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Effects of the RH-40 Cremophor Concentration on the Formulation of the *Vaccinium varingiifolium* (Blume) Miq leaf Extract Nanoemulsion

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ABSTRACT

Cantigi (*Vaccinium varingiaefolium* (Blume) Miq.) contains anthocyanins, chlorophyll, phenols, saponins, steroids, tannins, triterpenoids, flavonoids, and antioxidant activity. This study aimed to obtain the concentration of cremophor RH-40 as an optimal and stable surfactant during storage in Cantigi leaf extract nanoemulsion formulation process. Cantigi leaf extract was made by kinetic maceration in stages with n-hexane, ethyl acetate, and 96% ethanol as solvent, then evaporated with an evaporator. The extract was tested for solubility using various solvents before making the nanoemulsion. Nanoemulsions were prepared by varying the amount of cremophor RH-40 in three formulas (5%, 7.5%, and 10%) with stirring at 400 rpm at 40 °C. The nanoemulsions were characterized by particle size, zeta potential, and storage for 5 days. The evaluation results of Formula 1, 2, and 3 have an average particle size of 224.7, 226.5, and 198.3 nm, with a polydispersity index of 0.565, 0.237, and 0.223. The zeta potential values are - 43.7, - 39.2, and - 42.3 mV, respectively. The results of the storage of nanoemulsions for 5 days showed that in formulas 1 and 2 a precipitate formed, while in formula 3, there was no precipitate. Based on the optimization results obtained, cremophor RH-40 10% obtained a stable nanoemulsion that does not occur with no observed sedimentation/precipitation during storage.

Keywords: Cremophor RH-40, nanoemulsion, nanopartikel, *Vaccinium varingiaefolium* (Blume) Miq

Introduction

The leaves and fruit of cantigi (*Vaccinium varingiifolium* (Blume) Miq.) contain anthocyanins which function as antioxidants. Research that has been carried out as an antifidant, containing anthocyanin aglycones, cyanidin and peonidin, found 34 volatile chemical compounds (terpenoids (80%) and methyl benzoate (18%) (Yulyana et al., 2016). The field of cosmetology is developing with nanoparticle technology for the manufacture of cosmetics. The cosmetics industry uses nano-sized materials because they have different characteristics in color, transparency, solubility, and deeper skin penetration. Innovations in nanotechnology include the manufacture of nanoemulsions. Nanoemulsions have the advantages of transparent characteristics, soft texture, translucent and are dispersion water oil stabilized by a film layer of surfactant or surfactant molecules (Jusnita et al., 2019).

The surfactant that is often used in formulas is cremophor RH40. Using surfactants with high HLB such as cremophor RH40 will increase the effic iency of spontaneous nanoemulsification (self-emulsification). In addition, cremophores RH40 have also been reported to inhibit P. *Ostwald ripening* on nanoemulsions, thereby increasing the stability of the preparation for up to several months (Syukri et al. ,2019). The characterization of nanoemulsions using the size and distribution of nanoparticles was measured using a Particle Size Analyzer (PSA) using the principles of Photon Correlation Spectroscopy and Electrophoretic Light Scattering. A small particle in suspension moves in random patterns, then a laser beam shines on them. The larger the particle size, the slower the Brownian motion.

Particle size and distribution are the most important characteristics in nanoparticle systems. It is used to estimate the in vivo distribution, biology, toxicity, and sightability of the nanoparticle system. The zeta potential was used to characterize the surface charge properties of nanoparticles, which are related to the electrostatic interactions of nanoparticles. Electrostatic interactions will determine the tendency of aggregation and repulsion. The zeta potential is a measure of the surface charge of the particles dispersed in the dispersing medium. Ideally, the zeta potential charge of the particles should be higher than that of the dispersing medium to prevent aggregation. Nanoparticles with zeta potential values of less than -30 mV and greater than +30 mV have higher stability. Dispersion systems with low zeta potential values are easier to form aggregates with along with Van der Waals forces in particle interactions (Abdassah, 2009; Cardoso and Barrandas, 2020).

Material and Methods

Materials

Analitical balance (Fujitsu, Japan), ovens (Memmert, Germany), glassware (Pyrex, Indonesia), *Particle Size Analyzer* (Malvren, USA), *Zeta sizer* (Malvren, USA), stirrer (Thermo, Korea).

Table 1. Cantigi leaf extract nanoemulsion optimization formulation

Bahan	Formula (% b/v)		
	1	2	3
Cantigi leaf extract	0,2	0,2	0,2
Isopropyl myristate	5	5	5
Cremophor RH-40	5	7,5	10
Etanol 96%	10	10	10
Pure water ad	100	100	100

The materials used in this study were cantigi leaves (Kawah Putih, Bandung), isopropyl myristate (making cosmetics), cremophor RH-40 (PT. Bahtera Adi Jaya), 96% ethanol (PT. Palapa Muda Perkasa), and distilled water (Lux chemicals).

Experiment

1. *Nanoemulsion preparation*

   A procedure for making nanoemulsions The preparation was carried out by way of 100 mg of cantigi leaf extract of formulas 1, 2, and 3 dissolved with isopropyl myristate. 5%, 7.5%, and 10%) and 96% ethanol were added to the previous solution while stirring with a stirrer at 400 rpm at 40°C until completely dispersed (Amit et al. 2019; Larasati and Jusnita 2020; Deore et al., 2019).

2. *Nanoemulsion optimization*

   Nanoemulsion optimization was carried out by varying the concentration of cremophor RH-40 (5, 7.5, and 10%). Results of optimization of cremophor RH-40 on the best formula (by particle size, polydispersity index, and zeta potential).

3. *Evaluation of nanoemulsions*

   Particle size was analyzed by dissolving 1 mL of nanoemulsion with 19 mL *of ultra pure water* in a measuring cup. A total of 4 mL of the solution is pipetted and put into a cuvette. The cuvette that has been filled with samples is inserted into the *sample holder* (Hakim et al., 2018).

   Zeta potential was analyzed by mixing 2 g of nanoemulsion with 5 ml of deionized water. Then the zeta potential measurement was determined using electrophoretic light scattering (Yulyana, 2019).

Results and Discussion

The results of optimization of the volume of cremophor RH-40 by measuring the distribution and size of nanoparticles of nanoemulsion cantigi leaf extract are shown in the table 2. Based on the results of nanoemulsion optimization, the amount of surfactant (cremophor RH-40) of 5.0 mL, 7.5 mL, and 10.0 mL was used. After making the nanoemulsion, the stability of the nanoemulsion was observed for 5 days and a precipitate formed in formula 1 and formula 2, while in formula 3 no precipitate formed after being stored for 5 days.

Optimization of zeta potential measurement in 3 formulas with different amounts of surfactants to see the effect of the amount of surfactant incorporated or added into the oil phase on the resulting zeta potential value. Formula 1 received 43.7 mV, Formula 2 received 39.2 mV, and Formula 3 received - 42.3 mV (Syukri et al. 2019). Formula 1 added less surfactant than formulas 2 and 3, the larger the particle size produced. On the other hand, in formula 3, more surfactants were added than in formulas 1 and 2, so that the resulting particle size would be smaller. This is because by increasing the amount of surfactant, it will reduce the surface tension between the particles, so that it can produce a small particle size. The use of surfactants is proven to reduce the particle size of the formed nanoemulsion due to the stabilization of the oil droplets produced as a result of the o/w interface surfactant molecules, and the use of cosurfactants can also reduce the particle size (Soleha, Suleza, and Hermiyanti 2020). This is because cosurfactants can dissolve large amounts of hydrophilic or hydrophobic surfactants in the nanoemulsion carrier (Syukri et al. 2019; Dipahayu and Kusumo 2021).

The Zeta potential is used as an indicator that shows the stability of a system containing dispersed particles through the repulsion between particles of the same charge when they are close together (Nurfauziah et al., 2018). When the nanoparticles dissociate in the dispersing medium, the opposite ions will approach the particle surface and act as a barrier, which reduces the electrostatic attraction between the particles that can cause the particles to combine. A high zeta potential value (above +/-30 mV) is recommended to achieve nanoemulsion preparations to prevent coalescence (Adi et al. 2019; Nurfauziah et al., 2018).

Conclusion

Based on the research, the best formula was obtained at a concentration of 10% cremophor RH40. The resulting particle size is 198.3, the polydispersity index value is 0.223, the zeta potential is -42.3, and the resulting nanoemulsion is stable for 5 days of storage.

Table 2. Results of optimization of concentration of cremophor RH-40

Formula	Cremophor RH 40 (mL)	Results	Stability 5th day	Particle size (nm)	Polydispersity index
1	5.0	Homogeneous nanoemulsion	Precipitate ++	224.7	0.565
2	7.5	Precipitated homogeneous	Nanoemulsion +	226.5	0.237
3	10.0	Homogeneous nanoemulsion	No precipitate formed	198.3	0.223

Table 3. Results of optimization of zeta potential measurement

No	Formula	Cremophor RH 40 (ml)	Zeta potential (mV)
1	1	5.0	-43.7
2	2	7.5	-39.2
3	3	10.0	-42.3

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