Media Farmasi: Jurnal Ilmu Farmasi (Journal of Pharmaceutical Science) e-ISSN 2503-5223
Vol. 19, No. 2, September 2022, pp. 133-139
http://journal.uad.ac.id/index.php/Media-Farmasi/index

Formulation of self-nano emulsifying drug delivery system (SNEDDS) Red Ginger extract (*Zingiber Officinale* var. rubrum)

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ARTICLE INFO

Article history
Received: 02-09-2021
Revised: 10-12-2021
Accepted: 02-09-2022

Keywords
Diabetes Mellitus
Red Ginger
SNEDDS

ABSTRACT

Red ginger extract is one of the new medicinal discoveries made from natural substances that has pharmacological benefits in the treatment of diabetes. Many gingerol components in red ginger can aid in the treatment of diabetes mellitus. However, the administration of red ginger extract is not so effective, a delivery system such as SNEDDS (Self-Nano Emulsifying Drug Delivery System) must be developed. When compared to standard formulations, SNEDDS can boost the oral bioavailability of lipophilic medicines by up to 2.4 times. The oil phase of SNEDDS red ginger extract was virgin coconut oil, with tween 80 as a surfactant and PEG 400 as a co-surfactant. The fourth formula of the SNEDSS preparation of red ginger rhizome extract satisfied the requirements for a good nanoemulsion particle size in this study, with a percent T value of 99.7% and PSA test data showing that this formulation met the requirements for a good nanoemulsion particle size.

1. Introduction

There are around 40.000 plant species in Indonesia, and 1.300 of these plant species can be cultivated as potential medicinal plants (Anindhita & Oktaviani, 2016). Currently, Indonesians are beginning to use Trend Back to Nature medicine since medications made from herbal plants are simpler to get, less costly, and have less adverse effects (Sutomo et al., 2010). The use of ginger as a medicinal plant is increasing quickly, as is the use of natural components for therapy. Red ginger is a traditional diabetic treatment. Red ginger (Zingiber officinale var. Rubrum) is one of the medicines and spices discovered (Rahmadani et al., 2008). Identification of chemical components from red ginger (Zingiber officinale var. Rubrum), particularly gingerol, shogaol, and zingerone, which have been shown to have antioxidant, anti-inflammatory, analgesic, and anticarcinogenic properties (Febriani et al., 2018). However, because red ginger extract is an active material that is difficult to dissolve in water, it is manufactured in the form of a Self Nano Emulsifying Drug Delivery System (SNEDDS) to boost the active substance's solubility.

Self-Nano Emulsifying Drug Delivery System (SNEDDS) is a formulation made up of oil, surfactant, and cosurfactant in the proper proportions to form a stable isotropic combination (Nugroho & Sari, 2018). SNEDDS employs a nano-particle technology to improve medication absorption and bioavailability in the body, particularly for medicines with limited water solubility (Nugroho et al., 2017).

The capacity to distribute medications in dissolved form in the lumen of the gastrointestinal (GI) tract, offering a wider interfacial area for drug absorption, is one of the benefits of SNEDDS (Nugroho & Sari, 2018). A nano emulsion is a transparent, translucent emulsion system that is an oil-water dispersion stabilized with a surfactant film layer or surfactant molecules with droplet sizes ranging from 100 to 500 nm (Martien et al., 2012). Tween 80 is a surfactant that may be used with oil to generate a stable nano emulsion. Tween 80 has an HLB of 15 and is typically considered harmless

and nonirritant (Raymond, 2015). A cosurfactant in the form of PEG 400 is added to complement the performance of surfactants. The inclusion of cosurfactants reduces interfacial tension and disrupts the liquid crystal structure, resulting in the creation of nano emulsions (Muzaffar et al., 2013). Because the oil phase that dissolves the therapeutic material is lipophilic, VCO as the oil phase here works as a key component in the nano emulsion formulation. Furthermore, oil can enhance the proportion of lipophilic medicines absorbed by the lymphatics, gastric, and transdermal routes. Lauric acid accounts for 43-53 percent of the fatty acid content of VCO (Raymond, 2015). Lauric acid is capable of increasing penetration and absorption.

Based on the above, research was undertaken on the production of a Self-Nano Emulsifying Drug Delivery System (SNEDDS) formulation from red ginger extract (Zingiber officinale var. Rubrum), which provides the most recent alteration to increase solubility and hence bioavailability. chemicals that are active in the body.

2. Materials and Methods

This study is being conducted in the Pharmaceutical Technology Laboratory at Ahmad Dahlan University. The ingredients used are red ginger rhizome, tween 80, PEG 400, 95% ethanol (Onemed), aquadest, toluene, ethyl acetate. The tools used are oven, blender, rotary evaporator, water bath, vortex (Labinco), sonicator (Elma), magnetic stirrer, flacon, glass bottle, analytical balance (Ohaus), glassware, stopwatch (ZSD-808), UV-Vis spectrophotometer (Shimadzu Pharma spec UV-1700), white tip, blue tip, 50-200 µL micropipette, Particle Size Analyzer (PSA) (Horiba SZ-100) micropipette, filter paper, aluminum foil, porcelain cup, glass stirrer, thermometer

2.1.Preparation of samples

The red ginger rhizome (Zingiber officinale Rosc. Var. Rubrum) utilized in this study was acquired at Beringharjo Market Yogyakarta in May 2021. Fresh red ginger rhizome was cleaned, sliced, and dried in the oven for 24 hours before being mashed with a blender. The powdered ginger rhizome simplicia is kept in a firmly sealed jar. The yield of simplicia is computed as follows:

$$\text{Yield} = \frac{\text{Final Weight}}{\text{Initial Weight}} x\ 100\%$$

2.2 Red Ginger Extract

The maceration process was used to extract red ginger. As a solvent, 95 percent ethanol is used in the maceration process. Every 50 grams of simplicia powder is placed in a container, followed by 250 mL of 95 percent ethanol, which is then mixed, carefully covered, and left for 5 days with daily shaking for 1 hour to ensure equitable distribution. The filtrate was removed from another bottle and filtered, after which the residue was repressed for 24 hours, stirred, and filtered. The filtrate was then evaporated using a rotary evaporator at 50oC and proceeded with evaporation in a water bath until a thick extract was produced (Febriani et al., 2018). The extract yield was estimated by comparing the beginning weight of the simplicia to the final weight of the extracted simplicia.

2.3 Identify Gingerol Compounds

The TLC technique was used to identify gingerol compounds. The stationary phase was a silica GF 60 aluminum plate that was activated for 1 hour in a 100oC oven, and the mobile phase was a 7:3 solution of toluene and ethyl acetate that was combined and saturated in a jar. The extract was spotted on a labeled TLC plate and then examined under 366 nm UV light. Gingerol's Rf value is 0.54 according to extant studies (Febriani et al., 2018).

2.4 Creating SNEDDS

In each formula, oil phase (VCO), surfactant (Tween 80), and cosurfactant (PEG 400) were combined and homogenized by vortex for 5 minutes, followed by sonication for 15 minutes (Wahyuningsih & Putranti, 2015).

Table 1. SNEDDS formula for red ginger extract

Component	F1	F2	F3	F4
Tween 80	2.0 mL	2.0 mL	2.0 mL	2.0 mL
PEG 400	2.5 mL	2.5 mL	2.5 mL	2.5 mL
VCO	0.2 mL	0.3 mL	0.4 mL	0.5 mL
Red Ginger Extract	500mg/mL	500mg/mL	500mg/mL	500 mg/mL

2.5 Clarity Test

The clarity test was performed with a spectrophotometer and the percent Transmittance parameter at 650 nm, with distilled water as a control. The clearer the transmittance, the closer the emulsion droplets to the nanoscale size. The determination of its qualities will proceed with the highest percent transmittance (Wahyuningsih & Putranti, 2015).

2.6 Emulsification Time Test

The emulsification time of red ginger extract was determined using three media: aquadest, Artificial Gastric Fluid (AGF) without pepsin, and Artificial Intestinal Fluid (AIF) without pancreatin (Wahyuningsih & Putranti, 2015). SNEDDS red ginger extract was swiftly placed into the appropriate medium and the time it took for the extract to dissolve was recorded. The full dissolution of SNEDDS red ginger extract in the medium characterized the generated nano emulsion.

2.7 Particle Size Determination

Determination of SNEDDS particle size Red Ginger Extract was dispersed in aquabidest at a ratio of 1:250, and the dispersed nano emulsion solution was tested on the Particle Size Analyzer for particle size and polydispersity index (IP) (PSA).

3. Results and Discussion

3.1 Yield of Red Ginger Simplicia Powder

In May 2021, fresh red ginger was acquired at Beringharjo Market in Yogyakarta. The weight of fresh red ginger is 8.5 kg, while the weight of simplicia powder produced is 1.6 kg. The purity of the simplicia powder was 18.82 percent.

3.2 Red Ginger Extract

The weight of the red ginger extract obtained was 58.1002 grams, with a yield of 3.63 percent gained from the findings of this investigation. The organoleptic test findings of red ginger extract (Table 2).

Table 2. Organoleptic Test Results

Organoleptic	Results
Smell	Aromatic
Flavor	Spicy
Texture	Thick
Color	Dark chocolate

3.3 Identification of Gingerol Compounds

The TLC test of red ginger extract using toluene: ethyl acetate (7:3) mobile phase and silica GF 60 stationary phase aluminum plate produced satisfactory spot separation. A 366 nm UV light was used to generate a green spot with an Rf value of 0.58 on the chromatogram. Results of gingerol chemical discovery in red ginger extract (Figure 1).

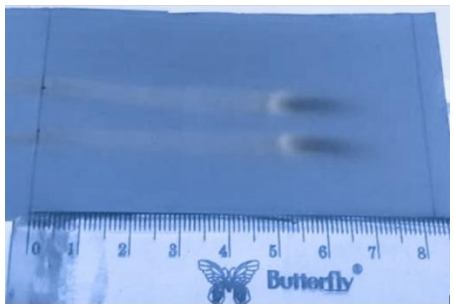

Figure 1. TLC findings obtained with a 366 nm GF silica plate and a toluene:ethyl acetate (7:3) developer

3.4 Making SNEDDS using Red Ginger Extract

Red ginger extract, which has been shown to contain gingerol components, was synthesized in SNEDDS preparations using the table 1 formulation. In each recipe, the red ginger extract SNEDDS produced was stable (Table 3). At 24 hours, the physical stability of SNEDDS red ginger ethanol extract was bright yellow, liquid, uniform, and did not separate. This demonstrates that the preparation is stable since it has the same organoleptic qualities as when it was initially produced. This is consistent with Stephanie et al, (2016) research, which claims that nano emulsion preparations are regarded to be excellent and stable if they have a clear appearance with no phase separation. The homogeneity, drug solubility, absorption, and particle size of SNEDDS red ginger extract will be affected by its stability.

Table 3. Stability of SNEDDS

Formulation	Stability
1	Stable
2	Stable
3	Stable
4	Stable

3.5 SNEDDS Clarity Test

The percent transmittance measurement was performed to demonstrate that the emulsion droplets had attained the nanoscale size of less than 100 nm. Observation of the percent transmittance value with a spectrophotometer at a wavelength of 650 nm if it is more than 90% (Winarti et al., 2018). The following table shows the results of the % transmittance test of SNEDDS red ginger ethanol extract (Table 4).

Table 4. Yield % Transmits

Formula	Replication	%T	Mean %T± SD
Formulation 1	1	92.529	92.549 ± 0.137
	2	92.480	
	3	92.639	
Formulation 2	1	99.500	99.553 ± 0.046
	2	99.573	
	3	99.585	
Formulation 3	1	99.646	99.613 ± 0.031
	2	99.585	
	3	99.609	
Formulation 4	1	99.713	99.744 ± 0.013
	2	99.756	
	3	99.744	
Aquadest	1	10.122	100.002 ± 0.114
	2	99.896	
	3	99.987	

The results of the % transmittance observation at 650 nm in the table above demonstrate a formula with a high transmittance, namely formulation 4. A clearer emulsion with a transmittance value similar

to aquadest implies the production of smaller emulsion droplets, which are believed to be 10-200 nm in size (Syukri et al., 2018).

The size of the dispersed phase has a significant impact on the appearance of the emulsion, such as whether it is clear or foggy. This is because to the size of the oil droplets scattered in the aqueous phase. The light beam will be transmitted as it passes through the created nano emulsion, resulting in a higher transmittance value. The findings of the transmittance test will then be carried over to the emulsification time test.

3.6 Emulsification Time Determination

The emulsification time calculation aims to provide an overview of SNEDDS preparations that can easily form emulsions in the body due to peristaltic movements in the gastrointestinal tract, so that the SNEDDS preparation of red ginger ethanol extract is diluted in various media with a pH that corresponds to the fluids in the gastrointestinal tract.

The faster the emulsification time, the faster the medication absorption time (Thakur et al., 2013). SNEDDS is stated to be excellent if the emulsification time generated on the three media, distilled water, artificial gastric fluid (AGF/gastric fluid), and artificial intestinal fluid(AIF), is less than one minute (intestinal fluid). The following table shows the results of the SNEDDS emulsification time test for red ginger ethanol extract (Table 5).

Table 5. Results of the emulsification time test

Formulation	Media AGF (s)	Media AIF (s)	Aquadest (s)
1	55.23	29.66	60.04
2	20.14	25.48	55.24
3	18.58	24.45	52.21
4	16.74	24.30	43.82

According to Indratmoko et al., (2021), an emulsion is considered satisfactory when the emulsification duration is shorter than one minute and the visuals are clear or transparent. In the emulsification time calculation above, all of the formulae produced good results because they had an emulsification time of less than 1 minute, however formulation 4 had the shortest emulsification time of all. The optimum emulsification time test results would be followed by a particle size test, assuming that SNEDDS preparations have a size range of 10-200 nm (Syukri et al., 2018).

3.7 Particle Size Test Results

The nano emulsion droplet size was determined using particle size parameters. The size of the nano emulsion is 10-200 nm (Syukri et al., 2018). The smaller the particle size, the larger the surface area, which can improve medication absorption in the gastrointestinal system (Winarti et al., 2018). The findings of the particle size test in formulation 4 are shown in the table below (Table 6).

Table 6. Particle size test results

Formulation	Particle Size	Polydispersity Index
4	17.8nm	0.173

According to the data in the table above, the nano emulsion particle size in formulation 4 was in the range of 10-200 nm. While a Polydispersity Index (PI) value less than one implies that the size of the nano emulsion generated is uniform. A PI value less than one has a homogenous size distribution indicator function that may be utilized to reliably prepare nano emulsion.

4. Conclusion

Based on the findings of this investigation, the fourth formulation of the Self Nano Emulsifying Drug Delivery System (SNEDSS) preparation of red ginger extract (Zingiber officinale var. Rubrum) had a percent T value of 99.7%. The PSA test likewise revealed that this fourth formula, with a particle

size of 17.8 nm, matched the parameters for a suitable nano emulsion particle size. The SNEDDS technique is easy, rapid, and accurate to create.

Author Contributions: Mila Erliyana conceived. Mila Erliyana, Widyanari Febriana Wulansari, dan Dea Anggraini Wumu designed the study, performed all data analyses, interpreted the result and revised the paper.

Funding

The Ministry of Education, Culture, Research and Technology has provided grant funds for this research in the Student creativity program.

Competing Interests

The authors disclose no conflict.

Acknowledgment

We would like to express our gratitude to KEMENDIKBUD has provided grant funding for this research.

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