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DEVELOPMENT OF LABRASOL®-BASED SNEDDS FOR ENHANCED DELIVERY OF COMBINATION PROPOLIS, SEA CUCUMBER, AND *CENTELLA ASIATICA* EXTRACTS

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ABSTRACT
The therapeutic efficacy of natural extracts such as propolis, sea cucumber or gamat (*Stichopus hermanii*), and pegagan (*Centella asiatica*) is supported by their anti-inflammatory, antioxidant, and regenerative properties. However, their pharmaceutical application is limited due to poor solubility and low bioavailability. This study aimed to develop and characterize a Self-Nanoemulsifying Drug Delivery System (SNEDDS) using Labrasol to enhance the delivery and stability of a combination of these three extracts, that exhibit synergistic effects as tissue regeneration, antimicrobial, anti-inflammatory, and antioxidant properties. SNEDDS formulations were prepared by a high energy method with Labrasol, Tween 80, and propylene glycol. The formulations were evaluated for droplet size, polydispersity index (PDI), zeta potential, and thermodynamic stability test. The optimized SNEDDS exhibited nano-sized droplets (151.13 nm ± 17.26) with low PDI (0.39 ± 0.01) and zeta potential (-50.30 ± 1.04) within the stable range, indicating a uniform, physically stable nanoemulsion, and passed the thermodynamic stability test. In conclusion, the optimized SNEDDS formulation demonstrated nano-sized droplets with low PDI and stable zeta potential, indicating good physical stability.

Keywords: Labrasol; SNEDDS; Nanotechnology; Natural Product Delivery

1. INTRODUCTION

Nanotechnology-based drug delivery systems have emerged as a transformative strategy in enhancing the bioavailability and therapeutic efficacy of poorly water-soluble natural products (Ruiz et al., 2022). Among these, the *self-nanoemulsifying drug delivery system* (SNEDDS) is widely recognized for its ability to spontaneously form fine oil-in-water nanoemulsions when it comes into contact with gastrointestinal fluids, thereby enhancing solubility, absorption, and stability of lipophilic compounds (Annisa et al., 2023). The effectiveness of SNEDDS formulations is largely influenced by the selection of oil, surfactant, and co-surfactant components, with Labrasol (caprylocaproyl macrogol-8 glyceride) frequently chosen for its excellent solubilizing properties (Hayat et al., 2024; Wu et al., 2025).

Surfactants and cosurfactants are known for reducing surface tension between oil as a carrier of active ingredients and GI tract and significantly influence emulsification efficiency (Buya et al., 2020; Syukri et al., 2024). Gamat extract, which naturally contains glycosaminoglycans and saponins, in synergy with the phenolic content of propolis and pegagan, may have contributed to better emulsification by reducing interfacial tension, allowing

for finer droplet formation during self-emulsification (Farooq et al., 2021; Ramos-Hernández et al., 2023; Tan & McClements, 2021).

Bioactive natural compounds in pharmaceutical development continue to attract considerable attention, particularly for their multifaceted pharmacological effects and safety profiles. Among the most extensively studied natural agents are propolis, sea cucumber or gamat (*Stichopus hermanii*), and *Centella* asiatica, locally called pegagan, each of which has antimicrobial, anti-inflammatory, antioxidant, and wound-healing properties (Aszrin et al., 2024; Fitria et al., 2021; Pillai et al., 2024). Despite their therapeutic promise, the clinical application of these extracts is often constrained by inherent physicochemical limitations, such as low aqueous solubility, chemical instability, and poor gastrointestinal absorption, leading to suboptimal bioavailability (Balasubramaniam et al., 2025). These challenges call for advanced formulation strategies capable of enhancing the solubilization, stability, and systemic delivery of lipophilic phytoconstituents. This study seeks to address this unexplored formulation approach by developing and characterizing a novel SNEDDS loaded with propolis, gamat, and pegagan extract.

This research uses high-energy emulsification techniques to make PGP-SNEDDS that can employ mechanical devices such as high-pressure homogenizers, ultrasonication probes, or high-shear mixers to generate intense disruptive forces that effectively overcome the interfacial tension between immiscible oil and aqueous phases (Håkansson & Rayner, 2018). These mechanical forces facilitate the formation of nano-sized oil droplets by breaking down larger droplets into finer, more uniform particles, thereby enhancing the stability and homogeneity of the resulting emulsion system. Compared to low-energy methods, mechanical approaches offer greater control over droplet size distribution, reproducibility, and formulation scalability, making them particularly advantageous in the production of robust and kinetically stable nanoemulsions for pharmaceutical applications (K. & Kumar, 2022).

Previous research has reported promising outcomes for each individual extract incorporated into SNEDDS formulations. A study by (Fitria et al., 2021) developed propolis-loaded SNEDDS and reported improved solubility and enhanced immunostimulant activity. Similarly, pegagan, (Jusril et al., 2024) showed that nanoemulsion of pegagan ethanolic extract (NanoSECA) significantly improved memory-related biomarkers in normal adult rats by enhancing cholinergic activity and elevating antioxidant levels. Furthermore, NanoSECA administration reduced oxidative stress and neuroinflammatory mediators, indicating its potential as a cognitive enhancer. But there are no researches reported about gamat extract in the SNEDDS form. While these findings confirm the feasibility and benefits of SNEDDS for each extract individually, their combined delivery in a single nanoemulsion system remains unexamined, warranting further investigation into formulation optimization, characterization, and potential synergistic effects.

The combination of propolis, gamat, pegagan extract in the SNEDDS (PGP-SNEDDS) formulation offers a novel synergistic approach for developing multifunctional therapeutic agents to increase the solubility. Characterization of physicochemical properties for SNEDDS, such as droplet size, polydispersity index (PDI), and zeta potential. Labrasol®-based systems are advantageous for both hydrophobic and amphiphilic phytoconstituents, making it a promising oil phase in this dual-extract system.

This study aims to develop and characterize a PGP-SNEDDS formulation with Labrasol® as a carrier. The outcome of this research is expected to contribute to the design of more effective delivery systems for marine and bee-derived natural products, supporting future pharmaceutical and cosmeceutical applications.

2. METHODS

Materials

Propolis and gamat were bought from Merapi Farma, Yogyakarta, Indonesia. Polysorbate 80 (Tween 80) and propylene glycol were obtained from Brataco Indonesia Ltd. Labrasol® were obtained from Gattefose (France).

Preparation of PGC-loaded SNEDDS

Propolis (1 gram), gamat (1.5 gram), and 0.5 grams pegagan were dissolved in 4 mL mixture of an Labrasol®, Tween 80, and propylene glycol, that conducted by ultrasonic homogenizer (model 300 V/T, USA). The process is typically carried out at 40-60% amplitude for 3-10 minutes while maintaining the sample temperature at 25-30°C for solubilization to obtain clear solution **(Table 1)** (Sinsuebpol & Changsan, 2020; Syukri et al., 2019).

Table 1. PGP-SNEDDS Formulation

Materials	Concentration (%)
Propolis	14.29
Gamat	21.43
Pegagan	7.14
Labrasol®	14.28
Tween 80	28.58
Propylene Glycol	14.28

PGC-Loaded SNEDDS Characterization

PGC-Loaded SNEDDS characterization was droplet size, polydispersity index (PDI) and zeta potential that were measured by particle size analyzer from Horiba SZ 100; Japan followed by 100-fold dilution factor of SNEDDS samples in purified water for enhanced readability with PSA (Fitriani et al., 2021).

Thermodynamic Stability Test

Centrifugation test

The formulations were subjected to centrifugation at 5000 rpm for 30 minutes, followed by visual assessment to verify instability, including cracking, phase separation, drug precipitation, or creaming. The formulations devoid of any indications of weakness were chosen for the heating-cooling test (Agrawal et al., 2015).

Heating and cooling cycle test

The heating and cooling cycle was conducted in three repetitions within a temperature range of 4°C to 45°C, with a minimum storage duration of 48 hours. The duration consisted of a single repetition lasting 8 hours at a temperature of 4°C and 8 hours at a temperature of 45°C. The formulations that withstood such conditions without exhibiting signs of creaming or phase separation were chosen for the freezing and thawing cycle (Kassem et al., 2016).

Freezing and thawing cycle test

The freeze and thaw test were performed three times at temperatures ranging from −20°C to +25°C, with a minimum storage duration of 48 hours. The duration consisted of a single repetition of 8 hours at a temperature of 4°C, followed by 8 hours at a temperature of 45°C. Subsequent analysis was conducted on the formulations that withstood the thermodynamic stress test (Kassem et al., 2016).

3. RESULTS AND DISCUSSION

PGC-Loaded SNEDDS Characterization

The preparation and characterization of PGP-SNEDDS have revealed promising results, particularly in terms of the system's particle size, PDI, and zeta potential, which are critical indicators of a stable and efficient nanoemulsion system. The average droplet size of the optimized formulation was found to be 151.13 nm ± 17.26, which was determined to be in the nanometer range, specifically within the range of 50-200 nm (Date et al., 2010; Syukri et al.,

2019). This nano-size range is optimal for ensuring efficient cellular uptake and improved drug absorption, as smaller particles are known to traverse biological membranes more easily than larger particles (Yun et al., 2025).

Labrasol®'s amphiphilic properties have led to its extensive use as both an oil and a surfactant in the formulation of SNEDDS. It primarily comprises a complex mixture of mono-, di-, and triglycerides, along with mono- and diesters of polyethylene glycol and fatty acids-predominantly caprylic and capric acids. Its widespread application is attributed to its ability to significantly enhance the aqueous solubility of lipophilic drug compounds, such as piroxicam, also facilitating the improved bioavailability of hydrophilic drugs, including gentamicin, through modulation of intestinal permeability (*Labrasol*®, 2025.; Li et al., 2013; Rama Prasad et al., 2003; Yüksel et al., 2003).

Table 2. PGP-SNEDDS Characterization

Replication	Particle Size (nm)	PDI	Zeta Potential (mV)
1	131.40	0.38	-49.10
2	163.40	0.39	-50.90
3	158.60	0.39	-50.90
Average ± RSD	151.13 ± 17.26	0.39 ± 0.01	-50.30 ± 1.04

The polydispersity index (PDI) values for PGP-SNEDDS were consistently low, 0.39 ± 0.01. This value indicates a narrow and uniform size distribution of droplets, confirming the homogeneity of the SNEDDS (López Angulo et al., 2024). A PDI below 0.7 is typically accepted as a threshold for homogenous nanoemulsions, and the results obtained fall well within this parameter, indicating that the emulsification process was highly efficient (Syukri et al., 2019). The low PDI values also reflect that the formulation process did not produce significant numbers of larger or aggregated particles, which can compromise drug delivery performance, and contribute to the formation of a highly monodisperse system (Fitriani et al., 2021). This uniformity is crucial in ensuring consistent therapeutic outcomes and controlled release behavior, especially for formulations aimed at delivering bioactive components such as polyphenols, triterpenes, and marine peptides (Sun et al., 2025).

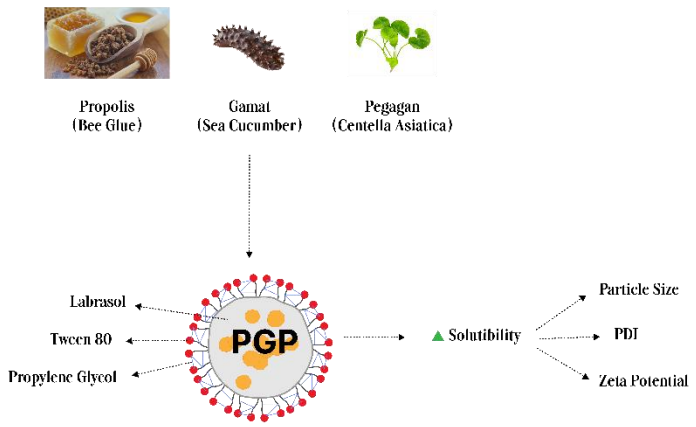


Figure 1. PGP-SNEDDS

Zeta potential measurements provided further insight into the stability of the SNEDDS system. The zeta potential of the PGP-SNEDDS was -50.30 mV ± 1.04. These negative values indicate the presence of sufficient surface charge to produce electrostatic repulsion among the droplets, thereby minimizing the risk of aggregation. A zeta potential magnitude greater than ±30 mV is generally considered adequate for physical stability, and the values obtained suggest that the SNEDDS formulation is electrostatically stable over time (Reddy & Gubbiyappa, 2022).

Thermodynamic Stability Test

Kinetic stability is essential for distinguishing nanoemulsions from emulsions, indicating the thermodynamic stability of the systems. The nanoemulsion system of SNEDDS is established through in situ solubilization, and stability prevents creaming, cracking, or precipitation (Syukri et al., 2019). The formulation involves an examination of thermodynamic stability, which includes heating and cooling cycles, as well as freezing and thawing cycles. PGP-Loaded SNEDDS exhibit no indications of phase separation, turbidity, or drug precipitation **(Table 3)**.

Table 3. Thermodynamic stability test of PGP-Loaded SNEDDS (n=3)

Replication	Visual Clarity	Heating and Cooling	Freezing and Thawing
1	Clear	Allowed	Allowed
2	Clear	Allowed	Allowed
3	Clear	Allowed	Allowed

Based on the data that have been characterized, the PGP-SNEDDS demonstrated desirable physicochemical characteristics, including nanoscale droplet size, uniform distribution, and electrostatic stability.

4. CONCLUSION

The PGP-SNEDDS formulation resulted in a nano-sized, homogenous, and electrostatically stable formulation. The formulation demonstrated desirable physicochemical properties, suggesting potential for enhanced stability and bioavailability, which warrants further pharmacokinetic-pharmacodynamic studies, and long-term stability test. This study was limited to in vitro physicochemical characterization of the optimized SNEDDS formulation, without assessing its in vivo pharmacokinetics, bioavailability, or therapeutic efficacy. Future studies should include animal and clinical evaluations to confirm the enhanced absorption and therapeutic benefits, as well as long-term stability and safety assessments to support potential pharmaceutical applications.

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