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Formulation and Characterization Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) of Ethanolic Extract of Rambutan (*Nephelium lappaceum* l.) Leaves

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Abstract

Rambutan (*Nephelium lappaceum l.)*, especially the leaf part, contains large quantity of secondary metabolites, such as flavonoid, tannin, and quercetin. Oral administration is considered the most convenient route for medicines. However, several studies reported the lack of absorption rate of the extract when it is given orally. To increase its bioavailability, a strategy is required and SNEDDs (Self Nanoemulsifying Drug Delivery Systems) emerges to answer the challenge by facilitating the less water-soluble substances and alleviates its potential to permeate through lipid system of the body tissue. Therefore, the aim of the study is to formulate and characterization the SNEDDs of ethanolic extract of Rambutan leaves. The Rambutan leaves was extracted using 70% ethanol as solvent through maceration continued by rotary evaporation and freeze-dried. The solubility test for premixture concentrate (Smix) suggested Caprylic Acid/Capryol® 90 as oil phase, Tween® 80/Cremophor® RH-40 as surfactant and Propylene Glycol/PEG-400 as co-surfactant. The formulas were evaluated for its visual appearance, droplets particle size, Z-potential, and physiochemical stability. Extract yield reached 7,85%. Only Formula F1 (Caprylic Acid, Tween® 80, Propylene Glycol/PEG-400) and F6 (Capryol® 90, Cremophor® RH-40, Propylene Glycol/PEG-400) have met the standard size of SNEDDs particle (23,86 and 43,62 nm). Zeta potential measurement for Formula F1 and F6 were within the range of negative charge (-7,381 and -9,822 mV). Stability test demonstrated homogenous appearance without phase separation.

Keywords: Characterization; Nanoemulsion; *Nephelium lappaceum* l.; Rambutan leaves, SNEDDs.

INTRODUCTION

Indonesia possesses wide range of ethnomedicinal resources, from plants to marines. Most of them have been studied thoroughly, especially to identify the possible advantages for medicinal purpose (Putra et al., 2023). Rambutan (*Nephelium lappaceum l.)* fruit is one of the infamous ethnical plants with unique taste and appearance. Rambutan is a tropical plant belonging to the *Sapindaceae* family and the genus *Nephelium*. This plant is widely found and cultivated in Southeast Asia, particularly Indonesia and Malaysia, and is widely distributed in various regions of Indonesia, including Sumatra, Java, and Kalimantan (Purba et al., 2023). Other body parts such as its skin, stems, roots and leaves have also been used for empirical purpose but it is limited due to various factors (Luh Komang Wahyuni & Putu Eka Leliqia, 2023a; Tingting et al., 2022). Preliminary studies suggest vast potential benefits for the leaves part since it may serve property as antioxidant, antibiotics, and anti-hyperglycemia (de Santana Santos et al., 2021). The ability to provide ailments for disease treatments are majority due to their important secondary metabolites, such as saponin, alkaloid, monoterpene, sesquiterpene, quinone, polyphenol, terpenoid, flavonoid and tannin (Karim et al., 2023; Luh Komang Wahyuni & Putu Eka Leliqia, 2023b). Flavonoid, for example, delivers scavenging system for antioxidant property in particular mechanism by preventing further cellular injury due to the formation of reactive oxygen species (ROS) in precise concentration (Álvarez-Valverde et al., 2024; Jantapaso & Mittraparp-Arthorn, 2022; Mistriyani et al., 2018). The flavonoid compound that is abundant in rambutan leaves is quercetin. Quercetin has semipolar properties because it contains five hydroxyl groups (-OH) which provide polar properties and aromatic benzene rings which are arranged to provide nonpolar properties. The conjugated bond system in the quercetin compound gives it lipophilic properties so that quercetin

is neither very polar nor nonpolar (Magar & Sohng, 2020).

Many experiments that focus on in-vitro experiments suggested major activities of Rambutan leaves in inducing immune capacity to triggering cell inhibition (Hidayah Base et al., 2018; Ratna et al., 2018; Rizkita, Ariani, et al., 2024; Sukatta et al., 2021). Emphasize the available preclinical studies even further to in-vivo and clinical experiments should be carried out carefully, especially optimizing the formulation (Algharably et al., 2022). The natural and origin state of flavonoid and other typical semi-polar metabolites create a classic barrier of challenge during oral administration due to its poor bioavailability (Arshad et al., 2024). With large quantities of lipid bilayer system across the body tissue, the strategy to overcome the problem is mandatory prior examining the pharmacology effect. The answer centers on how the active ingredients are delivered safely to systemic circulation by formulating the optimal carrier system (Patra et al., 2018; Rizkita, Putri, et al., 2024; Sercombe et al., 2015).

Robust drug delivery system research helps to resolve the main issue in regards low absorption rate of certain substances. Various known strategies, from polymer to lipid-based delivery system, are largely studied not only to facilitate conventional medicines but also traditional plants extract. Lipid-based delivery system including liposomes, phytosomes (phytosomes), niosomes, transferosomes, ethosomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), nanoemulsions, microemulsions, self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), and self-nanoemulsifying drug delivery system (SNEEDS) is mostly selected to navigate non-polar compounds since it allows interaction without electrostatic process (Pandey et al., 2021; Sriwidodo et al., 2022; Yokota & Tokudome, 2017). Histologically, human body also provide better permeation for lipid-based molecules. Thus, it creates greater plasma concentration and sustained releasing speed in the circulation (Rizkita, Putri, et al., 2024). Although most of the biological compounds found in natural products could maintain its stability once it interacts with body system, the effective period for it to hold the therapeutic capacity is usually less sufficient and incompatible when it must be encapsulated for oral administration (Pratiwi et al., 2018). Among all the available lipid-based delivery system, SNEDDs relieve the obstacles by allowing efficient drug transport through most of the biological membranes. Technically, to obtain optimum SNEDDs formula, the soluble pre-concentrate is required prior mixture it with the active compounds. Then, a few drops of premixture concentrate (Smix) are exposed to the water and it should rapidly generate clear oil-in-water emulsions in nano-size (20-100 nm) (Shrirang et al., 2026a). Several studies have confirmed how SNEDDs formulation could stabilize the physiochemical characters of the extracts within and mediates higher absorption uptakes in the gastrointestinal tracts (Yandi Syukri et al., 2025).

By utilising the various advantages of SNEDDS, such as the spontaneous formation of nanoemulsions within the gastrointestinal tract, a significant increase in solubility, protection of active compounds from degradation by extreme pH levels and digestive enzymes, and enhanced absorption via the lymphatic pathway (Priani et al., 2025). Therefore, this study aims to develop the formulation of ethanolic extract of Rambutan (*Nephelium lappaceum l.*) leaves in SNEDDs, characterization of the SNEDDs particle, and confirming the formula stability.

MATERIALS AND METHODS

Study Design

This study was a semi-quantitative research performed by analyzing the optimal formula based on several predictors, such as visual appearance, solubility and stability. Then, the obtained formulas were characterized by measuring the particle size, particle size distribution and zeta potential. Experiments were conducted in Laboratorium Penelitian Terpadu dan Pengujian (LPTP) Fakultas Farmasi dan Laboratorium Farmakologi Fakultas Kedokteran, Universitas Ahmad Dahlan starting from February to July 2026.

Materials

The primary material in this study was dried Rambutan (*Nephelium lappaceum l.)* collected from the Special Region of Yogyakarta. The Smix used were olive oil, corn oil, sunflower oil, virgin coconut oil (VCO), isopropyl myristate, oleic acid, Capryol® 90 (Gattefosse), Caprylic Acid (Oleokimia), Cremophor® RH 40 (BASF), Tween® 20 (Labotiq), Tween® 80 (Labotiq), polyethylene glycol 400 (PEG-400), glycerin, propylene glycol. Other materials include: (1) Solvents and chemicals: 70% pure ethanol, NaCl, distilled water, (2) Equipments: Grinder (Orion), maceration apparatus, rotary evaporator (Heidolph), water bath (Memmert), oven (Memmert), autoclave (GEA), vortex (Thermo Scientific), Freeze-dryer (Buchi), Particle Size Analyzer (Malvern Zetasizer Instrument), Benchtop Centrifuge (Hettich EBA 200), Freezer (GEA) and various laboratory glassware and consumables.

Sample preparation

Rambutan leaves procurement

Rambutan leaves were collected from mature plants in Special Region of Yogyakarta, Indonesia. The healthy and undamaged leaves were hand-picked and separated from its stem branch. The collection process was repeated until the raw weight of leaves reached at least 3 kg. Then, all leaves were washed with flowing stilled water until the impurities were removed. The cleaned and

fresh leaves were dried at room temperature to preserve the active compounds. The drying process last for at least 48 hours to reduce the moisture and continued by oven-drying for 24 hours preserved at temperature at 40ºC. Oven drying produces extracts with higher flavonoid content than sun-drying. Dried leaves were stored in air-tight and light-resistant container (Lestari et al., 2023; Rizkita, Ariani, et al., 2024).

Extraction of Rambutan leaves

The dried leaves were then separated from the veins and put in a grinder until it formed simplicia. Simplicia was sieved with 100 mesh to obtain a homogeneous particle size. The simplicia powder was macerated, with a ratio of ingredients and solvent 1:10 (w/v). To obtain a thick extract from rambutan leaves, several extraction methods could be applied. In research conducted by Tambunan et al. (2024), the maceration followed by evaporation process was considered the suitable method to gain thick rambutan leaf extract (Mistryanto Tambunan et al., 2024). A total of 200 mg of simplicia was weighed and then soaked in 2 liters of 70% ethanol. The soaking process lasted for 24 hours. After 24 hours, the maceration results were filtered using Whattman 0.1 paper and continued with the evaporation process using a rotatory evaporator with a rotation speed of 100 rpm and a temperature of 50°C. The thick extract that has been evaporated was heated furtherly using a water bath at a temperature of 50°C for 4 hours. (Ratna et al., 2018; Tingting et al., 2022). Extract yield was calculated to determine the percentage of thick extract obtained by measuring the ratio between the weight of the extract obtained to the dry weight of simplicia, expressed in percentage (%) (Ahsan et al., 2018; Taiyeb et al., 2024). To reduce the large amount of water content resulting from the use of 30% ethanol solvent, the thick rambutan leaf extract that has been made was freeze-dried. The freeze-dried solid extract is filtered using a mesh filter to form a solid powder (Shofian et al., 2011; Vareltzis et al., 2023).

SNEDDs formulation

Selection of SNEDDs component and solubility test

Solubility test was performed to select the material with the highest solubility for the active ingredient. At this stage, the solubility testing process uses all components in the SNEDDs without the active ingredient first (Hernawan Nugroho et al., 2017). SNEDDs premixture concentrate (Smix) consist mainly of oil phase, surfactant and co-surfactant. The oil phase used in this study included olive oil, corn oil, sunflower oil, virgin coconut oil (VCO), isopropyl myristate, oleic acid, caprylic acid, and Capryol® 90. The surfactants employed were Tween® 20, Tween® 80, and Cremophor® RH 40, while the co-surfactants consisted of PEG 400, glycerin, and propylene glycol. Emulsification ability between each oil phase and surfactant was observed by mixing them with ratio 1:1. To obtain optimal dissolving appearance, gentle shaking was given to each vials. The similar process applied between the surfactant and co-surfactant with ratio 2:1. For best optical clarity, set alone the vials for 2 hours and observed the dispersion (Mustika et al., 2019).

Premixture concentrate (Smix) formulation

The SNEDDS mixture that exhibited the highest drug solubility in the solubility study was selected as the optimal Smix for subsequent formulation procedures. 30 mg of solid thick extract of Rambutan leaves was added in each vial of selected premixture formulas. Various SNEDDS formulations were developed by varying the proportions of oil (25–70% w/w), surfactant (30–75% w/w), and co-surfactant (0–25% w/w) (Mustika et al., 2019). The composition of the formula is shown in Table 1. Each formula mixture was homogenised by vortexing it for five minutes, then sonicating it for fifteen minutes and conditioning it in a water bath at 40ºC for ten minutes (Suryani et al., 2019). The best possible combination of oil, surfactant, and co-surfactant was used to formulate SNEDDS of Rambutan leaf extract.

Table 1. The Composition of SNEDDs Formula.

Extract (mg)	The Oil Phase (ml)	Surfactants (ml)	Co-surfactants (ml)
30	1	2	2
30	2	2	1
30	3	1	1
30	2	1	2
30	1	3	1

SNEDDs dosage formulation

The chosen Smix formula that contained 30 mg of Rambutan leaves extract was added into the distilled water until it formed self-emulsification. For better dissolution, vortex could be applied for at least 1 minute on 3000 rpm. The Rambutan leaves extract-loaded SNEDDs were kept in tightly closed glass vial at room temperature for further analysis. The freshly created nanoemulsions underwent visual analysis. Oil-water nanoemulsions, which are transparent and have a great flow-like nanoemulsion (N.E.), make up the initial phase. Microemulsion (M.E.), a translucent solution with a somewhat medium flow, is the second phase. The third phase, known as emulsion (E), is a milky solution with good flow, and the last phase, known as emulgel (M), is a milky gel with good flow. The grading system score could also be applied to determine the self-emulsification by naked eye examination (Table 2) (Mohite et al., 2024).

Table 2. Dispersibility grading system.

Grade	Observation	Time
A	Transparent or bluish appearance	Rapid formation (less than 1 minute)
B	Less transparent, bluish-white appearance	Rapidly forming (less than 1 minute)
C	Fine white milkfish avant-grade emulsion	Within 2 minutes
D	Greyish white emulsion	Slow to emulsification process
E	Large globules of oil are visible on the surface	Slow to emulsification process

Adapted from (Mohite et al., 2024)

Characterization of SNEDDs

A Malvern Zetasizer Instrument was used to assess globule size (nm), polydispersity index, zeta potential (mV), and percent transmittance (%) in mixtures that did not undergo phase separation (Dewi et al., 2025). The particle size distribution of the formulation was determined using dynamic light scattering (DLS) which measures the hydrodynamic diameter of particles based on fluctuations in light scattering caused by their Brownian motion. All measurements were performed in triplicate at 25 °C using sterile disposable cuvettes. The zeta potential was measured by electrophoretic light scattering (ELS), a technique that determines the surface charge of particles by monitoring their electrophoretic mobility under an applied electric field. Zeta potential values were used to assess the physical stability of the formulation, with higher absolute values indicating greater stability. The obtained data were analyzed using Zetasizer software, and the results were expressed as the mean particle size, polydispersity index (PDI), and zeta potential, along with their corresponding standard deviations (Sapra et al., 2026).

Stability Test

Thermodynamic stability tests included centrifugation, heat-cold cycles, and freeze-thaw cycles. The formula was centrifuged at 5000 rpm for 30 minutes (Pratiwi et al., 2018). Heat and cooling cycles were carried out in three cycles at temperatures ranging from 4°C to 45°C with a minimum storage duration of 48 hours. Freeze-thaw cycle tests were carried out in three freeze-thaw cycles at temperatures between -20°C and +25°C with storage at each temperature for at least 48 hours, followed by centrifugation for 15 minutes at 3500 rpm (Asita et al., 2024).

RESULTS AND DISCUSSION

Result

Extraction yield

The exact extract yield produced from 200 g simplicia was 15,7 g. The simplicia was macerated for 24 hours in room temperature and regular stir in every 6 hours in 70% ethanolic solvent. From 2 liters of evaporated and water-bathed liquid extract, approximately 72 ml of thick extract was produced. Thus, it made the extract yield reached 7,85%. Series of extraction process was conducted in several batches. The thick extract exhibited a deep green to dark brownish-black color with a distinctive leafy aroma.

A total of 27 grams of thick extract was made into solid freeze-dried form and shrinkage of the extract occurred. The extract in solid form after freeze-dried was filtered using 200 mesh and produced a final total of 16.8 grams of solid powder extract. Apart from reducing water content to the maximum, the freeze-dried method is also useful for maintaining the levels of secondary metabolites contained in crude plant extracts. In general, freeze-dried is widely used for drying and preserving foods such as fruit and vegetables. Research conducted by Shofian, et al (2011) and Vareltzis et al (2023) shows that carrots and oregano leaves processed using the freeze-dried method can maintain the content of antioxidant compounds in them, such as beta-carotene, phenolic compounds, etc (Shofian et al., 2011; Vareltzis et al., 2023).

Rambutan leaves extract dosage determination

The solubility test results of the crude extract of rambutan leaves show that the maximum weight of the extract that can be dissolved in the solvent (1 ml propylene glycol) is 30 mg. Thus, the weight of the extract used for the SNEDDS formulation was not exceed 30 mg to prevent insolubility. A study conducted by Fidrianny, et al (2015) by testing the ethanol extract of rambutan leaves from five different varieties showed that 50 µg/mL ethanol leaf extract from five rambutan varieties (rapiah rambutan, rajah rambutan, binjai rambutan, lebak bulus rambutan and non-consumable rambutan) which was reacted with 50 µg/mL DPPH solution provided a scavenging capacity for antioxidants of 93.18%, respectively. 93.04%, 94.63%, 92.21%, 91.70% (Fidrianny & Sukowati, 2015). Using the assumption that a dose of 5-10% ethanol extract of rambutan leaves has an antioxidant effect, then 1-2 mg of the extract that undergoes emulsification at the end (in 5.7 ml of water) is sufficient to provide an antioxidant effect.

Thus, the concentration ratio of Rambutan leaves extract loaded-SNEDDS: water is as follows (Table 3):

Table 3. SNEEDs formulation ratio.

Smix (ml)	Water (ml)	Total Volume (ml)
0,3	5,7	6

Solubility test of Smix components

Rambutan leaf extract in 70% ethanol solvent was proven to be classified as a semi-polar extract. When dissolved in distilled water as the most polar solvent, the extract still shows debris. When the extract is dissolved in a long chain oil such as sunflower oil, clear debris appears at the bottom of the vial. This indicates that the extract produced in this research is a semi-polar extract. Solubility testing was carried out on several components in the SNEDDs pre-mix and it was found that the extract could dissolve well in the propylene glycol (Figure 1). After thorough observation and Smix solubility analysis, the optimal oil phase to enable steady and stable formula physically were Capryol® 90 and Caprylic Acid. No phase separation appeared after 48 hours leaving in glass vial in room temperature. The mixture also could maintain the formulation consistency when it was exposed with the Rambutan leaves extract. This finding was also relevant with study reported by Ghiffari, et al. (2025) that mentioned how the n-hexane fraction of *Pandanus odorifer* unable to dissolve to form SNEDDs molecule. It implied that the SNEDDs formula could allow self-emulsification with semipolar to polar extract (Ghiffari et al., 2025).



Figure 1. Appearance of ethanolic extract of rambutan leaves with propylene glycol

Rambutan leaves extract loaded-SNEDDs formula

The solubility test suggested ten different formula (F1, F2, F3, F4, F5, F5, F6, F7, F8, F9, F10) for further analysis. Formula F1 to F5 mixture consist of Caprylic Acid, Tween® 80 and propylene glycol/PEG-400, while formula F6-F10 combined Capryol® 90, Cremophor®-RH40 and propylene glycol/PEG-400. All Smix formulas tested had good solubility (Figure 2). Then, self-emulsification could be observed after giving a few drops (0,3 ml) of Smix in 5,7 ml of distilled water (Figure 3). The final SNEDDs results showed that formula F1 and F6 created optimum optical clarity without forming debris at the bottom of the vial. Meanwhile, F2, F3, F4, F7, F8, F9 looked cloudy with typical milky solution appearance. Formulas F5 and F10 formed a bright yellowish emulgel and fell to the bottom of the vial. This was possibly caused by the emulsification process occurring too quickly after interacting with water molecules. Thus, the optimal SNEDDs formula was F1 and F6 based on physical appearance.

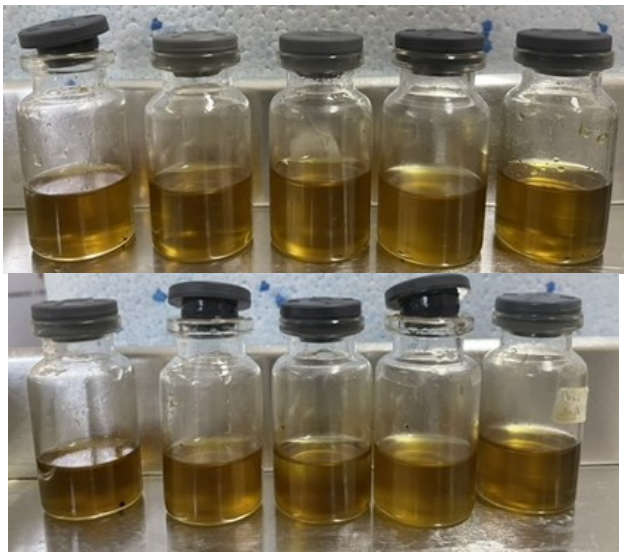


Figure 2. Smix formula, from left to right (formula F1 to F10)



Figure 3. Self-emulsification appearance after dripping the Smix to the distilled water, from left to right (formula F1 to F10)

SNEDDs characterization

SNEDDs characterization was carried out by assessing the particle size, polydispersity index (PI) and zeta potential of the candidate formulas that showed a clear appearance (formula F1 and F6), as shown in Table 4. The particle size distribution curve for formula F1 (Figure 4) showed 2 peaks with details of 50% (D50) of particles having a size smaller than 24.13 and 90% of particles having a size smaller than 526.9 nm. This could be caused by slight droplet aggregation, incomplete emulsification or the presence of a large droplet population. This event can affect the stability of the formulation (Shrirang et al., 2026b). However, the PI from the F1 formula shows a value of 0.283, which

indicates that the size distribution is still quite good and is still within generally accepted limits. Thus, for formula F1, the majority of SNEDDS droplets are at nano size (indicated by D50 of 24.13 nm and PDI of 0.283 which is still within the homogeneous limit). PDI value less than 0.3 indicated that the droplet size distribution was relatively homogeneous, in which the nanoemulsion formation process was well performed. A narrow size distribution was a desirable characteristic in SNEDDS formulations because it contributed to the physical stability and consistency of the system (Danaei et al., 2018; Ghiffari et al., 2025). Zeta potential formula F1 which showed a value of -9.822 mV indicated that the SNEDDS droplet has a negative surface charge, but the charge is still relatively low. This value shows that the droplet has a negative charge with a relatively low charge (Arshad et al., 2024).

Table 4. Physical characteristics and compositions of all SNEDDS formulations loaded with extract from Rambutan leaves.

Formulation	Oil	Surfactant	Co-surfactant	Z-ave (nm)	Zeta potential (mV)	PDI	Appearance
F1	Caprylic acid	Tween® 80	Propylene glycol/PEG 400	23,88	−9.822	0.283	Clear
F6	Capryol® 90	Cremophor® RH-40	Propylene glycol/PEG 400	41,44	−7.382	0.15	Clear

Formula F6 showed more stable particles. The particle size distribution looked more homogeneous with the presence of a single peak (Figure 5). A total of 10% of particles have a size of <26.1 nm, 50% of particles have a size of <43.82 nm and 90% of particles have a size of <76.56 nm. The median particle value is <100 nm, indicating that all particles are at nanometer size. The polydispersity index of formula F6 was 0.15, indicating the same level of uniformity in particle size distribution as observed for formulation F1. The zeta potential of formulation F6 was slightly lower than that of formulation F1, with a value of −7.382 mV.

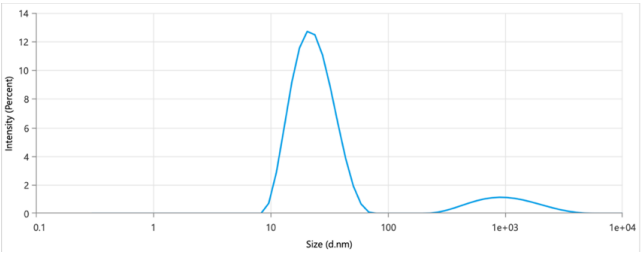


Figure 4. Distribution of particle size of formula F1

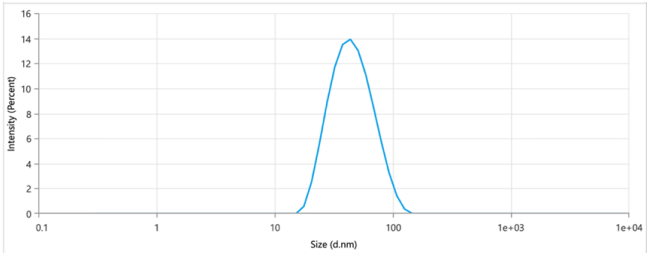


Figure 5. Distribution of particle size of formula F6.

Stability performance of Rambutan leaves extract-loaded SNEDDs

Stability of formulas F1 and F6 were carried out by centrifugation and hot cold cycles. By using a centrifuge set at a speed of 5000 rpm for 30 minutes, there was no phase separation, creaming or cracking. However, minimal sedimentation was found at the bottom of the tube (Figure 6). The test was continued using two different conditions, 4°C and 40°C for 48 hours each and repeated for 6 cycles. The formula sample was then continued with a freeze-thaw test, namely by running six freezing and thawing cycles using a temperature range of -21°C to 25°C, with a storage duration of 48 hours in each cycle. From the results of the temperature stability test, it was found that there was no phase separation, creaming or cracking. The physical appearance is still the same as after centrifugation.



Figure 6. Post physiochemical stability test of formula F1 (left) and F6 (right).

Discussion

Significant debris could be found at the base of glass vial during solubility test of premix with the solid form of extract. Although the extract size had been minimized by reducing the water content and 200-mesh filtering process, the visible insoluble molecules were prominently formed. Furtherly, when the extract met water as the highest polarity substance, the similar phenomena also occurred. This finding indicated the extract was majorly constructed as semi-polar. After mixing the extract with premix that contained propylene glycol as co-solvent, immediate dissolution was developed. The use of propylene glycol as a co-surfactant has been widely investigated in various studies related to SNEDDs. Propylene glycol is often chosen as a solvent for bioactive compounds in extracts because it has a proven and wide safety range, including for cosmetic, pharmaceutical and food grade preparations. In addition, it emerges a greater biocompatibility. Chemically,

propylene glycol has been widely used to dissolve compounds such as polar and semi-polar phytochemicals such as phenolic compounds. Propylene glycol as an additional surfactant can reduce interfacial tension so that the system has sufficient flexibility to form nanoemulsions with larger compositions (Ermawati et al., 2020; Myo et al., 2025). In addition, propylene glycol can increase the solubility of lipophilic compounds and is classified as an ideal option for the formulation of drug dosage forms to increase the solubility of this class of drugs (Dewi et al., 2025; Sapra et al., 2026).

This study chose Tween® 80 and Cremophor as surfactants and propylene glycol/PEG400 as co-surfactant because many studies reported good solubility levels for both. The solubility test also revealed both components produce better clearance and dissolution. Tween 80 could dissolve more oil, thus it may emit better nanoemulsion system. Furthermore, Tween 80 is considered as a solubilizing agent due to the lipophilic properties so it could mix with oil and has HLB 15 which is stable to form an oil-in-water (o/w) type emulsion (Nirmalayanti, 2021; Tresia Pramasta Diva et al., 2023). Cremophor® RH40 was also included in the premix composition as surfactant since it had HLB range 14-16. Thus, it would increase the efficiency of nano-emulsification directly (spontaneous nanoemulsification) and had the ability to maintain the nanoemulsions stability when stored for a long time (months). The addition of surfactants in the formulation would reduce the surface tension between particles, resulting in small particle sizes. Good combinations between suitable surfactant and co-surfactant may benefit with the globule formed in the water phase. According the study finding, both formula F1 and F6 interacted well inside the water by giving clear solution appearance. However, the ratio of each Smix composition was responsible for the clarity view. Ideally, the designated ranges for oil (10–50%), surfactant (30–70%), and cosurfactant (20–60%) (Dewi et al., 2025). This study also applied the similar theory and revealed less oil mixture within the Smix may design better stability. The use of surfactants had been proven to reduce the particle size of nanoemulsions formed due to the stabilization of oil droplets produced as a result of the o/w interface of surfactant molecules, and the use of co-surfactants (Christian et al., 2023). PEG 400 is a medium-chain hydrocarbon that can be placed between the gaps of the nanoemulsion system by forming hydrogen chains so that it could maximize the emulsification process during nanoemulsion assembly. Propylene glycol could penetrate the surface of the monomer effectively and helped to solubilize hydrophilic surfactants or drugs in oil bases. The combination of PEG 400 with propylene glycol as a cosurfactant furtherly increased the stability of oil droplet shape in the air and reduced interfacial tension. The oils used in the study were Capryol® 90 and Caprylic Acid. Both are the medium-chain fatty acids. The use of Capryol® 90 has been widely used as the oil phase for SNEDDs and is considered a good solvent for compounds that have less solubility in air (e.g., semi-polar) (Fitria et al., 2021; Putri, 2024).

Through dynamic light scatter projection, Formula F1 exhibited two peaks due to less homogenous SNEDDs particle dispersion. It could be caused by slight droplet aggregation, incomplete emulsification or the presence of a large droplet population formulation (Shrirang et al., 2026b). The first taller peak was still in range <100 nm, meaning most particles were still around in nano-scale size. However, the other peak with lowest altitude (526.9 nm) may indicate the presence of a small portion of larger droplets which causes the size distribution to widen. This condition was most likely induced by some droplet aggregation or the self-emulsification process which has not completely produced uniform droplet sizes. More homogenous dispersity index was presented in formula F6. Particularly for the formulations with a high ratio of Smix, which showed a PDI value of less than 0.2, suggesting the uniformity of the particle size, the PDI values of these formulations were less than or roughly 0.4. These formulas are offered as unambiguous fixes (Morakul et al., 2024). The larger particle analyzed not more than 80 nm. Thus, formula F6 could be projected as the finest formula compared to formula F1. All optimal formula (F1 and F6) performed less than ±30 mV but within the range of weak loading capacity. In electrostatically stabilized dispersion systems, zeta potential values greater than ±30 mV generally indicate good stability because the repulsive force between droplets is strong enough to prevent aggregation. However, in the SNEDDS system, stability is not only determined by the electrostatic mechanism, but also by the steric stabilization mechanism provided by the nonionic surfactant (Arshad et al., 2024). Formula F6 contains Cremophor® as a nonionic surfactant, Capryol® 90 as the oil phase, and propylene glycol/PEG400 as a cosurfactant. Cremophor® works by forming a protective layer on the droplet surface, thereby preventing coalescence through steric hindrance. Therefore, as long as the droplet size stays tiny, the size distribution is uniform, and there is no phase separation during stability testing, a relatively low zeta potential value is still acceptable. This behaviour in SNEDDS formulations based on nonionic surfactants has been extensively documented (Öztürk et al., 2024).

Both formula F1 and F6 showed stable visual appearance after sequence of stability test under various different conditions. The physical appearance is still the same as after centrifugation. The addition of surfactants such as Tween® 80 which was classified as a non-ionic surfactant. Tween® 80 was not easily affected by acidic conditions and electrolytes so it remained active as a surface layer between oil and water. A nanoemulsion system stabilized by ionic surfactants, the surface charge comes from the ions contained in the hydrophilic groups of the constituent surfactants. The surface charge of nanoemulsion systems stabilized by non-ionic surfactants

originates from the adsorption of ions in the water phase or friction between the droplets and the dispersion medium (Fitria et al., 2021; Pratiwi et al., 2018).

CONCLUSIONS

Our study suggested the optimal formula of Rambutan leaves (*Nephelium lappaceum l.*) extract-loaded SNEDDs showed good characteristics with formula contained Caprylic Acid/Capryol® 90, Tween® 80/Cremophor® RH-40 and propylene glycol/PEG 400 (1:2:2) with globule size 23,88 and 41,44 nm, polydispersity index 0,283 and 0,15, zeta potential -9,822 and -7,382 mV. Each formulation also demonstrated good stability throughout the stability study.

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REFERENCES

Ahsan, M., Hidayah Base, N., Farmasi Yamasi Makassar, A., & Studi AKFAR Yamasi Makassar, P. (2018). Uji Daya Hambat Sediaan Gargarisma Ekstrak Daun Rambutan (Nephelium lappaceum L.) terhadap Streptococcus mutans. *Jurnal Kesehatan YAMASI Makassar*, *2*(2), 1–6.

Algharably, E. A., Di Consiglio, E., Testai, E., Pistollato, F., Mielke, H., & Gundert-Remy, U. (2022). In Vitro–In Vivo Extrapolation by Physiologically Based Kinetic Modeling: Experience With Three Case Studies and Lessons Learned. *Frontiers in Toxicology*, *4*. https://doi.org/10.3389/ftox.2022.885843

Álvarez-Valverde, V., Alfaro-Zúñiga, C., Passos-Pequeno, A., Carvajal-Miranda, Y., Rodríguez-Rodríguez, J., Rodríguez, G., & Jiménez-Bonilla, P. (2024). Antioxidant and antibacterial extracts from rambutan (Nephelium lappaceum) skins: Exploring the Potential of Transforming Agricultural Byproducts into Functional Supplements. *Revista Tecnología En Marcha*. https://doi.org/10.18845/tm.v37i7.7298

Arshad, A., Arshad, S., Alamgeer, Mahmood, A., Asim, M. H., Ijaz, M., Irfan, H. M., Rubab, M., Ali, S., & Hashimi, A. R. (2024). Zeta potential changing self-nanoemulsifying drug delivery systems: A newfangled approach for enhancing oral bioavailability of poorly soluble drugs. *International Journal of Pharmaceutics*, *655*(123998). https://doi.org/https://doi.org/10.1016/j.ijpharm.2024.123998

Asita, N., Zubair, M. S., Syukri, Y., & Sulastri, E. (2024). Formulation of self-nanoemulsifying drug delivery system (SNEDDS) of combined 70% ethanolic of Begonia medicinalis herbs and Moringa oleifera leaves. *Pharmacy Education*, *24*(3), 304–309. https://doi.org/10.46542/pe.2024.243.304309

Christian, Y. E., Rahmat, D., & Farida, Y. (2023). Effects of the RH-40 Cremophor Concentration on the Formulation of the Vaccinium varingiifolium (Blume) Miq leaf Extract Nanoemulsion. *PHARMACY: Jurnal Farmasi Indonesia*, *20*(2), 147–149.

Danaei, M., Dehghankhold, M., Ataei, S., Hasanzadeh Davarani, F., Javanmard, R., Dokhani, A., Khorasani, S., & Mozafari, M. R. (2018). Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. *Pharmaceutics*, *10*, 1–17. https://doi.org/10.3390/pharmaceutics10020057

de Santana Santos, A., Karoline de Souza Oliveira, A., Oliveira Pereira, R., Vieira Barbosa Junior, E., de Lima Sayão, A., & Mara de Oliveira Silva, A. (2021). Composition and Biological Properties of Rambutan (Nephelium lappaceum). In D. N. Chauhan & K. Shah (Eds.), *Phytopharmaceuticals: Potential Therapeutic Applications* (Vol. 1, pp. 403–436). Wiley Online Library.

Dewi, S. N., Martien, R., Novitasari, L., & Nuringtyas, T. R. (2025). Formulation and Characterization Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) Chloroform Extract of Gaharu Leaves (Gyrinops verstegii (Gilg.) Domke. *Jurnal Sains Farmasi & Klinis*, *11*(3), 179–188. https://doi.org/10.25077/jsfk.11.3.179-188.2024

Ermawati, D. E., Yugatama, A., & Wulandari, W. (2020). Optimization Of Olive Oil, Tween 80, And Propylene Glycol of Self-nanoemulsifying Drug Delivery System Of Zinc Oxide by D-Optimal Method. *Journal of Pharmaceutical Sciences and Community*, *17*(2), 92–101. https://doi.org/10.24071/jpsc.001649

Fidrianny, I., & Sukowati, A. (2015). In Vitro Antioxidant Activities Of Various Leaves Extracts From Five Varieties of Rambutan (Nephelium Lappaceum) And It's Correlation With Total Flavonoid, Phenolic, Carotenoid Content. *Asian Journal of Pharmaceutical and Clinical Research*, *8*(2), 139–143.

Fitria, A., Hanifah, S., Chabib, L., Uno, A. M., Munawwarah, H., Atsil, N., Pohara, H. A., Weuanggi, D. A., & Syukri, Y. (2021). Design and characterization of propolis extract loaded self-nano emulsifying drug delivery system as immunostimulant. *Saudi Pharmaceutical Journal*, *29*(6), 625–634. https://doi.org/10.1016/j.jsps.2021.04.024

Ghiffari, H. D., Suhendra, A., & Vonikartika, A. (2025). Formulasi Dan Uji Evaluasi Sediaan Self-Nanoemulsifying Drug Delivery System (SNEDDs) Dari Ekstrak Metanol Akar Pandan Laut (Pandanus Odorifer). *Jurnal Ilmiah Manuntung: Sains Farmasi Dan Kesehatan*, *11*(2), 187–197. https://doi.org/10.51352/jim.v11i2.964

Hernawan Nugroho, B., Citrariana, S., Nurma Sari, I., & Nadya Oktari, R. (2017). Formulation and evaluation of SNEDDS

(Self Nano-emulsifying Drug Delivery System) of papaya leaf extracts (Carica papaya L.) as an analgesic Formulasi dan evaluasi SNEDDS (Self Nanoemulsifying Drug Delivery System) ekstrak daun pepaya (Carica papaya L.) sebagai analgesik. *Jurnal Ilmiah Farmasi*, *13*(2), 77–85. http://journal.uii.ac.id/index.php/JIF

Hidayah Base, N., Rezky Husnul, D. K., Farmasi Yamasi Makassar, A., & Studi AKFAR Yamasi Makassar, P. (2018). Uji Daya Hambat Ekstrak Etanol Daun Rambutan (Nephelium lappaceum L.) terhadap Streptococcus mutans. *Jurnal Kesehatan YAMASI Makassar*, *2*(2), 1–7.

Jantapaso, H., & Mittraparp-Arthorn, P. (2022). Phytochemical Composition and Bioactivities of Aqueous Extract of Rambutan (Nephelium lappaceum L. cv. Rong Rian) Peel. *Antioxidants*, *11*(5). https://doi.org/10.3390/antiox11050956

Karim, S. F., Lewikinta, M. N., & Sadsyam, S. (2023). Formulasi dan Uji Aktivitas Antibakteri Pasta Gigi Ekstrak Daun Rambutan (Nephelium lappaceum L.) terhadap Streptococcus mutans. *Jurnal Ilmiah Fitomedika Indonesia*, *2*(1), 20–29.

Lestari, A., Rusli, R., & Aryati, F. (2023). Skrining Fitokimia dan Uji Aktivitas Tabir Surya Ekstrak Etanol Daun Rambutan (Nephelium lappaceum L.). *Proceeding of Mulawarman Pharmaceuticals Conferences*, *18*, 192–198. https://doi.org/10.25026/mpc.v18i1.726

Luh Komang Wahyuni, N., & Putu Eka Leliqia, N. (2023a). Review: Kandungan Fitokimia, Aktivitas Antibakteri, dan Toksisitas dari Rambutan (Nephelium lappaceum L.). *International Safety Management of Central Cytotoxic Reconstitution*, *2*, 2023.

Luh Komang Wahyuni, N., & Putu Eka Leliqia, N. (2023b). Review: Kandungan Fitokimia, Aktivitas Antibakteri, dan Toksisitas dari Rambutan (Nephelium lappaceum L.). *Prosiding Workshop Dan Seminar Nasional Farmasi 2023*, *2*, 174–183. https://doi.org/10.24843/WSNF.2022.v02.p14

Magar, R. T., & Sohng, J. K. (2020). A Review on Structure, Modifications and Structure-Activity Relation of Quercetin and Its Derivatives. *Journal of Microbiology and Biotechnology*, *30*(1), 11–20. https://doi.org/10.4014/jmb.1907.07003

Mistriyani, Riyanto, S., & Rohman, A. (2018). Antioxidant activities of rambutan (Nephelium lappaceum L) peel in vitro. *Food Research*, *2*(1), 119–123. https://doi.org/10.26656/fr.2017.2(1).150

Mistryanto Tambunan, P., Nadia, S., Maulida Ulfa, N., & Studi Farmasi, P. (2024). Skrining dan Uji Aktivitas Antioksidan Ekstrak Etanol Daun Rambutan (Nephelium lappaceum L.) Wilayah Kabupaten Deli Serdang Desa Suka Raya dengan Metode FRAP (Ferric Reducing Antioxidant Power). *Forte Journal*, *4*(1), 57–65. https://www.ojs.unhaj.ac.id/index.php/fj

Mohite, P., Sule, S., Pawar, A., Alharbi, H. M., Maitra, S., Subramaniyan, V., Kumarasamy, V., Uti, D. E., Ogbu, C. O., Oodo, S. I., Kumer, A., Idowu, A. O., & Okoye, O. N. N. (2024). Development and characterization of a self-nano emulsifying drug delivery system (SNEDDS) for Ornidazole to improve solubility and oral bioavailability of BCS class II drugs. *Scientific Reports*, *14*(1). https://doi.org/10.1038/s41598-024-73760-7

Morakul, B., Teeranachaideekul, V., Limwikrant, W., & Junyaprasert, V. B. (2024). Dissolution and antioxidant potential of apigenin self nanoemulsifying drug delivery system (SNEDDS) for oral delivery. *Scientific Reports*, *14*(1). https://doi.org/10.1038/s41598-024-59617-z

Mustika, A., Fatimah, N., & Sari, G. M. (2019). Formulation and characterizations of self-nanoemulsifying drug delivery system of extract Petiveria alliacea (Singawalang) leaves. *International Journal of Applied Pharmaceutics*, *11*(Special Issue 5), 61–65. https://doi.org/10.22159/ijap.2019.v11s5.T0050

Myo, H., Khat-udomkiri, N., Sam-ang, P., & Phanumartwiwath, A. (2025). Propylene glycol-based green extraction of polyphenols from industrial hemp stems: process optimization and bioactivity assessment. *Chemical and Biological Technologies in Agriculture*, *12*(1). https://doi.org/10.1186/s40538-025-00870-3

Nirmalayanti, N. L. P. K. V. (2021). Skrining Berbagai Jenis Surfaktan Dan Kosurfaktan Sebagai Dasar Pemilihan Formulasi Nanoemulsi. *Jayapangus Press Metta : Jurnal Ilmu Multidisiplin*, *1*(3), 158–166.

Öztürk, K., Kaplan, M., & Calis, S. (2024). Effects of nanoparticle size, shape, and zeta potential on drug delivery. *International Journal of Pharmaceutics*, *666*(124799). https://doi.org/https://doi.org/10.1016/j.ijpharm.2024.124799.

Pandey, R., Bhairam, M., Shukla, S. S., & Gidwani, B. (2021). Colloidal and vesicular delivery system for herbal bioactive constituents. *DARU Journal of Pharmaceutical Sciences*, *29*(2021), 415–438. https://doi.org/10.1007/s40199-021-00403-x

Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M. D. P., Acosta-Torres, L. S., Diaz-Torres, L. A., Grillo, R., Swamy, M. K., Sharma, S., Habtemariam, S., & Shin, H. S. (2018). Nano based drug delivery systems: Recent developments and future prospects. *Journal of Nanobiotechnology*, *16*(1), 1–33. https://doi.org/10.1186/s12951-018-0392-8

Pratiwi, L., Fudholi, A., Martien, R., & Pramono, S. (2018). Uji Stabilitas Fisik dan Kimia Sediaan SNEDDS (Self-nanoemulsifying Drug Delivery System) dan Nanoemulsi Fraksi Etil Asetat Kulit Manggis (Garcinia mangostana L.) Physical and Chemical Stability Test of SNEDDS (Self-nanoemulsifying Drug Delivery System) and Nanoemulsion Ethyl Acetate Fraction of Garcinia mangostana L. *Traditional Medicine Journal*, *23*(2), 84–90.

Priani, S. E., Nurhaliza, A., Aryani, R., Wilar, G., Chaerunisaa, A. Y., & Sopyan, I. (2025). Recent progress in supersaturation-based SNEDDS: Formulation, mechanism, and biopharmaceutical performance. In *OpenNano* (Vol. 25). Elsevier Inc. https://doi.org/10.1016/j.onano.2025.100252

Purba, M. R., Dian Soraya Tanjung, & Rona Angelin Purba. (2023). Comparison of Antibacterial Effectiveness of Rambutan Leaf Extract (Nephelium lappaceum L.) and Tin Leaf Extract (Ficus carica L.) to Streptococcus mutans. *Bioscientia Medicina : Journal of Biomedicine and Translational Research*, *6*(18), 2976–2979. https://doi.org/10.37275/bsm.v6i18.744

Putra, N. R., Yustisia, Y., Heryanto, R. B., Asmaliyah, A., Miswarti, M., Rizkiyah, D. N., Yunus, M. A. C., Irianto, I., Qomariyah, L., & Rohman, G. A. N. (2023). Advancements and challenges in green extraction techniques for Indonesian natural products: A review. In *South African Journal of Chemical Engineering* (Vol. 46, pp. 88–98). Elsevier B.V. https://doi.org/10.1016/j.sajce.2023.08.002

Putri, N. E. K. (2024). Uji Kelarutan Pada Seleksi Fase Minyak, Surfaktan Dan Kosurfaktan Dalam Preparasi Self-Nano Emulsifying Drug Delivery System (SNEDDS) Ekstrak Herba Kerokot (Lygodium Microphyllum. *Prosiding Seminar SAFANA 2024*, *1*(1), 99–102.

Ratna, Hidayah Base, N., & Rezky Husnul, D. K. (2018). Uji Daya Hambat Ekstrak Etanol Daun Rambutan (Nephelium

lappaceum L.) Terhadap Streptococcus mutans. *Jurnal Pengabdian Masyarakat Yamasi*, *2*(2), 1–7.

Rizkita, L. D., Ariani, R., Farid, M., Rastrani, A., Ramadhania, W. A., & Putri, R. A. E. (2024). Inhibitory effects of rambutan (Nephelium lappaceum l.) leaves ethanolic extract on Methicillin-Resistant Staphylococcus aureus (MRSA) and Streptococcus pyogenes. *Sains Medika: Jurnal Kedokteran Dan Kesehatan*, *15*(2), 68. https://doi.org/10.30659/sainsmed.v15i2.40155

Rizkita, L. D., Putri, R. G. P., Farid, M., Rizkawati, M., & Wikaningtyas, P. (2024). Liposome drug delivery in combating the widespread topical antibiotic resistance: a narrative review. In *Beni-Suef University Journal of Basic and Applied Sciences* (Vol. 13, Number 1). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1186/s43088-024-00545-2

Sapra, K., Sharma, R., Samaddar, S., & Sardana, S. (2026). Formulation and optimization of self-nanoemulsifying drug delivery systems (SNEDDS) for enhancing the solubility, bioavailability, and anticancer activity of flutamide. *Discover Pharmaceutical Sciences*, *2*(1), 4. https://doi.org/10.1007/s44395-026-00037-5

Sercombe, L., Veerati, T., Moheimani, F., Wu, S. Y., Sood, A. K., & Hua, S. (2015). Advances and challenges of liposome assisted drug delivery. *Frontiers in Pharmacology*, *6*(286), 1–13. https://doi.org/10.3389/fphar.2015.00286

Shofian, N. M., Hamid, A. A., Osman, A., Saari, N., Anwar, F., Dek, M. S. P., & Hairuddin, M. R. (2011). Effect of freeze-drying on the antioxidant compounds and antioxidant activity of selected tropical fruits. *International Journal of Molecular Sciences*, *12*(7), 4678–4692. https://doi.org/10.3390/ijms12074678

Shrirang, V. A., Pande, S. D., Bobade, N. N., Wankahde, V., Mankar, A. D., & Bijore, I. (2026a). A Comprehensive Review On Sneeds: A Simple Tool To Enhance Drug Solubility. *Asian Journal of Pharmaceutical Research and Development*, *14*(3), 163–172. https://doi.org/10.22270/ajprd.v14i3.1775

Shrirang, V. A., Pande, S. D., Bobade, N. N., Wankahde, V., Mankar, A. D., & Bijore, I. (2026b). A Comprehensive Review On Sneeds: A Simple Tool To Enhance Drug Solubility. *Asian Journal of Pharmaceutical Research and Development*, *14*(3), 163–172. https://doi.org/10.22270/ajprd.v14i3.1775

Sriwidodo, Umar, A. K., Wathoni, N., Zothantluanga, J. H., Das, S., & Luckanagul, J. A. (2022). Liposome-polymer complex for drug delivery system and vaccine stabilization. *Heliyon*, *8*(2), 1–16. https://doi.org/10.1016/j.heliyon.2022.e08934

Sukatta, U., Rugthawon, P., Khanoonkon, N., Anongjanya, P., Kongsin, K., Sukyai, P., Harnkarnsujarit, N., Sothornvit, R., & Chollakup, R. (2021). Rambutan (Nephelium lappaceum) peel extract: Antimicrobial and antioxidant activities and its application as a bioactive compound in whey protein isolate film. *Journal of Science and Technology*, *43*(1), 37–44.

Suryani, Zubaydah, W. O. S., Sahumena, M. H., Adawia, S., Wahyuni, R., Adjeng, A. N. T., Nisa, M., Kasmawati, H., Ihsan, S., Ruslin, & Aswan, M. (2019). Preparation and characterization of self-nanoemulsifying drug delivery system (SNEDDS) from Moringa oleifera L.and Cassia alata L. leaves extracts. *AIP Conference Proceedings*, *2199*. https://doi.org/10.1063/1.5141325

Taiyeb, M., Hartati, H., Arwansyah, A., Dahlia, Muis, A., Mu'nisa, A., Arif, A. R., & Salleh, L. M. (2024). Self-Nanoemulsifying Drug Delivery System (SNEDDS) formulation and molecular docking of mahogany seed extract (Swietenia mahagoni) as anti-hyperglycemic. *Informatics in Medicine Unlocked*, *47*. https://doi.org/10.1016/j.imu.2024.101517

Tingting, Z., Xiuli, Z., Kun, W., Liping, S., & Yongliang, Z. (2022). A review: extraction, phytochemicals, and biological activities of rambutan (Nephelium lappaceum L) peel extract. *Heliyon*, *8*(11). https://doi.org/10.1016/j.heliyon.2022.e11314

Tresia Pramasta Diva, M., Gusti Ngurah Agung Dewantara Putra, I., Desi Laminiati, K., Haridas Chandra Gayatri, P., & Ayu Ratih Tri Bhuwana Putri, K. (2023). Uji Kelarutan Flavonoid Ekstrak Kulit Salak Pondoh dalam Minyak, Surfaktan, dan Kosurfaktan untuk Preformulasi SNEDDS sebagai Nutrasetikal. *Prosiding Workshop Dan Seminar Nasional Farmasi 2023*, *2*, 2023.

Vareltzis, P., Stergiou, A., Kalinderi, K., & Chamilaki, M. (2023). Antioxidant Potential of Spray- and Freeze-Dried Extract from Oregano Processing Wastes, Using an Optimized Ultrasound-Assisted Method. *Foods*, *12*(13). https://doi.org/10.3390/foods12132628

Yandi Syukri, Syafira Tri Nurmala Sari, & Arba Pramundita Ramadani. (2025). A Comprehensive Review of Solid Self Nano Emulsifying Drug Delivery System (S-SNEDDS) Technology to Enhance Nanoemulsion Stability. *Jurnal Sains Farmasi & Klinis*, *12*(1), 15–28. https://doi.org/10.25077/jsfk.12.1.15-28.2025

Yokota, M., & Tokudome, Y. (2017). Related topic: Liposomes-recent advances and future perspective. In K. Sugibayashi (Ed.), *Skin Permeation and Disposition of Therapeutic and Cosmeceutical Compounds* (1st ed., pp. 137–142). Springer Japan. https://doi.org/10.1007/978-4-431-56526-0_11