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The effect of surfactant on the solubility of kencur (*Kaempferia galanga L.)* rhizome ethanol extract in self nanoemulsifying drug delivery system

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ABSTRACT

Kencur (*Kaempferia galanga L.)* rhizome ethanol extract contains a lipophilic compound of ethyl p-methoxycinnamate. Self-nanoemulsifying drug delivery system (SNEDDS) formulation can increase the solubility of the extract in water. The purpose of this study was to determine the effect of surfactant combination on the kencur rhizome extract in the SNEDDS system. The SNEDDS formulations were carried out by selecting the surfactant ratio of Tween 80:Span 80 and Tween 80:Chremophor RH 40, followed by selecting the ratio of surfactant mixtures to polyethylene glycol 400 as co-surfactant, and to virgin coconut oil as the oil phase. The clarity, transmittance, emulsification time, particle size, and polydispersity index were evaluated. The stability test was carried out in aquadest, artificial gastric fluid, and artificial intestinal fluid for 4 hours at 37°C. The results showed that the combination of Tween 80: Chremophor RH 40 produced better SNEDDS than Tween 80:Span 80. The combination of surfactant-cosurfactant of Tween 80:Chremophor RH 40:PEG 400 at ratio 3:1 and 1:1 could produce homogenous dispersed SNEDDS showing droplet size of 23,0 and 21,8 nm; transmittance of 95.63% and 93.83%, and SNEDDS preconcentrate emulsified less than 35 seconds. The single surfactant Tween 80:PEG 400 at the ratio 3:1 produce better dispersed SNEDDS than the combined surfactant with droplet size 16.3 nm, transmittance 97.85%, and SNEDDS preconcentrate emulsified less than 45 seconds. The SNEDDS system could produce a smaller droplet size than the extract in aquadest.

Keywords: Kencur rhizome ethanol extract, SNEDDS, surfactant, nanoemulsion

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INTRODUCTION

The extract of kencur rhizomes (*Kaempferia galanga* L.) contains ethyl-p-methoxycinnamate (EPMS) that has an anti-inflammatory and analgesic (Riasari et al., 2016; Tambunan & Lubis, 2017; Umar et al., 2012) antidiabetic (Ernawati et al., 2017) and antioxidative effects (Riasari et al., 2016). EPMS is a lipophilic compound and low water solubility, resulting in low systemic bioavailability (Ekowati et al., 2017). Self-nanoemulsifying drug delivery system (SNEDDS) dosage form could be an alternative formulation to improve solubility and oral bioavailability. SNEDDS forms spontaneous emulsions in the digestive tract. The small size of the nanoemulsion is less than 100 nm. Its size could increase the surface area of particles and the solubility in the gastrointestinal fluid (Makadia et al., 2013).

The SNEDDS formulation consists of a drug, oil, surfactant, and co-surfactant. An appropriate composition would create a stable emulsion mixture (Date et al., 2010). Tween 80 is a hydrophilic surfactant, it can decrease the surface tension of the oil and water phase and maintains the stability of nanoemulsion in the formed system (Maestro et al., 2008; Dizaj, 2013). Tween 80 can form oil-in-water emulsion systems with small particles, increasing the solubility and bioavailability of the drug (Chinwong et al., 2012; Sheu et al., 2011). Span 80 is a lipophilic surfactant. A combination of hydrophilic and lipophilic surfactants could form a stable nanoemulsion (Makadia et al., 2013). Otherwise, the lipophilic surfactant can increase the drug loading of SNEDDS (Chen et al., 2011). Chremophor is a hydrophilic surfactant with the lowest HLB than Tween 80, resulting in a stable nanoemulsion system combined with Tween 80 (Basalious et al., 2010).

The research of Tween 80 with Span 80 and Chremophor RH 40 as a surfactant in SNEDDS preparation of kencur rhizome extract has not been carried out. This study was purposed to determine the effect of surfactant combination on the kencur rhizome extract in the SNEDDS system by evaluating the droplet size, polydispersity index, clarity, transmittance, and emulsification time.

MATERIALS AND METHOD

Materials

The materials used in this research were an ethanolic liquid extract of Kencur (*Kaempferia galanga L.)* rhizome (Indesso Aroma), Virgin Coconut Oil (Loba Chemie), Tween 80 (Avantor), Span 80 (Merck), Chremophor RH 40 (BASF), and PEG 400 (ChemWorld). All of the excipients were pharmaceutical grade. Based on the CoA, the ethanolic liquid extract of kencur rhizome is a dark brown suspension with an aromatic odor and has a specific gravity (25°C) of 0,949.

Methods

Formulation of kencur rhizomes extract SNEDDS

Selection of surfactant combination ratio

Various combinations of surfactant (Tween 80:Span 80 and Tween 80:Chremophor RH 40) were selected at 1:1, 1:3, 1:5, 3:1, and 5:1 ratios. The mixture was homogenated for 5 minutes. The clarity and stability were visually observed for three days. A clear and stable mixture was chosen for further selection.

Selection of surfactant and co-surfactant ratio

The combination of chosen surfactants and polyethylene glycol (PEG) 400 as co-surfactant were selected at 3:1, 3:2, 3:3, 3:4, and 3:5 ratios. The mixture was homogenated for 5 minutes. The clarity and stability were visually observed for three days. A clear and stable mixture was chosen for further selection. In this research, the combination of single surfactants Tween 80: PEG 400 at a ratio of 3:1 was also evaluated.

Selection of surfactant, co-surfactant, and oil phase ratio

The composition of selected surfactant and co-surfactants were mixed with VCO as the oil phase with a ratio of surfactant-cosurfactant and VCO at 1:1 to 10:1. The mixture was homogenated for 5

minutes. The clarity and stability were visually observed for three days. A clear and stable mixture was chosen as the selected SNEDDS base system.

Construction of SNEDDS' base system

The SNEDDS of kencur rhizome extract was formulated with varying concentrations of the surfactant, co-surfactant, and oil phase based on the previous selection study (Table 1). For any mixture, the total was 100%. Each formulation was stirred at 250 rpm for 10 minutes and vortex at high speed for 5 minutes.

Construction of the kencur rhizome ethanol extract SNEDDS

Table 1. The composition of kencur rhizome ethanol extract SNEDDS

Formulation	Concentration (%v/v)					
	F1	F2	F3	F4	F5	F6
Kencur Rhizome Extract	20	20	20	20	20	20
Tween 80	25	20	17	23	25	51
Chremophor RH 40	25	20	17	-	-	-
Span 80	-	-	-	23	25	-
PEG 400	16	28	36	16	16	17
VCO	14	12	10	18	14	12

Drug loading

The drug loading was obtained by mixing the kencur rhizomes extract into each SNEDDS system until saturated. The clarity of the mixture was visually observed. Each formulation of kencur rhizome extract SNEDDS was stirred at 250 rpm for 10 minutes and vortex at high speed for 5 minutes. Then each formulation was scaled up for the characteristics evaluation.

Characterization of SNEDDS' physical properties

Each formulation of kencur rhizome extract SNEDDS was evaluated for its physical and stable properties. The SNEDDS preconcentrate was evaluated for organoleptic and emulsification time, whereas the dispersed SNEDDS was evaluated for clarity, transmittance, droplet size, polydispersity index, and physical stability.

Clarity and transmittance

An amount of 200.0 µL of each SNEDDS was added by aquadest up to 10.0 mL. The mixture was homogenated with the vortex at low speed for 30 seconds. The sample was evaluated for clarity by visual observation and the transmittance percent at a wavelength of 650 nm by using a UV-Vis spectrophotometer, using aquadest as a blank (Patel et al., 2010).

Emulsification time

The emulsification time was evaluated in three media: aquadest, AIF (artificial intestinal fluid), and AGF (artificial gastric fluid) at 37°C. 1.0 mL SNEDDS preconcentrate was dropped into the 500 mL media and stirred at 120 rpm (Pratiwi et al., 2017). The time needed to form an emulsion in media was observed as an emulsification time.

Droplet size and polydispersity index

The droplet size and polydispersity index were obtained using a particle size analyzer with a dynamic light scattering type. 5.0 µL of each kencur rhizome extract SNEDDS preconcentrate was mixed into 1.0 mL of aquadest and analyzed by the instrument. The droplet size of dispersed SNEDDS was compared to kencur rhizomes extract in aquadest.

Physical stability

An amount of 100.0 µL SNEDDS preconcentrate was added by each media up to 5.0 mL. Nanoemulsion dispersion was homogenated with the vortex for 30 seconds. A nanoemulsion solution was observed every hour for 4 hours at 37ºC to examine its stability (Suryani et al., 2019).

Data Analysis

The physical properties and stability data of SNEDDS were analyzed to the obtained selected formulation and determine the effect of the combination of surfactant to extract solubility, compared to extract in aquadest and formulation with only Tween 80 surfactant. The clarity and stability data were analyzed descriptively. The transmittance percent, emulsification time, particle size, and polydispersity index were analyzed quantitatively.

RESULT AND DISCUSSION

Selection of SNEDDS components

Surfactant is a vital component of SNEDDS (Shahba et al., 2012). The surfactants are the main component to stabilize the SNEDDS system by decreasing the surface tension of the oil and water phase and maintaining the stability of nanoemulsion in the formed system (Dizaj, 2013). The proper mixture may also lower the interfacial tension to facilitate the dispersion process by forming a flexible film that can readily deform around the droplet (Winarti, 2016). The selection results of the surfactant combination ratio showed that the clear and stable mixture produced at Tween 80 ratio is equal to or greater than Span 80 or Chremophor RH40. The selected ratio of each surfactant combination is 1:1. The combination of Tween 80:Span 80 at a ratio of 1:1 can increase the stability of the emulsion (Rowe et al., 2009). The same result of (Basalious et al., 2010) showed that optimum and stable SNEDDS formulation was obtained at the combination of Tween 80:Chremophor RH40 at a ratio of 1:1.

PEG 400 as a co-surfactant is a short-chain amphiphilic molecule that helps surfactant to reduce surface tension and produce nanoemulsions (Parmar et al., 2011). The result of the composition ratios of Tween 80:Chremophor RH40 and PEG 400 showed a clear and stable mixture at a ratio of about 3:1 until 1:1 (F1, F2, and F3). While the combination of surfactant Tween 80:Span 80 and PEG 400 can only form a clear and stable mixture at a ratio of about 3:1 (F4 and F5). The combination of Tween 80:Chremophor RH 40 showed a larger range of surfactant-cosurfactant ratios than Tween 80:Span 80 because Span 80 is a lipophilic surfactant that is more difficult to combine with PEG 400 at the large ratio. The interaction between surfactants and co-surfactants occurs due to the presence of hydroxy groups in both components as a hydrophilic group. The balance of interaction was better in a greater ratio of the surfactant: PEG 400 (3:1) because it tends better ability to bind the hydroxy group on PEG 400 and maintain the mixture during storage (Dizaj, 2013).

The oil phase has an important role in the formation of nanoemulsion because it is related to the ability of the oil phase to dissolve drugs (Priani et al., 2017). The appropriate composition of the oil phase will affect the optimal extract loading. The differences in surfactant-cosurfactant composition affect their interaction ability with the oil phase. The result of the selection ratio of the oil phase showed that the clear and stable mixture produced at ratio oil:surfactant-cosurfactant about 1:4 until 1:7. Based on the selection, the composition of the selected base formulation for the SNEDDS system used to determine the extract loading.

The visual observations on the clarity test of SNEDDS formulation showed a transparent mixture on F1, F3, and F6, which indicated the systems could produce nanoemulsion (Figure 2). The results of visual observations on the clarity test correlated with a quantitative analysis of the transmittance. The transmittance showed the turbidity of dispersed SNEDDS in aqueous media that was evaluated by using a visible spectrophotometer with λ 650nm (Table 2). Transparency of the system since droplets of the dispersed phase are smaller than 1/4th of the wavelength of visible light. The nanoemulsion scatters light and appears transparent (Sintov & Shapiro, 2004). F4 and F5 can not be read by spectrophotometer because of their turbidity. (Winarti, 2016) showed the dispersed SNEDDS was more turbid due to lipophilic Span 80.

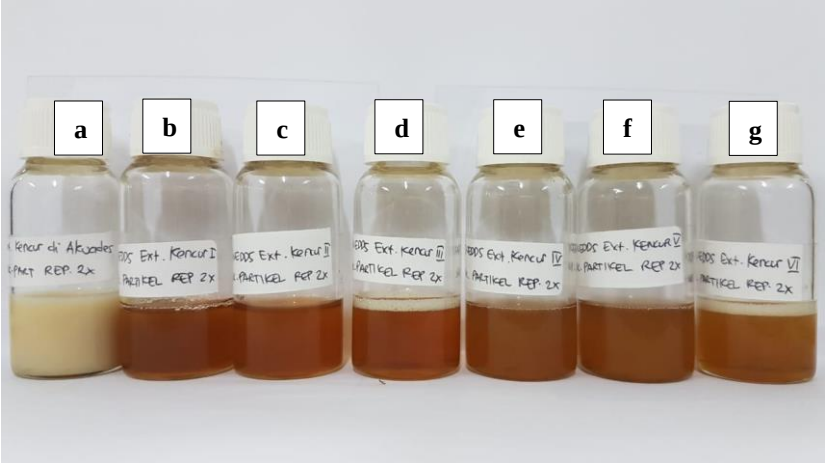

Figure 1. The SNEDDS of kencur rhizome ethanol extract, a) extract in aquadest, b) F1, c) F2, d) F3, e) F4, f) F5, g) F6

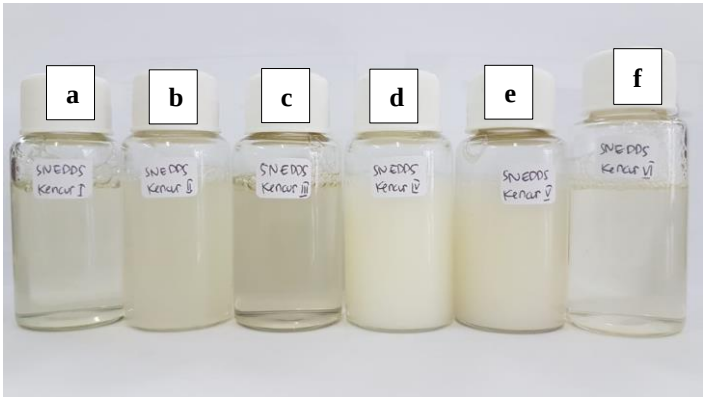

Figure 2. The result of the clarity test of kencur rhizome ethanol extract SNEDDS, a) F1, b) F2, c) F3, d) F4, e) F5, f) F6

The emulsification time testing showed that the SNEDDS preconcentrate system could be emulsified on all media (Table 2). Its test illustrates the spontaneous emulsification of SNEDDS in the digestive tract by using small energy that represents peristalsis in the digestive tract for an emulsification process. The emulsification time of a good SNEDDS is less than a minute and produces a clear and transparent appearance (Balakumar et al., 2013). Tween 80 is a surfactant in the SNEDDS that reduces the interface tension between an extract and aqueous media of gastrointestinal liquid so that an emulsification process will occur. PEG 400 in the SNEDDS system is a co-surfactant that helps to produce nanoemulsion rapidly with a transparent appearance due to the high polarity index of PEG 400 (Vilas et al., 2014). Co-surfactant will slip and form a space between surfactants so that the structure expands, the fluidity increase, and forming nanoemulsion faster in the test media (Parmar et al., 2011). The combination of Tween 80 and PEG 400 also could increase emulsification time in piroxicam SNEDDS (Wahyuningsih et al., 2018). The emulsification time at the three mediums showed the same pattern. F6 with only Tween 80 resulted in a slower emulsification time than others. The combination of two surfactants produced faster emulsification time because the properties of the surfactant that less hydrophilic than Tween 80, so they increase the interaction between the oil phase and medium, especially in Span 80 combination. The value of hydrophilicity can see from the HLB value. HLB of surfactant with < 10 is hydrophobic, whereas over > 10 is hydrophilic. The bigger ratio between hydrophilic and hydrophobic surfactants, the HLB is higher (Singh et al., 2009). Span 80 (HLB 4.3) is less hydrophilic than Chremophor (HLB 13.5), while HLB Tween HLB is 15.0.

Characterization of SNEDDS' physical properties

Table 2. The characteristic of kencur rhizome ethanol extract SNEDDS

Characteristic	Results					
	F1	F2	F3	F4	F5	F6
Organoleptic	Clear, Brown	Turbid, Brown	Clear, Brown	Turbid, Brown	Turbid, Brown	Clear, Brown
Appearance of clarity	Clear	Turbid	Clear	Turbid	Turbid	Clear
Transmittance (%)	95.63 ± 2.02	10.51 ± 2.57	93,83 ± 1.06	Not readable	Not readable	97,85 ± 0,90
Emulsification time in aquadest (seconds)	34.3 ± 2.1	26.3 ± 1.5	19.0 ± 1.7	10.7 ± 2.5	11.7 ± 2.1	44.7 ± 1.5
Emulsification time in AGF (seconds)	24.7 ± 1.5	27.0 ± 2.0	22.7 ± 1.5	12.0 ± 2.0	9.7 ± 1.5	22.3 ± 1.2
Emulsification time in AIF (seconds)	12.3 ± 1.2	11.3 ± 0.6	10.7 ± 0.6	9.3 ± 1.5	6.3 ± 0.6	19.3 ± 2.1
Droplet size (nm)	23.0 ± 0.5	296.3 ± 9.7	21.8 ± 0.2	484.1 ± 67.1	723.1 ± 30.8	16.3 ± 0.2
Polydispersity index	0.05 ± 0.01	0.36 ± 0.04	0.06 ± 0.05	0.43 ± 0.02	0.49 ± 0.05	0.02 ± 0.01

The droplet size analysis of the dispersed SNEDDS system ensures the formation of nanoemulsion with a droplet size of less than 100 nm. Nanoemulsion size was influenced by the ratio of surfactants to cosurfactants. The research showed that the higher ratio of surfactant to cosurfactant could produce a smaller size of the nanoemulsion droplets. Table 2 shows the nanometer droplet size of the kencur rhizome extract obtained in F1, F3, and F6. This proved that the SNEDDS preconcentrate formulation was capable to produces nanoemulsion. Whereas a droplet size of kencur rhizome extract in aquadest showed a microparticle system at 26430 ± 381.8 nm. At the same extract concentration, the dispersed SNEDDS system could produce a smaller emulsion droplet than the extract in aquadest. These results correlated with the clarity test and transmittance percent results. The reduction of droplet size can increase the surface area and could affect the increase in solubility of kencur rhizomes extract. Further study is needed to prove this.

The value of PI (polydispersity index) expresses the homogeneity of nanoemulsion particles. PI values are from 0.0 to 1.0. The closer to the 0 value, the more homogeneous system is (Binarjo et al., 2015; Patel et al., 2010). Table 2 shows that the PI values of the dispersed SNEDDS of F1, F3, and F6 are smaller than other formulations, indicating better homogeneity of their system than others.

Physical stability testing at 37ºC for 4 hours was carried out to determine the stability of the nanoemulsion dispersion that had formed during the transit time in the digestive tract under conditions of human body temperature. No sedimentation or phase separation occurred up to 4 hours of observation, so it could state that the emulsions formed were stable.

From the characteristic evaluation, F1, F3, and F6 are the potential for further development. It combines Tween 80 with Chremophor RH 40 in 3:1 and 1:1 ratio, or only Tween 80 in 3:1 ratio to co-surfactant. Further research could be determining the saturated drug loading of kencur rhizome extract or using the synthetic compound of EPMS to increase the effectiveness of therapy. The pharmacokinetics evaluation could be evaluated to determine the therapeutic effect in a volume of SNEDDS delivery.

CONCLUSION

The combination of Tween 80:Chremophor RH 40 produced SNEDDS better than Tween 80:Span 80. The surfactant-cosurfactant of Tween 80:Chremophor RH 40:PEG 400 at a ratio of 3:1 (F1) and 1:1 (F3) is a selected formulation that could produce dispersed SNEDDS. The single surfactant Tween 80:PEG 400 at the ratio 3:1 (F6) results in dispersed SNEDDS better than the combined surfactant. The SNEDDS systems could produce a smaller droplet size than the extract in aquadest.

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