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# Characteristics and Physical Stability of Nanoemulsion as a Vehicle for Anti-Aging Cosmetics: A Systematic Review

Eva Syariefah Rachman, Widji Soeratri*, Tristiana Erawati
Departement of Pharmaceutics, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

*Corresponding author: widji-s@ff.unair.ac.id

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***Abstract***
***Background****: Skin aging can be overcome by applying anti-aging cosmetics. Many active ingredients that have anti-aging potential are derived from plants, and these materials must be delivered with a sound skin delivery system, namely nanoemulsion. The characteristics of nanoemulsion are closely related to physical stability.* ***Objective****: This study aims to conduct a systematic review of in vivo and in vitro study designs to examine the characteristics and physical stability of nanoemulsions used in topical anti-aging cosmetics.* ***Methods****: A systematic literature review based on the PRISMA statement was used to review the articles regarding nanoemulsions' characteristics and physical stability. The article search was accessed from an internet search database: Scopus, Pubmed, and Web of Science, published between January 2012 and June 2022.* ***Results****: Of the 244 articles, 44 were found to be related to the characteristics and physical stability of nanoemulsions in anti-aging cosmetics. These showed that active ingredients with antioxidant activity, filter UV rays, moisturizing agents, and cell-repairing agents are delivered by a nanoemulsion system with various types and ratios of surfactants, cosurfactants, and oil phases. Tween 80, Span 80, Transcutol HP, and Caprylic/capric triglyceride are the most widely used nanoemulsion compositions.* ***Conclusion****: The type and composition of the oil phase, surfactant, and cosurfactant affect the characteristics of the nanoemulsion (droplet size, polydispersity index, viscosity, zeta potential) and the physical stability of the nanoemulsion so that it can deliver active ingredients that have the potential as anti-aging well.*

***Keywords****: Characteristics, Physical Stability, Nanoemulsions, Cosmetics, Skin Aging*

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## INTRODUCTION

Aging is a natural phenomenon of a decline in physiological function and skin structure that cannot be avoided but can be slowed down (Li et al., 2021) . Two factors, i.e. intrinsic factors such as genotype, endocrine metabolism, and hormone levels, and extrinsic factors such as air pollution, UV radiation, and nutritional levels, can influence skin aging (Ahmed et al., 2020). UV radiation is the main external factor that significantly influences the rapid occurrence of premature aging. When UV rays reach the skin surface, UV rays increase free radicals in the skin, causing damage to DNA, skin peroxidation, and protein cross-linking. Highly reactive molecules called free radicals have one or more unpaired electrons. Free-radical formation triggers signs of aging such as thinning of the epidermis and dermis layers, reduced elastic fibers, decreased collagen synthesis, and decreased number of fibroblasts (Cao et al., 2020).

Invasive and non-invasive treatments can be done to slow down the aging of the skin. Invasive treatment is an action that is carried out on the body through incisions, punctures or using a tool that goes into the skin(Cousins et al., 2019). The non-invasive treatment is a procedure that does not require a device that goes into the skin. One example of non-invasive anti-aging treatments is the use of topical anti-aging cosmetics. All circles of society can use topical cosmetics because it is easy to use and can be done anywhere. Therefore, anti-aging cosmetics are an easy alternative to treat skin aging. Based on the function, anti-aging cosmetics are divided into three categories: antioxidant cosmetics, moisturizing cosmetics, and biological activity of cosmetics (Li, 2015).

Several innovative cosmetic delivery systems are used in cosmetic products, one of which is nanoemulsion. Nanoemulsion is one type of drug delivery by mixing the water phase and the oil phase with the help of surfactants and co-surfactants with a certain HLB value to produce a droplet size of 20-500 nm, which varies depending on the composition of the nanoemulsion system and the method of manufacture (Harwansh et al., 2019). Nanoemulsions can deliver both lipophilic and hydrophilic drugs. There are several nanoemulsions, i.e. oil in water (O/W), water in oil (W/O) nanoemulsions, and double nanoemulsions such as oil in water in oil (O/W/O) or water in oil in water (W/O/W). W/O nanoemulsion is a nanoemulsion consisting of water as the dispersed phase or internal phase and oil as the dispersion medium or external phase. The W/O nanoemulsion can protect the degradation of hydrophilic drugs so that the hydrophilic drugs can become an internal phase protected by oil as an external phase, and vice versa O/W nanoemulsions can protect the degradation of lipophilic drugs.

Nanoemulsions are very attractive for cosmetics due to the aesthetic properties of nanoemulsions, i.e. stability, low viscosity, transparent visual aspect, and high surface area, enabling effective delivery of the active ingredients to the skin. Nanoemulsions are formed from the dispersion process from one liquid phase into another liquid phase to form droplets. Nanoemulsion has a tiny and homogeneous globule size that can prevent creaming, sedimentation, and coalescence. The advantage of using nanoemulsions as topical preparations is that more active substances can be formulated in one preparation due to an increase in solubility capacity and can increase the bioavailability of the active substance to increase the thermodynamic activity of the active substance on the skin. In addition, it has high effectiveness in penetrating the skin's stratum corneum (Marzuki et al., 2019). The composition and characteristics of the oil phase, surfactants, and cosurfactants affect nanoemulsions stability and oxidative stability. The characteristics of the physical properties of nanoemulsions can evaluate through several tests such as organoleptic, homogeneity, phase separation, nanoemulsion type, measurement of pH, percent transmittance, viscosity, droplet size, and polydispersity index. The characteristics of the nanoemulsion are related to physical stability and clarity because they will have an important effect on the resulting droplet size (Marzuki et al., 2019).

Studies related to nanoemulsions for topical anti-aging products have been carried out. However, to our knowledge, a systematic review that summarizes the characteristics and physical stability of nanoemulsions in topical anti-aging products has not been performed. Therefore, this systematic review intend to fill the gap by efficiently integrating accurate information and providing a basis for making a dicision from the related literature that systematically reviewed all available related studies for characteristics and physical stability of nanoemulsion systems for topical anti-aging products. This study aims to conduct a systematic review of *in vivo* and *in vitro* study designs of examine the characteristics and physical stability of nanoemulsions used in topical anti-aging cosmetics.

## RESEARCH METHOD

This research is a systematic (Systematic Literature Review) using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) method, which is carried out systematically by following or doing research. This systematic review technique consists of multiple parts, including 1) Establishing the background and objectives, 2) Formulating research questions, and 3) Conducting a literature search. 4) Criteria for selection, 5) Practice screens, 6) Checklist and quality procedures 6) Strategy for Data Extraction, and 7) Strategy for Data Synthesis.

### Keywords

The search for articles relevant to this research topic was conducted using the keywords: 'cosmetics,' 'skincare,' 'skin aging,' 'stability,' 'characteristics,' and 'nanoemulsion.' These keywords are obtained through the formulation of PICO. Table 1 gives a detailed explanation of the search technique.

### Eligibility criteria

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Inclusion criteria were studies that used quantitative data obtained from experimental results with *in vitro* or *in vivo* study, products tested for topical use and no additional anti-aging therapy was used. Articles that discuss the characteristics and/or stability of nanoemulsions that contain ingredients that counteract free radicals can repair skin cells, provide moisture to the skin, and protect the skin from UVA/UVB rays.

Exclusion criteria were articles in the form of reviews, reports, or chapters in books, products tested for internal use and the presence of additional accompanying therapeutic methods. Research article on the topic of the problem is not related to the characteristics and/or stability of nanoemulsions that contain ingredients that counteract free radicals can repair skin cells, provide moisture to the skin, and protect the skin from UVA/UVB ray.

**Literature searches and selection**

The data collection process required in this study was obtained from three web databases: Scopus, Pubmed, and Web of Science, published between January 2012 and June 2022. Required data collection online in May - June 2022. No regional, language, or temporal restrictions were applied when searching for literature.

**Data extraction**

After obtaining the appropriate keywords, a search can be carried out on the database to be used through the official website of each database. After the search of the articles, screening was carried out on each article obtained. The screening was done through the Mendeley tools. In the first stage of screening, it was done by checking for duplication of search results. After separating the duplicate articles, it was continued by sorting based on the suitability of the title and abstract with the topic of this research, namely nanoemulsion in anti-aging topical preparations. Furthermore, the eligibility test was carried out, and each article filtered from the title and abstract selection will be read in its entirety to see whether it is in accordance with the inclusion criteria previously set.

**Data analysis and reporting**

Article review analysis was used to collect data so that it could produce findings to answer the objectives of this study. The data will be presented in the form of a table consisting of the authors, active ingredients, constituent materials (oil phase, surfactants, cosurfactants), characteristics (droplet size, polydispersity index, zeta potential), physical stability and research results.

## RESULTS AND DISCUSSION

**Results**

A total of 244 articles were successfully obtained from searching in three databases, i.e. Scopus, Web of Science, and Pubmed. Furthermore, as many as 37 duplicate articles were issued, and there were 207 articles left in the screening process by reading the title and abstract. As many as 132 articles were rejected throughout the screening phase because they did not match the inclusion criteria; consequently, only 75 articles were included in the full-text reading assessment step. Furthermore, as many as four articles must be issued because they do not have full access to read the entire article, so 71 articles remain in the assessment process for eligibility. Finally, as many as 27 articles must be issued because they do not have exposure of interest to get 44 articles that meet all inclusion criteria used in the Systematic Literature Review as shown in Table 2.

**Table 1**. Description of search strategy

| Database | Search Strategy |
|---|---|
| Scopus | [('Cosmetics' or 'Skin Care' or 'Skin Aging') and ('Stability' or 'Characteristics') and ('Nanoemulsion')] |
| Pubmed | [('Cosmetics' or 'Skin Care' or 'Skin Aging') and ('Stability' or 'Characteristics') and ('Nanoemulsion')] |
| Web of science | [('Cosmetics' or 'Skin Care' or 'Skin Aging') and ('Stability' or 'Characteristics') and ('Nanoemulsion')] |

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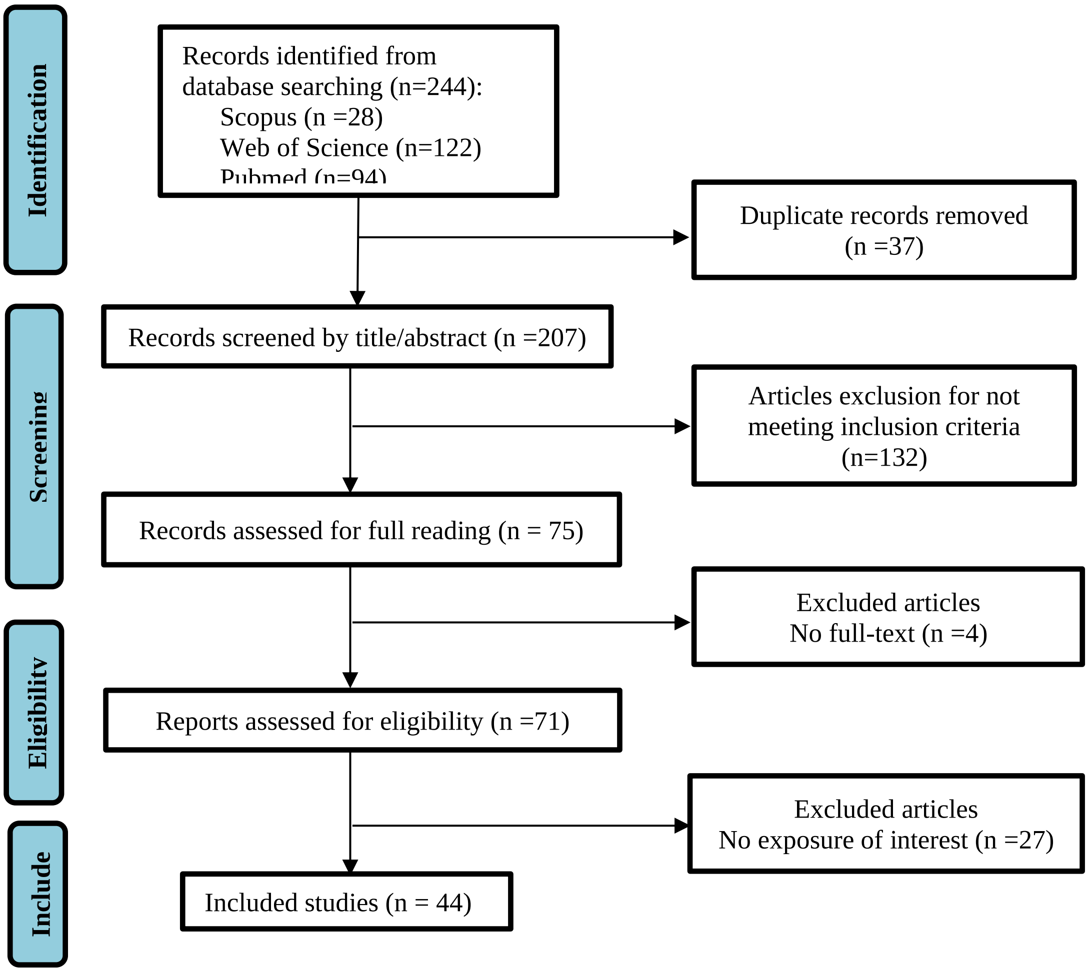


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram of the study

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**Tabel 2**. Summary of studies on characteristics and physical stability of nanoemulsion for anti-aging effects

| **Active Ingredients** | **Ingredients** | **Characteristics** | **Stability** | **Anti-aging Effects** |
|---|---|---|---|---|
| Leaf and Stem *Vellozia squamata* | Oil phase: Babacu oil<br>Surfactant: Sorbitan monoestearate, PEG- 40 hydrogenated castor oil | • Droplet size:<br>Leaf 154.6±9.59 nm<br>Stem 147.6±33.32 nm<br>• Polydispersity Index:<br>Leaf 0.284±0.034<br>Stem 0.351±0.254<br>•Viscosity:<br>Stem 99.70 Cp<br>Leaf 99.70 Cp | Accelerated stability assay: Thermal cycle<br>• Droplet size after 7 days<br>(stem 157.4±6.90 nm)<br>(leaf 144.5±4.02 nm)<br>• Polydispersity index after 7 days<br>(stem 0.490±0.128)<br>(leaf 0.310±0.022)<br>(Quintão et al., 2013) | • The total phenol content in plant extracts is proportional to the free radical inhibition of the antioxidants. Both of these effects also depend on the concentration of the plant extract.<br>• Hydroalcoholic extracts from *V. squamata* as potential natural ingredients with antioxidant properties. |
| Tocotrienol | Oil phase: Palm oil esters<br>Surfactant: Tween 80, Span 80 | - | Centrifugation test:<br>Sedimentation rates at earth gravity decreased with the increased in the percentage of the oil phase (10%, 20% and 30%).<br>(Han et al., 2013) | The greatest elasticity was produced by the nanoemulsion containing 30% oil. |
| • Octyl Methoxycinnamate (OMC)<br>• Titanium Dioxide | Oil phase: Avocado oil<br>Surfactant: Ultrol® L70, Ultrol® CE200 | • 10 w/w % avocado oil and 12 and 14 w/w % Ultrol® L70 w/w: no nano size<br>• 5 w/w % avocado oil and 12 and 14 w/w % Ultrol® L70: 6 – 10 nm but destabilized after 5 days<br>• 12 and 14 w/w % Ultrol® CE200, with 5 w/w % avocado oil: 6-10 nm | Stability study was conducted by visual observation for 1 month. There was no precipitation in the nanoemulsion containing 5% avocado oil/0.25% TiO2/12% Ultrol® CE200/water. The average droplet size is in the range of 400 to 500 nm.<br>(Silva et al., 2013) | The formulation containing (w/w) 5% avocado oil/12% nonionic surfactant/83% water, 1% w/w for chemicals (OMC) and 0.25% for Titanium Dioxide was a stable nanoemulsion formulation. |

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| • Ethyl Hexyltriazone (EHT)<br>• Diethylamino Hydroxybenzoyl Hexyl Benzoate (DHHB)<br>• Bemotrizinol (Tinosorb S)<br>• Avobenzone (AVO)<br>• Octyl Methoxycinnamate (OMC) | Oil phase: Miglyol 812<br>Surfactant: Pluronic F68 | • Droplet size (nm)<br>NE-OMC 190.6 ± 20.1<br>NE-AVO 170.4 ± 14.3<br>NE-EHT 198.4 ± 7.2<br>NE-TINO 191.2 ± 11.9<br>NE-DHHB 186.5 ± 20.3<br>NE-UVMIX 118.2 ± 4.4<br>Unloaded NE 290.4 ± 18.7<br>• Polydispersity Index<br>NE-OMC 0.26 ± 0.02<br>NE-AVO 0.23 ± 0.03<br>NE-EHT 0.23 ± 0.03<br>NE-TINO 0.22 ± 0.01<br>NE-DHHB 0.23 ± 0.01<br>NE-UVMIX 0.22 ± 0.03<br>Unloaded NE 0.39 ± 0.04<br>• Zeta Zeta potential (-mV)<br>NE-OMC 13.3 ± 0.5<br>NE-AVO 22.8 ± 1.1<br>NE-EHT 37.7 ± 1.5<br>NE-TINO 28.6 ± 1.2<br>NE-DHHB 27.2 ± 1.9<br>NE-UVMIX 20.5 ± 1.8<br>Unloaded NE 24.9 ± 0.6 | -<br>(Puglia et al., 2014) | Both NLC and nanoemulsion can protect the photostable active ingredients. |
| Retinyl Palmitate | Oil phase: Labrafac lipophile<br>Surfactant: Labrasol<br>Cosurfactant: Plurol oleique | Droplet size: 14.42±1.10 nm<br>Polydispersity Index: 0.680<br>Viscosity 55.28 ± 0.08 mPas | -<br>(Clares et al., 2014) | Nanoemulsion with Retinyl Palmitate loaded penetrate deeper than SLN and Liposome. |

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| Propolis Extract | Oil phase: Rice bran oil<br>Surfactant: Tween 80, KollipHor RH40<br>Cosurfactant: Glycerin, Propylene | Droplet size: 23.72 nm<br>Polydispersity index: 0.338 | After stability test for 63 days at $25^0$C and passing through 6 cycles of Freeze Thaw test there was no separation, propolis nanoemulsion was a stable formula.<br>Droplet size when thermal cycling test<br>Cycle 0 18.4 ± 0.36 nm<br>Cycle 6 23.53 ± 3.25 nm<br>Polydispersity Index when thermal cycling test<br>Cycle 0 0.29 ± 0.04<br>Cycle 6 0.4 ± 0.14<br>(Mauludin et al., 2015) | Propolis nanoemulsion consisting of 26.25% KollipHor RH40; 8.75% glycerin; 5% RBO; 3% EEP; and 57% water can reduce 58% of DPPH free radicals. |
| Fullerene | Oil phase: Palm kernel oil esters<br>Surfactant: Span 80, Tween 80 | Droplet size: 140 - 170 nm | Fullerene nanoemulsion showed good stability by visual observation.<br>(Ngan et al., 2015) | Fullerene could increase collagen production, skin hydration by observing collagen score and corneometric units. |
| Swiftlet Nest | Oil phase: Jojoba oil, Olive oil<br>Surfactant: Tween 80 | Droplet size: 136.35 nm<br>Zeta potential: 40.2 mV | There was no separation after centrifugation and during 3 months of storage, this indicates that formulation was stable.<br>(Mohd Taib et al., 2015) | Stable formula with homogenization time of 17 minutes consisted of 3.99% Tween 80; 90.03% deionized water and 3.4% other ingredients and contains 2.58% Swifle Nest. |

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| *Opuntia ficus-indica* (L.) Mill Extract | Oil phase: Capric/Caprilic triglycerides<br>Surfactant: Tween 80, Span 80 | Droplet size: 92.2 - 233.6 nm<br>Polydispersion Index: 0.200<br>Zeta potential: −26.71- −47.01 mV | •Droplet size (nm)<br>at t0 119.0±7.4<br>at 4°C 121.6±8.8<br>at 25°C 233.6±30.1<br>at 45°C 92.71±6.1<br>•Polydispersity Index<br>at t0 0.257±0.038<br>at 4°C 0.251±0.020<br>at 25°C 0.305±0.126<br>at 45°C 0.228±0.044<br>•Zeta potential (mV)<br>at t0 -26.71±6.67<br>at 4°C -41.71±4.55<br>at 25°C -39.77±5.99<br>at 45°C -41.21±6.02<br>(Ribeiro et al., 2015) | Nanoemulsion 1% *Opuntia ficus-indica* (L.) Mill hydroglycolic extract can enhance the water content in the stratum corneum with the mechanism of action of humectants. |
| Quercetin | Oil phase: Capric/Caprilic triglycerides<br>Surfactant: Oleth-20, Oleth-3, Cetyl Trimethyl Ammonium Chloride (CTAC) | - | Quercetin nanoemulsion was stable at low and room temperature.<br>(Dario et al., 2016) | Nanoemulsion has good capability as a topical formulation and has low skin irritation. |
| *Clinacanthus nutans (L.)* Leaves | Oil phase: Guava seed oil/palm kernel oil<br>Surfactant: Tween 80, Span 80 | Droplet size 97.38±1.63 nm<br>Zeta potential -25.1±0.57 mV<br>Polydispersity index 0.25±0.01 | During different storage conditions for 90 days (room temperature and 45 °C), visual inspection revealed no phase separations, indicating the nanoemulsion's stability.<br>(Che Sulaiman et al., 2016) | A good Clinacanthus nutans nanoemulsion formula consisted of 8.13% of surfactant, 5% of oil, 1% of xanthan gum, 84.97% of water, 0.1% of bioactive extract, and 0.8% of preservative. |

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| B-D Glucan Polysaccharides Extract | Oil phase: Palm olein<br>Surfactant: KollipHor®RH40 (Polyoxyl 40 Hydrogenated Castor Oil) | Droplet size: 263 nm<br>Polydispersity index: 1.85<br>Viscosity: 0.244 cP | After 24 h<br>Droplet size: 289.6 nm<br>Polydispersity Index: 0.312<br>At a concentration of less than 1%of β-D-glucan, the nanoemulsion showed better stability compared to a concentration of 85% of β-D-glucan at storage for 90 days at 4 °C and at 25 °C.<br>(Alzorqi et al., 2016) | A good nanoemulsion formulation consists of 85% water and an oil/surfactant ratio of 3, using ultrasonic for 300 seconds and a power of 700 W. |
| Quercetin | Oil phase: Capric/Caprilic triglycerides<br>Surfactant: Oleth-20, oleth-3, Cetyl Trimethyl Ammonium Chloride (CTAC). | Droplet size: 19.99±0.07 nm<br>Polydispersity Index: 0.082<br>Zeta potential: 19.6±2.2 mV<br>Viscosity: 7.1 cP | Ostwald ripening occurred in an accelerated stability test for 90 days at 45ºC with an increase in droplet size of 1000%, but observations were not carried out at room temperature.<br>(Dario et al., 2016) | The optimum 0.5% Quercetin nanoemulsion formula was 5.6 % Oleth-20 and 3.4% Oleth-3, CTAC 1% using surfactant mixture HLB equal to 12.5. |
| Ethoxylated Lanolin (El)<br>Acetylated Lanolin (Al) | Oil phase: Rubus idaeus (Raspberry seed Oil), Passiflora edulis seed oil, Prunus persica (Peach kernel oil)<br>Surfactant: Sorbitan Monooleate, PEG 36 Castor Oil | Droplet size 48.0±7.2 nm | There was no change in droplet size in the formula containing 6.0% EL but at the addition of 2.0% AL, the droplet size increased.<br>(Pereira et al., 2016) | The nanoemulsion formula containing 6.0% EL was more stable than the nanoemulsion formula with 2.0% AL which contained lanolin derivatives. |
| Thistle Oil | Oil phase: Thistle oil<br>Surfactant: Tween 80, Decyl Glucoside | • 4% Decyl glucoside<br>Droplet size<br>189.0 ± 5 - 179.8 ± 10 nm<br>Polydispersity index<br>• 0.216 - 0.303<br>Viscosity:<br>580 ± 50- 562 ± 30 mpa<br>• 4% Tween 80<br>Droplet size: 191.1 ± 9 nm<br>Polydispersity index: 0.335<br>Viscosity: 690 ± 100 mpa<br>• 6% Tween 80<br>Droplet size: 159.5 ± 8 nm | After 60 days<br>• 4% Decyl glucoside<br>Droplet size 168 ± 9 - 233 ± 12 nm<br>Polydispersity index 0.232 - 0.325<br>• 4% Tween 80<br>Droplet size 201 ± 3 nm<br>Polydispersity index 0.269<br>• 6% Tween 80<br>Droplet size 164 ± 6 nm<br>Polydispersity index 0.295<br>(Miastkowska et al., 2016) | More amount of Tween 80 up to 6% could decrease droplet size. The concentration of Decyl glucoside as natural surfactant needed lower amount to obtain optimal formula. |

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| | | Polydispersity index: 0.257<br>Viscosity: 587 ± 22 mpa | | |
| Vitamin E | Oil phase: palm olein<br>Surfactant: Polyoxyethylene (4) Lauryl Ether (Brij 30) | Droplet size O/S ratio 4:6<br>31.45±0.06 - 46.50±3.83 nm<br>Droplet size O/S ratio 5:5<br>28.63±6.97 - 42.66±7.25 nm<br>Viscosity 0.04 - 0.07 Pa.S | Formulas with added vitamin E and without added vitamin E were stable by visual observation during 12 h storage with four freeze-thaw cycle tests at 4 °C, 25 °C, and 40 °C. (Ramli et al., 2017) | The right formula for carrying vitamin E was an oil:surfactant ratio of 4:6, 5:5 and 6:4 and contains 20-50% by weight of water. |
| *Agave sisalana* | Oil phase: Caprylic/Capric Triglyceride<br>Surfactant: Tween 80, Span 80 | • Nanoemulsion with extract<br>Droplet size 155.0 ± 1.29 nm<br>Polydispersity Index I 0.10 ± 0.01<br>Zeta potential -17.67 ±0.40 mV<br>pH 4.47±0.09<br>• Nanoemulsion with extract and polysaccharide-enriched fraction<br>Droplet size 155.80 ± 3.99 nm<br>Polydispersity Index 0.09 ± 0.02<br>Zeta potential −20.41 ± 2.58 mV<br>pH 5.01 ± 0.05 | Accelerated stability test after 24 h and 90 days<br>• Nanoemulsion with extract<br>Droplet size<br>t0 171. 23 ± 3.49 nm<br>4 °C 165.0 ± 4.27 nm<br>25 °C 174.86 ± 2.29 nm<br>45 °C 237. 84 ± 3.84 nm<br>Polydispersity Index<br>t0 0.12 ± 0.02<br>4 °C 0.09 ± 0.02<br>25 °C 0.09 ± 0.01<br>45 °C 0.08 ± 0.03<br>Zeta Potential<br>t0 −15. 77 ± 2.20 mV<br>4 °C −18. 02 ± 1.78 mV<br>25 °C −16. 10 ± 2.73 mV<br>45 °C −18. 91 ± 3.14 mV<br>• Nanoemulsion with extract and polysaccharide-enriched fraction<br>Droplet size<br>t0 174. 81 ± 5.37 nm<br>4 °C 172.71 ± 10.6 nm<br>25 °C 175.97 ± 6.19 nm<br>45 °C 215.79 ± 11.11 nm<br>Polydispersity Index<br>t0 0.11 ± 0.02<br>4 °C 0.09 ± 0.03 | The formula containing *Agave sisalana* extract with an additional 0.5% polysaccharide-enriched fraction was considered safe for the skin. The formula contained 40% oil phase, 50% water phase, and 10% surfactant additive. |

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| | | | 25 °C 0.10 ± 0.02<br>45 °C 0.09 ± 0.04<br>Zeta Potential<br>t0 −23. 03 ± 1.94 mV<br>4 °C −20.78 ± 2.19 mV<br>25 °C −22. 78 ± 3.04 mV<br>45 °C −19.04 ± 2.31 mV<br>(Barreto et al., 2017) | |
| Coffee Oil<br>Algae Oil | Oil phase: Coffee oil/Algae oil<br>Surfactant:Tween 80, Span 80 | Droplet size: 36.7±0.2 nm | Droplet size during storage for 1 day and 90 days<br>4°C 37.7±0.3 and 31.9±0.2 nm<br>25°C 37.5±0.2 and 35.3±0.2 nm<br>40°C 36.8±0.2 and 47.5±1.2 nm<br>Polydispersity Index during storage for 1 day and 90 days<br>4°C 0.065 and 0.087<br>25°C 0.093 and 0.124<br>40°C 0.076 and 0.050<br>(Yang et al., 2017) | 0.1% coffee oil-algae oil nanoemulsion could decrease water loss and erythema the HLB value 12.86 |
| • Curcumin<br>• Benzylisothiocyanate | Oil phase: a-tocopherol<br>Surfactant: Sodium Stearoyl Lactate, Tween 80<br>Cosurfactant: Ethanol | • Droplet size<br>Pure NE: 38 ± 3 nm<br>BITC loaded: 45 ± 2 nm<br>Curcumin loaded: 49 ± 3 nm<br>BITC + curcumin: 53 ± 2 nm<br>• Viscosity<br>Pure NE: 1.41 ± 0.01 cP<br>Curcumin loaded: 1.46 ± 0.02 cP<br>BITC loaded: 1.45 ± 0.01 cP<br>BITC + curcumin: 1.48 ± 0.01cP | • NE with addition of ethanol has good stability than NE without ethanol.<br>• At 25$^0$C, NE without ethanol showed increasing of droplet size.<br>• At 4$^0$C, NE showed increased size both NE and NE without ethanol.<br>• BITC was loaded in NE showed high stability in alkaline conditions. Pure NE was stable under acidic and neutral condition.<br>(Kaur et al., 2017) | When compared with empty nanoemulsion and curcumin nanoemulsion, benzilisothiocyanate nanoemulsion acted as a better antioxidant.<br>The smallest droplet size was obtained at a concentration of 2% ethanol. |

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| Jaboticaba (*plinia peruviana*) Extract | Oil phase: Caprylic/Capric Triglyceride<br>Surfactant: Tween 80 | Droplet size: 184.5 ± 3.96 nm<br>Polydispersity Index: 0.185 ± 0.012<br>Zeta potential: -15.5 ± 5.37 mV | Stability studies of nanoemulsion were performed at room temperature over 120 days: Zeta potential nanoemulsion with extract: -21.5 - -36.7 mV<br>(Mazzarino et al., 2017) | The nanoemulsion formula with 10% jaboticaba extract consisted of 5 % oil, 1 % surfactant, and 500 bar of homogenization pressure and also contained high phenolic activity. |
| Ubiquinone (Co-Q10) | Oil phase: Virgin Coconut Oil<br>Surfactant: Tween 80, Span 80<br>Cosurfactant: Ethanol | Droplet size: 93.2 ± 2.78 nm<br>Viscosity: 8.5 cPas | -<br>(Erawati et al., 2018) | Co-Q10 nanoemulsion formula penetrated deeper than Co-Q10 emulsion formula. |
| Co-Q10 | Oil phase: Isopropyl Myristate<br>Surfactant: Tween 80<br>Cosurfactant: Transcutol HP | Droplet size: 11.76 ± 1.1 nm<br>Polydispersity Index: 0.228<br>Zeta potential: 14.7 ± 1.23 mV<br>Viscosity 199.05 ± 0.35 cP | 18 formulations with various Surfactants: Co-surfactant ratio and drug concentration were evaluated for their thermodynamic stability using centrifugation, heating-cooling, and freeze-thaw tests, and a formula that passed three of the tests was selected.<br>(El-Leithy et al., 2018) | The right formula to deliver Co-Q10 was a formula containing 10% w/w isopropyl myristate (Oil phase), 60% w/w of Tween 80: Transcutol HP mixture (S/cosmix) at ratio 2:1, 30% w /w water and 2% w/w Co-Q10. |
| Ellagic Acid | Oil phase: Isopropyl Myristate<br>Surfactant: EL -40<br>Cosurfactant: Glycerol | Droplet size: 24.28 nm<br>Zeta potential: −2.93 mV | The stability study consisted of the constant-temperature accelerated test, the high-speed centrifugation test, and the high-temperature test, after which no precipitation and no change in droplet size were observed in EA nanoemulsion.<br>(Zhang et al., 2018) | Higher concentration of ellagic acid nanoemulsion,greater anti-aging effects. |
| • Caffeine (CAF)<br>• Ethyl Ximenynate (EXM) | Oil phase: Isononanoate (EI), Dicaprylyl Ether (DE)<br>Surfactant: Potassium Lauroyl Wheat Amino Acids, Palm Glycerides, Capryloyl Glycine | Droplet size: 30 - 50 nm | The stability of the nanoemulsion at room temperature (RT), $4^0$C and 50 °C over 3 months was conducted to 15 formulas and 2 formulas was chosen with each 0.4% CAF and 0.8% EXM by visual inspection. Both of them were stable.<br>(Musazzi et al., 2018) | Higher Dicaprylyl Ether concentration, higher clearness of system.<br>Better EXM release When water content is higher at different oil and water ratios. Even though EXM and CAF have different polarities, there was no significant difference in permeation. |

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| *Tetraselmis tetrathele* extract | Oil phase: Palm Kernel Oil Esters (PKOEs)<br>Surfactant:Tween 80 | Droplet size: 102.3 - 249.5 nm<br>Zeta potential: - 33.2 to - 71.7 mV<br>Viscosity: 79.19 Pa.s | In the 10-week stability test at 4, 25, and 45 °C T1 (20 wt% Tween 80) and T2 (15 wt% Tween 80) were stable but T3 (10 wt% Tween 80) precipitated at week eight. Of the three formulas, T1 has the best stability.<br>(Farahin et al., 2019) | 1% of *Tetraselmis tetrathele* extract was chosen in formula with 20% tween 80 and 8%. |
| Sunflower Oil | Oil phase: Sunflower oil<br>Surfactant: Tween 80<br>Cosurfactant: Sorbitol | Droplet size: 124.47 nm<br>Viscosity: 225 ± 25 cP | 3 formulas were observed stability of its droplet size during 12 weeks and F1 was stable than others:<br>• Droplet size F1<br>0-week 124.47 nm<br>6 weeks 307.17 nm<br>12 weeks 393.78 nm<br>• Viscosity F1<br>0 week 225.0 ± 25.00<br>4 weeks 437.5 ± 21.65<br>6 weeks 562.5 ± 0.00<br>12 weeks 750.0 ± 50.00<br>(Arianto & Cindy, 2019) | For 12 weeks of storage at room temperature, low temperature, and high temperature, a nanoemulsion mixture containing 5% sunflower oil with a ratio of 38:22 surfactant Tween 80 and sorbitol with an SPF value of 5.43±0.03 demonstrated good stability. |
| Grape Seed Oil | Oil phase: Grape Seed Oil<br>Surfactant: Tween 80<br>Cosurfactant: PEG 400 | Droplet size: 163.82 nm<br>Viscosity: 210 cP | Physical stability was observed during 8 weeks storage:<br>Droplet size 438.50 nm<br>Viscosity 550 cp<br>(Sumaiyah & Leisyah, 2019) | F3 with 6% grape seed oil was chosen from 3 formulas of nanoemulsion due to its highest improvement in anti-aging activity (moisture, evenness and pore, spots, and wrinkles). |
| • Centella Asiatica<br>• *Lycopersicon esculentum* Mil.<br>• *Moringa oleifera* Lam. Extract | Oil phase: Virgin Coconut Oil<br>Surfactant: Tween 80 | Droplet size: 197 ± 2.18 nm<br>Polydispersity Index: 0.23 ± 0.01<br>Zeta potential: -17.1 ± 0.26 mV<br>Viscosity: 2.55 ± 0.03 cP | At a temperature of 25ºC, droplet size and polydispersity index values were constant while the zeta potential value changed for 3 days. However, at low temperature and high temperature, droplet size increases. Thus, the appropriate temperature for nanoemulsion stability is 25ºC.<br>(Limthin & Phromyothin, 2019) | A good formulation is a nanoemulsion containing 1% extract with a ratio of water, virgin coconut oil and surfactant Tween 80 is 80:10:10 with a homogenization of 4000 rpm for 20 minutes. |

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| Sucupira Oil | Oil phase: Sucupira oil<br>Surfactant: Span 80, Tween 80 | Droplet size: 150 nm<br>Polydispersity Index: 0.2<br>Conductivity: 90 to 100 µs/cm | Stability Droplet size<br>Day 1<br>4°C: 152.4±5.7 nm<br>25°C: 151.1±4.1 nm<br>45°C: 149.6±6.0 nm<br>Day 90<br>4°C: 150.9±5.2 nm<br>25°C: 149.8±4.5 nm<br>45°C: 161.6±5.9 nm<br>(Pacheco et al., 2019) | Treatment with a concentration of 5 g/ml Sucupira could significantly inhibit interleukin IL-6 and IL-8 in irradiated keratinocytes. It was very suitable for UVA radiation treatment. |
| • Retinyl Palmitate<br>• Dead Sea Water | Oil phase: Sunflower Seed Oil, Arlamol™ HD oil<br>Surfactant: Brij 96 | Droplet size: 50 to 180 nm | -<br>(Garcia-Bilbao et al., 2020) | 4.2%, w/w of Retinyl Palmitate (mixed with sunflower seed oil) dissolved in 15.8% w/w of Arlamol™ HD oil); 7% w/w of Dead Sea Water, 7% w/w of Brij 96, and 66% w/w of triple distilled water was chosen as final formula of nanoemulsion. |
| • Gotu kola<br>• Mangosteen Rind<br>• Cucumber<br>• Tomato Extract | Oil phase: Avocado oil<br>Surfactant: Tween 80, Span 80 | Droplet size: 1.64 ± 0.99 µm<br>Viscosity: 1638 ± 1294 cP | • Viscosity after 60 days<br>5 °C: 2180 cP<br>Ambient: 830 cP<br>40 °C: – (not stable)<br>• Droplet size after 60 days<br>5°C: 822.2 nm<br>Ambient: 836.3 nm<br>40°C: 6511.7 nm<br>(Septiyanti & Meliana, 2020) | 2% Gotu kola extract, 2% mangosteen rind extract, 2 % tomato extract and 4% cucumber extract with 2 % of avocado oil was chosen as suitable anti-aging formula. |
| Mangostin Peel Extract | Oil phase: Virgin Cocunut Oil (VCO)-PG<br>Surfactant:Tween 20, Span 20 | Droplet size: 28.67 ± 0.58 nm<br>Polydispersity Index: 0.37 ± 0.01<br>Zeta potential: -48.50 ± 2.27 mV | After freeze-thaw cycle test, droplet size of formula with HLB value of 15.1 increased not significant.<br>(Sungpud et al., 2020) | Ratio Span 20 and Tween 20 is 4:1 having an HLB value of 15.1 with 10% extract and VCO-PG was chosen as best formula. |

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| • Vitamin C<br>• Vitamin E<br>• Curcumin (CAC) | Oil phase: Capmul MCM C8 (CA)<br>Surfactant: Bacillus Subtilis as Surfactin<br>Cosurfactant: Transcutol | • Droplet size (nm)<br>SF:TR:CA 69.3±1.4<br>SF:TR:Vitamin C 176.46±0.50<br>SF:TR:Vitamin E 183.9±7.64<br>SF:TR: CAC 89.18±1.35<br>• Polydispersity Index<br>SF:TR:CA 0.084±0.019<br>SF:TR:Vitamin C 0.108±0.014<br>SF:TR:Vitamin E 0.328±0.01<br>SF:TR: CAC 0.371±0.02<br>• Zeta potential (mV)<br>SF:TR:CA -77.36±1.61<br>SF:TR:Vitamin C -82.7±1.9<br>SF:TR:Vitamin E -95.03±5.11<br>SF:TR: CAC -43.57±7.10 | Stability was observed for 195 days at 25$^0$C, formula of curcumin (CAC) was not stable.<br>Droplet size of Vitamin C formula increased: 190.57±0.3 nm<br>Droplet size of Vitamin E decreased: 147.6 ± 1.9 nm<br>Polydispersity index of Vitamin C: 0.183±0.06<br>Polydispersity index of Vitamin E: 0.126 ± 0.016<br>Zeta potential of Vitamin C: - 77.57±0.8 mV<br>Zeta potential of Vitamin E: - 89.7±1.14 mV<br>(Lewińska et al., 2020) | 50% surfactin from Bacillus subtilis as surfactant, 30% Transcutol as cosurfactant and 20% Capmul MCM C8 (CA) as oil phase was the suitable formula to carry vitamin C and vitamin E which has anti-aging effects. |
| *Ocimum Sanctum* Linn | Oil phase: Tea seed oil<br>Surfactant: Tween 20<br>Cosurfactant: PEG-400 | Droplet size: 170.0±0.6 nm<br>Polydispersity index: 0.143±0.010<br>Potential Zeta: -24.0±0.6 mV | Droplet size, PI and Zeta potential was stable and remained constant after heating-cooling cycles was conducted.<br>(Chaiyana et al., 2020) | 15% tea seed oil; 7.5% Tween 20; 7.5% PEG 400 and 70% Water was nanoemulsion formula to encapsulate 0.1% w/w *O. Sanctum* ethanolic extract. |
| *Cordyceps Militaris* | Oil phase: Sea buckthorn oil<br>Surfactant: Tween 80<br>Cosurfactant: Chitosan | Droplet size: 87.0±2.1 nm<br>Polydispersity Index: 0.089±0.023<br>Zeta potential: -26.20±2 mV | • Droplet size (nm)<br>RT 87.0±2.1<br>4$^0$C 87.1±3<br>25$^0$C 114.5±2<br>60$^0$C 161.8<br>• Polydispersity Index<br>RT 0.089±0.023<br>4$^0$C 0.100±0.030<br>25$^0$C 0.122±0.04<br>60$^0$C 0.106±0.04<br>• Zeta potential (mV)<br>RT -26.20±2<br>4$^0$C -25.94±0.7<br>25$^0$C -19.81±0.5<br>60$^0$C -12±1.2<br>(Rupa et al., 2020) | 88% Water (*Cordyceps*); 6% sea buckthorn oil; 6% surfactant; 0.1% chitosan cosurfactant is safe for topical use that contain good antioxidant. |

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| Microbial Carotenoids | Oil phase: Buriti oil<br>Surfactant:Tween 80, Span 80<br>Cosurfactant: Propylene glycol | Droplet size:<br>142.11 ± 0.92 nm<br>Polydispersity index:<br>0.198 ± 0.017 | Stability was conducted during 30 days<br>Droplet size<br>0 day 142.11 ± 0.92 nm<br>15 days 148.47 ± 2.68 nm<br>30 days 147.72 ± 1.63 nm<br>Polydispersity index<br>0 day 0.198 ± 0.161<br>15 days 0.133 ± 0.018<br>30 days 0.092 ± 0.011<br>(Mansur et al., 2020) | 12% Tween 80; 3% Span 80; 2% Propylene glycol; 3% Buriti oil; 0.2% Microbial carotenoids and 0.1% Vitamin E with 10% OMC; 3% EHMC and 3% BZF-3 had SPF of 36 ± 1.5. |
| Retinyl Palmitate | Oil phase: Capryol 90 and Captex 355<br>Surfactant: KollipHor EL<br>Cosurfactant: Transcutol HP | Droplet size:<br>16.71 nm<br>Polydispersity index: 0.015<br>Zeta potential: -20.6 mV<br>Viscosity: 77.48±1.73 cp | Stability of droplet size and polydispersity index was observed during 90 days at ambient conditions then no significant changes were observed.<br>Droplet size: 16 nm<br>Polydispersity index: 0.05<br>(Algahtani et al., 2020) | 10% oil phase (ratio 2:1); 30% KollipHor EL; 15% Transcutol HP and 45% Water was chosen as best formula with drug content 98.87±0.55%. |
| *Cordyceps militaris* Extracts | Oil phase: Sugar squalene<br>Surfactant: Tween 85 | Droplet size: 157.1±2.6 nm<br>Zeta potential: -15.8±0.3 mV | After heating-cooling cycle test, the droplet size increased that were less than 300 nm and polydispersity index was less than 0.4.<br>(Marsup et al., 2020) | 5% Tween 85; 10% Sugar squalene with 1% of *Cordyceps militaris* extract was chosen as best formulation of nanoemulsion that potent to deliver high amount extract to skin layer. |
| Curcumin | Oil phase: Medium Chain Triglycerides, Eucalyptol<br>Surfactant: Tween 80<br>Cosurfactant: Soybean lecithin | Droplet size: 69 - 128 nm | -<br>(Nikolic et al., 2020) | 5% MCT; 5% Eucalyptol; 1% soybean lecithin; 9% Tween 80; 80% water was best formula and monoterpene eucalyptol could modify nanoemulsion strongly. |
| Green Coffee Beans Extract | Oil phase: Green Coffee Oil<br>Surfactant: Poloxamer<br>Cosurfactant: Soy lecithin | Droplet size: 224±0.98<br>Polydispersity index:<br>0.204±0.01<br>Zeta potential: −37.4±0.49 mV | -<br>(Buzanello et al., 2020) | Higher content of green coffee oil, higher its antioxidant activity. |

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| Carrot Seed Oil | Oil phase: Carrot Seed Oil<br>Surfactant: Tween 80<br>Cosurfactant: Sorbitol 40 and 20 | Droplet size: 338.34 nm<br>Viscosity: 499.00±0.00 mpa | • Droplet size<br>4-weeks 411.86 nm<br>8-weeks 512.27 nm<br>Viscosity<br>4-weeks 454.33±1.15 mpa<br>8-weeks 439.00±1.73 mpa<br>(Arianto et al., 2021) | 4% carrot seed oil; 40% Tween 80; 20% sorbitol as best formula had SPF value 20.28±0.218. |
| Bakuchiol | Oil phase: Bakuchiol Rich Extract<br>Surfactant: Coco betaine, Surfactin | Droplet size: 221±4 nm<br>Polydispersity index: 0.182±0.01<br>Zeta potential: 73±5 mV | Stability test with freeze-thaw 6 cycles was observed by visual inspection if there was no precipitation.<br>(Lewińska et al., 2021) | The best formula of nanoemulsion was 5% Surfactant (Coco betaine: Surfactin = 4:1); 1% Oil phase and 94% water phase. |
| Ceramide-Like Molecule | Oil phase: Oleic acid<br>Surfactant: Tween 80 | Droplet size: 231 – 277 nm<br>Polydispersity index: 0.137 – 0.365<br>Zeta potential:<br>– (29±3) to – (34±5) mV | 30 days stability test resulted that nanoemulsion preparation was stable by visual inspection.<br>(Guzman et al., 2021) | Oil: surfactant ratio was 1 and 73% water could encapsulated up to 2.0% ceramide-like molecule. |
| Levan | Oil phase: Ascorbyl Tetraisopalmitate<br>Surfactant: Sodium Surfactin Powder<br>Cosurfactant: Transcutol HP | Droplet size:<br>143.9±74 - 385.2±26.6 nm<br>Polydispersity Index:<br>0.171±0.02 – 0.430±0.01<br>Zeta potential:<br>– 18.04±0.42 to 40.34±0.84 mV | After 90 days<br>Droplet size: 91.6±5.5 – 195.7±7.5 nm<br>Polydispersity Index: 0.094±0.010 – 0.650±0.120<br>Zeta potential: – 14.07±1.36 to 38.27±1.26 mV<br>(Lewińska et al., 2021) | 50% sodium surfactin powder;30% Transcutol HP; 20% ascorbyl tetraisopalmitate was a formula of nanoemulsion and this formula was added by pentylene glycol, 1.2-hexanediol and butylene glycol as preservatives to enhance its stability during 90 days. |

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**Discussion**

The stability of the nanoemulsion is determined by the composition and characteristics of the oil phase, surfactant, and cosurfactant. Stability tests on nanoemulsions were carried out to investigate the stability of the droplet size and to observe changes in stability, such as no phase separation. Stability consists of physical and chemical stability. The stability of nanoemulsion can be interpreted that the preparation does not change or change within the permissible limits related to physical, chemical, microbiological, therapeutic, and toxicological characteristics (Rai et al., 2018). Physical and chemical stability is one of the important criteria for the success of a preparation. Physical stability was observes physical changes in preparation such as organoleptic examination, pH, homogeneity, specific gravity, and changes in nanoemulsion characteristics. Physical stability can be reviewed by comparing the physical properties of the preparation before and after the centrifugation test, thermal cycling, and real-time methods (Zothanpuii et al., 2020) .

The instability of nanoemulsions occurs through several mechanisms such as gravity separation, flocculation, coalescence, and ostwald ripening. This instability affects the increase in droplet size. Gravity separation occurs were characterized by the appearance of creaming and sedimentation because the density of internal phase is lower or higher than the surrounding environment. Gravity separation can be overcome by adding a thickening agent so that the viscosity of the nanoemulsion increases. Flocculation and coalescence are aggregating droplet events and can be prevented by increasing repulsion rather than attraction (Bhattacharjee, 2019).

Table 2 shows ingredients that function as antioxidants, UV rays filters, moisturizing agents, and cell repairing agents that can help skin cope with aging in accordance with topical anti-aging functions (Li, 2015). Leaf and stem of Vellozia Squamata (Quintão et al., 2013), Tocotrienol (Han et al., 2013), propolis extract (Mauludin et al., 2015), quercetin (Dario, Oliveira, et al., 2016), vitamin E (Ramli et al., 2017), *Clinacanthus nutans* (L.) leaves (Che Sulaiman et al., 2016), β-D-glucan polysaccharides extract (Alzorqi et al., 2016), curcumin (Nikolic et al., 2020) and benzyl isothiocyanate (Kaur et al., 2017), Jaboticaba (*Plinia peruviana*) extract (Letícia Mazzarino et al., 2018), *Tetraselmis tetrathele* (Farahin et al., 2019), grape seed oil (Sumaiyah & Leisyah, 2019), Centella Asiatica/*Lycopersicon esculentum* Mill./*Moringa oleifera* Lam. extract (Limthin & Phromyothin, 2019), Gotu kola/mangosteen rind/cucumber/tomato extract (Septiyanti & Meliana, 2020), Mangostin peel extract (Sungpud et al., 2020), *Cordyceps militaris* (Marsup et al., 2020; Rupa et al., 2020) and Green coffee beans extract (Buzanello et al., 2020), vitamin C/vitamin E (Lewińska et al., 2020) are an antioxidant compounds that play a role in protecting the skin from UV radiation, cigarette smoke and also hypoxia. Antioxidants can protect the skin from free radicals that cause aging by increasing collagen production. Antioxidants are stable compounds that donate electrons to reactive free radicals and neutralize them, reducing their capacity to damage surrounding cells. Antioxidants delay or inhibit cell damage. Free radicals come from endogenous sources (fibroblast, respiratory chain, inflammatory cells, epithelial cells) as well as from exogenous sources such as exposure to ultraviolet light, smoking, air pollution, and industrial chemicals. Antioxidants have two mechanisms for carrying out their functions. The first mechanism is chain cleavage, in which primary antioxidants give electrons to free radicals. The second mechanism is to help regenerate primary antioxidants, deactivate singlet oxygen, absorb ultraviolet radiation, bind metal ions, and reduce free radicals (Gulcin, 2020).

Cell repairing agents are retinyl palmitate (Clares et al., 2014), fullerene (Ngan et al., 2015), swiftlet nest (Taib et al., 2015), coffee oil/algae oil (Yang et al., 2017), co-Q10 (El-Leithy et al., 2018; Erawati et al., 2018), ellagic acid (Zhang et al., 2018), caffeine (CAF)/ethyl ximenynate (EXM) (Musazzi et al., 2018), *Ocimum sanctum* Linn (Wantida Chaiyana et al., 2020), bakuchiol (Lewińska et al., 2021), ceramide-like molecule (Guzman et al., 2021), and thistle oil (Miastkowska et al., 2016). The cell repairing agent stimulates and increases skin collagen production by increasing the ability to proliferate old dermis fibroblast cells (Li, 2015). When collagen production decreases with increasing age, the result is an increase in the process of "dry skin" and its elasticity properties.

Levan (Lewińska et al., 2021), *Opuntia ficus-indica* (L.) Mill Extract (Ribeiro et al., 2015), Ethoxylated Lanolin (EL)/Acetylated Lanolin (AL) (Pereira et al., 2016), and *Agave sisalana* (Barreto et al., 2017) are some of the active compounds from the articles in Table 2 which function as moisturizing agents. Moisturizing agents help maintain water in the skin's uppermost layer to prevent it from dry out. Based on the mechanism of action, moisturizers are divided into three types: occlusive, humectant, and emollient (Dini & Laneri, 2021). The action of occlusive moisturizer is to prevent transepidermal water loss (TEWL) in the stratum corneum so that dehydration does not occur in the skin. The mechanism of action of humectants as moisturizers is to attract water from the environment to enter the skin to be able to hydrate the stratum corneum. Emollients work by softening and filling cracked skin with oil droplets.

Exposure to UV rays on the skin can cause thinning of the skin barrier, the appearance of wrinkles, and also damage the DNA structure, causing skin cells to reduce their ability to regenerate to form new cells (Cao et al., 2020). Using an ultraviolet light scattering agent or UV absorber can reduce the negative impact of UV exposure. Hence, sunscreen to slow down aging is needed. From the selected articles, several active compounds that act as ultraviolet light scattering agents or UV absorbers are octyl methoxycinnamate (OMC)/titanium dioxide (Silva et al., 2013), ethyl hexyltriazone (EHT)/diethylamino hydroxy benzoyl hexyl benzoate (DHHB)/bemotrizinol (Tinosorb

S)/avobenzone (AVO)/ octyl methoxycinnamate (Puglia et al., 2014), sucupira oil (Pacheco et al., 2019), sunflower oil (Arianto & Cindy, 2019), retinyl palmitate and dead sea water (Garcia-Bilbao et al., 2020), microbial carotenoids (Mansur et al., 2020), and carrot seed oil (Arianto et al., 2021).

Furthermore, Table 2 describes the different types of surfactants, cosurfactants, and oil phases used in each study. The most important factors to avoid unstable formulas are surfactants, cosurfactants, and the oil phase. Surfactants are the first factor that plays a major role in the creation of nanoemulsions by reducing the interfacial tension between two immiscible liquids and causing them to become miscible as a result of the hydrophilic and hydrophobic groups that are present at the head and tail of each surfactant, respectively. The choice of surfactant depends on its solubility in oil and water, the HLB value, and its non-irritating properties to the skin (Rai et al., 2018). Table 1 shows several articles using two types of surfactants, single surfactants and the addition of cosurfactants with various oil phases. The combination of tween 80 and span 80 was the most commonly utilized surfactant among the 44 selected articles (Barreto et al., 2017; Erawati et al., 2018; Han et al., 2013; Mansur et al., 2020; Ngan et al., 2015; Pacheco et al., 2019; Ribeiro et al., 2015; Septiyanti & Meliana, 2020; Sulaiman et al., 2016; Yang et al., 2017). Next, among the ten articles that used a combination of tween 80 and span 80, the smallest droplet size of nanoemulsion with 36.7±0.2 nm was conducted by adding 0.1% coffee oil/algae oil phase (Yang et al., 2017) and it was stable at storage condition for 90 days by visual observation and the largest particle size of nanoemulsion with 170 nm was conducted with a palm kernel oil ester as the oil phase by Ngan et al. (2015) and the polydispersity index (PI) value close to zero which means the particle size distribution is good, so that showed good stability during 90 days of storage by centrifugation and freeze-thaw cycle tests. Tween 80 is a hydrophilic nonionic surfactant with an HLB value of 15.0, and Span 80 is a lipophilic nonionic surfactant with an HLB value of 4.3. In addition to its non-irritating nature, combining these two types of nonionic surfactants can reduce droplet size by providing steric stabilization. Steric stabilization is produced by nonionic surfactants having long polyoxyethylene chains with polar groups on the surfactant head. The polyoxyethylene chain of Tween 80 and the ring of Span 80 can form steric stabilization. The smaller the droplet size resulted in the smaller the aggregation rate, so this nanoemulsion is difficult to coalesce. In addition, the small particle size can be stored longer, is not easily damaged, the texture is not easy to change, and is easily absorbed by the skin.

The use of a single surfactant is also not infrequently used in nanoemulsion formulations such as tween 80 (Farahin et al., 2019; Guzman et al., 2021; Limthin & Phromyothin, 2019; L Mazzarino et al., 2018; Mohd Taib et al., 2015), tween 85 (Marsup et al., 2020), kolliphor®RH40 (polyoxyl 40 hydrogenated castor oil) (Alzorqi et al., 2016), brij 96 (Garcia-Bilbao et al., 2020) and pluronic F68 (Puglia et al., 2014). Among these studies, research by Garcia-Bilbao et al. (2020) produced the smallest droplet size of 50 nm with 7% brij 96 as a surfactant, a mixture of sunflower seed oil and arlamol™ HD oil as the oil phase, and the largest droplet size from the research conducted by (Guzman et al., 2021) of 277 nm with a ratio of oleic acid and Tween 80 of 1, the polydispersity index value of 0.365, the zeta potential value of (-34±5) mV and also stable at storage for 30 days. The electrostatic repulsion between the scattered droplets close to each other is directly connected to the zeta potential, which is the difference between tightly bonded surface ions around a solution-neutral droplet (Marzuki et al., 2019). A high zeta potential value indicates that the emulsion is both physically and chemically stable, as repulsive forces tend to prevent flocculation. A good zeta potential value (positive and negative charge) indicates a stable nanoemulsion system, thereby reducing the droplet aggregation potential by 30 mV. If the zeta potential is positive, it implies that the positively charged particles in the suspension are dispersed. On the other hand, a negative zeta potential means that the negatively charged in the suspension is dispersed.

The second factor is the cosurfactant; cosurfactants are amphiphilic in a state without a tendency to be partitioned in large quantities at the surfactant interfacial monolayer (Harshitha et al., 2020). The cosurfactants commonly used are short to medium-chain alcohols (C3-C8), which assist the solubility of solutes in the dispersion medium by increasing the flexibility of the layer around the droplet area and lowering the surface free energy so that stability can be maintained. In addition, with the use of cosurfactants, the concentration of surfactant used can be reduced to reduce the risk of irritation that can be caused. In the articles reviewed, the most commonly used cosurfactant was Transcutol HP (Algahtani et al., 2020; El-Leithy et al., 2018; Lewińska et al., 2021; Agnieszka Lewińska et al., 2020) and ethanol (Buzanello et al., 2020; Erawati et al., 2018; Kaur et al., 2017) as well as several articles using sorbitol (Arianto et al., 2021; Arianto & Cindy, 2019), glycerine (Mauludin et al., 2015; Zhang et al., 2018), propylene glycol (Mauludin et al., 2015), PEG-400 (W. Chaiyana et al., 2020; Sumaiyah & Leisyah, 2019), chitosan (Rupa et al., 2020) and plurol oleique (Clares et al., 2014). Nanoemulsion with Transcutol HP as cosurfactant, ascorbyl tetraisopalmitate as oil phase, and sodium surfactin powder as surfactant had the largest droplet size of 385.2±26.6 nm, polydispersity index 0.430±0.01 and zeta potential value –18.04±0.42 (Lewińska et al., 2021). The polydispersity index value from this study is classified as polydispersity, indicating an extensive droplet size distribution so that the droplet size is very diverse and sedimentation is prone to occur. According to Stokes' Law, the speed of deposition is directly proportional to the size of the diameter of the particle, where if the diameter of the particle is small, then the speed of deposition is also low (long). The zeta potential value, smaller than 30 mV, also indicates less stability (Rai et al., 2018). Furthermore, the smallest

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droplet size was 11.76 ± 1.1nm, Zeta potential - 14.7 ± 1.23mV, and Viscosity 199.05 ± 0.35 cp with Transcutol HP as cosurfactants, Tween 80 as surfactant, and isopropyl myristate as the oil phase (El-Leithy et al., 2018). The study showed good stability by visual observation.

From the above explanation, using single and combined surfactants produced good nanoemulsion characteristics, but the resulting stability was different. Nanoemulsions with combined surfactants produce better stability than single surfactants because they can provide a better balance of HLB values according to the desired type of nanoemulsion. The addition of cosurfactants is not something that must be added in a nanoemulsion system, but the cosurfactant itself can positively impact the nanoemulsion's stability (Sadoon & Ghareeb, 2020). Cosurfactants can increase the hydrocarbon tail's mobility so that the oil's penetration in the tail becomes greater.

When compared with studies using two surfactants and a single surfactant, the addition of cosurfactants and also the increase in surfactant concentration as in the study of El-Leithy et al. (2018) that 60% of the surfactant Tween 80 and cosurfactant Transcutol HP resulted in smaller emulsion droplet sizes due to the increase in surfactant molecules to absorb around the interface area to reduce the oil-water interfacial tension and dissolve large amounts of hydrophilic surfactants or hydrophobic drugs on the nanoemulsion system. Transcutol HP has advantages over other cosurfactants because it is non-volatile, almost odorless and transparent (Osborne & Musakhanian, 2018). When compared to ethanol, Transcutol HP has a higher boiling point so it does not limit the processing temperature.

The third most important factor is the selection of the type of oil; oil selection also plays an important role in nanoemulsion characteristics and stability. Oils contain long-chain triglycerides (LCT) because they contain more than 12 carbon chains. Apart from LCT, there are two other triglycerides classifications: medium-chain triglycerides (MCT) containing 6-12 carbon chains and short-chain triglycerides (SCT) containing less than six carbon chains (Zulkanain et al., 2020). Based on Table 2, the most frequently used type of oil is caprylic/capric triglyceride (Barreto et al., 2017; Dario et al., 2016; Mazzarino et al., 2017; Ribeiro et al., 2015). 19.99±0.07 nm is the smallest droplet size among research articles using caprilyc/capric triglyceride as the oil phase, oleth-20, oleth-3, cetyltrimethylammonium chloride as a surfactant (Dario et al., 2016). This study showed a positive zeta potential (+19.6±2.2 mV). These were due to the presence of the cationic surfactant cetyltrimethylammonium chloride. The polydispersity index value of 0.082 is classified as polydispersity, which means that the particle size distribution in the system varies. Caprylic/capric triglycerides are triglyceride oils from coconut oil or fatty acids and glycerin. This oil spreads easily and doesn't feel occlusive.

The lowest viscosity was 7.1 cP because Caprilyc/capric triglyceride was only 5% (Dario et al., 2016). Caprylic/capric triglycerides are classified as medium-chain triglycerides (MCT). MCTs have unique physical properties. For example, MCTs are more polar than LCTs, so MCTs are more soluble in water. Oils with medium chain triglycerides (MCT) are stable at low and high temperatures, have low viscosity, and produce smaller droplet sizes than nanoemulsions with high viscosity oils (Erawati et al., 2018). This study showed the occurrence of ostwald ripening in the preparation during 90 days of storage. Although it produces a small droplet size, ostwald ripening also affects the stability of the nanoemulsion due to its low viscosity. Based on stokes' law (McClements, 2005), the lower the viscosity, the more distant the distance between the droplets, so they tend to bond with each other, and the kinetic energy will increase so that the deposition rate is high. Oils that have short to medium chains are more stable than long chains. These are because oils with short to medium chains are easier to break the chain and produce clearer formula when compared to oils with long chains.

The largest droplet size was 277 nm with oleic acid as its oil phase, tween 80 as a single surfactant with 75% water percentage, and a potential zeta value (-29±3) mV (Guzman et al., 2021). However, when the water percentage decreased to 73%, the percentage of oleic acid and surfactant was increased, the droplet size became smaller, and increased the encapsulation of the ceramide-like molecule. These are because the solubility of the ceramide-like molecule to oleic acid increases so that the ceramide-like molecule is easily trapped in the oleic acid, and the concentration of surfactant used can reduce the surface tension so that it has good stability. Oleic acid (C18:1) is an unsaturated fatty acid that is lipophilic and non-polar (Rowe et al., 2006). These are in accordance with the statement of Harshitha et al. (2020) that the oil phase used can also affect the droplet size and stability of the formed nanoemulsion. The oil phase in the nanoemulsion acts as a carrier that can dissolve hydrophobic active substances and form droplets in the dispersion medium in the presence of surfactants and cosurfactants. The fatty acids generate a negative charge on the zeta potential in oleic acid (Zhao et al., 2010). Due to the wide range of absolute zeta potential values, limiting zeta potential values cannot be used to predict the stability of nanoemulsions. The physical stability of the produced emulsion may be partially determined by the zeta potential.

## CONCLUSION

The effectiveness of anti-aging ingredients like antioxidants, photoprotective agents, moisturizing agents, and cell repairing agents could be improved by using nanoemulsions as carriers. The physical stability of nanoemulsions is affected by factors such as droplet size, zeta potential, polydispersity index, and viscosity. The composition and characteristics of the oil, surfactant, and cosurfactant have an impact on the characteristics and physical stability of the nanoemulsion itself. According to the findings of the literature research, Tween 80, Span 80, Transcutol HP, and caprylic/capric triglyceride, which is referred to as MCT oil, were found to be the most often used surfactants, cosurfactants, and oils in the review articles. The type of surfactant and cosurfactant used, as well as their ratio, influence the characteristics and stability of nanoemulsions. Since the oil's physicochemical characteristics (molecular weight, polarity, and viscosity) have a significant impact on the nano emulsification spontaneously, nanoemulsion droplet size, and drug solubility, the oil phase plays a key role in the nanoemulsion formulation. The oil chosen for the nanoemulsion formulation is one that can produce nanoemulsions with tiny droplet sizes and can dissolve the drug as much as possible. The characteristics of the nanoemulsion also affect the physical stability. According to Stokes' law, physical stability is affected by particle size and viscosity. Characteristics that include particle size and viscosity will affect the physical stability of a preparation. As stated by Stokes' law, particle size and viscosity are important characteristics because they determine the homogeneity of the formed system, namely: the separation rate increases with increasing particle size, the more significant the difference between the density of the medium and the particles and the decrease in viscosity.

## LIMITATIONS

Some articles published in 2022 are not fully accessible, and the author did not investigate the chemical stability of these articles; Chemical stability is one of the stabilities regarding the length of time a preparation maintains its chemical content and potency.

## CONTRIBUTION

The author states that a potential conflict of interest does not exist in this article review.

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