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Stability Study of Super Saturable Catechin-Self Nano Emulsifying Drug Delivery System as Antidiabetic Therapy

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Abstract: Diabetes mellitus is a metabolic syndrome characterized by hyperglycemic and increased ROS production, which causes oxidative stress. Catechin isolated from the tea plant has oxidative stress inhibitor activity and anti-diabetic activity with low absorption in circulation systemic. Therefore, it is formulated in a super saturable catechin-self nano emulsifying drug delivery system (SSC-SNEDDS). Stability is one of the factors that affect the safety, quality, and efficacy of SSC-SNEDDS. This study aims to evaluate the stability of the formulated oil phase using oleic acid, crodurett as a surfactant, and propylene glycol as a co-surfactant. Stability studies were carried out by several tests, namely heating-cooling cycle assay, freeze-thaw cycle assay, centrifugation, and endurance assay. Droplet characterization in the form of changes in diameter, zeta potential, and mobility in evaluating stability tests using dynamic light scattering-particle size analyzer (DLS-PSA). Real-time stability was also evaluated by observing changes in the infrared spectrum pattern using FTIR-ATR. After the stability test, the emulsion droplet size of SSC-SNEDDS was still below 100 nm and showed good stability. It can be concluded that the formula has a good stability profile.

Keywords; catechin; self-nano emulsifying; stability study; heating-cooling; freeze-thaw; FTIR-ATR.

1. Introduction

Diabetes mellitus is a cause of death with a high risk of complications. Diabetes is an endocrine, metabolic disorder whiches still be epidemic and one of the main causes of death. Type 2 diabetes is characterized by hyperglycemia, insulin resistance, chronic inflammation causes, induced free radicals, and damage to the endogenous antioxidant defense system [1,2]. Based on scientific publications in recent years, there is a correlation between oxidative stress and type 2 diabetes, both of which play a relevant role in pathogenesis [3,4]. Hyperglycemia can contribute to oxidative stress through glucose autoxidation, which collectively increases reactive oxygen species (ROS) [5]. Hyperglycemic conditions can increase the production of ROS that can initiate oxidative stress [6]. Many catechins are isolated from leaves tea (*Camellia* *sinsensis*) and can be an oxidative stress inhibitor. Catechins have been shown to reduce ROS with the support of polyphenol structure, which can ward off free radicals [7]. Therefore, the antioxidant agents and anti-diabetic continuously to be learned, especially the natural sources of the polyphenol group.

Catechin has better antioxidant properties than tocopherol, butylated hydroxyanisole, or butylated hydroxytoluene [8,9]. It has been reported that the antioxidant activity of catechin has the most important benefit in counteracting free radicals [10]. Several studies have reported that consumption of catechin in green tea can increase plasma catechin and reduce oxidative stress [11]. Catechin has the benefit of increasing insulin sensitivity in type 2 diabetes. Still, catechin is unstable in physiological conditions and can quickly degrade if given intravenously, and some of them will be degraded before reaching the target [12,13].

The formulation in the form of super saturable catechin-self nano emulsifying drug delivery system (SSC-SNEDDS) is an alternative to increase bioavailability by lipophilic. This strategy will increase clinical efficacy, simplify permeability, and decrease the dose to clinical effects [14-16]. The stability of SNEEDS and the nanoemulsion formed is very important to be evaluated. The stability depends on constituent components, the courante of clots in the SNEDDS system, and the droplet size of the nanoemulsion formed. The small droplet size can increase emulsion stability by decreasing gravitation and Brown motion to prevent creaming and flocculation [17]. In this study, SSC-SNEDDS stability is observed with several tests such as heating-cooling, freeze-thaw, centrifugation, and endurance assay, which evaluate physical thermodynamic stability; hopefully that a stable SSC-SNEDDS will be obtained further as a better diabetes therapy agent.

2. Materials and Methods

2.1. Chemical materials.

Catechin used products purchased from Sigma-Aldrich (Singapore). The materials such as oleic acid, croduret, propylene glycol were purchased from Bratachem (Jakarta, Indonesia). Other materials such as aquadest, aquabidest, aqua pro injection, and ethanol were purchased from Embacang Multi Jaya (Palembang, Indonesia).

2.2. Super saturable catechin-self nano emulsifying drug delivery system formulation.

Preparation of SNEDDS was initiated by dissolving catechin in the oil phase using a vortex followed by a sonicator for 5 minutes at room temperature. Addition of surfactant and co-surfactant in oil-catechin. The mixture formed was stored in a rotary shaker at 25 - 30 °C for 12 hours and left for 12 hours. The composition of the formula composition is in Table 1.

Table 1. Design formula of super saturable catechin-self nano emulsifying drug delivery system.

Material	Function	Quantity
catechin	active ingredient	30 mg
oleic acid	oil phase	895 uL
croduret	surfactan	1598 uL
propylenglicol	co-surfactan	823 uL

2.3. Clarity determination using spectrophotometer UV-Vis.

Samples in the form of SSC-SNEDDS and the obtained emulsion form were put into a cuvette of 3 mL each. Clarity was measured as percent transmission (%T) at a maximum wavelength of 650 nm using a Genesys 10s series Spectrophotometer (Thermo Scientific, USA). The blank used in the measurement of the percent transmission was distilled water [18].

2.4. Heating-cooling cycle assay.

The assay was carried out in 3 (three) cycles. Each cycle consists of storage at a temperature of approximately 45 °C) and then cooling at -21 °C with a storage time of 24 hours each. Observation of in stability parameters such as separation, sediment, creaming, and cracking was carried out.

2.5. Freeze-thaw cycle assay.

The assay was carried out in 3 (three) cycles. In each cycle, the samples were stored at a freezing temperature of -21°C, then thawed at 25°C, with 24 hours storage for each temperature. Observation of in stability parameters such as separation, sediment, creaming, and cracking was carried out.

2.6. Centrifugation assay.

Stability test by centrifugation using the BKC-TL4IV Biobase series centrifugator (Shandong, China). Samples were tested by centrifugation at a speed of 3500 rpm for 30 minutes. Observation of in stability parameters such as separation, precipitation, creaming, and cracking was carried out.

2.7. Endurance test.

The SSC-SNEDDS formula was emulsified with dilution levels of 100, 250, and 500 times using aquadest as a solvent. The emulsion formed was observed for the separation phase that was formed until the presence or absence of a precipitate. The evaluation was also carried out using the centrifugation method at a speed of 3500 rpm for 30 minutes. The endurance parameter is determined by the formation of a precipitate.

2.8. FTIR-ATR spectra.

FTIR-ATR spectra were measured in the FTIR spectrophotometer Nicolet iS10 (Thermo Scientific, USA) and the detector used was deuterated triglycine sulfate. The FTIR spectra were measured in the region of 4000-500 cm^{-1} with a resolution of 4 cm^{-1} and 16 scans/min controlled by Omnic 4.2 software (Thermo Scientific, USA). FTIR spectra were stored as a data point table [19,20].

2.9. Determination droplet using particle size analyzer.

Droplet diameter, polydispersity index, and zeta potential were measured using particle size analyzer Zetasizer Nano ZSP (Malvern Panalytical, UK) by applying the dynamic light scattering (DSL-PSA) method. The test steps were described as follows, 500 µL catechin carrier SNEDDS drop by drop were put into 5 mL (emulsion 1:10) aquabidest on the magnetic stirrer with a speed of 150 rpm. The emulsion formed was inserted into the microcuvette, and the measurements were carried out with predetermined specifications. The analysis was assisted using Zetasizer 7.12 software so that the results obtained were droplet size (d.nm), polydispersity index, and zeta potential (mV) [21].

3. Results and Discussion

3.1. SSC-SNEDDS formula.

Super saturable catechin (SSC) was successfully formulated in the form of a SNEDDS using oleic acid oil as a carrier, croduret as a surfactant, and propylene glycol as a co-surfactant. SSC-SNEEDS shows a yellow-orange color due to the formation of colloidal dispersion, as in Figure 1a. SSC-SNEEDS can form an oil-in-water nanoemulsion when interacting with aqueous media, which changes the color to clear or cloudy, as shown in Figure 2b. Both the SNEDDS system and the emulsion were tested for thermodynamic stability using heating-cooling and freeze-thaw methods. The SNEDDS formula before the test was marked with information number 1, number 2 for the heating-cooling test, and number 3 for results after freeze-thaw.

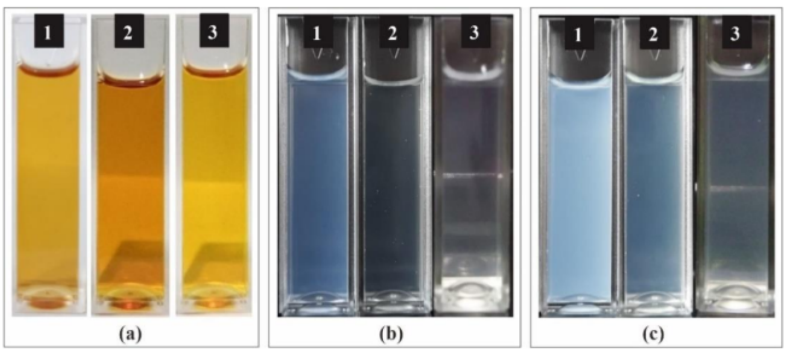

Figure 1. Visualization of SSC-SNEDDS and nanoemulsion: (a) SSC-SNEDDS formula; (b) nanoemulsion; (1) normal before testing; (2) after heating-cooling; (3) after freeze-thaw.

3.2. Stability in the form of SSC-SNEDDS.

SNEDDS stability is thermodynamically tested using heating-cooling, freeze-thaw, and centrifugation methods. Testing at this stage aims to evaluate the stability of selected formulas based on various temperature and centrifugation variations. Observation of the stability of SSC-SNEDDS is done visually to see its clarity, physical changes (creaming, cracking), sediment, and phase separation [17,22]. Stability test results by several methods are obtained results that the formula SSC-SNEDDS remains stable. Figure 1 proves there is no phase separation and no visual precipitate.

Tabel 2. Result of stability study for SSC-SNEDDS formula.

Replication	Centrifugation	Heating-cooling cycle assay	Freeze-thaw cycle assay
1	stable	no phase separation	no phase separation
2	stable	no phase separation	no phase separation
3	stable	no phase separation	no phase separation
4	stable	no phase separation	no phase separation
5	stable	no phase separation	no phase separation
6	stable	no phase separation	no phase separation

Evaluation on the form of SSC-SNEDDS indicates fairly good stability. Table 2 shows that there was no separation and precipitate from 6 replications in the centrifugation, heating-cooling, and freeze-thaw tests. Stability at this stage greatly affects pharmaceutical quality. In addition, the stability of the SNEDDS isotropic system will affect the emulsion formed.

Tabel 3. Stability test of SSC-SNEDDS (*n*=6).

Parameters	Colors	Precipitation	Clarity (%T)
before test	pure orange	none	82.38 ± 1.70
heating-cooling	pure orange	none	85.93 ± 2.86
freeze-thaw	brownish orange	none	91.24 ± 0.71

The results of heating cooling, freeze-thaw, and centrifugation tests on SSC-SNEDDS can be seen in Tables 2 and 3. No separation and sediment were found from the three tests. These thermodynamic stability results indicate that the SNEDDS formula is stable both in storage and in temperature changes. So, the SSC-SNEDDS formula already meets the desired characteristics.

3.3. Evaluation of stability using FTIR-ATR spectra for SSC-SNEDDS.

The stability of the SSC-SNEDDS formula was also observed using FTIR-ATR instrumentation by qualitatively evaluating spectra patterns. The SSC-SNEEDS spectra pattern the first day after it is formulated and after 30 days if stored at room temperature is presented in Figure 2. Both spectra show the same pattern; there is no significant difference between the two spectra. Several peaks were detected with a relatively weak percentage of transmittance (%T), at 3853.01 absorptions; 3648.64; 1652.83; 1558.26; 1540.69, and 1506.77.

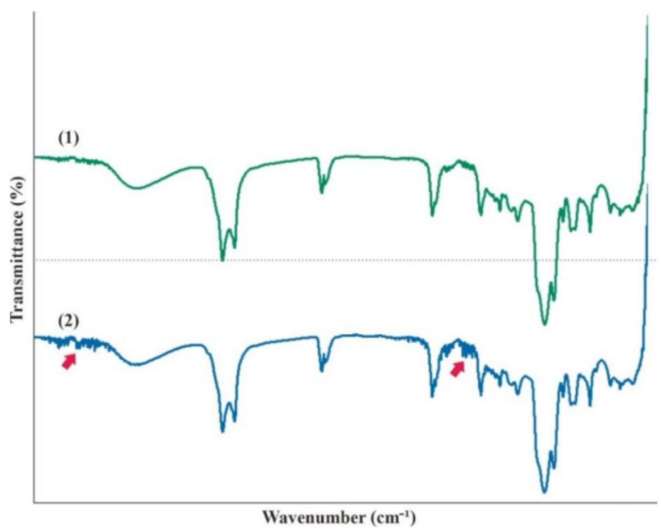

Figure 2. SSC-SNEDDS FTIR-ATR spectra pattern, (1) first-day formulation, (2) storage of room temperature (25 – 30 °C) for 30 days.

Tabel 4. Wavenumber and intensity of SNEDDS spectra on days 0 and 30.

1: Day 0		2: Day 30		Bonding type
Wavenumber (cm^{-1})	Intensity (% T)	Wavenumber (cm^{-1})	Intensity (% T)	
504.06	115.64	503.69	121.13	C-O; C-C
668.22	84.20	668.20	84.80	C=C-H, Ar-H
837.44	79.86	837.49	80.11	C=C-H, Ar-H
945.77	80.15	945.62	80.39	C-O-C

1: Day 0		2: Day 30		Bonding type
Wavenumber (cm^{-1})	Intensity (% T)	Wavenumber (cm^{-1})	Intensity (% T)	
990.48	82.68	990.47	82.66	C=C-H, Ar-H
1043.15	61.67	1042.58	62.51	C-O bond, hydroxy
1095.28	55.34	1096.01	55.72	stretch C-O, hydroxyl and ether
1248.84	82.76	1248.84	83.36	C-O bond, epoxy, ester stretch
1348.71	85.46	1348.76	85.66	C=O symmetric, deprotonation of carboxyl
1456.73	84.37	1456.87	82.88	asymmetric CHx bond
-	-	1506.77	93.56	stretch C=C (aromatic and aliphatic)
-	-	1540.69	93.75	stretch C=C
-	-	1558.26	94.08	stretch C=O, protonated carboxyl
-	-	1652.83	93.97	stretch C=O
1732.20	84.17	1732.91	82.57	stretch C=O, carbonyl, protonated carboxyl
2359.82	90.35	2359.82	89.90	stretch -C≡C-, C≡N
2854.80	75.67	2854.78	75.68	symmetrical CH_2 stretch
2922.97	72.28	2923.01	72.77	asymmetric CH_2 stretch
3419.36	91.54	3420.22	91.61	O-H stretch of a liquid such as water or a Lewis base
-	-	3648.64	95.58	O-H stretch of water
-	-	3853.01	96.40	O-H stretch of water

A more detailed evaluation of spectra 1 and 2 can be seen from the wavenumber absorption data in Table 4. The intensity of the same wavenumber does not differ much between spectra 1 and 2. Absorption occurs in wave number areas 3648.64 cm^{-1} and 3853.01 cm^{-1} in spectra 2, which in this area indicates the presence of OH tension from water [23]. The storage of SSC-SNEDDS at room temperature for 30 days allows the degradation process of oil components to produce a small amount of water. The presence of this water can be read in FTIR-ATR instrumentation at wavenumbers between 3400-3800 cm^{-1}. The results of organoleptic testing for formulas stored for 30 days a little has a rancid smell. However, in general, the physical condition of SNEDDS is still relatively good and stable. The evaluation results on the FTIR-ATR spectra also did not show any differences in the spectra that differed in both of the absorption patterns, the number of waves, and the intensity.

3.4. Nanoemulsion stability.

Dilution of 500, 250, and 100 times performed aims to see the emulsion stability of the resulting SSC-SNEDDS. The lower the dilution done, the longer the emulsification time will be. In addition, to see the occurrence of a sediment or phase separation that occurs. The observations showed stable results, both 500; 250; and 100 times dilution. Because none of the deposits or phase separation in the nanoemulsion was formed, this endurance essay explains the level of dilution in the emulsification process affecting the final stability resulting from nanoemulsions. The three dilution levels tested did not cause the emulsion to separate or precipitate to form. These results prove that the emulsion obtained from the SSC-SNEDDS formula is stable.

Kinetic stability can be achieved by heating-cooling and freeze-thaw because in a short time, it can be detected the separation of phases occur [17]. Physical stability is performed to know the maximum storage length that can lead to the separation of the emulsion phase (creaming or cracking). Testing is conducted as many as 3 cycles. The results of heating-cooling and freeze-thaw show no phase separation from both tests. So that nanoemulsion can be said to be stable during storage. Observations of nanoemulsions can be visually seen in Tables 5 and 6.

Table 5. Stability study of nanoemulsion.

Replication	Centrifugation	Heating-cooling cyle assay	Freeze-thaw cyle assay
1	stable	no phase separation	no phase separation
2	stable	no phase separation	no phase separation
3	stable	no phase separation	no phase separation
4	stable	no phase separation	no phase separation
5	stable	no phase separation	no phase separation
6	stable	no phase separation	no phase separation

Nanoemulsions are more stable with spheric droplet morphology. The results of heating-cooling and freeze-thaw also showed that the resulting nanoemulsion was stable caused none of phase separation. Centrifugation tests also support the stability of the nanoemulsions formed as the results show no phase separation.

Table 6. Nanoemulsion stability and droplet determination using DLS-PSA (*n*=6).

Parameter	Color	Clarity (%T)	Droplet (nm)	PDI	Zeta Potential (mV)	Mobility (µmcm/Vs)
nanoemulsion	cloudy white	32.19 ± 5.55	55.39 ± 1.85	0.212 ± 0.03	29.87 ± 0.40	2.30 ± 0.51
heating-cooling	clear	85.57 ± 2.75	57.21 ± 1.90	0.358 ± 0.05	27.95 ± 1.21	2.05 ± 0.09
freeze-thaw	clear	78.01 ± 2.11	54.89 ± 0.71	0.295 ± 0.05	28.64 ± 0.73	2.12 ± 0.34

The results of the measurement of droplet diameter, charge, and mobility before and after the stability test of the formed emulsion are shown in Table 6. There was no significant difference in the emulsion before the test and after the heating-cooling and freeze-thaw test. Droplet size has 55.39 d.nm values with a polydispersity index of 0.212.

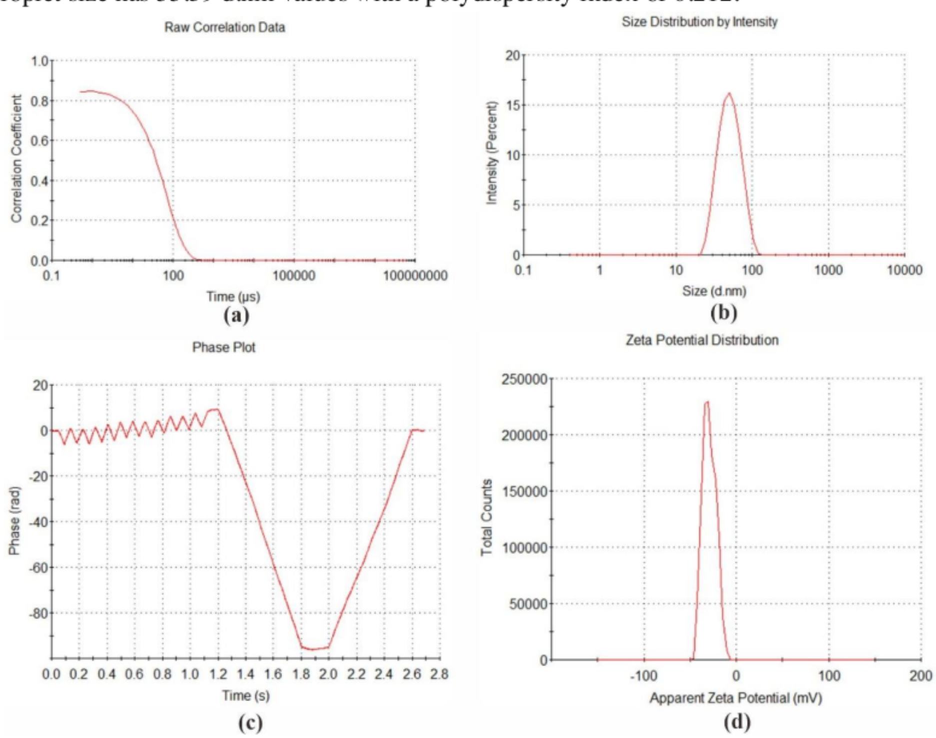

Figure 3. Droplet determination using DLS-PSA, (a) raw correlation data, (b) intensity of droplet size, (c) phase plot of zeta potential, and (d) total counts of zeta potential.

A polydispersity index below 0.5 means that the uniformity of droplet nanoemulsion size is getting better. The potential zeta is 29.87 mV, a value that is further away from the number 0, indicating more stable [21,24]. The electrophoresis mobility value of 2.30 µmcm/Vs is a significant result. This electrophoresis mobility is important to see the movement of the resulting nanoemulsion; the faster the mobility movement, the more stable the SNEDDS produced. Figure 3 shows an example of emulsion measurement results in the form of droplet size diameter (Figure 3a and 3b) and zeta potential with a negative charge (Figure 3c and 3d) from SSC-SNEDDS.

The viscosity of preparation greatly affects the value of the resulting emulsification time; the lower the viscosity value (diluted), the smaller the droplet size [25], the viscosity value obtained by 231.4 mPa.s. The resulting emulsification time shows a time of 10.30 seconds which indicates an excellent emulsification time, a good emulsification time of fewer than 5 minutes [25]. The resulting drug load value of 22.62 mg/mL means the active substance can enter the SNEDDS system perfectly that will have a good effect on the body. The formula stored for 30 days has a slightly rancid smell; this is due to the strain of the OH group releasing a little water. Therefore, it is still necessary to study optimization and the addition of antioxidants to the development formula.

4. Conclusions

Catechins have been successfully formulated in the form of super saturable-SNEDDS and have a good stability profile. The heating-cooling, freeze-thaw, centrifugation and endurance assay tests analyze the stability.

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Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the study's design, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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GENERAL COMMENTS

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.