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Original Article

PHYSICAL STABILITY AND DISSOLUTION TEST OF SNEDDS (SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM) DICHLOROMETHANE FRACTION OF MANGOSTEEN RIND (*GARCINIA MANGOSTANA* L)

ARI WIDAYANTI[1,2*], MAHDI JUFRI[2], SILVIA SURINI[2], BERNA ELLYA[2]

[1]Faculty of Pharmacy and Sciences, Universitas Muhammadiyah Prof. Dr. Hamka, East Jakarta-13460, Indonesia. [2]Faculty of Pharmacy, Universitas Indonesia, Depok-16424, West Java, Indonesia

*Corresponding author: Ari Widayanti; *Email: ariwidayanti@uhamka.ac.id

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ABSTRACT

Objective: Mangosteen rind (*Garcinia mangostana* L) is a plant that is quite popular in Indonesia. Mangosteen rind extract contains alpha-mangostin. Poor water solubility of alpha mangostin limits its oral bioavailability. The formulation in the form of SNEDDS is expected to increase the solubility and bioavailability of the active fraction of mangosteen rind. Dichloromethane (dcm) fraction has high antioxidant activity so it is used as an active substance in SNEDDS formulation. To optimize a self-nanoemulsifying drug delivery system (SNEDDS) to enhance solubility, dissolution, and oral delivery of alpha mangostin.

Methods: Solubility screening was performed in various oils, surfactants, and co-surfactants. The optimized SNEDDS was evaluated for droplet size, PDI, zeta potential, and stability under centrifugation, heating–cooling, and freeze–thaw cycles. Dissolution studies were conducted *in vitro*, and cumulative release profiles were analyzed kinetically.

Results: The optimized SNEDDS (1.64:7.34:1.02, isopropyl myristate: Tween 20: propylene glycol) formed nanoemulsions with droplet size 50.6±1.37 nm, PDI 0.206±0.0036, and zeta potential-15.35±0.81 mV. Stability tests showed no significant change after stress conditions. Transmittance was 70.125%, indicating adequate clarity. Dissolution was significantly improved compared to dcm fraction. The R^2 calculation results obtained for the zero-order data were 0.5882, first-order 0.8852, Higuchi 0.6945 and Korsmeyer-Peppas 0.8556. Therefore, it can be concluded that the release kinetics for the dcm fraction of SNEDDS follows a first-order model, with the R^2 value approaching 1. This means that the drug release rate is directly proportional to, or dependent on, the remaining drug concentration in the dosage matrix.

Conclusion: Optimized SNEDDS improved dissolution and demonstrated robust physical stability under stress conditions, highlighting its potential for oral delivery of α-mangostin.

Keywords: SNEDDS, Dichloromethane fraction, Phisical stabiliy, *Garcinia mangostana*

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by damage or impaired insulin secretion. This disease is characterized by increased blood sugar levels as a result of impaired metabolic system in the body, where the pancreas is unable to produce insulin hormone according to the body's needs. Here the body cannot use insulin optimally. Mangosteen (*Garcinia mangostana*) is one of the plants that can be used as an antidiabetic treatment. The discarded mangosteen rind can be used as a drug candidate. Mangosteen rind has very high antioxidants. Compounds that have high antioxidant activity are alpha mangostin, beta mangostin and garcinon. Alpha mangostin is the main secondary metabolite of mangosteen rind [1]. Xanthone has a unique chemical structure consisting of a tricyclic aromatic system (C_6-C_3C_6). The xanthone compound found in mangosteen rind is a phenolic compound that is included in the polyphenol class. The alpha mangostin compound is yellowish in color, has various benefits such as anti-inflammatory, anti-tumor, cardioprotective, antidiabetic, antifungal, antiparasitic, antioxidant, and antiobesity [2]. Alpha mangostin as an antioxidant by deactivating free radicals in the form of singlet oxygen, superoxide anions and radicals peroxyl [1]. The antioxidant effect of mangosteen peel extract shows that alpha mangostin as the main constituent, has antioxidant potential. The solubility of alpha mangostin in water is 2.03 x 10-4 mg/ml. Solubility is one of the important parameters to achieve the desired drug concentration in systemic circulation to achieve the required pharmacological response [3]. Poor solubility is the most common cause associated with low oral bioavailability [4]. So that the need for strategies to increase the solubility and dissolution of drugs that are not soluble in water is very important in the development of oral preparations.

Drug delivery in lipid-based formulations is a solution for types that have low solubility characteristics in water. Lipid-based drug delivery systems include SNEDDS, which are technologies to increase the rate of absorption in the category of poorly water-soluble drugs [5]. SNEDDS is a drug delivery technique consisting of an isotropic mixture of drugs, oils and surfactants, and if necessary can add cosurfactants, this system when it meets water media with light agitation will be able to form a nanoemulsion, with a size below 100 nm. In another study of mangosteen peel using dcm fractions obtained an IC_{50} value of 37.53 ppm. This is a good antioxidant because it has quite high antioxidant power [6].

In this study, SNEDDS formula was developed from the dcm fraction of mangosteen peels (*Garcinia mangostana* L), which provides new modifications to improve solubility, so that it can improve the bioavailability of active substances in the body. The dichloromethane fraction of mangosteen rind has high antioxidant activity compared to the water and n-hexane fractions, namely 34.66 ug/ml [7].

Based on this background, research will be developed on the formulation of SNEDDS from the dcm fraction of mangosteen rind (*Garcinia mangostana* L), which provides new modifications to improve solubility, so that it can improve the bioavailability of active substances in the body. Alpha-mangostin, the main active constituent of mangosteen (*Garcinia mangostana* L.) rind extract, has promising biological activities, including anti-inflammatory and anticancer properties. However, its utilization in oral therapy is severely hampered by significant biopharmaceutical challenges, primarily its very low aqueous solubility (classified as BCS Class II or IV poorly soluble) and poor oral bioavailability [8, 9].

These major challenges are caused by its slow dissolution rate in the aqueous gastrointestinal tract and extensive first-pass metabolism in the liver. Therefore, this study aimed to develop and optimize a SNEDDS formulation containing isopropyl myristate as the oil phase, Tween 20 as a surfactant, and propylene glycol as a cosurfactant to enhance the solubilization and absorption potential of alpha-mangostin.

The characteristic tests that will be carried out on the SNEDDS formula include particle size, zeta potential, polydispersity, emulsification time and stability tests. Furthermore, *in vitro* characterization of drug release was carried out through dissolution tests.

MATERIALS AND METHODS

The materials used are thick extract of mangosteen rind (BRIN Serpong), n-hexane, dcm, reagent solution, alpha mangostin (Sigma Aldrich, USA), isopropyl myristate, virgin coconout oil (VCO), caprylic acid, Tween 20, lecithin, PEG 400, propylene glycol, aqua dest, acetonitrile, methanol, phosphate buffer pH 7.4. The tools used in this study are glassware (Pyrex), digital analytical balance (Ohauss), vortex mixer (Velp, Itali), ultrasonicator, Ultra High Performance Liquid Chromatography (Waters Arc Acquity CH-30A, USA) autosampler, C-18 column (Xbridge), micro pipette, chamber, Particle Size Analyzer (Beckman coulter, USA), centrifugator (Gemmy, Taiwan), hot plate stirrer, oven (Memmert), aluminum foil, porcelain exchanger, thermometer, evaporator cup, desicator.

Preparation of plant fraction

The thick extract of mangosteen rind was then added with 500 ml of distilled water to obtain a liquid solution, then partitioned with 500 ml of n-hexane p. a three times, then partitioned with 500 ml of dcm p. a twice. The dcm fractionation results were concentrated with a water bath at 40 °C±0.5 until all solvents were lost and the dcm fraction powder was produced [10].

Determination of alpha mangostin levels in the dichloromethane fraction of mangosteen rind using Ultra High Performance Liquid Chromatography (HPLC), Xbridge C18 Column with Phosphoric Acid: Methanol (12:88) mobile phase, with an average retention time of 2.848. The validation parameters of the analysis method are as follows: linearity, precision and accuracy.

Formulation of SNEDDS

Solubility screening of dcm fraction in oil/surfactan/co-surfactant

The solubility of dcm fraction was measured in a panel of oils (isopropyl myristate, virgin coconout oil, caprylic acid), surfactants (Tween 20, Lecithin), and co-surfactants (propylene glycol, PEG 400). Excipients exhibiting the highest drug solubility were selected for phase diagram construction. A total of 10 mg of dcm fraction was added to 10 ml as the oil phase, surfaktan and co-surfactan. This mixture was conditioned in a water bath at 40 °C for 10 min. The process of dissolving the fraction in a carrier was maximized by a sonicator for 15 min and left for two days at room temperature. After two days, insoluble part was separated by centrifugation at 3000 rpm for 20 min. The sample that dissolved the most of the oil phase, surfactant, and co-surfactant was selected for the next optimization phase

Pseudo-ternary phase diagrams were generated using varying oil: Smix ratios (1:9, 2:8, 3:7, 4:6, 5:5). Each mixture was titrated with water until a clear or transparent nanoemulsion was formed. The largest nanoemulsion region indicates the strongest self-emulsifying state. Mixture design was used with Design Expert software to optimize the SNEDDS composition and responses such as particle size, transmittance percentage, polydispersity index, and zeta potential. Experimental runs were generated within the nanoemulsion region identified from the pseudo tenary diagram.

The optimum SNEDDS was made with a combination of oil, surfactant and cosurfactant, namely isopropyl myristate, Tween 20 and propylene glycol with a ratio of 1.64:7.34:1.02. Furthermore, dcm fraction 100 mg/10 ml SNEDDS was added. The mixture was conditioned in a water bath at a temperature of 40 °C for 10 min. The fraction dissolution process was maximized with a sonicator for 15 min.

SNEDDS evaluation

% Transmittance

Preconcentrate formula of 100.0 µl** plus distilled water to a final volume of 5 ml. Homogenization of the mixture is carried out with the help of a vortex tool for 30 sec. The emulsion that has been obtained is measured for its absorbance at a wavelength of 650 nm with a distilled water blank to determine its clarity level [11]. The clearer or the absorbance is closer to the absorbance of the distilled water, it is an indicator that the emulsion droplets have reached nanometer size.

Droplet size, zeta potential and PDI

Measurement using a particle size analyzer (PSA) tool determines the size and distribution of nanoparticles. A total of 1 ml of SNEDDS was mixed with distilled water up to 5 ml, then homogenized by inverting for 1 min. After that, 3 ml was taken and put into a cuvette for analysis. The particle size data obtained as output on the computer were the average particle size, particle size distribution, and deviation from the average. Particle Size and Zeta Potential were measured based on the principle of dynamic light scattering. The sample was placed in a disposable zeta cell [12, 13].

Physical stability test

The test used centrifugation at 5000 rpm for 30 min. Then observations were made on the preparation on the parameters of instability, including separation, sedimentation, creaming, cracking. Stable preparations were further tested, namely heating and cooling [14].

Heating and cooling

In this test, 6 cycles were carried out using temperatures of 4 °C and 48 °C with a storage period of 48 h. Formulations that did not experience instability parameters included separation, sedimentation, creaming, cracking. Stable preparations were further tested, namely, freeze thaw

Freez thaw

A total of 6 freezing and thawing cycles using temperatures of-21 °C and 25 °C with a storage period of 48 h. After centrifugation at a speed of 5000 rpm for 5 min, observations were made, including separation, sedimentation, creaming, cracking.

Emulsification time

500 ml of distilled water was stirred on a magnetic stirrer at 120 rpm. One ml of the mangosteen rind active fraction was quickly added to the medium. The time required for the emulsion to form a homogeneous mixture was observed, indicated by the complete mixing of the SNEDDS of the mangosteen rind dichlormethane fraction into the medium [12].

Dissolution test of SNEDDS preparation

The release test of the dcm fraction of mangosteen rind from SNEDDS was conducted using a modified dissolution method, with a dissolution test apparatus consisting of a beaker and a dialysis bag containing phosphate buffer pH 7.4 with a magnetic stirrer. The *in vitro* drug dissolution test aims to evaluate the release of the drug from SNEDDS. The system is maintained at body temperature, which is 37 °C. The temperature of the compartment must be maintained because changes in temperature can affect the rate of drug release through the membrane. Before use, the membrane is immersed in dissolution medium. The receptor compartment is stirred at a speed of 100 rpm to keep the compartment fluid homogeneous. A sample of 2 ml was placed into the donor compartment of the dialysis bag and tied with thread. The sample was tested at minutes 30, 60, 120, 180, 240, 300, 360, 420, and 480, with a 1 ml sample being taken and replaced with a 1 ml buffer solution in the receptor compartment to maintain a constant dissolution medium volume.

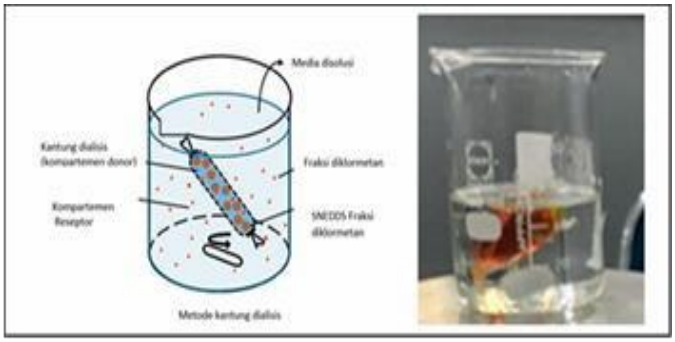


Fig. 1: Dissolution of SNEDDS dcm fraction

RESULTS AND DISCUSSION

Determination of alpha mangostin

After validation of the analysis method, the alpha mangostin content in 3 fractions was measured to see how much alpha mangostin content was contained in each fraction. The results were as follows: for the n-hexane fraction, the average alpha mangostin content was 25.18%±0.003 and for the dichloromethane fraction, 31.24%±0.0222.

Alfa mangostin of dcm fraction exhibited the highest solubility in isopropyl myristate, followed by Tween 20 and propilenglicol, compared with other screened excipient.

Pseudo-ternary phase diagrams were generated using varying oil: Smix ratios (1:9, 2:8, 3:7, 4:6, 5:5). Each mixture was titrated with water until a clear or transparent nanoemulsion was formed. The largest nanoemulsion region indicates the strongest self-emulsifying state.

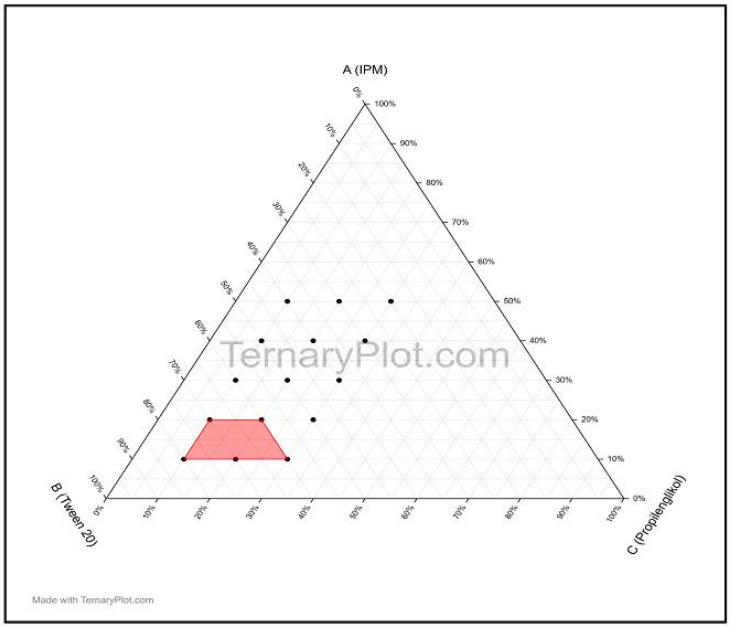


Fig. 2: Pseudo-ternary phase diagrams

Mixture design was used with Design Expert software to optimize the SNEDDS composition and responses such as particle size, transmittance percentage, polydispersity index, and zeta potential. Experimental runs were generated within the nanoemulsion region identified from the pseudo-ternary diagram.

The resulting ratio of isopropyl myristate, Tween 20, and propylene glycol was 1.64:7.34:1.02, which minimized droplet size and maximized clarity while maintaining physical stability.

Characteristics of SNEDDS dcm magosteen peel

% Transmittance

Based on the results of transmittance measurements, the three formulas above have a transmittance value of more than 70.125±0.090%. Although the transmittance values indicate slight turbidity, the claims regarding the "stable nature" of this formulation are supported by the results of rigorous physical stability testing, including thermodynamic stability testing: a successful formulation must pass freeze-thaw cycle testing and centrifugation testing without exhibiting phase separation, creation, or sedimentation. The color of the dcm fraction is dark brown, so although transparent, it is dark in color and not cloudy.

According to [15] a good nanoemulsion is one that has a clear visual appearance with high transmittance, the formula will become a nanoemulsion when emulsified in water media. The clearer the emulsion, the smaller the particle size and the more turbid the emulsion, the larger the particle size.

Droplet size analysis and zeta potential

Analysis of droplet size and zeta potential examination on optimized dcm mangosteen peel. Observation of nanoemulsion droplet size is carried out to ensure that the size of the nanoemulsion droplet formed is smaller than 100 nm. Droplet size distribution is used as a parameter of uniformity and reliability of the nanoemulsion

manufacturing method. This test was carried out on aquadest media. which has an average nanoemulsion size of less than 100 nm. This proves that the SNEDDS formula made is capable of producing nanoemulsions. Theoretically, the size of the nanoemulsion is greatly influenced by the ratio of surfactant to cosurfactant. The higher the ratio of surfactant to cosurfactant, the smaller the size of the nanoemulsion obtained. The particle size of nanoemulsions is influenced by the composition of oil and surfactant. Oil SNEDDS can increase the ability to carry drugs but causes the size of the nanoemulsion to be larger so that the ratio of oil used is always smaller than oil. Some literature states that the particle size of SNEDDS is in the range of 17.9-101.3 nm. In general, the particle size produced has met the requirements (<100 nm) [16]. An emulsion system with a droplet size range between 20-500 nm is included in the nanoemulsion category. The particle size of the SNEDDS dcm fraction of mangosteen rind is 50.6 nm ±1.37, this indicates that the droplet size is within the required range, so it is included in the nanoemulsion category. The PI (polydispersity index) value indicates the homogeneity of the nanoemulsion particles. The PI value varies from 0.0 to 1.0 and the value of 0, the closer the particles are to homogeneity. In this study, the PI value was 0.206±0.0036. The PI value was obtained from testing the size and distribution of particle size of the distilled water media. It can be concluded that the nanoemulsion has a uniform particle size distribution and the nanoemulsion manufacturing method has good reliability. The zeta potential in this study was-15.35±0.81. The value in the range of ±30 mV is the limit value that is able to maintain the stability of the emulsion because the value is close to neutral, thus reducing the possibility of particles forming aggregates. As noted in the colloidal stability literature, high absolute zeta potential values (e. g., ≥±30 mV) are generally considered indicative of strong electrostatic repulsion and stability in nanoemulsions. This threshold has been adopted as a benchmark in many formulations to predict the physical stability of colloidal systems. However, we now substantiate our findings by referring to studies in which nanoemulsions with moderate zeta potential values (<|30 mV|), when combined with non-ionic surfactants or steric stabilizers, exhibited stable behavior due to steric and mixed stabilization mechanisms [17].

Table 1: Evaluation result of SNEDDS DCM fraction

Sample	% Transmittan	Droplet size (nm)	PDI (-)	Zeta potential (mV)
SNEDDS dcm fraction	70.12±0.09	50.6±1.37	0.206±0.003	-15.35±0.81

Note: All tests were repeated (n=3)

Physical stability test

Physical stability is an important parameter that must be met by the optimum SNEDDS formula because it describes the durability of a product according to certain limits during storage and use where the product still has the same properties and characteristics as at the time of manufacture. Based on the results of the physical stability test, it is known that all test samples showed no separation, precipitation, cracking or creaming. Surfactants greatly affect the surface of the emulsion droplet by reducing the interfacial free energy and providing a mechanical barrier for coalescence to occur and producing spontaneous thermodynamic dispersion [18]. Co-surfactants increase the fluidity interface by penetrating the surfactant film creating empty spaces between surfactant molecules [19].

Table 2: Quantitative stability assessment

Test condition	Droplet size (nm)		PDI		Zeta potential (mV)	
	Before	After	Before	After	Before	After
Centrifugation	50,6±1,375	50,1±1,005	0,206±0,004	0,206±0,002	-15,35±0,809	-16,24±0,20
Heating–Cooling	50,1±1,376	100,5±2,009	0,204±0,005	0,206±0,023	-16,62±0,129	-26,03±0,21
Freeze–Thaw	50,6±1,377	50,8±1,5	0,202±0,002	0,205±0,004	-16,245±0,18	-15,34±0,809

Note: Note: All tests were repeated (n=3)

The emulsification time was 1 min 12.67 sec. It was 500 ml of distilled water, which was conditioned on the top stirrer at 120 rpm. A total of 1 ml of SNEDDS was dropped into the medium quickly. SNEDDS are designed to emulsify spontaneously and rapidly (within seconds to minutes) upon contact with aqueous fluids. An optimal formulation should emulsify rapidly [20, 21].

Dissolution test

The release test was carried out for 8 h to see the amount of alpha-mangostin in both the SNEDDS preparation and its fractions. The percentage value of drug release in the SNEDDS preparation is shown in the fig. below.

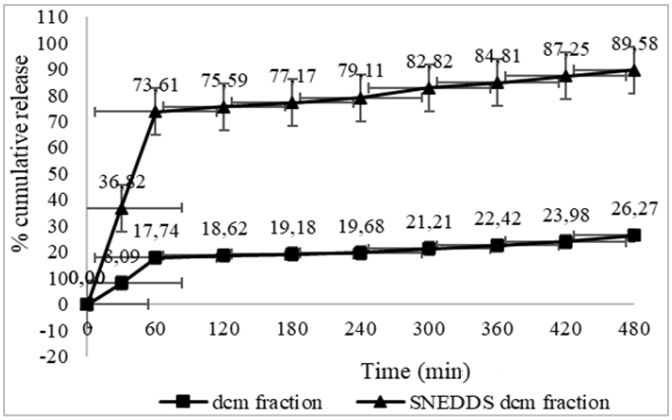


Fig. 3: Cumulative release profile of alfa mangostin in dcm fraction and SNEDDS dcm fraction (*Note: over 8 h in phosphat buffer pH 7,4; n=3*)

The results of the release test of the dcm fraction preparation showed that the release of alpha mangostin at the 30th min was 8.085±0.0015%, while at the 480th min (8 h) it produced a release of 26.27±0.004%. Meanwhile, the release test of the SNEDDS preparation of the dcm fraction showed that the alpha mangostin content at the 30th min was 36.82±0.367% and at the 480th min (8 h) it produced a % release of 89.58±0.0215%. This shows that there is a difference in the % release between the particle forms of the preparation, the smaller the particle size, the easier it is to dissolve in the carrier and this is evident if the release of the dcm fraction in powder form is smaller than the release value of the SNEDDS preparation of the dcm fraction. The dissolution results of SNEDDS are greater than without SNEDDS because SNEDDS increases the solubility and absorption of drugs, especially drugs that are difficult to dissolve in water. SNEDDS forms nanoemulsions that increase the surface area of drug interaction with water, thereby accelerating the dissolution and absorption process into the body [22, 23].

When SNEDDS is added to water, this system spontaneously forms nanoemulsions (oil particles that are evenly distributed in water). The size of these nanoparticles is very small, increasing the surface area of drug interaction with water. With the increase in surface area, the drug can dissolve faster and more in body fluids, thereby increasing the dissolution rate.

In general, SNEDDS enhance drug dissolution, particularly for poorly water-soluble drugs (BCS Class II and IV) through several key mechanisms such as increasing the specific surface area (nanoplet size), keeping the drug dissolved in the lipid core, and presenting the drug in a pre-dissolved state. The very small nanodroplet size (typically 20–200 nm) that spontaneously form when SNEDDS mix with body fluids (such as gastric or intestinal fluids) results in a very large total surface area. This drastic increase in surface area allows for more efficient and rapid interaction between the drug and the surrounding fluid, significantly accelerating the dissolution rate [24].

The drug (which is often hydrophobic or insoluble in water) is pre-dissolved in the lipid core (oil phase) of the emulsified droplets. This system stabilizes the drug in the dissolved state and prevents it from precipitating or recrystallizing in the aqueous environment of the gastrointestinal tract. The drug remains dissolved and ready for absorption. The SNEDDS formulation maintains a high drug load within the lipid droplet core, effectively keeping the hydrophobic drug in a dissolved state even after dilution in aqueous gastrointestinal media [25].

Because the drug is molecularly dissolved in the lipid formulation before consumption, SNEDDS essentially "bypasses" the dissolution stage that is typically time-consuming for conventional solid dosage forms (such as tablets or powder capsules). The drug is available in a dissolved state, ready for absorption by the body immediately after emulsifying. The pre-dissolved drug delivery in a nanoemulsion system itself bypasses the rate-limiting dissolution stage, resulting in a more rapid onset of action and improved bioavailability [26].

The enhanced *in vitro* dissolution of SNEDDS explicitly correlates with the hypothesis of enhanced *in vivo* oral bioavailability, primarily because SNEDDS overcome the rate-limiting stage of dissolution for poorly water-soluble drugs (BCS Class II and IV).

While the dialysis bag method is a common technique for assessing *in vitro* drug release from colloidal carriers, it is important to recognize its limitations for lipid-based systems such as SNEDDS. In this approach, the released drug must diffuse across a semipermeable membrane before being quantified in the external medium. Because the diffusion through the dialysis membrane can become rate-limiting, especially when drug release from the carrier is fast or the membrane has restricted permeability, the resulting profiles may underestimate the actual release from the formulation and distort kinetic interpretation. This barrier effect has been demonstrated in studies of nanoparticle and liposomal carriers, where membrane resistance rather than release from the carrier dominated the apparent release kinetics, leading to lower measured release rates or lag phases that are not indicative of the true delivery performance.

Alternative or complementary methods, such as direct sampling with ultrafiltration or continuous-flow dissolution systems, may provide additional insight into the intrinsic release behavior of dispersed lipid systems and improve *in vitro–in vivo* correlation predictions. However, due to the convenience and widespread use of the dialysis approach, careful interpretation and acknowledgment of its limitations are required when applied to lipid-based drug delivery systems [27].

A limitation of the present study is that we did not include a pure α-mangostin suspension as an independent control in the dissolution experiments. Including such a suspension control is considered a standard practice in *in vitro* release/dissolution studies of lipid-based drug delivery systems because it allows direct quantification of the enhancement provided by the formulation relative to the unformulated drug. For example, recent work with SNEDDS and lipid nanocarrier systems has shown that the dissolution of poorly water-soluble drugs in formulation can be significantly higher than the corresponding pure drug, with unformulated drug suspensions often exhibiting very low dissolution rates under identical test conditions.

Therefore, while the present comparison between the DCM fraction and SNEDDS-DCM fraction demonstrates improved dissolution behavior, we recognize that the lack of an explicit pure α-mangostin suspension control may underestimate the relative magnitude of enhancement. Future studies should include this control to fully quantify the formulation's impact on dissolution and support better *in vitro–in vivo* correlation [28].

Based on the dissolution test results obtained, it was continued with a release kinetic analysis including calculations with standard models (zero-order, first-order, Higuchi, Korsmeyer-Peppas). And the results of the R2 calculation obtained data for order 0 were 0.5882, order 1 0.8852, Higuchi 0.6945 and Korsmeyer-Peppas of 0.8556. So we can conclude that the release kinetics for SNEDDS dcm fraction follows order 1 where the R2 value approaches 1. This means that the drug release rate is directly proportional or depends on the remaining drug concentration in the dosage matrix. First-order release generally occurs in systems where the dissolved drug concentration in the release medium is low, or when the drug diffuses through a porous matrix. The n value has also been interpreted in the text to provide mechanistic insights into drug release behavior. The Korsmeyer–Peppas model is used to characterize the drug release mechanism from dispersed systems, where the exponent n indicates the type of transport mechanism (e. g., Fickian diffusion vs. non-Fickian/anomalous transport). Below, we include the interpretation of the n value according to established criteria (e. g., $n \leq 0.45$ for Fickian diffusion, $0.45<n<0.89$ for anomalous transport, and $n \geq 0.89$ for Case II transport in a plate system). The resulting n value is 0.993, which represents a non-Fickian (Case II) transport interpretation involving diffusion and interfacial relaxation, which is in accordance with currently published standards for kinetic modeling in controlled delivery systems and colloids. The release rate will slow down as the amount of drug remaining in the dosage decreases [24, 29].

Table 3: Summary of release kinetic model fits and parameters

Kinetic model	Regresion equation	R^2	k (rate constant)	n	Release mechanism interpretation
Zero order	y = 4,563x+57,844	0,5882	4,563	—	Poor fit; release does not occur at a constant rate
First order	y = 0,3739x+0,8531	0,8852	0,3739	—	Concentration-dependent release; best kinetic fit
Higuchi	y = 17,849x+42,611	0,6945	17,849	—	Diffusion contributes, but is not the sole rate-limiting step
Korsmeyer–Peppas	y = 0,933x-1,2716	0,8556	0,053	0,933	Non-Fickian (Case-II) transport involving diffusion and interfacial relaxation

R^2: coefficient of determination; k: release rate constant; n: Korsmeyer–Peppas exponent

Mechanistically, excipients in SNEDDS play distinct roles beyond merely composing the formulation: Isopropyl myristate functions primarily as the lipophilic solvent for α-mangostin, enhancing drug solubility in the preconcentrate and supporting spontaneous nanoemulsion formation upon aqueous dilution. The oil's physicochemical properties, such as chain length and polarity, govern the curvature of the oil–water interface, influencing both droplet size and drug loading capacity. Lower oil content typically facilitates rapid emulsification and smaller droplet radii, while higher oil loading can increase capacity at the expense of emulsification efficiency. This balance is crucial for optimizing SNEDDS performance. Tween 20 is a non-ionic surfactant with a high hydrophilic–lipophilic balance (HLB), which reduces interfacial tension and stabilizes the newly formed nanoemulsion droplets. Its polyoxyethylene chains provide steric stabilization, limiting coalescence and contributing to uniform droplet size distribution. The presence of Tween 20 also enhances wettability of the oil-drug phase, a factor directly linked to improved drug dispersion and dissolution in gastrointestinal fluid. Propylene glycol acts as a cosurfactant/solvent modifier that increases the flexibility of the surfactant film at the oil-water interface, lowering the energy barrier for spontaneous emulsification. It improves the miscibility between the surfactant and oil, facilitating more efficient packing at the interface and potentially leading to finer droplet formation. Its relatively low molecular weight and amphiphilic character help tailor the microstructure of the nanoemulsion, which can impact drug release kinetics and robustness against dilution.

Collectively, the oil surfactant cosurfactant interplay dictates the self-emulsification region in phase behavior and ultimately modulates droplet size, release kinetics, and physical stability. Our targeted selection of isopropyl myristate, Tween 20, and propylene glycol was guided by solubility screening and emulsification efficiency considerations, consistent with recent formulation strategies in SNEDDS research [30].

CONCLUTION

Physical evaluation of SNEDDS dcm fraction showed an average particle size of 50.6 nm, zeta potential-15.35±0.81 mV, PdI value 0.206±0.0036, transmittance 70.125%, emulsification time 1 min 12 sec. The results of physical stability observations showed no physical changes in separation, precipitation, creaming and cacking of the SNEDDS dcm fraction preparation. Dissolution tests of SNEDDS dichlormethane fraction and dcm fraction preparations showed significant differences quantitatively of 26.27±0.004% and 89.58±0.0215%. This study successfully developed a stable SNEDDS formulation that significantly enhanced the in vitro dissolution rate and extent of alpha-mangostin from the dcm (dichloromethane) fraction of mangosteen rind. This substantial dissolution enhancement,–which effectively overcomes the compound's intrinsic solubility limitations, demonstrates a highly feasible and effective strategy to address the solubility-limited bioavailability of mangosteen xanthones. Characterization of the physical stability and superior dissolution performance validates SNEDDS as a promising drug delivery platform for future alpha-mangostin therapeutic applications.

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Nil

AUTHORS CONTRIBUTIONS

Author contributions: Ari Widayanti: concept and design, data acquisition, data analysis, manuscript. Mahdi Jufri: concept and research design, critical revision of manuscript, supervision, and final approval. Silvia Surini: data analysis, critical manuscript, supervision, supporting materials, final approval. Berna Ellya: data analysis, critical manuscript, supervision, supporting materials, final approval.

CONFLICT OF INTERESTS

We declare that we have no conflict of interest with this research

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