycles with storage at -4 °C for 24 hours and followed by storage at 25 °C for 24 hours. Then, the instability parameters such as separation and precipitation were observed²¹.

5 Endurance Test:

The formula generated from the freeze-thawing cycle test is then used to perform an endurance test. The formula was diluted with dilution levels of 100, 250, and 500 times using aquadest. Observations were made for seven cycles, where one cycle was counted for 24 hours at room temperature^{20,22}.

Data Analysis:

The design of the catechin-SNEDDS formula uses the simplex centroid design (SCD). The analysis used a multivariate statistical approach with the PCA-CA method. Minitab software (State College, PA, USA) was used to analyze the data. The resulting PCA-CA output is in the form of a scree plot, a score plot, a loading plot, a biplot, and a dendrogram.

RESULT AND DISCUSSION:

Catechin-SNEDDS formulation:

The catechin-SNEDDS formulation in this study used oil (oleic acid), surfactant (croduret 50-SS), and co-surfactant (propylene glycol). The upper and lower limits were searched using references in previous studies, then processed using the SCD to see the range, producing 12 formulas with different concentrations. The properties of oil, surfactant, co-surfactant, ingredient ratio and concentration greatly influence the SNEDDS formulations and nanoemulsions formed after contact with water^{23,24,25}. The catechin-SNEDDS and nanoemulsion formed from the 12 runs are shown in Fig. 1.

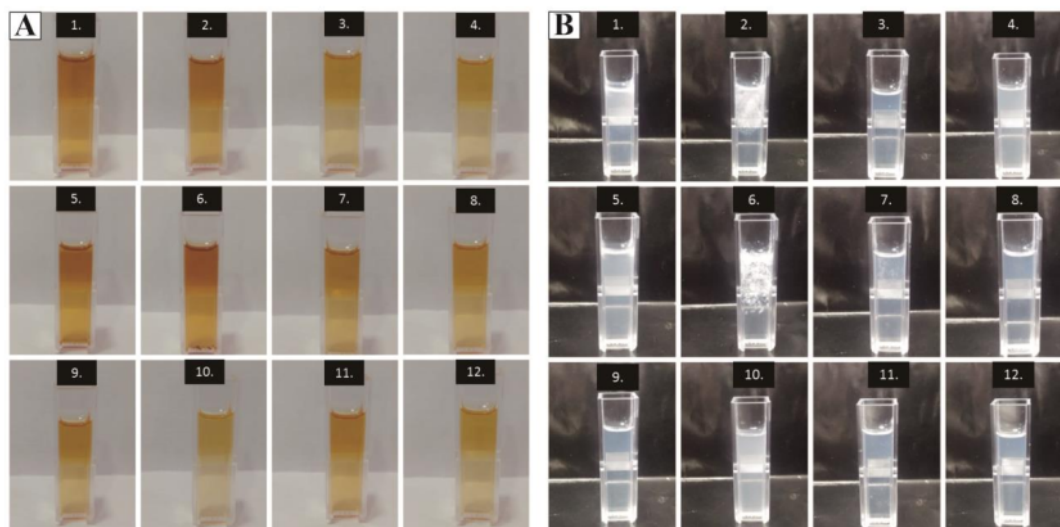


Fig. 1: (A) Catechin-SNEDDS and (B) Nanoemulsion, Numbers 1-12 are Run Codes of the SNEDDS Formula

The results show that the %T values close to 100% are formulas 3, 4, and 10. The results obtained indicate that the SNEDDS preparations made have precise characteristics so that when dispersed in the medium, it forms a clear solution. These results are supported by propylene glycol as a co-surfactant that helps the solubility of croduret and the solubility of drugs in the oil phase²⁶. While the results of formulas 1, 2, 5, 6, 7, 8, 9, 11, and 12 have a %T value that is less than 90%, this is due to the concentration ratio between the different phases of oil, surfactant, and co-surfactant.

Principal Component Analysis and Cluster Analysis to Assess Response Correlation and Its Classification:

The results of the chemometric analysis using PCA and CA methods are presented in Fig. 2. PCA analysis aims to simplify the observed variables by reducing the data dimensions consisting of many interrelated variables without changing the information contained therein^{4,17,27}. The score plot in Fig. 2A shows a formula that can be classified based on the proximity of the measured response characters. The results of the CA can provide information about the relationship and grouping of objects based on similarities. The purpose of this analysis is to emphasize objects that are classified in specific clusters based on the measured response so that

formulas that have similarities can provide more accurate information.

Fig. 2A shows the results of the PCA analysis with the score plot output. Twelve SNEDDS are separated at different distances from each other, where the distance between samples shows the degree of similarity. The dendrogram in Fig. 2B provides information about the level of SNEDDS similarity assessed from the response. The PCA-CA analysis in this study resulted in four clusters, and the response parameters evaluated on SCD were positively correlated.

The calculation results of the similarity index are depicted in a dendrogram and presented in Fig. 2B. Each of these formulas is classified according to its similarity. Formulas 2 and 5 have proximity with a value of 93.63%, formulas 7 and 9 have proximity with a value of 76.56%, formulas 8 and 12 have a proximity value of 58.02%, and formulas 4 and 10 have a proximity value of 35.28%. The result of the score plot shows very clearly that there are four different groups (classifications). Details of the classification and grouping formulas are presented in Fig. 2A and 2B. The classification formed is a function of the composition of the formula (the factors specified in the SCD) with the response parameter²⁷.

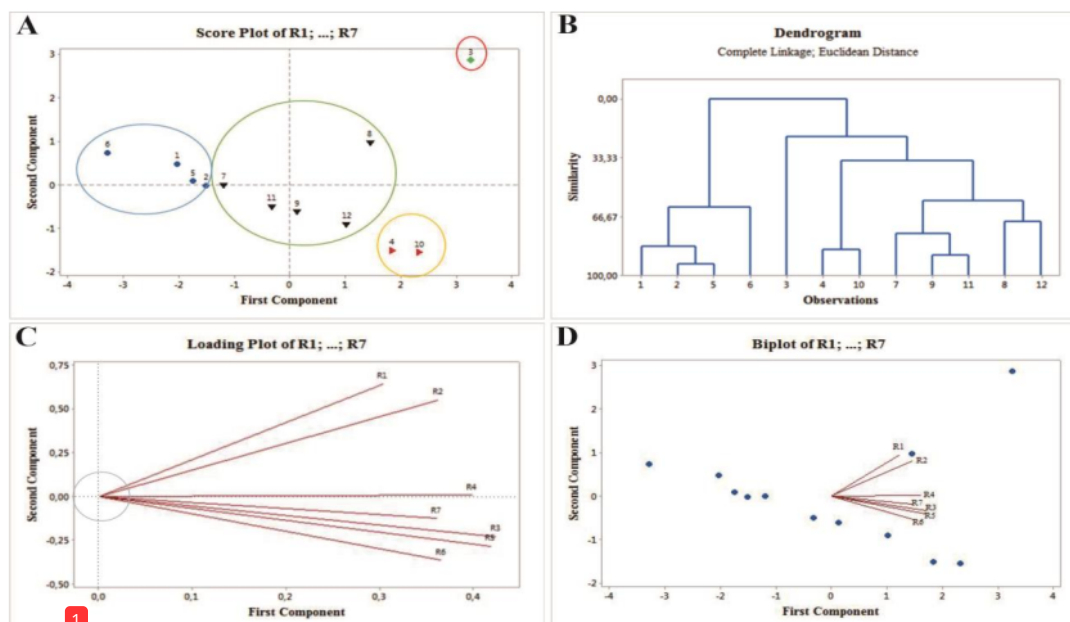


Fig. 2: (A) Score plot, (B) Dendrogram, (C) Loading Plot, (D) Biplot, Symbols numbered 1-12 are Catechin-SNEDDS, (R₁) Emulsification time before a freeze-thaw assay, (R₂) Emulsification time after the freeze-thaw Assay, (R₃) %T of SNEDDS, (R₄) %T of nanoemulsion after a freeze-thaw assay at 100x dilution, (R₅) %T of nanoemulsion after the freeze-thaw assay at 500x dilution, (R₆) %T of nanoemulsion before the freeze-thaw assay at 100x dilution, (R₇) %T of nanoemulsion before the freeze-thaw assay at 500x dilution.

The group A formulations showed similarities in the characteristics and concentrations of the constituent components, while the similarities included the emulsification time after the freeze-thaw test and the constituent components, namely surfactants (croduret 50-SS). This group A formulation showed the same amount of emulsification time, and the 50-SS croduret concentrations that were nearly the same as each other. The group B formulas show similarities in the characteristics of each formula and concentration. Formulas 7, 9, and 11 show similarities in the concentration of co-surfactant; besides that, they show similarities to the resulting characteristics. Formulas 9 and 11 have the same concentration, namely oil, surfactant, and co-surfactant. Formulas 8 and 12 show similar characteristics. Group C in formulas 4 and 10 had almost the same characteristics, such as emulsification time, %T value, and clarity. Group C only in formula 3 with a distance from other groups showed no similarities between formulas, the concentration on each constituent component, and the characterization of each formula.

The loading plot aims to determine the variable of a sample or formula that most contributes to principal component values formation. The contribution of the sample variable to the loading plot can be seen from a distance used. The distance away from the starting point indicates the more significant the contribution of this variable in PCA. Data analysis using loading plots from PCA illustrates the angle that shows a correlation between the responses of the 12 formulas. The vectors on R₁ and R₂ form a narrow-angle (below 45°), indicating a positive relationship between the two responses. These areas contribute to forming the first component (PC1), both of which correlate because they show that they both describe the same response. A positive correlation is also generated from the vectors in the responses R₄-R₇, R₃-R₅, and R₅-R₆. In general, if the vector (response; R_n) forms an angle below 45°, it indicates that the correlation formed is positive. This area has a contribution to the formation of the second component. The five responses (R₃, R₄, R₅, R₆, and R₇) are %T responses, which in these five responses only show differences in the level of dilution and treatment. The response to R₃ is %T from the 12 catechin-SNEDDS formulations, R₄ and R₅ are the %T responses of nanoemulsions with different dilution levels that have been carried out in the freeze-thaw test, and in the response, R₆ and R₇ are the %T response of nanoemulsion with different dilution rates of catechins-SNEDDS. The five of them correlated because they show the same response.

The biplot graph in Fig. 2D illustrates the correlation between the sampling areas as a whole. Biplot analysis

shares information about the relationship between variables, the relative similarities between observation objects, and the variables relative positions. This biplot graph curve shows which variable has the most contribution or impact at a point by examining the distance between the variable and the sample. The distance between the sample and the variable illustrates the relationship between the variable and the sample. The biplot display results in Fig. 2D illustrate that the observation points are formulas that spread across all quadrants in the biplot. The adjacent points are shown in formulas 7, 11, 9, 12, 8, 4, and 10, where these formulas are located adjacent to the seven responses. The proximity relationship between these points is because the characteristics of this formula are relatively close.

Emulsification Time:

The emulsification time showed that of the 12 formulas, 5 SNEDDS formulas could form nanoemulsions in 10 mL of aquadest medium with an average time needed less than one minute. These results indicate that the composition of croduret 50-SS and propylene glycol can form a homogeneous mixture. The stability of the nanoemulsion is affected by the surfactant composition. The higher the amount of surfactant will increase the stability^{24,28,29}. However, in oral formulations, there must be restrictions on the use of surfactants because too much will irritate the gastrointestinal tract.

Stability Study:

Table 2 shows formulas 1, 5, 10, and 12 that did not undergo phase separation after 22 h. Surfactants and co-surfactants provide the ability to reduce the interface stress between the oil phase and the water phase to influence this phase separation. The formation of stable nanoemulsions is due to the ability of surfactants and co-surfactants to reduce interfacial tension^{23,30}. The process of reducing surface tension by propylene glycol helps to produce a smaller droplet emulsion size. Stability is an important parameter, either SNEDDS when outside the body or nanoemulsion while in the digestive tract.

The fastest emulsification time is shown in formula 1, and the longest time of more than 1 minute is given by formula 3. Surfactants significantly affect the surface of the droplets by providing a mechanical barrier. It also reduces the free energy of the interface to combine and results in spontaneous thermodynamic dispersion³¹. The interface fluidity is enhanced by using co-surfactants by penetrating the surfactant film, which leaves empty spaces between surfactant molecules^{32,33}. The nanoemulsion that is formed is clear, not cloudy, and colored after adding water. The emulsification time requirement for SNEDDS preparation is less than 1 minute. The emulsification time was less than 5 minutes

for formulas 1, 4, 5, and 10, and the nanoemulsion was clear.

Endurance Test:

The physical stability of SNEDDS can be evaluated using an endurance assay with various dilutions. This assay is critical regarding the use of the oral route in the future. The endurance test results in Table 3 show that

the catechin-SNEDDS does not undergo separation at all dilution levels, namely in formulas 3, 4, and 10, so it can be interpreted that the nanoemulsion is stable. The stability of the nanoemulsion indicated that the droplets remained stable on the media. There was no sediment formation in the nanoemulsion from the results of visual observations carried out.

Table 2: Stability Study of Catechin-SNEDDS

| Formula | Emulsification Time (minutes) | | Separation | Precipitation |
|---------|-------------------------------|-----------------------------|------------|---------------|
| | Before the Freeze Thaw Assay | After the Freeze Thaw Assay | | |
| 1 | 0.22 ± 0.12 | 0.14 ± 0.02 | - | - |
| 2 | 0.21 ± 0.01 | 0.22 ± 0.02 | + | + |
| 3 | 1.70 ± 1.01 | 1.99 ± 0.50 | + | + |
| 4 | 0.52 ± 0.06 | 1.18 ± 0.11 | + | + |
| 5 | 0.32 ± 0.00 | 0.22 ± 0.01 | - | - |
| 6 | 0.22 ± 0.03 | 0.21 ± 0.01 | + | + |
| 7 | 0.25 ± 0.01 | 0.22 ± 0.03 | + | + |
| 8 | 0.64 ± 0.33 | 0.89 ± 0.30 | + | + |
| 9 | 0.28 ± 0.04 | 0.25 ± 0.03 | + | + |
| 10 | 0.39 ± 0.09 | 0.30 ± 0.11 | - | - |
| 11 | 0.28 ± 0.02 | 0.24 ± 0.01 | + | + |
| 12 | 0.42 ± 0.08 | 0.39 ± 0.05 | - | - |

Note: (+) separation occurs, (-) there is no separation.

Table 3: Catechin-SNEDDS Endurance Test Results.

| Formula | 100x Dilution (Day) | | | | | | 250x Dilution (Day) | | | | | | 500x Dilution (Day) | | | | | | | |
|---------|---------------------|---|---|---|---|---|---------------------|---|---|---|---|---|---------------------|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 1 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 2 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 3 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 4 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 6 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 7 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 8 | + | + | + | + | + | + | + | + | + | - | - | - | - | - | + | + | + | + | + | + |
| 9 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 10 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 11 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 12 | + | + | + | + | + | + | + | - | - | - | - | + | + | - | - | - | - | - | - | - |

Note: (+) undergoes separation and precipitation (-) does not undergo separation and deposition.

Table 4: Appearance and pH of Catechin-SNEDDS

| Formula | Color | Clarity | Phase Separation | Odor | Homogeneity | pH |
|---------|-----------------|-------------|------------------|----------|-------------|----|
| 1 | Brownish Yellow | Transparent | No separation | Specific | Homogeneous | 4 |
| 2 | Brownish Yellow | Transparent | No separation | Specific | Homogeneous | 4 |
| 3 | Yellow | Transparent | No separation | Specific | Homogeneous | 5 |
| 4 | Yellow | Transparent | No separation | Specific | Homogeneous | 5 |
| 5 | Brownish Yellow | Transparent | No separation | Specific | Homogeneous | 4 |
| 6 | Brownish Yellow | Transparent | No separation | Specific | Homogeneous | 4 |
| 7 | Yellow | Transparent | No separation | Specific | Homogeneous | 4 |
| 8 | Brownish Yellow | Transparent | No separation | Specific | Homogeneous | 5 |
| 9 | Brownish Yellow | Transparent | No separation | Specific | Homogeneous | 4 |
| 10 | Yellow | Transparent | No separation | Specific | Homogeneous | 4 |
| 11 | Brownish Yellow | Transparent | No separation | Specific | Homogeneous | 4 |
| 12 | Brownish Yellow | Transparent | No separation | Specific | Homogeneous | 4 |

Note: Characteristic odor of oleic acid oil

Appearance and pH of SNEDDS:

The results of visual and pH observations in the table above show formulas 1 to 12, which have brownish-yellow visuals for formulas 1, 2, 5, 6, 8, 9, 11, 12 and exact yellow color for formulas 3, 4, 7, 10 then the formula is non-separating and has a distinctive and homogeneous odor. Nanoemulsion is said to be excellent or stable if it has a pH that matches the condition of the stomach (pH. 2.0) and intestine (pH. 6.8)²⁶. The pH values in Table 4 from formulas 1 to 12 have a pH of 4-5, which has not yet entered the predetermined range. According to research, an inadequate decrease in pH value is caused by the breakdown of fat, hydrolysis, oxidation, the influence of light, and the growth of microorganisms³².

In our best review, there are no publications related to combination chemometric with SCD in the field of pharmaceutical analysis. The modeling procedure at the Catechin-SNEDDS optimization stage has not been carried out. Therefore, it is necessary to immediately carry out the next steps to obtain the perfect formula. Several parameters that are more reflective to strengthen the development of SNEDDS, such as zeta potential, TEM morphology, drug load, and diameters droplets, are very influential at the optimization stage^{34,35}. There have been many publications on applications of DoE in filtering and optimization, such as simplex lattice design (SLD) in formula optimization^{36,37}, central composite design (CCD)³⁸, or factorial design (FD) in extraction³⁹. Chemometric studies to evaluate this design will provide more accurate and precise information. The final result of the chemometric analysis can strengthen the modeling, prediction, and determination of optimal conditions in DoE.

CONCLUSION:

Catechins-SNEDDS can emulsify well in aquadest media, have adequate visualization and %T, the resulting pH does not meet due to oxidation, hydrolysis, the influence of light, and bacterial growth. PCA-CA can describe the correlation and similarity of characteristics of each evaluation by classifying formulas to describe the evaluation of design and response in a comprehensive manner.

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15 CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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GENERAL COMMENTS

Instructor

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RUBRIC: 6TH-8TH SCIENCE ARGUMENT (CER)

CLAIM

Take an arguable position on the scientific topic and develop the essay around that stance.

| | |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ADVANCED | The essay introduces a precise, qualitative and/or quantitative claim based on the scientific topic or text(s), regarding the relationship between dependent and independent variables. The essay develops the claim and counterclaim fairly, distinguishing the claim from alternate or opposing claims. |
| PROFICIENT | The essay introduces a clear, qualitative and/or quantitative claim based on the scientific topic or text(s), regarding the relationship between dependent and independent variables. The essay effectively acknowledges and distinguishes the claim from alternate or opposing claims. |
| DEVELOPING | The essay attempts to introduce a qualitative and/or quantitative claim, based on the scientific topic or text(s), but it may be somewhat unclear or not maintained throughout the essay. The essay may not clearly acknowledge or distinguish the claim from alternate or opposing claims. |
| EMERGING | The essay does not clearly make a claim based on the scientific topic or text(s), or the claim is overly simplistic or vague. The essay does not acknowledge or distinguish counterclaims. |

EVIDENCE

Include relevant facts, definitions, and examples to back up the claim.

| | |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ADVANCED | The essay supplies sufficient relevant, accurate qualitative and/or quantitative data and evidence related to the scientific topic or text(s) to support its claim and counterclaim. |
| PROFICIENT | The essay supplies relevant, accurate qualitative and/or quantitative data and evidence related to the scientific topic or text(s) to support its claim and counterclaim. |
| DEVELOPING | The essay supplies some qualitative and/or quantitative data and evidence, but it may not be closely related to the scientific topic or text(s), or the support that is offered relies mostly on summary of the source(s), thereby not effectively supporting the essay's claim and counterclaim. |
| EMERGING | The essay supplies very little or no data and evidence to support its claim and counterclaim, or the evidence that is provided is not clear or relevant. |

REASONING

Explain how or why each piece of evidence supports the claim.

| | |
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| ADVANCED | The essay effectively applies scientific ideas and principles in order to explain how or why the cited evidence supports the claim. The essay demonstrates consistently logical reasoning and understanding of the scientific topic and/or text(s). The essay's explanations anticipate the audience's knowledge level and concerns about this scientific topic. |
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| PROFICIENT | The essay applies scientific reasoning in order to explain how or why the cited evidence supports the claim. The essay demonstrates logical reasoning and understanding of the scientific topic and/or text(s). The essay's explanations attempt to anticipate the audience's knowledge level and concerns about this scientific topic. |
| DEVELOPING | The essay includes some reasoning and understanding of the scientific topic and/or text(s), but it does not effectively apply scientific ideas or principles to explain how or why the evidence supports the claim. |
| EMERGING | The essay does not demonstrate clear or relevant reasoning to support the claim or to demonstrate an understanding of the scientific topic and/or text(s). |

FOCUS

Focus your writing on the prompt and task.

| | |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ADVANCED | The essay maintains strong focus on the purpose and task, using the whole essay to support and develop the claim and counterclaims evenly while thoroughly addressing the demands of the prompt. |
| PROFICIENT | The essay addresses the demands of the prompt and is mostly focused on the purpose and task. The essay may not acknowledge the claim and counterclaims evenly throughout. |
| DEVELOPING | The essay may not fully address the demands of the prompt or stay focused on the purpose and task. The writing may stray significantly off topic at times, and introduce the writer's bias occasionally, making it difficult to follow the central claim at times. |
| EMERGING | The essay does not maintain focus on purpose or task. |

ORGANIZATION

Organize your writing in a logical sequence.

| | |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ADVANCED | The essay incorporates an organizational structure throughout that establishes clear relationships among the claim(s), counterclaims, reasons, and evidence. Effective transitional words and phrases are included to clarify the relationships between and among ideas (i.e. claim and reasons, reasons and evidence, claim and counterclaim) in a way that strengthens the argument. The essay includes an introduction and conclusion that effectively follows from and supports the argument presented. |
| PROFICIENT | The essay incorporates an organizational structure with clear transitional words and phrases that show the relationship between and among ideas. The essay includes a progression of ideas from beginning to end, including an introduction and concluding statement or section that follows from and supports the argument presented. |
| DEVELOPING | The essay uses a basic organizational structure and minimal transitional words and phrases, though relationships between and among ideas are not consistently |

clear. The essay moves from beginning to end; however, an introduction and/or conclusion may not be clearly evident.

EMERGING

The essay does not have an organizational structure and may simply offer a series of ideas without any clear transitions or connections. An introduction and conclusion are not evident.

LANGUAGE

Pay close attention to your tone, style, word choice, and sentence structure when writing.

ADVANCED

The essay effectively establishes and maintains a formal style and objective tone and incorporates language that anticipates the reader's knowledge level and concerns. The essay consistently demonstrates a clear command of conventions, while also employing discipline-specific word choices and varied sentence structure.

PROFICIENT

The essay generally establishes and maintains a formal style with few possible exceptions and incorporates language that anticipates the reader's knowledge level and concerns. The essay demonstrates a general command of conventions, while also employing discipline-specific word choices and some variety in sentence structure.

DEVELOPING

The essay does not maintain a formal style consistently and incorporates language that may not show an awareness of the reader's knowledge or concerns. The essay may contain errors in conventions that interfere with meaning. Some attempts at discipline-specific word choices are made, and sentence structure may not vary often.

EMERGING

The essay employs language that is inappropriate for the audience and is not formal in style. The essay may contain pervasive errors in conventions that interfere with meaning, word choice is not discipline-specific, and sentence structures are simplistic and unvaried.