Formulation of Super Saturable-Self Micro Emulsifying Loaded Centella asiatica L. Extract and FTIR-based Fingerprinting Combinated Chemometrics Analysis

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Formulation of Super Saturable-Self Micro Emulsifying Loaded *Centella asiatica* L. Extract and FTIR-based Fingerprinting Combinated Chemometrics Analysis

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In this study, self-emulsifying method was applied to formulate the *Centella asiatica* L. urban extract (CeCa). The presence of groups in the extract was established on the basis of FTIR-ATR spectra using a chemometric approach. Further, the super saturable-CeCa-self micro emulsifying (SS-CeCa-SME) extracts were formulated using an oleic acid carrier oil, Tween 80 as surfactant and propylene glycol as co-surfactant with nine variations of component concentration. The FTIR-ATR spectra obtained were evaluated using a chemometric approach. The chemometric analysis method uses principal component analysis (PCA) and cluster analysis (CA). The score plot provides precise classification results by forming three large groups. The results were obtained to become a reference in the optimization process and further development of pharmaceutical preparations.

Keywords: *Centella asiatica* L. Urban, Self-micro emulsifying, Chemometrics, Principal component analysis, Cluster analysis.

INTRODUCTION

Centella asiatica L. Urban is a cosmopolitan plant, especially in the tropical and subtropical areas. This herb has several pharmacological properties, including antibacterial and antimicrobial, antifungals, antioxidants, anti-inflammatory, anticancer, improving cognitive function and neuroprotective [1-3]. This herb contains the active ingredients saponins, tannins, flavonoids, steroids and triterpenoids [4,5]. Bioactive triterpenoid compounds include asiaticoside, madecassoside, asiatic acid and madecassic acid [6]. This compound is difficult to dissolve in water; its sizeable molecular structure results in difficult absorption, unstable to the environment, thus affecting storage stability [7,8].

Therefore, it is formulated as a delivery improvement in super saturable-self micro emulsifying (SS-SME). A sound delivery system will increase the bioavailability of the drug and improve the stability of *Centella asiatica* extract (CeCa). The development of SS-CeCa-SME formula is highly determined from the constituent components consisting of oil, surfactant and co-surfactant. Metabolomic is a comprehensive analysis of metabolites in organisms with a multivariate approach [9]. However, in its development, metabolomic properties can be applied to specific materials, such as in the formulation of drug delivery systems by utilizing the characteristics of chemicals [10]. This approach can display detected chemical profiles and evaluate forms of change as a typical response in various circumstances. Therefore, it can be utilized in classifying an SS-CeCa-SME formula.

Some of the published results describe changes in metabolite profile and its correlation with bioactivity in plants with a combination of FTIR and chemometric. This approach has been used for metabolite correlation and bioactivity to identify function groups, which correlate with antioxidant activity, authentication and adulteration [11,12]. However, no studies have been reported for the classification of an SS-CeCa-SME formula. Moreover, no analysis is also reported through the infrared fourier transform-attenuated total reflection (FTIR-ATR) spectra pattern in evaluating the characteristics of the SE formula. The chemometric analysis used in this study was principal component analysis (PCA) and cluster analysis (CA). PCA is used for sample classification according to its different formulae.

EXPERIMENTAL

Centella asiatica was obtained from Omah Djamoe Arroyyan (Klaten, Indonesia). Chemicals such as oleic acid, Tween 80, propylene glycol (PG), ethanol 70% were purchased from Bratachem (Jakarta, Indonesia).

Sample preparation and extraction: Extract preparation was done using the ultrasound-assisted extraction (UAE) technique from the pollination and extraction process. The UAE procedure uses a force of 48 kHz, within 15 min, using 70% ethanol solvent.

Super saturable-self microemulsifying formulation: The design compositions of SS-CeCa-SME for nine formulae in this study are shown in Table-1. The preparation of SS-CeCa-SME samples were done by dissolving CeCa in oil using a vortex *i.e.* continued sonicator for 5 min at room temperature followed by the addition of surfactants and co-surfactants in the oil-extract solutions. The formed mixture was stored in a rotary shaker temperature of 25-30 ºC for 12 h and then left for 12 h.

TABLE-1
DESIGN FORMULA OF SS-CeCa-SME

Formula	Oil: Oleic acid (%)	Surfactan: Tween 80 (%)	Co-surfactant: PG (%)
F_1	60.00	30.00	10.00
F_2	40.00	50.00	10.00
F_3	20.00	70.00	10.00
F_4	47.50	37.50	15.00
F_5	27.50	52.50	20.00
F_6	20.00	60.00	20.00
F_7	32.50	42.50	25.00
F_8	40.00	30.00	30.00
F_9	20.00	50.00	30.00

Emulsification time, viscosity and drug load: A 10 mL of SS-CeCa-SME was added into 5 mL of media with the help of a magnetic stirrer with a speed of 120 rpm at 37 ºC. The emulsion formed was characterized by the complete dissolution of SS-CeCa-SME in the medium [13]. SS-CeCa-SME viscosity was measured using the Oswald viscometer instrumentation in mPa.s units. The quantity of extract or drug load contained in SS-CeCa-SME was determined using the centrifugation technique at 3500 rpm for 30 min. The precipitate formed was weighed as an extract.

Percentage transmittance: The emulsion obtained from the emulsification time measurement is used to determine the clarity value or transmittance (%) measurement at a wavelength of 650 nm using a UV-Vis Genesys 10S spectrophotometer (Thermo Scientific, USA).

Droplet size, polydispersity index, zeta potential and mobility: The size of the droplet diameter (nm), polydispersity index (PI), zeta potential (mV) and electrophoretic mobility (cm^2/Vs) of the SS-CeCa-SME formula was measured using a particle size analyzer (Horiba, Japan) [14].

FTIR-ATR spectra: FTIR-ATR spectra were measured using FTIR spectrophotometer Nicolet iS10 (Thermo Scientific, USA) equipped with a deuterated triglycine sulfate (DTGS) detector. The FTIR spectra were measured in the region of 4000-525 cm^{-1} with a resolution of 4 cm^{-1} and 16 scans/min controlled by Omnic 4.2 software (Thermo Scientific, USA). FTIR spectral data were stored as a data point table [14,15].

Chemometrics analysis: Rough spectra obtained from instruments are processed using Omnic software. The obtained data is inputted in excel. Classification of SS-CeCa-SME according to the various formula was performed using principal component analysis-cluster analysis (PCA-CA). The PCA technique is used in classifying formulae based on the absorbance of 13 predetermined peaks. Plot score data is emphasized by cluster analysis (CA) [16,17].

RESULTS AND DISCUSSION

SS-CeCa-SME formulation: *Centella asiatica* extract (CeCa) was successfully formulated in self-emulsifying using oleic acid oil as its carrier, Tween 80 as a surfactant and propylene glycol as co-surfactant. The first mixing in preparation between carrier oil and extract using vortex for 5 min is intended to mix all active substances as well in the oil with constant speed and strength. Surfactants and co-surfactants were dissolved into oil solutions and extracts that have been perfectly fused. Ultrasonication aims to reduce the particle size of the mixture so that the homogeneity of the mixture increases. The formed mixture was stored at 25-30 ºC for 24 h before the evaluation process. Visualizations of SS-CeCa-SME extracts obtained on nine different composition are presented in Fig. 1. The resulting SS-CeCa-SME colours range from bright yellow to dark yellow. Colour is influenced by the concentration between oil mixture, surfactant and co-surfactant.

When the oil phase meets the water phase in the stomach, it forms spontaneous emulsification so that the SS-CeCa-SME directly spreads to the gastrointestinal tract (GI). Motility in the stomach can affect self-emulsification so that smaller droplets form and have a wide surface and trigger a faster absorption process [18]. Analysis of emulsification time is carried out observations to obtain an overview of the time and it takes SS-CeCa-SME to form nanoemulsions when it meets the gastrointestinal fluid. The condition of emulsification time was less than 5 min. Emulsification time on nine formulae meets the requirements with the fastest time of 60 s for formula 1.

The viscosity of SS-CeCa-SME can affect the droplet size of the formed emulsion. High viscosity values also affect the speed of emulsification time. Formula 4 has low viscosity with an emulsification time of 63 s. The highest drug load was found in formula 5 of 232.57 mg/mL. The transmittance (%T) test was conducted to investigate the ability of the sample solution to pass on light fired from UV spectrophotometry, while the value of %T of a formula describes the emulsification process capability of a surfactant. The transmittance was measured using a spectrophotometric method at a wavelength of 650 nm. The

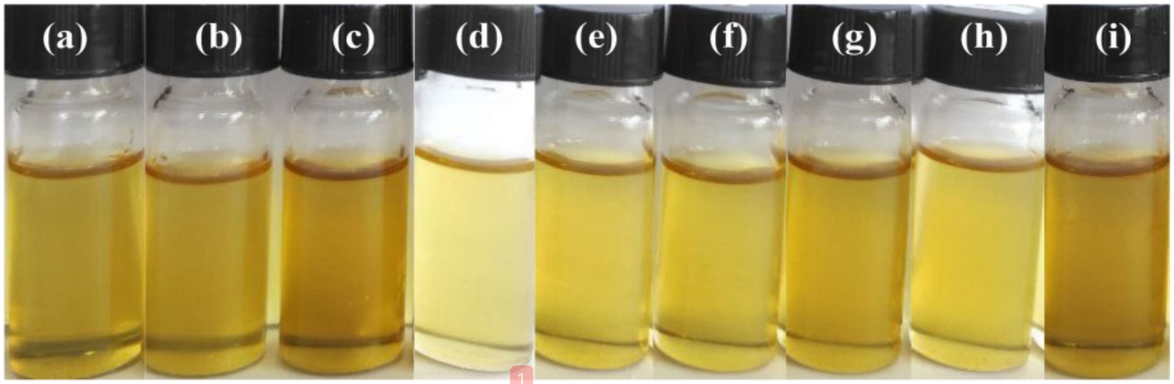

Fig. 1. Visualization of SS-CeCa-SME formulas, (a) F1; (b) F2; (c) F3; (d) F4; (e) F5; (f) F6; (g) F7; (h) F8 and (i) F9

transmittance value close to 100% indicates that SS-CeCa-SME produces a clear and transparent dispersion with a droplet size estimated to reach nanometers.. The transmitting value of 9 formulae that are close to 90% is formula 6. The higher %T value, the better surfactant capability would be used in the emulsification process and the clearer nanoemulsion will obtained. Among the nine formulae, formula 3 has the highest %T. Evaluation of the emulsification time, viscosity, drug load, SS-CeCa-SME transmittance and emulsion transmittance is presented in Table-2.

Measurements using DLS-PSA resulted in the formation of the tiniest droplet of 0.25 µm in formula 3, while formula 9 consist the largest droplet diameter of 1.93 µm. Formulae 2 and 8 have zeta potential values close to 0. This condition is consistent with the visual observations that rapidly form deposits and separations. In contrast to other formulae (F1, F3, F4, F5, F6, F7 and F9), the potential zeta value exceeds 30 mV with a negative charge. Fig. 2 shows the results of droplet measurements using the DLS-PSA instrumentation. This zeta potential value correlates with mobility. If the zeta potential is high, the mobility is also high. The results of droplet measurements, including size diameter, polydispersity index, zeta potential and electrophoretic mobility of the entire formula, are presented in Table-3.

TABLE-2
RESULTS OF SS-CeCa-SME CHARACTERIZATION

Formula	Emulsification time (s)	Viscosity (m.Ps)	Drug load (mg/mL)	Transmittance SS-CeCa-SE (%)	Transmittance emulsion (%)
F_1	41 ± 3.61	7.57 ± 0.07	363.88 ± 8.93	80.65 ± 1.57	83.46 ± 2.58
F_2	86 ± 2.65	10.07 ± 0.29	279.96 ± 10.00	79.38 ± 0.88	81.34 ± 2.42
F_3	70 ± 2.00	7.06 ± 0.10	399.20 ± 5.47	80.49 ± 1.91	85.72 ± 1.90
F_4	63 ± 3.61	6.56 ± 0.27	364.66 ± 4.64	80.65 ± 1.77	82.89 ± 2.12
F_5	191 ± 2.00	4.44 ± 0.15	232.57 ± 7.95	81.51 ± 1.58	57.99 ± 2.44
F_6	61 ± 1.00	5.66 ± 0.23	427.57 ± 9.04	88.91 ± 0.87	55.36 ± 1.05
F_7	64 ± 1.00	7.70 ± 0.20	350.58 ± 2.55	78.33 ± 0.90	83.71 ± 2.05
F_8	136 ± 2.00	9.87 ± 0.09	395.09 ± 4.56	81.44 ± 2.33	78.53 ± 1.19
F_9	118 ± 2.00	6.92 ± 0.15	67.88 ± 1.77	83.09 ± 2.53	59.66 ± 1.49

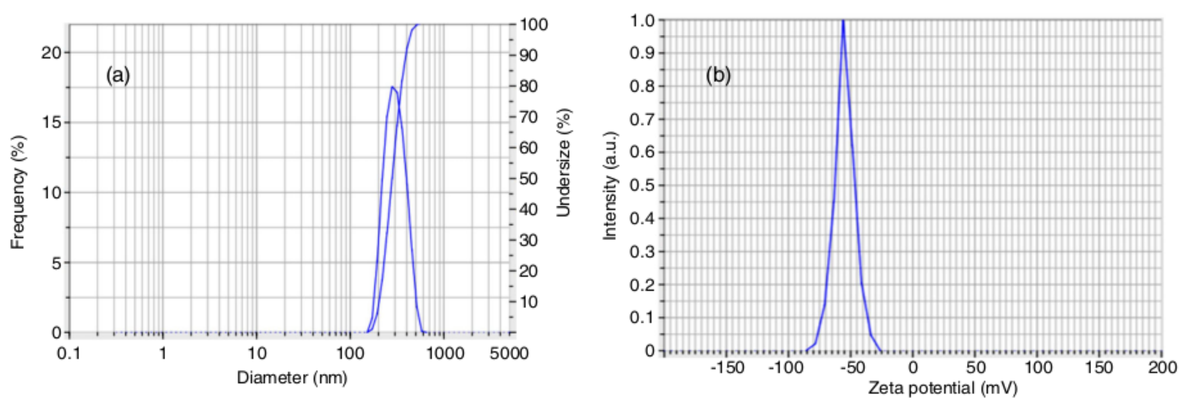

Fig. 2. Droplet size from DLS-PSA measurement (a) diameter, (b) zeta potential

TABLE-3
DROPLET CHARACTERISTICS OF NANOEMULSION SAMPLES USING PARTICLE SIZE ANALYZER

Formula	Droplet size (d.nm)	Polydispersity index	Zeta potential (mV)	Description
F_1	1013.9 ± 4.09	0.556 ± 0.007	-45.2 ± 1.00	Clear
F_2	1300.4 ± 0.93	0.595 ± 0.003	-14.7 ± 0.72	Clear
F_3	253.4 ± 1.63	0.393 ± 0.004	-54.9 ± 0.72	Clear
F_4	759.8 ± 2.94	0.830 ± 0.044	-57.8 ± 1.13	Clear
F_5	892.5 ± 1.75	0.503 ± 0.005	-45.3 ± 0.91	Clear
F_6	290.9 ± 0.97	0.504 ± 0.008	-53.8 ± 0.81	Clear
F_7	1413.5 ± 7.14	0.534 ± 0.012	-32.3 ± 0.93	Clear
F_8	974,5 ± 4.75	0.554 ± 0.005	-13.5 ± 0.79	Clear
F_9	1934.3 ± 4.34	0.497 ± 0.003	-58.3 ± 1.84	Clear

Correlation of evaluation parameters on the characterization of SS-CeCa-SME: Several responses evaluated from nine formulae were analyzed using multivariate statistical techniques. The correlation between responses from the loading plot and dendrogram is shown in Fig. 3. The size of the droplet diameter has a positive correlation with the emulsification time. The smaller droplet size will accelerate the spontaneous formation of emulsion and *vice-versa*. The positive correlation between droplet size and emulsification time was indicated by the formation of angles below 45º from both vectors. A positive correlation is formed between the droplet distribution values as reflected in the polydispersity index and transmittance (%T). This phenomenon follows visual observations where more evenly distributed droplets of uniform size produce SS-CeCa-SME with a transparent appearance.

The absence of correlation between the responses is indicated by forming an angle of 90º between the two adjacent vectors [16]. Viscosity does not directly correlate with emulsification time and between droplet diameter size and transmittance (%T) formed. Two vectors forming an angle of approximately 180º indicate a negative correlation. This phenomenon is formed between the zeta potential and viscosity. Drug load (DL) also negatively correlates with emulsification time. The higher the drug load value, the longer the spontaneous emulsification process will take. The size of the droplets formed strongly influences the number of catechins that enter the SNE system. The smaller the droplet size in SS-CeCa-SME, the higher the drug load.

FTIR-ATR studies: The FTIR-ATR spectral analysis is very helpful in evaluating the properties or characteristics of . A function cluster at a specific wave number indicates a unique fingerprinting area. Similar to metabolites in extract analysis, metabolomics also works on SS-CeCa-SME formula samples. Therefore, these distinctive properties can be used in evaluating different formulae. Fig. 4 shows the spectra patterns of all nine formula components.

Fig. 5 presents nine FTIR spectra patterns from the SS-CeCa-SME formula. No differences are obtained from the IR spectra in the peak position or each extract has a similar pattern and only differ in their intensities.

Classification of SS-CeCa-SME using chemometrics: The data of formulation and characterization results to nine Formulae of SS-CeCa-SME obtained will be processed using chemometric analysis with principal component analysis (PCA) and cluster analysis (CA) methods processed using Minitab software. The chemometric analysis is a science that connects measurements performed in a system or chemical process with the state of the system through the application of mathematics and statistical methods. The processing of infrared spectrum data is carried out using multivariate statistical methods [19]. The benefit of the multivariate statistical method is its ability to extract the necessary spectrum information from the infrared spectrum and use that spectrum information for qualitative and quantitative applications [20].

Classification is indispensable in the pre-optimization evaluation as a first step in determining the top and bottom

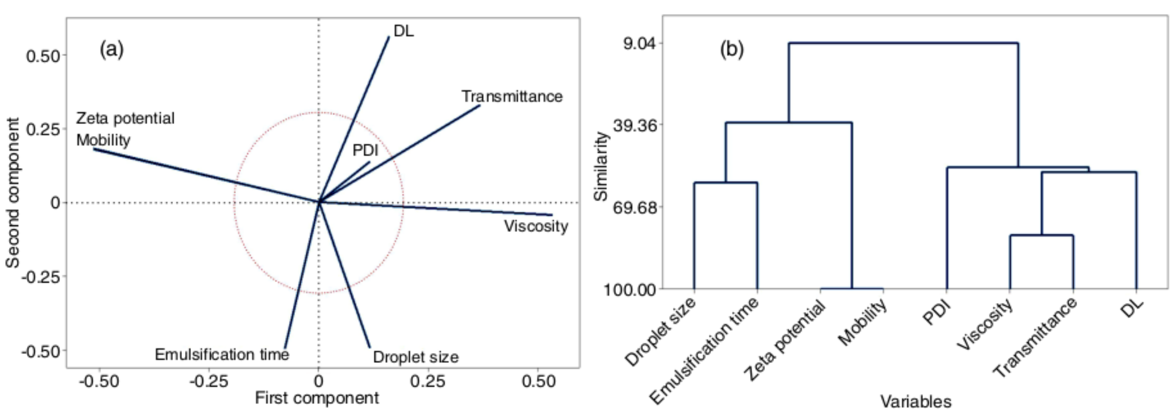

Fig. 3. Loading plot that describes the relationship between responses, (a) loading plot, (b) dendogram

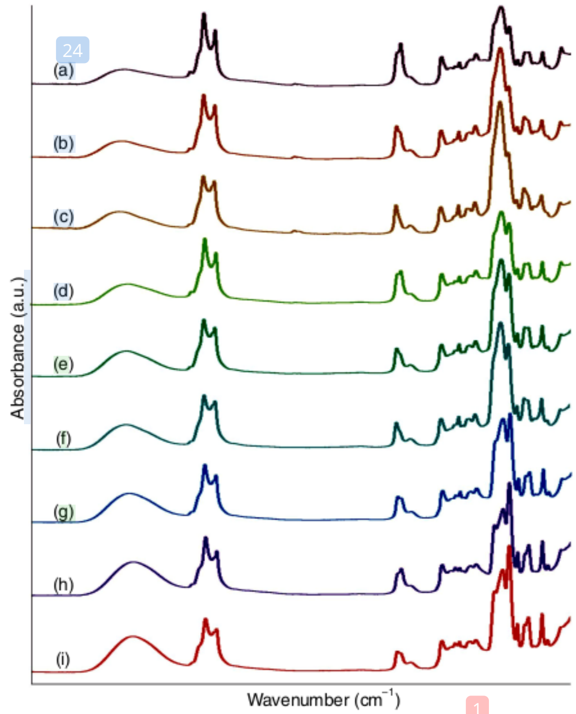

Fig. 4. FTIR-ATR spectrum of SS-CeCa-SME Formulae, (a) F1, (b) F2, (c) F3, (d) F4, (e) F5, (f) F6, (g) F7, (h) F8, dan (i) F9

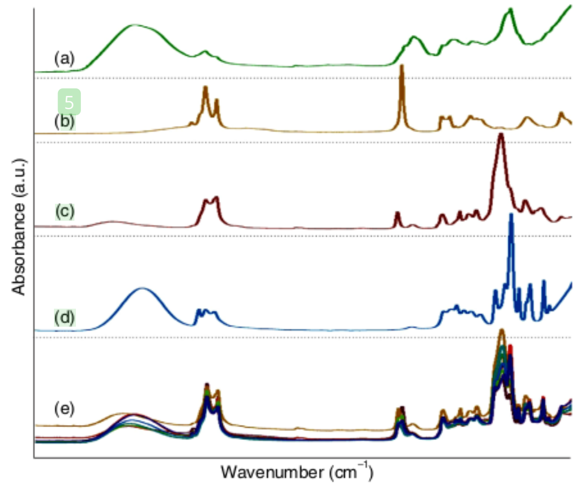

Fig. 5. IR spectral profile of the SS-CeCa-SME formula and its constituent components, (a) SS-CeCa-SE, (b) Oleic acid, (c) Tween 80, (d) propylene glycol

levels. Provides an insight into the range of concentrations that can affect the properties and characteristics of the obtained formula. The results of the score plot in the form of three groups are shown in Fig. 6a. Formulae 1, 2 and 4 have a close resemblance or character in one group. The second group formed consisted of formulae 3, 5 and 6. While the group of three consists of formulae 7, 8 and 9.

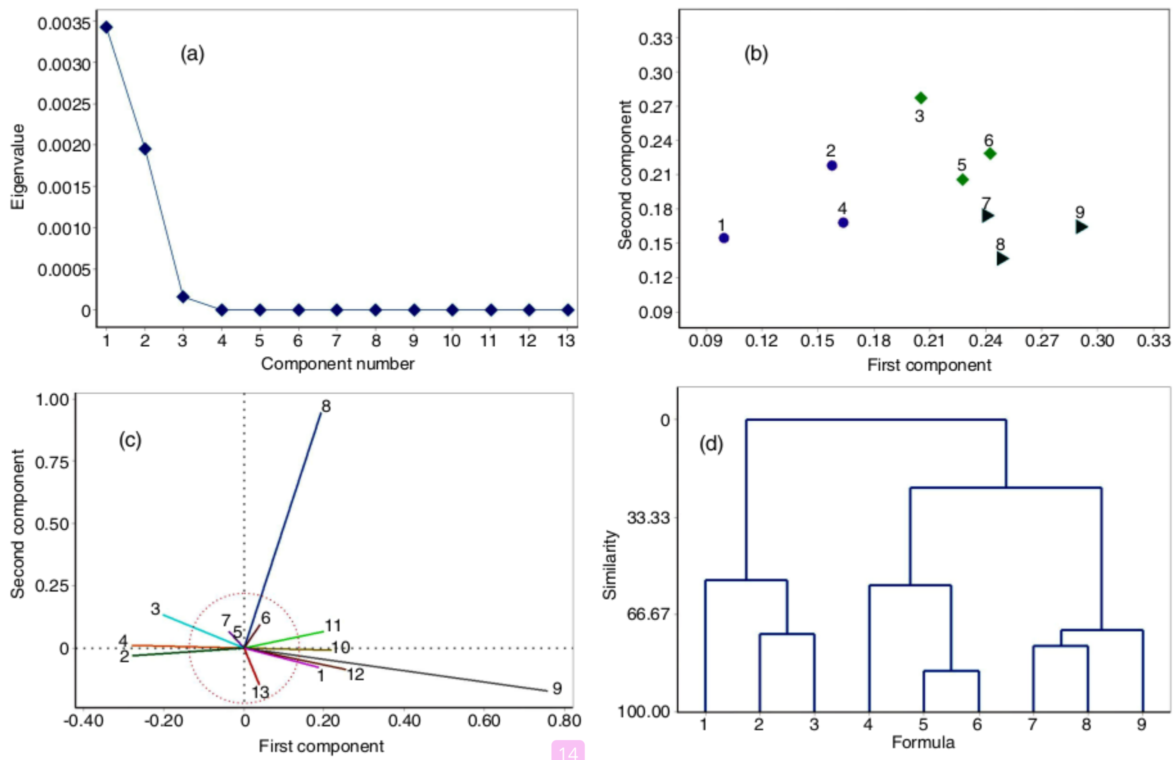

Fig. 6. PCA plot of SS-CeCa-SME, (a) Score plot, (b) Score plot, (c) loading plot and (d) dendogram

TABLE-4
ABSORBANCE OF SELECTED WAVENUMBER ON ALL IR SPECTRA OF SE-CeCa-SME FORMULA

	Absorbance												
	1	2	3	4	5	6	7	8	9	10	11	12	13
F_1	0.042	0.169	0.131	0.101	0071	0.058	0.077	0.183	0.139	0.064	0.081	0.082	0.092
F_2	0.044	0.149	0.126	0.079	0.069	0.067	0.079	0.254	0.168	0.077	0.100	0.092	0.088
F_3	0.060	0.144	0.132	0.076	0.072	0.076	0.083	0.320	0.199	0.089	0.116	0.100	0.082
F_4	0.045	0.148	0.116	0.075	0.069	0.063	0.075	0.208	0.183	0.080	0.092	0.095	0.095
F_5	0.051	0.122	0.104	0.057	0.066	0.067	0.074	0.256	0.224	0.091	0.104	0.108	0.089
F_6	0.051	0.117	0.104	0.056	0.065	0.069	0.075	0.280	0.232	0.093	0.110	0.110	0.085
F_7	0.060	0.125	0.102	0.054	0.067	0.065	0.073	0.228	0.240	0.094	0.109	0.115	0.094
F_8	0.076	0.132	0.101	0.061	0.070	0.064	0.071	0.195	0.254	0.098	0.115	0.123	0.105
F_9	0.079	0.119	0.096	0.046	0.070	0.068	0.072	0.229	0.282	0.108	0.122	0.130	0.100

A dendrogram supports the classification results in Fig. 6b that emphasizes similarity. Each formula is grouped according to its similarity. Fig. 6c describes the correlation between the peaks set in the response. A total of 13 responses describes the absorbance value in the wavenumber (Table-4). There is a positive correlation, a negative and no correlation when referring to the initial IR function, which indicates the function cluster at these peaks.

Conclusion

Extracts from *Centella asiatica* were well formulated using the self-micro emulsifying method. The FTIR-ATR spectra pattern is successfully used in classifying the super saturable-CeCa-self microemulsifying (SS-CeCa-SME) formulas using a chemometric analysis approach. The classification obtained can be used in providing optimization direction at the next stage of development.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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Formulation of Super Saturable-Self Micro Emulsifying Loaded Centella asiatica L. Extract and FTIR-based Fingerprinting Combinated Chemometrics Analysis

GRADEMARK REPORT

FINAL GRADE	GENERAL COMMENTS
/100	**Instructor**

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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.

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.

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.