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EVALUATION OF RESPONSE CORELLATION USING CHEMOMETRICS ANALYSIS FOR PRE-OPTIMIZATION QUERCETIN – SELF EMULSION FORMULATION

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ABSTRACT

The optimization approach using the simplex centroid design (SCD) has many advantages, including a minimized number of experiments and a good description of the interactions between components. However, modeling with the SCD approach has not evaluated between responses. Therefore, this study aims to apply a chemometric analysis to evaluate the response of the optimization stage using the quercetin – self emulsion formulations (quercetin-SEFs) as a model. SEFs were prepared using grapeseed oil, Croduret, and PEG 400. The evaluated responses included emulsification time and transmittance. Both responses were performed in endurance test by centrifugation method and stability test using freeze-thaw. A chemometric analysis on cluster analysis (CA) generates a dendrogram, while pricipal component analysis (PCA) generates score plots, loading plots, scree plots, and biplots. The results of chemometric analysis show that between responses that have a positive correlation will increase each other or giving a comparable value between responses. Different results happens if there is a negative correlation between responses in chemometric analysis, then the results between responses will be inversely proportional. Emulsification time has a positive correlation with transmittance value. The quercetin-SEFs formula in SCD was classified into three groups based on the similarity of characters. Chemometric analysis was successfully applied in evaluating the response to the quercetin-SEFs optimization modeling.

Keywords: Emulsion; Chemometrics; Quersetin; Self-emulsion; Simplex centroid design

1. INTRODUCTION

Quercetin is a flavonoid compound found in various medicinal plants. The pharmacological effects of quercetin are antioxidant (Septembre-Malaterre et al., 2022), oxidative stress inhibitor (Kant et al., 2022), tonic (Racinowski et al., 2021), immunomodulatory (Manjunath & Thimmulappa, 2021), anti-inflammatory (Li et al., 2021; Zhao et al., 2021), anticancer (Li et al., 2021), and antidiabetic (Dhanya, 2022; Kant et al., 2021). The extraordinary pharmacological potential of quercetin does not guarantee a good therapy because it still has low bioavailability problems (Alizadeh & Ebrahimzadeh, 2022; Singh et al., 2021). Quercetin is classified as a hydrophobic compound or has low solubility in water (Kandemir et al., 2022). Therefore, developing a lipid-based drug delivery system in self-emulsifying formulations (SEFs). SEFs formulation will increase the bioavailability of quercetin as the active substance, which has hydrophilic properties (Moon et al., 2021).

SEFs consist of oils, surfactants, and co-surfactants with suitable compositions to form a stable mixture (Cholakova et al., 2022; Shiyan et al., 2022). SEFs emulsify spontaneously in the GI tract and effectively increase bioavailability (Cardona et al., 2021; Dhritlahre et al., 2021). Optimization procces is needed to meet the SEFs parameters. DoE is widely applied to optimization procedures for example (Pratiwi et al., 2020; Shiyan, Marketama, et al., 2021). simplex centroid design (SCD) (Maciel et al., 2020; Nunes Filho et al., 2021). Applying SCD in optimization can simplify the number of designs and provide good optimal predictions. However, modeling on SCD could not evaluate the response and its correlation to the test parameters. Therefore, a chemometric analysis approach was applied using the principal component analysis (PCA) method to evaluate the response.

This study aimed to analyze the response of pre-optimized design of quercetin-SEFs using a chemometric analysis approach. The modeling in determining the pre-optimization stages is designed using an SCD. Factors that optimize quercetin-SEFs included grapeseed oil concentration, croduret 50-SS concentration, and PEG 400 concentration. The evaluated responses included emulsification time and transmittance value. Both responses were developed in endurance test by centrifugation method and stability test using freeze-thaw. The chemometric approach analyzed the correlation between the responses generated through a statistical approach. The final information from this study will further clarify the correlation between responses that strengthen the modeling at the optimization stage of quercetin-SEFs.

2. METHODS

2.1. Material and Chemicals

Quercetin as the model active compound was obtained from Sigma-Aldrich (Singapore). Supporting materials such as PEG 400 (Dow Chemical), grape seed oil (Aceites Borges) and Croduret 50-SS (Croda) were purchased from local distributors in Palembang, Indonesia.

2.2. Design Quercetin-SEFs

The formula design for the optimization procedure used the simplex centroid design (SCD) approach. Determining factors are the percentage of grapeseed oil, croduret 50-SS, and PEG 400. The upper level used in the oil is 14-20%, a surfactant is 30-60%, and a co-surfactant is 10-30% (Shiyan et al., 2022). SEFs were designed using the design-expert (DX) software series 12 free trial (Start-Ease Inc, Minneapolis, MN, USA). The composition of the components of the quercetin-SEFs from the pre-optimized design and the complete results of the response parameters are presented in Table 1.

Table 1. The Design of Quercetin-SEFs Using Simplex Centroid Design

Formula	A: Grapeseed oil (% w/w)	B: Croduret 50-SS (% w/w)	C: PEG 400 (% w/w)
1	40.78	35.87	23.33
2	39.05	45.94	15.00
3	55.48	28.79	15.72
4	16.37	53.62	30.00
5	55.00	15.00	30.00
6	40.78	35.87	23.33
7	68.05	15.00	16.94
8	27.44	42.55	30.00
9	27.36	56.26	16.37
10	40.78	35.87	23.33
11	45.15	24.84	30.00
12	15.00	65.00	20.00

2.3. Preparation of Quercetin-SEFs

SEFs were prepared by dissolving quercetin in carrier oil using vortex and sonication for 3 minutes at room temperature. Surfactants and co-surfactants are added to the oil-quercetin mixture and mixed with vortex until it become a homogen quercetin-SEFs. Quercetin-SEFs were stored at 25-30°C for 24 hours. Quercetin-SEFs was dissolved into aquadest up to 5 mL and mixed by inverting the vial until the SEFs dissolved in aquadest and become quercetin emulsion (Halder et al., 2021; Shiyan, Zubaidah, et al., 2021).

2.4. Emulsification Time Measurement

A total of 5 mL of distilled water was used as a medium and placed on a magnetic stirrer at a speed of 120 rpm. An amount of 10 μL and 50 μL of SEFs was dripped onto the medium rapidly. Observations were made visually by looking at the color, shape change, separation phase, and the time required for quercetin-SEFs to form emulsions (Anwer et al., 2021).

2.5. Transmittance Measurement

An amount of 10 μL dan 50 μL of SEFs was diluted with 5 mL of distilled water. The transmission percentage can be seen on a UV-Vis spectrophotometer at a 650 nm wavelength, and distilled water was used as a blank (Jumaryatno et al., 2018).

2.6. Endurance Measurement

Emulsion resistance test with three different dilutions (100, 250 and 500) in distilled water medium using centrifugation. The main indicators include the precipitate formed after centrifugation and the change in appearance for seven days.

2.7. Thermodynamics using the Freeze-Thaw Method

The thermodynamic stability of SEF used the freeze-thaw method. Samples were stored at -20 °C for 24 hours and transferred to temperature of 25-30°C for 24 hours. The cycle in this test was repeated six times. Observation of the stability of quercetin-SEFs by visually observing the parameters of clarity, phase separation, and precipitate (Shiyan, Zubaidah, et al., 2021).

2.8. Chemometric Analysis

Response data were analyzed using a chemometric approach with the principal component analysis (PCA) method to produce scree plots, score plots, loading plots and biplots. Using the cluster analysis (CA) method, the score plot results will be strengthened from the dendrogram. Multivariate analysis on the chemometric approach was supported by Minitab software (Shiyan, Marketama, et al., 2021).

3. RESULTS AND DISCUSSION

3.1. Quercetin-SEFs Formula

Organoleptic observations include color, smell, and shape. The observed quercetin-SEFs were obtained from the optimization design of the SCD formula. The formula that has been made has a yellowish color, is clear, has a slightly pungent odor, and is a slightly thick liquid due to the addition of a surfactant, namely Croduret 50-SS. The transmittance value indicates the clarity indicator on quercetin-SEFs above 90% (formula 6, 9, and 12) showed in **Table 2** (R_3). In contrast, the other formulas have a transmittance value below 90%. The difference in concentration between the different components affected the appearance of quercetin-SEFs and resulted in different transmittance values. The pH test results are in the range of 5-6 and all the formulas were accepted the requirements that the requirements are 4.5-6.

The quercetin-SEFs of the 12 formulas are presented in **Figure 1** and descriptions in **Table 2**. All formulas have a visually uniform appearance. Quercetin-SEFs have a bright yellow color from a combination of oil components, surfactants, and the active compound quercetin. Emulsions are formed after quercetin-SEFs encounter water spontaneously (Tharmatt et al., 2021). The resulting emulsion has a clear to a cloudy character.

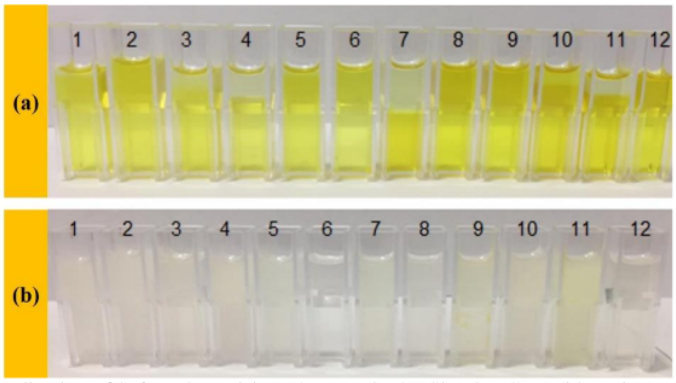

Figure 1. Visualization of Sefs and Emulsion 12 Formulas by Simplex Centroid Design. (A) Quercetin-Sefs Result and (B) Self-Emulsion Result.

Table 2. Visual Observations of Quercetin-SEFs

Formula	Color	Clarity	Phase	Smell	Homogeneity
1	Yellow	Clear	Separation	Typical	Homogeneous
2	Yellow	Clear	Separation	Typical	Homogeneous
3	Yellow	Clear	Separation	Typical	Homogeneous
4	Yellow	Clear	Separation	Typical	Homogeneous
5	Yellow	Clear	Separation	Typical	Homogeneous
6	Yellow	Clear	No separation	Typical	Homogeneous
7	Yellow	Clear	Separation	Typical	Homogeneous
8	Yellow	Clear	Separation	Typical	Homogeneous
9	Yellow	Clear	Separation	Typical	Homogeneous
10	Yellow	Clear	Separation	Typical	Homogeneous
11	Yellow	Clear	Separation	Typical	Homogeneous
12	Yellow	Clear	No separation	Typical	Homogeneous

3.2. Chemometric Analysis

The values of score plot, loading plot, biplot, scree plot, and dendrogram can help with correlation analysis. The grouping of data in each plot can show several different meanings. The loaded data follows the normal response, and in some of the responses entered, there is no value in the outlier plot. The eigenvalues of the scree plot components of the analysis formula can be seen in **Figure 1**.

Table 3. Results of Each Response from Pre-Optimization Quercetin-SEFs

Formula	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
1	10.17	8.73	71.16	89.917	31.247	3.941	5.471	6
2	5.95	7.36	67.18	55.666	26.522	1.288	12.984	5
3	8.36	7.11	52.94	62.262	13.619	1.290	7.725	5
4	8.36	7.11	64.75	23.273	32.609	0.188	5.958	5
5	7.72	6.95	51.82	40.500	40.485	0.900	2.331	5
6	8.73	7.59	94.00	99.749	66.363	89.274	66.556	6
7	9.29	10.14	47.62	65.487	7.520	1.242	11.649	5
8	7.86	6.86	85.35	62.113	23.009	1.726	28.232	5
9	22.96	9.54	93.60	47.261	16.815	1.404	21.639	6
10	6.46	7.70	74.96	84.664	24.708	0.947	5.654	5
11	5.50	8.69	72.10	39.153	19.549	0.198	3.688	5
12	10.41	27.73	92.80	97.402	82.605	87.662	80.441	5

Note: (R_1) normal emulsification time with 500x dilution (second); (R_2) emulsification time after freeze-thaw with 500x dilution (second); (R_3) transmittance of quercetin-SEFs (%T); (R_4) transmittance of emulsion from 500x dilution (%T); (R_5) transmittance of emulsion from 100x dilution (%T); (R_6) transmittance of emulsion after freeze-thaw at 100x dilution (%T); (R_7) transmittance of emulsion after freeze-thaw at 500x dilution (%T) and (R_8) pH test results of quercetin-SEFs.

Based on PCA analysis, in the five principal components (PC), the variance has exceeded 99% of the initial data (**Figure 2a**). These results follow the theory and indicate a good analytical process (Riswanto et al., 2021). Observations are clearer on the scree plot (**Figure 2a**). The scree plot is a plot between the dimensions versus the percentage variance. Plot visualizations useful in interpreting data from PCA results include score plots, loading plots, and biplots. The correlation between the responses of the parameters specified in the SCD was well described using a loading plot (Shiyan, Zubaidah, et al., 2021).

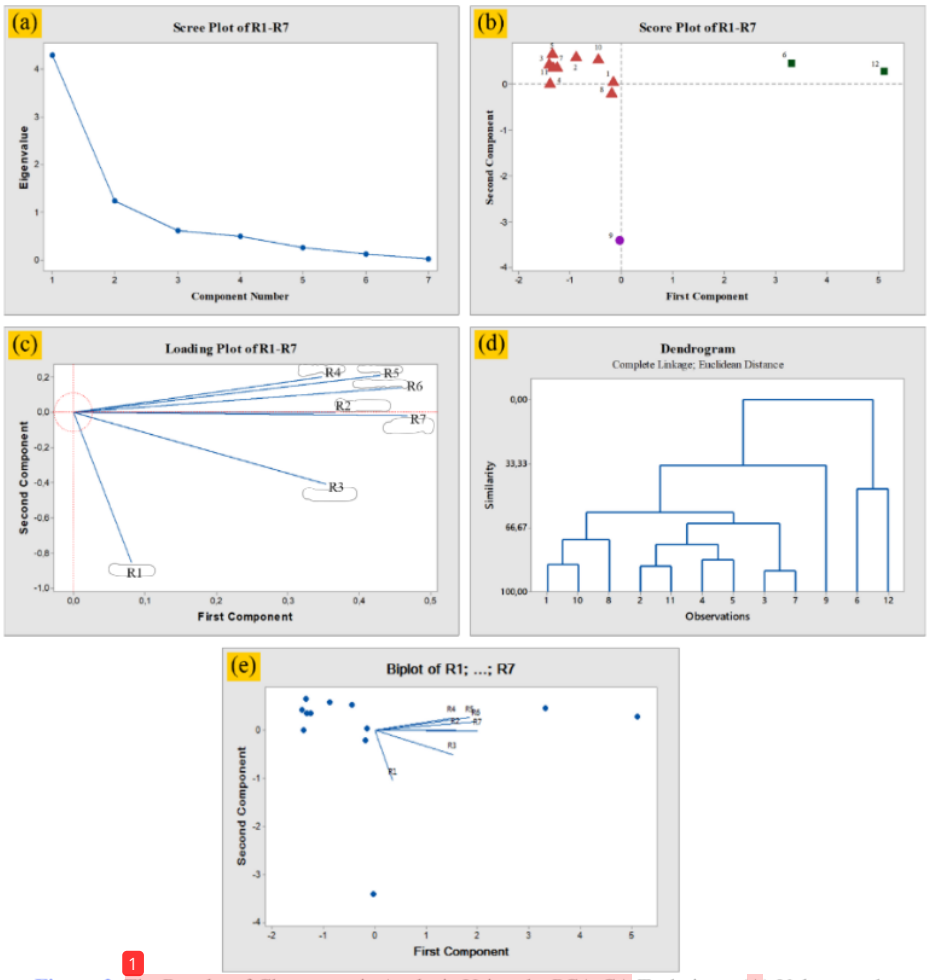

Figure 2. The Results of Chemometric Analysis Using the PCA-CA Technique. (A) Values on the Eigenvalues; (B) Scree Plot; (C) Loading Plot; (D) Dendogram; (E) Biplot. (R_1) Normal Emulsification Time With 500x Dilution; (R_2) Emulsification Time After Freeze-Thaw With 500x Dilution; (R_3) Transmittance Of Quercetin-Sefs; (R_4) Transmittance Of Emulsion From 500x Dilution; (R_5) Transmittance Of Emulsion From 100x Dilution; (R_6) Transmittance of Emulsion After Freeze-Thaw At 100x Dilution; (R_7) Transmittance of Emulsion After Freeze-Thaw at 500x Dilution.

Score plot can also be supported by cluster analysis in a dendrogram (Triyasmono et al., 2021; Widyastuti et al., 2021). A charge close to 0 indicates that the variable has a weak influence on the component. The results obtained from the score plot are reinforced with dendrogram diagrams to clarify the grouping of formulas based on similarity or similarity in character. Samples in one group will have similarities to each other. The PCA identification can be matched with the observations of the dendrogram diagram, as shown in **Figure 2d**. The score plot states

that observations of a certain group or class can be used to see an observation including a class based on the same characteristics (Hssaini et al., 2021; Yang et al., 2022).

Loading plot used to determine the response variables in large-scale grouping in the formation of PC values. **Figure 2c** shows the loading plot obtained, and the farther one variable is from the starting point, the greater the contribution of the variable to the PCA process. Loading plot states that the variables close to each other have a directly proportional relationship (directly proportional). Directly proportional is also called co-linearity, while variables far apart and opposite each other are inversely related (inversely proportional). **Figure 2c** through loading plot graph which graph below shows that R_1 and R_4 are approaching a 90-degree angle, indicating no correlation between the two responses (Widyastuti et al., 2021). Some responses, including R_1-R_5, R_1-R_6, R_1-R_2, and R_1-R_7, do not correlate. The two vectors between R_4-R_5, R_4-R_6, R_4-R_2, and so on form an angle of less than 90; both responses are positively correlated.

The biplot graph in **Figure 2e** explains the correlation between the sampling areas, which shows the variables that have the most contribution or impact by examining the distance between variables and samples. The distance between samples and variables describes the relationship between variables and samples. The closer the distance between the two variable points and the sample, the larger the variables contributing to the sample. Two response points close to the sample indicate a larger response contributed to the sample. Two samples with the same characteristics are described as two points close together (Riswanto et al., 2021). The analysis results through a biplot graph show that each point in the analyzed data illustrates that the observed points are samples that are spread in all quadrants in the biplot. All points displayed by the biplot data indicate that formulas 1 and 8 are located close to all response points.

3.3. Observed Response Evaluation

3.3.1. Normal emulsification time with 500x dilution (R_1)

The quercetin-SEFs formula was tested for emulsification time to measure the time required for the preparation to form an emulsion in the body according to the peristaltic motion of the gastrointestinal tract. **Table 3** (R_1) showed formulas 1, 9, and 12 tested had the slowest emulsification time, more than 10 seconds. The optimization design of quercetin-SEFs on SCD proves that each concentration of the mixture component of the formula can affect the emulsification time (**Figure 3**). The evaluation was carried out on twelve formulas using water media and stated that it was easier to use (Herbianto, 2018). Distilled water media has neutral properties to the SEFs components, so it will not affect its content. Emulsion that looks transparent or translucent when seen with the naked eye indicates a very small particle or droplet size. The requirement of good SEFs emulsification time is less than 1 minute. Emulsification time data from twelve experimental runs were judged to meet the requirements of good SEFs. The emulsification time of SEFs can decrease with the interaction of oil and PEG-400 concentration, while oil with oil concentration can increase, which affects the emulsification time.

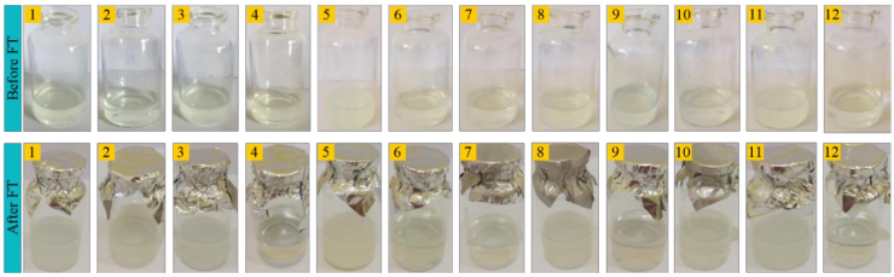

Figure 3. Appearance of Quercetin-Sefs (A) Before Freeze-Thaw and (B) After Freeze-Thaw

3.3.2. Emulsification time after freeze-thaw with 500x dilution (R_2)

A stable formula at temperature changes is important because it will determine the resistance of the formula to changes in storage and distribution conditions. The stability test results ensure that the product (formula) remains in good condition. The freeze-thaw method is a formula stability test technique with the principle of periodically transferring samples from a cold place to room temperature (Jumaryatno et al., 2018). The results of the freeze-thaw test that have been carried out can be seen that the formula made is stable to changes in temperature (**Table 3**; R_7). The most stable formulas and remain in very good condition are found in formulas 4 and 12, marked by a clear visual form. Several formulas showed that the emulsion appearance after freeze-thaw was cloudier except for formulas 4 and 12. This phenomenon occurred due to freezing time which caused the hydrophilic groups on the surfactant head to freeze. The freezing time that lasts will return to its original catch and cover the oil phase again. Overall, several statistical evaluations of seven response models that were obtained were feasible to be used as the design of the quercetin-SEFs optimization formula. Physical stability test of emulsion at freeze-thaw dilution of 500x has been conditioned on several storage cycles.

3.3.3. Transmittance of quercetin-SEFs (R_3)

The results obtained from UV-Vis spectrophotometry are important factors in seeing the shape of the SEFs formula made and revealed that the transmittance value close to 99% indicates the clarity of an emulsion (Artanti et al., 2021). Measurement of transmittance (%T) used a wavelength of 650 nm. The highest transmittance value SEFs results were found in formulas 6, 9, and 12 (**Table 3**; R_3).

3.3.4. Transmittance of emulsion from 500x dilution (R_4)

The measurement of the transmittance value of emulsions using a wavelength of 650 nm at the time of testing (Yuliani et al., 2016). Observation of clarity is seen from the transmittance value, which is close to 100 % in formulas 6, 9, and 12. If the emulsion has a transparent appearance, it can be estimated that the droplet size reaches nanometers. Apart from measuring the clarity of SEFs, it is also necessary to measure the transmittance of emulsions to control the dispersion formation of emulsions. The dispersed phase strongly influences the appearance of the emulsion in the form of droplet size formed. Light can pass through a very small droplet size, and the light will be transmitted so that the readings on the spectrophotometer produce a high transmittance value.

3.3.5. Transmittance of emulsion from 100x dilution (R_5)

The droplets in the emulsion reach the nanometer size, which is directly proportional to the transmittance value close to 100% (Jumaryatno et al., 2018). SEFs produce clear dispersions and have a potential droplet size of up to nanometers. The transmittance results of emulsions carried out in this study have a lower range than emulsions with 500x dilutions, namely 13-82% (**Table 3**; R_5).

3.3.6. Transmittance of emulsion after freeze-thaw at 100x dilution (R_6)

The test results of the transmittance of the freeze-thaw nanoemulsion at 100x dilution showed that the nanoemulsion had a color change to become cloudier but without phase separation. The percentage produced statistically shows a significant difference between the conditions before and after the nanoemulsion was carried out in the freeze-thaw stage stated that the turbidity that occurs can be caused by changing cycles in the freeze-thaw test because at a temperature of -20°C, the hydrophilic group at the head of croduret-50SS will freeze and will have difficulty in capturing or enclosing the oil phase as before. This process makes the droplets combine and form a larger size, causing turbidity in the formula (**Table 3**; R_6).

3.3.7. Transmittance of emulsion after freeze-thaw at 500x dilution (R_7)

The clarity of the percentage of transmittance of nanoemulsion in freeze-thaw dilution of 500x is higher than that of 100x dilution. The transmittance value of the freeze-thaw

nanoemulsion at 500x dilution ranged from 5-80%. The transmittance value obtained by each formula is not uniform due to differences in concentration, and the designed formula may have varying droplet sizes. Before the freeze-thaw cycle, the physical form of the formula underwent changes that were not too significant when viewed from the shape and appearance (Table 4; R_6).

Table 4. Endurance Test Results of Quercetin-SEFs

Formula	dilution level of 100							dilution level of 250							dilution level of 500						
	Days to							Days to							Days to						
	1	2	3	4	5	6	7	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: (↓) precipitated. (≠) not precipitated

3.4. Endurance Test

The endurance test aimed to see the similarity of the properties of quercetin-SEFs formed from various dilutions. Endurance test can also be used to ensure proper drug release and ensure that there are no deposits at various dilution levels so as not to hinder drug absorption (Jumaryatno et al., 2018; Yuliani et al., 2016).

The replication results stated that the had the same conditions at each level of dilution. The formula that did not experience precipitation was found in runs 1, 4, 6, 8, 9, 10 and 12 at the dilution level of 100. The formula made in the 250 dilutions did not find any precipitation at runs 3, 4 and 10. While in the 500 dilutions, no precipitation was found (on runs 3, 4, 10 and 12).

4. CONCLUSION

Chemometric analysis was successfully applied in evaluating the response to the quercetin-SEFs optimization modeling. Chemometric analysis of PCA and CA on simplex centroid design optimization of quercetin-SEFs includes score plot, loading plot, scree plot and dendrogram with three large scale groups. The results of chemometric analysis show that between responses that have a positive correlation will increase each other or giving a comparable value between responses. Different results happens if there is a negative correlation. The loading plot can clarify the correlation between responses. In this pre-optimization model, the transmittance value is positively correlated with the emulsification time. The diluent factor at the time of emulsification and freeze-thaw was also correlated. It means, all of the respons that positively correlated will giving the comparable value between the respons. If the first response is higher, than the other respones that positively correlated with first reponse will getting higher too. Therefore, this explanation supports evaluating response in the optimization stage so that formula is obtained according to the expectations and requirements. Based on the findings of this study, can clarify the correlation between responses, so that further modeling can be developed at the optimization stage of quercetin-SEFs

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6. CONFLICT OF INTEREST

The author declares that there are no competing conflicts of interest.

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