Study of Liquid Self-nanoemulsifying Drug Delivery System (L-SNEDDS) that Use Oleic Acid as the Oil Phase: Literature Review

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Abstract

Self-Nanoemulsifying Drug Delivery System (SNEDDS) is a nanoemulsion system that can be used to increase the bioavailability of drugs that are hardly soluble in water and have low bioavailability. Oleic acid, a saturated fatty acid that is found in many vegetable oils, is an oil that is often used for the oil phase in SNEDDS. Therefore, this review article aims to review, study, analyze and explore the optimum formula of SNEDDS that use oleic acid as the oil phase. The articles were searched via Google Schoolar, Science Direct, and Pubmed. The total number of articles is 464 articles. The total number articles that include exclusion criteria is 453 articles. The total article that use is 11 articles. SNEDDS, which uses oleic acid as the oil phase, produces droplet sizes of 19.75-190.03 nm with a polydispersity index of 0.278-0.532. Zeta potential value, only 2 articles have a zeta potential value above +/-30, that is mefenamic acid SNEDDS and furosemide SNEDDS. Overall, SNEDDS which uses oleic acid as the oil phase has a better dissolution and bioavailability profile compared to the commercial product or the pure drug. If solubility and bioavailability increase, it can increase the pharmacological activity of the drugs.

Keywords: *SNEDDS, oleic acid, characteristics*

INTRODUCTION

A nanoemulsion technology called SNEDDS can be used to improve the bioavailability of medications that have low bioavailability (<25%) and are difficult to dissolve in water (<0.1 mg/mL) (Beg *et al*., 2017). A homogenous mixture of drugs, oil, surfactant, and cosurfactant is used to make SNEDDS, which can produce nanoemulsions with an O/W (oil in water) system. (Makadia *et al*., 2013). SNEDDS has a globule size of 20–200 nm when dispersed in water (Hashem *et al*., 2015) because nanometer-sized droplets can increase drug bioavailability (Michaelsen *et al*., 2019), increase drug dissolution into the intestine so that the drug will go to the lymphatic tract, prevent first-pass metabolism (Aisy *et al*., 2021), increase absorption and permeation of drugs (Zhang *et al*., 2020). In agreement with Date *et al* (2010), another advantage of orally distributed SNEDDS is that it accelerates drug onset and can reduce drug doses by increasing the maximum concentration value (Cmax). A number of drugs, including atorvastatin (Hashem et al., 2015), rosuvastatin (Dabhi et al., 2011), gemfibrozil (Villar et al., 2012), and other drugs with low solubility that fall under the Biopharmaceutical Classification System (BCS) Class II, which has poor solubility and high permeability have been formulated as SNEDDS.

The oil phase is the most crucial component in the SNEDDS formulation because it functions as a solvent to dissolve lipophilic drugs, facilitates the formation of emulsions, and increases the drug levels of lipophilic drugs to be able to pass through the lymphatic system in the gastrointestinal tract. The physicochemical characteristics of the oil

phase (polarity, viscosity, and molecular size) greatly affect the nanoemulsion formation process, nanoemulsion droplet size, drug solubility, and nanoemulsions in biological fluids (Pouton and Porter, 2008). Generally, the selected oil phase in the SNEDDS formulation is the oil that has the best ability to dissolve the active substance because it will correlate with drug loading and bioavailability. The oil phase selection phase must be determined based on its ability to dissolve lipophilic drugs and be able to produce nanoemulsions that have small droplet sizes (Larsen *et al*., 2013), less than 200 nm (Bhikshapathi and Priya, 2018) to obtain maximum drug loading.

The globul size of the nanoemulsion is directly correlated with the lipophilicity and total oil phase in the SNEDDS formulation (Sadurní et al., 2005). It is challenging to create nanoemulsions from oils with long hydrocarbon chains, such as long-chain triglyceride oils and soybean oil. Meanwhile, triglyceride oils with medium chains and short chains such as ethyl oleate, will easily form nanoemulsions. Hashem et al (2015) state that the oil phase is a critical component that can affect the response of droplet size, zeta potential, and conductivity of Atorvastatin SNEDDS. One of the oil phases that is often used in SNEDDS is oleic acid. Oleic acid or cis-9-octadecanoic acid is a saturated fatty acid that is found in many vegetable oils. The largest content of oleic acid is in olive oil, which is around 50-80%, and in palm oil around 30-45%. Oleic acid has the benefit of increasing HDL lipoproteins, so it plays an important role in treating atherosclerosis, thrombosis, blood vessel blockages, and high blood pressure (Mora et al., 2013). As a result, the goal of this research is to examine, investigate, evaluate, and determine the ideal SNEDDS formula that uses oleic acid as the oil phase. This work will help future research in preparing SNEDDS from different medications using oleic acid as the oil phase by providing details on the properties and in vitro and in vivo evaluation of the SNEDDS preparation of diverse drugs.

METHODS

Research Design

This type of research is a literature review for identifying, analyzing, and interpreting all findings. Several stages in a literature study include planning, searching and retrieval, filtering and sorting, final inclusion, data extraction, and reporting. The SNEDDS formula contains oleic acid as an oil phase with favorable properties.

Inclusion Criteria

The article inclusion criteria used for this literature review were the original research article related to SNEDDS, published between 2016-2023, written in English or Bahasa Indonesia, about the topic related to SNEDDS formulations with oleic acid as the oil phase without combination with other oil. In addition, the research articles should showed examination of SNEDDS in vitro and in vivo, including droplet size, polydispersity index, transmittance, and zeta potentials, dissolution profiles, bioavailability, the effectiveness of drugs with pure drugs, conventional preparations, or market products, and all articles available in full text.

Exclusion Criteria

Books, review papers, duplicate articles, non-full text articles, and irrelevant articles met the study's exclusion criteria. The articles discussing alternative formulation to liquid SNEDDS (nanoemulsions,microemulsions, nanocream, microemulgel, emulgel, SMEDDS). The articles that use natural ingredients as active substances (extracts and fractions), using a combination of two or more oil phases, and publication of manuscripts that have not yet been published in journals (pre-proof or accepted manuscripts) also waived.

Data Collection

Data Source

Based on the findings of the research and their publishing in national and international online journals, publications and reports were

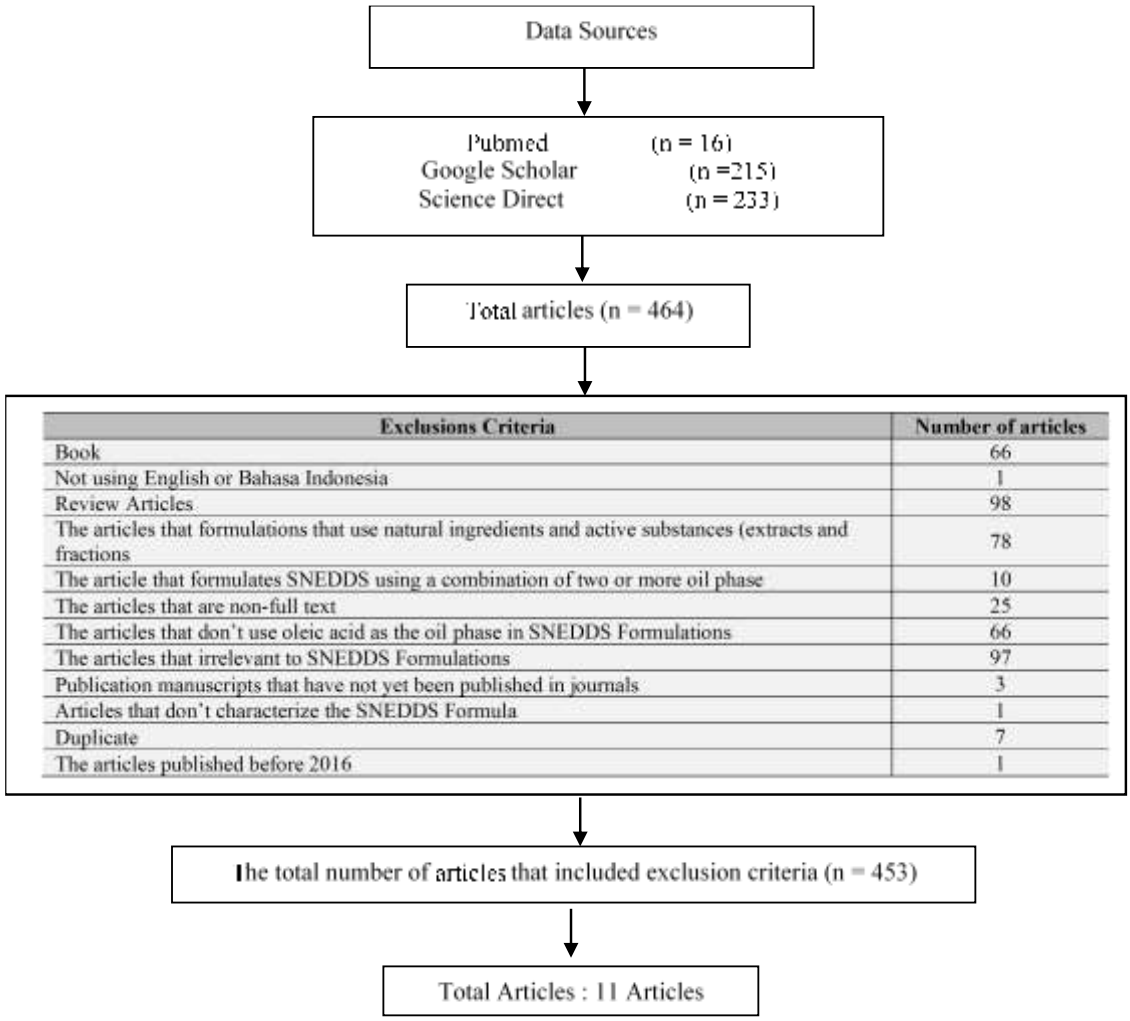

Figure 1. Data Collection Process and The Total Number of Aricles Used

searched for data. Science Direct, Pubmed, and Google Scholar were used to search for the articles. **Figure 1** shows the data collection process and the total number of aricles used.

Article Search Strategy

Searches for national and international articles were carried out on Google Scholar, PubMed, and Science Direct sites. The article search process uses keywords: (((((SNEDD) OR (SNEDDS)) OR ("Self nanoemulsifying Drug Delivery System")) OR ("Self-nanoemulsifying Drug Delivery System")) OR ("Self nanoemulsifying Drug Delivery Systems")) OR ("Self-Nanoemulsifying Drug Delivery Systems")) AND ((Oleic Acid) OR (Oleic Acid*)), which obtain 16 articles from PubMed, 215 articles from Google Scholar, and 233 articles from Science Direct. The total number of articles is 464 articles.

Article Extraction

The articles that fulfilled the requirements for inclusion were gathered and condensed into a table with their names, the SNEDDS optimal formula (which comprises the oil phase, surfactant, and cosurfactant and their percentage), medications, the SNEDDS characterization, and the in vitro and in vivo evaluation. Subsequently, the study aims and contents of the article summaries were evaluated to determine the similarities and differences across the publications.

RESULT AND DISCUSSION

Characterization of SNEDDS

In SNEDDS, the active drug substance will be formulated into the oil, surfactant, and cosurfactant phases. The selected articles use the same oil phase, which is oleic acid, as a dispersing phase that can dissolve lipophilic drugs. In this study, the characteristics of SNEDDS, and the in vitro and in vivo evaluation of the formula were studied. SNEDDS characteristics include percent transmittance, droplet size produced, polydispersity index, emulsification time, and zeta potential. Review the optimum SNEDDS and their characterization as shown in **Table 1**. This table includes informations about optimum formula of SNEDDS, drugs, and thei characteristics such as droplet size, zeta potential value, emulsification time, and polydispersity index.

Droplet Size

Based on the literature study that has been carried out, the results obtained are that SNEDDS, which uses oleic acid as the oil phase with various active substances, surfactants, and cosurfactants produces a droplet size range of 19.75-190.03 nm. In general, the droplet size of SNEDDS < 200 nm when dispersed in water (Hashem *et al*., 2015). The size of the resulting nanoemulsion is strongly connected to the lipophilicity and total oil phase in the SNEDDS formulation (Sadurní et al., 2005).

Globule size can directly influence the results of *in vitro* evaluation (dissolution and stability) and also pharmacokinetic profiles such as drug absorption. Drugs encapsulated in SNEDDS that have smaller particle sizes have better oral biological availability because the increased surface area from the smaller particles can improve the drug's permeability and solubility (Li *et al*., 2015). Based on research by Astuti *et al*., (2017) the size showed that droplet size is positively proportional to the addition of the percentage of oleic acid in the SNEDDS formula. In the polynomial equation from the design expert, the most notable effect on increasing droplet size is caused by oleic acid. The amount of surfactant cannot cover the oil droplets if the oil ratio is higher. As a result, the droplets will flocculate to reduce the interface area, which increases the droplet size (Astuti *et al*., 2017). This is contradictory to the results of the characteristics of SNEDDS Tetrandrine which contains the highest oleic acid with a percentage of 40%, with a combine of Soybean phosphatidylcholine and Cremophor RH-40 as surfactant and PEG 400 as cosurfactant has the smallest droplet size, which is 19.75 nm (Liu *et al*., 2018).

Zeta Potentials

Zeta potential characterization aims to determine the colloidal stability or physical stability of nanoemulsions. The zeta potential value indicates the surface charge of the nanoemulsion globules formed. The smaller the zeta potential value, then it will be greater the possible flocculation, which integrates small globules into large globules. This is because the smaller the zeta potential value, the more attractive force of the globul will be greater (Listyorini et al., 2018). The requirements for a good zeta potential value are more than ±30 mV (Ali and Hussein, 2017). In the articles reviewed, 2 articles met the requirements, that the Mefenamic Acid SNEDDS formula (44.1 ± 1.69 mV) (Ali and Hussein, 2017) and Furosemide SNEDDS (-34.8mV)(Wahyuningsih *et al*., 2019). Some SNEDDS formulas did not meet the requirements for zeta potentials value, such as Tetrandrine SNEDDS (1.87 ± 0.26 mv) (Liu *et al*., 2018), Nystatin SNEDDS (-19.5 ± 4.20) (Kassem *et al*., 2016), and cyclovirobuxine D SNEDDS (-25.5mV) (Ke *et al*., 2016). Stability evaluations are necessary for SNEDDS because zeta potential levels that do not match the criteria have a significant likelihood of flocculation. However, through physiological barriers like mucus and cell membranes, the zeta potential value in nanoemulsions might influence the drug delivery systems' penetration abilities. The mucus layer has a negative charge because it contains sulfonic acid and sialic

Table 1. Literature Review of the Scientific Articles Collected.

Authors	Optimum SNEDDS Formula	Drugs	SNEDDS characteristics
(Ansari *et al*., 2021)	Oil: Oleic acid 10% Surfactant: Tween 20 45% Cosurfactant: Diethylene Glycol Monoethyether 45%	Brigatinib	Droplet size 50 nm; PDI 0.532 Emulsification time in acidic pH 2 is 25 s, 24 s in basic pH 8; Appearance: Clear Transmittance >95%; Zeta potential -4.05
(Astuti *et al*., 2017)	Oil : Oleic acid 18,6% Surfactant: Tween 20 and Labrasol (1:1) 51, 4 % Cosurfactant: PEG 400 30%	Pentagamavunon-0	The droplet size 77.34 ± 9.41 nm
(Tungadi *et al*., 2021)	Oil: Oleic acid 10% Surfactant: Tween 20 72% Cosurfactant: Propylene glycol 18%	Astaxanthin	Transmittance 95% Droplet size 105,75nm Polydispersity index 0.392 Emulsification time 21 s
(Nuari *et al*., 2021)	Oil: Oleic acid 8% Surfactant: Tween 80 66% Cosurfactant: Propylene Glycol 26%	Piroxicam	Transmittance 99.16% ± 0.06 Emulsification time 44.82 ± 0.53 seconds
(Liu *et al*., 2018)	Oil : Oleic acid 40 % Surfactant: Soybean phosphatidylcholine and Cremophor RH-40 (15: 30%) Cosurfactant: PEG 400 (15%)	Tetrandrine	Droplet size is 19.75±0.37nm Zeta potential was 1.87±0.26 mv
(Syukri *et al*., 2020)	Oil: Oleic acid 10% Surfactant: Tween 80 80% Cosurfactant: PEG 400 10%	Mefenamic Acid	Transmittance 88.5% Particle size 190.03 ± 1.18 nm The Polydispersity Index is 0.469 ± 0.03 Zeta potential is -44.1 ± 1.69 mV
(Kassem *et al*., 2016)	Oil: Oleic Acid 9% Surfactant: Tween 20 (54%) Cosurfactant: Dimethyl sulfoxide (DMSO) 27%	Nystatin	Droplet size was 83.89 ± 9.02 nm The polydispersity index is 0.487 Zeta potential -19.5 ± 4.20 Spectroscopic Absorbance 0.172
(Alothaid *et al*., 2021)	Oil: Oleic Acid 5% Surfactant: Tween 20 65% Cosurfactant: PEG 600 30%	Albendazolum	The polydispersity index (PDI) of 0.278 indicates that the mean globul size value of 89.2 nm has good dispersion qualities, preserving the supersaturated state of albendazolum.pH 6.8 Percentage transmittance 100%
(Wahyuningsih *et al*., 2019)	Oil: Oleic acid 8% Surfactant: Tween 80 66% Cosurfactant: Propylene glycol 26%	Furosemide	Transmittance 95.87% Globul size 89..5 nm Emulsification time 25.7 s Zeta potential -34.8mV
(Ke *et al*., 2016)	Oil: Oleic acid 24% Surfactant: Solutol SH 15 38% Cosurfaktan: Propylene glycol 38%	Cyclovirobuxine D	Globul size of 64.80±3.58 nm Zeta potentials -25.5mV Transmittance 98.5% ±0.03%
(Priani *et al*., 2017)	Oil phase: Oleic acid 10% Surfactant: Tween 80 67.5% Cosurfactant : Transcutol 22.5%	Glimepirid	Transmittance 95,7 ± 2,797 % Emulsification time 14,26 ± 1,00 detik Thermodynamically stable; Droplet size 45 nm

nanoparticles due to electrostatic interactions. Therefore, SNEDDS with a negative value of zeta potentials can more effortlessly penetrate the mucus approach to SNEDDS with a positive value of zeta potentials (Gershanik and Benita, 1996).

The lowest zeta potentials contain the highest oleic acid phase (40%) in the SNEDDS Tetrandrine formulation (Liu *et al*., 2018). Increasing oil and surfactant concentrations can cause an improve in viscosity resulting in a decrease in zeta potential. Surfactants can help droplet breakup by lowering interfacial tension to reduce resistance to droplet deformation. Surfactants can prevent the recombination of newly formed droplets through rapid adsorption and stabilization of the interface formed (Leong *et al*., 2009). The highest zeta potential value is SNEDDS Mefenamic acid, which uses oleic acid (10%) as oil, with tween 80 (80%) and PEG 400 (10%) as surfactant and cosurfactant (Syukri *et al*., 2020). SNEDDS Tetrandrine has the lowest zeta potential value (1.87 ± 0.26 mv) with phosphatidylcholine and Cremophor RH-40 as surfactants and PEG 400 as cosurfactant (Liu *et al*., 2018). The addition of ionic and nonionic surfactant types to SNEDDS can affect the zeta potential value. In addition to the charge on the dispersed phase, the dispersing medium's physicochemical characteristics, such as pH, ionic strength, dielectric constant, conductivity, and viscosity, have an impact on the zeta potential value (Ansari *et al*., 2021).

Emulsification Time

Dissolution test equipment can be used to measure the emulsification time. The amount of time needed to create a transparent dispersion is called the emulsification time. The amount of oil or surfactant in the SNEDDS recipe determines how long the emulsification process takes (Czajkowska-Košnik *et al*., 2015). According to Nurismawati and Priani (2021), the SNEDDS formula is said to be good if the emulsification time required is less than 2 minutes. The emulsification time characteristics of all the articles studied met the requirements. The results obtained show that the SNEDDS formula containing oleic acid as the oil phase meets the requirements because it can self-emulsify in the time range of 14.26 – 44.82 seconds.

Polydispersity Index (PDI)

The significance of the polydispersity index value lies in its correlation with the nanoemulsion's size homogeneity. More homogeneity in size is indicated by a small polydispersity index value. According to Suciati *et al* (2014), a polydispersity index number above 0.5 suggests that the globule size distribution is non-uniform, whereas a value below 0.5 indicates a good polydispersity index. Based on the article reviewed by Brigatinib SNEDDS has a less uniform globule size with a polydispersity index value of 0.532 (Ansari *et al*., 2021). Astaxanthin SNEDDS (PDI 0.392) (Tungadi *et al*., 2021), Mefenamic acid SNEDDS (PDI 0.469 ± 0.03) (Syukri *et al*., 2020), and Nystatin SNEDDS (Kassem *et al*., 2016) have the polydispersity index value is less than 0.5 so they are categorized as monodisperse. Brigatinib SNEDDS (Ansari *et al*., 2021) and Mefenamic acid SNEDDS (Syukri *et al*., 2020) have the same oleic acid concentration (10%) as an oil phase. According Rusdi (2017) the smaller the surfactant concentration used, the more polydisperse the mixture formed will be and have a higher polydispersity index value, but this is not following the results of the article study where Mefenamic acid SNEDDS (Syukri *et al*., 2020) contains more surfactant, that is Tween 80 with a percentage of 80% compared to the amount of surfactant in Brigatinib SNEDDS (Ansari *et al*., 2021) use Tween as surfactant with percentage 45%.

***In vitro* and *In vivo* Evaluation**

In the article review, several articles did not carry out *in vitro* or *in vivo* evaluation. Overall, SNEDDS which uses oleic acid as the oil phase has a better dissolution and bioavailability profile than market product or

Table 2.In vitro and In vivo Evaluation of Research Articles

Authors	*In vitro* Evaluations	*In vivo* Evaluations
(Ansari *et al*., 2021)	*In vitro* release profile 2 fold higher than suspense Brigatinib SNEDDS has anticancer activity 2 fold higher than Brigatinib solution in buffer phosphate (MTT assays) Dissolution of Brigatinib SNEDDS increased 205 times	-
(Astuti *et al*., 2017)	PGV-0 solubility was 30.57 ± 1.48 mg/mL PGV-0 dissolved at the 45th minute (C45) had a concentration of 82,20%.	-
(Nuari *et al*., 2021)	-	Piroxicam SNEDDS showed % a anti-inflammatory effect significantly higher (42.5 ± 3.4 %) than positive control (11.8 ± 2.6%).
(Liu *et al*., 2018)	The dissolute rate of the Tettrandrine SNEDDS formulation in various dissolution media was remarkably faster than commercial tablets due to the small droplet size.	The Tmax value of Tetrandrine SNEDDS is faster (3.8±1.2 hours) compared to commercial tablets (6.6±1.6 hours) Cmax value Tetrandrine SNEDDS 2 times higher (1234.8±39.7 ng/mL) than commercial tablets (519.3±26.8 ng/mL) with relative bioavailability of 233.3%
(Kassem *et al*., 2016)	Drug release from SNEDDS was 98% after 48 h, whereas drug release from suspension did not exceed 47% after 48 h The ability of Nystatin SNEDDS to kill *C.albicans* bacteria is slower (less than 20 minutes) compared to nystatin suspension in the same dose	On treatment days 5 and 7, the Nystatin SNEDDS formulations effectively reduced the oral burden of Candida albicans compared to the marketed NYS solution.
(Wahyuningsih *et al*., 2019)	-	The total urine excretion volume of the test animal group given Furosemide SNEDDS was greater (2.32 ± 0.10 mL) compared to the urine volume of the test animal group given Furosemide suspension preparation (1.36 ± 0.05 mL) thus indicating that furosemide SNEDDS may increase the diuretic effect of furosemide
(Ke *et al*., 2016)	SNEDDS exhibited a 1.54 times higher drug permeation amount and 0.57 times lower drug excretion amount than that of market tablets at 4 hours. When SNEDDS cyclovirobuxine D was used as a cytotoxic agent on Caco-2 cells, the vitality of the cells was shown to be lower (91.32%±1.57%) in comparison to the market tablets (92.57%±1.26%).	The Cmax a of SNEDDS (224.72± 9.88 ng/mL) were much greater than those obtained from the commercial tablets (108.42±3.79ng/mL) The elimination half-life (t1/2) showed no significant differences between the SNEDDS and commercial tablets. The relative bioavailability of optimized SNEDDS was 200.22%.
(Priani *et al*., 2017)	Glimepiride was completely dissolved within 10 minutes in the form of SNEDDS. The dissolution rate of SNEDDS Glimepiride is higher than the dissolution rate of pure Glimepiride.	-

studies are shown in **Table 2**. In this table explains the *in vitro* and *in vivo* evaluation for each article.

In vitro Evaluation

Brigatinib SNEDDS (Ansari *et al*., 2021) and Nystatin SNEDDS (Kassem *et al*., 2016) were *in vitro* release profiles 2 fold than drug suspension, so they have higher pharmacological activity compared to pure drugs. Likewise, Tetrandrine SNEDDS with the same oleate percentage of 40% has a higher dissolution rate compared to the commercial tablet (Liu *et al*., 2018). Apart from increasing the dissolution rate, the dosage formulation in the form of SNEDDS with oleic acid as the oil phase can increase permease, compared to commercial tablets, SNEDDS showed 0.57 times reduced drug excretion and 1.54 times more drug permeation after 4 hours of cyclovirobuxine D. (Ke *et al*., 2016).

Drug relese from Nystatin SNEDDS was 98% after 48 hours, whereas drug release from suspension did not exceed 47% after 48 h. The ability of Nystatin SNEDDS to kill bacteria is slower than nystatin suspension (Kassem *et al*., 2016). *In vitro*, SNEDDS can increase solubility and drug release, this can increase *in vitro* activity such as the anticancer activity of Brigatnib (Ansari *et al*., 2021) and Cyclovirobuxine D (Ke *et al*., 2016). However, this is contrary to research (Kassem *et al*., 2016) which stated that there was a decrease in the antibacterial activity of SNEDDS Nystatin. Particle size influences the pharmacological activity of a compound. The smaller the particle size, the easier it will spread and increase its pharmacological activity.

***In vivo* Evaluation** Several articles on the formulation of SNEDDS preparations containing oleic acid as the oil phase show increased pharmacological activity. Piroxicam SNEDDS showed a significant increase in the % anti-inflammatory effect, which is 3.6 times higher than the positive control (Nuari *et al*., 2021). Furosemide SNEDDS has better diuretic activity compared to furosemide suspension as indicated by the total urine excretion volume of the test animal group given Furosemide SNEDDS being greater (2.32 ± 0.10 mL) compared to the urine volume of the test animal group given Furosemide suspension (1.36 ± 0.05 mL) (Nuari *et al*., 2021). The pharmacokinetic profile of the SNEDDS preparation formulation in the article studied shows an increase in the Cmax value and relative bioavailability, in addition to that, SNEDDS has a faster Tmax value. In Tetrandrine SNEDDS, the Cmax value is 2 times higher (1234.8 ± 39.7 ng/mL) than commercial tablets (519.3 ± 26.8 ng/mL) with relative bioavailability 233.3%. The Tmax value of Tetrandrine SNEDDS is faster (3.8 ± 1.2 hours) compared to commercial tablets (6.6±1.6 hours) (Liu *et al*., 2018). Similarly, in the in vivo test, the Cmax value of SNEDDS cyclovirobuxine D (224.72± 9.88 ng/mL) was significantly higher than that of the market tablets in the experimental animals, specifically in rabbits (108.42±3.79 ng/mL). The relative bioavailability of optimised SNEDDS was 200.22% when compared to commercial tablets (Ke *et al*., 2016). In the *in vivo*, SNEDDS preparations using oleic acid as the oil phase have better activity and pharmacokinetic profiles compared to drug suspensions or commercial products.

CONCLUSIONS

From the literature review articles, there are not many articles that use oleic acid as the oil phase in SNEDDS liquid formulations. Most of the SNEDDS developments are applied in the formulation of natural ingredients as active substances. SNEDDS which uses oleic acid as the oil phase produces droplet sizes of 19.75-190.03 nm

with a polydispersity index of 0.278-0.532. Zeta potentials value, only 2 articles have a zeta potentials value in a value above +/-30, that is Mefenamic Acid SNEDDS and Furosemide SNEDDS. Most SNEDDS in the reviewed articles have a transmittance percentage of >95%. In the article review, several articles did not carry out *in vitro* or *in vivo* evaluation. Overall, SNEDDS which uses oleic acid as the oil phase has a better dissolution and bioavailability profile compared to the commercial product or the pure drug. If solubility and bioavailability increase, it can increase the pharmacological activity of the drugs.

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References

Aisy, Z. H. R., Puspita, O. E., and Shalas, A. F. 2021. Optimasi formula nanoemulsi nifedipin dengan metode self-nanoemulsifying drug delivery system (snedds). Pharmaceutical Journal of Indonesia, 6(2), pp.85–95.

Ali, H. H., and Hussein, A. A. 2017. Oral nanoemulsions of candesartan cilexetil: formulation, characterization and in vitro drug release studies. Aaps Open, 3(1), pp.1–16.

Alothaid, H., Aldughaim, M. S., Yusuf, A. O., Yezdani, U., Alhazmi, A., Habibullah, M. M., and Khan, M. G. 2021. A comprehensive study of the basic formulation of supersaturated self-nanoemulsifying drug delivery systems (snedds) of albendazolum. Drug Delivery, 28(1), pp.2119–2126.

Ansari, M. J., Alnakhli, M., Al-Otaibi, T., Meanazel, O. Al, Anwer, M. K., Ahmed, M. M., Alshahrani, S. M., Alshetaili, A., Aldawsari, M. F., Alalaiwe, A. S., Alanazi, A. Z., Zahrani, M. A., and Ahmad, N. 2021. Formulation and evaluation of self-nanoemulsifying drug delivery system of brigatinib: improvement of solubility, in vitro release, ex-vivo permeation and anticancer activity. Journal of Drug Delivery Science and Technology, 61, 102204.

Astuti, I. Y., Marchaban, M., Martien, R., and Nugroho, A. E. 2017. Design and optimization of self nano-emulsifying drug delivery system containing a new anti-inflammatory agent pentagamavunon-0. Indonesian Journal of Chemistry, 17(3), pp.365–375.

Beg, S., Jain, S., Kushwah, V., Bhatti, G. K., Sandhu, P. S., Katare, O. P., and Singh, B. 2017. Novel surface-engineered solid lipid nanoparticles of rosuvastatin calcium for low-density lipoprotein-receptor targeting: a quality by design-driven perspective. Nanomedicine, 12(4), pp.333–356.

Bhikshapathi, D. V. R. N., and Priya, K. (2018). Development and in vivo Evaluation Lovastatin by Self-Nanoemulsifying Drug Delivery System. International Journal of Pharmaceutical Sciences and Drug Research, 10(03), pp.165–172.

Czajkowska-Košnik, A., Szekalska, M., Amelian, A., Szymańska, E., and Winnicka, K. 2015. Development and evaluation of liquid and solid self-emulsifying drug delivery systems for atorvastatin. Molecules, 20(12), pp.21010–21022.

Date, A. A., Desai, N., Dixit, R., and Nagarsenker, M. 2010. Self-nanoemulsifying drug

delivery systems: formulation insights, applications and advances. Nanomedicine, 5(10), pp.1595–1616.

Hashem, F. M., Al-Sawahli, M. M., Nasr, M., and Ahmed, O. A. A. 2015. Custom fractional factorial designs to develop atorvastatin self-nanoemulsifying and nanosuspension delivery systems--enhancement of oral bioavailability. Drug Design, Development and Therapy, 9, pp.3141–3152.

Kassem, A. A., Mohsen, A. M., Ahmed, R. S., and Essam, T. M. 2016. Self-nanoemulsifying drug delivery system (snedds) with enhanced solubilization of nystatin for treatment of oral candidiasis: design, optimization, in vitro and in vivo evaluation. Journal of Molecular Liquids, 218, pp. 219–232.

Ke, Z., Hou, X., and Jia, X. bin. 2016. Design and optimization of self-nanoemulsifying drug delivery systems for improved bioavailability of cyclovirobuxine D. Drug Design, Development and Therapy, 10, pp.2049–2060.

Larsen, A. T., Ohlsson, A. G., Polentarutti, B., Barker, R. A., Phillips, A. R., Abu-Rmaileh, R., Dickinson, P. A., Abrahamsson, B., Østergaard, J., and Müllertz, A. 2013. Oral bioavailability of cinnarizine in dogs: relation to snedds droplet size, drug solubility and in vitro precipitation. European Journal of Pharmaceutical Sciences, 48(1–2), pp.339–350.

Leong, T. S. H., Wooster, T. J., Kentish, S. E., and Ashokkumar, M. 2009. Minimising oil droplet size using ultrasonic emulsification. Ultrasonics Sonochemistry, 16(6), pp.721–727.

Li, F., Song, S., Guo, Y., Zhao, Q., Zhang, X., Pan, W., and Yang, X. 2015. Preparation and pharmacokinetics evaluation of oral self-emulsifying system for poorly water-soluble drug Lornoxicam. Drug Delivery, 22(4), pp.487–498.

Liu, C., Lv, L., Guo, W., Mo, L., Huang, Y., Li, G., and Huang, X. 2018. Self-nanoemulsifying drug delivery system of tetrandrine for improved bioavailability: physicochemical characterization and pharmacokinetic study. BioMed Research International, pp.1-10

Listyorini, N.M.D., Wijayanti, N.I.P.D., and Astuti, K.W. Optimasi pembuatan nanoemulsi virgin coconut oil. Jurnal Kimia, 12(1), pp.8-12.

Michaelsen, M. H., Siqueira Jørgensen, S. D., Abdi, I. M., Wasan, K. M., Rades, T., and Müllertz, A. 2019. Fenofibrate oral absorption from SNEDDS and super-SNEDDS is not significantly affected by lipase inhibition in rats. European Journal of Pharmaceutics and Biopharmaceutics, 142, pp. 258–264.

Mora, E., Emrizal Emrizal, and Selpas, N. 2013. Isolasi dan karakterisasi asam oleat dari kulit buah kelapa sawit (Elais guinensis Jacq.). Jurnal Penelitian Farmasi Indonesia, 1(2), pp.47–51.

Nuari, Y. R., Wahyuningsih, I., and Prabawati, S. 2021. Self-Nanoemulsifying Drug Delivery System (SNEDDS) of piroxicam. Pharmaciana, 11(2), pp.185.

Nurismawati, D. A., and Priani, S. E. 2021. Kajian formulasi dan karakterisasi self-nanoemulsifying drug delivery system (SNEDDS) sebagai penghantar agen antihiperlipidemia Oral. Jurnal Riset Farmasi, 114–123.

Pouton, C. W., and Porter, C. J. H. 2008. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Advanced Drug Delivery Reviews,

60(6), pp.625–637.

Priani, S. E., Nurrayyan, N., and Darusman, F. 2017. Formulation self nano emulsifying drug delivery system glimepiride using oleic acid as oil phase. Pharmaciana, 7(2), pp.267.

Rusdi, M. 2017. Karakteristik ukuran partikel dan indeks polidispersitas formulasi nanoemulsi pewarna alam ekstrak kayu secang. Jurnal Pertanian Terpadu, 5(2) pp.114-127

Sadurní, N., Solans, C., Azemar, N., and García-Celma, M. J. 2005. Studies on the formation of O/W nano-emulsions, by low-energy emulsification methods, suitable for pharmaceutical applications. European Journal of Pharmaceutical Sciences, 26(5), pp.438–445.

Suciati, T., Aliyandi, A., and Satrialdi. 2014. Development of transdermal nanoemulsion formulation for simultaneous delivery of protein vaccine and artin-m adjuvant. International Journal of Pharmacy and Pharmaceutical Sciences, 6(6), pp.536–546.

Syukri, Y., Nugroho, B. H., and Istanti, I.2020. Penggunaan D-optimal mixture design untuk optimasi dan formulasi self-nano emulsifying drug delivery system (SNEEDS) asam mefenamat. Jurnal Sains Farmasi and Klinis, 7(3), pp.180.

Tungadi, R., Thomas, N. A., and Gobel, W. G. Van. 2021. Formulasi, karakterisasi, dan evaluasi drops liquid self nano-emulsifying drug delivery system (snedds) astaxanthin. Indonesian Journal of Pharmaceutical Education, 1(3), pp.168–178.

Villar, A.M.S., Naveros, B.C., Campmany, A.C.C., Trenchs, M.A., Rocabert, C.B., and Bellowa, L.H.2012. Design and optimization of self-nanoemulsifying drug delivery systems (SNEDDS) for enhanced dissolution of gemfibrozil. International Journal of Pharmaceutics. 431, pp.161-175.

Wahyuningsih, S. I., Yuswanto, A., and Martien, R. 2019. Aktivitas diuretik self-nanoemulsifying drug delivery system (snedds) furosemid diuretic activity of a self-nanoemulsifying drug delivery system (snedds) of furosemide. Farmasains, 4(1), pp.33-38.

Zhang, N., Zhang, F., Xu, S., Yun, K., Wu, W., and Pan, W. 2020. Formulation and evaluation of luteolin supersaturatable self-nanoemulsifying drug delivery system (S-SNEDDS) for enhanced oral bioavailability. Journal of Drug Delivery Science and Technology.58.