

Solid lipid nanoparticles of mangosteen peel extract based on monoacylglycerol-diacylglycerol-rich fat and stearic acid: Study on physicochemical properties and encapsulation efficiency

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ABSTRACT

Mangosteen peel (*Garcinia mangostana L.*) contains phenolics and high antioxidant activity, but encapsulation including solid lipid nanoparticles (SLN), is required to provide stability and a good delivery system. Therefore, this study aimed to determine the characteristics of SLN of mangosteen peel extract produced using the double emulsion method based on monoacylglycerol (MAG) and diacylglycerol (DAG)-rich fat from coconut stearin and stearic acid. The results showed that higher concentrations of MAG-DAG-rich fat led to smaller particle sizes and increased entrapment efficiency (EE). However, the application of higher mangosteen peel extract increased the particle size and decreased EE. The use of 40 % MAG-DAG-rich fat and 15 % mangosteen peel extract produced the best SLN characteristics, with EE of $97.73 \pm 0.33\%$, particle size of 373.00 ± 20.30 nm, polydispersity index (PI) of 1.52 ± 0.08 , total flavonoid content of 3.19 ± 0.29 mg QE/g, and antioxidant activity (IC₅₀) of 235.12 ± 2.93 ppm. SLN showed spherulite-shaped particles, where mangosteen peel extract was trapped and dispersed in the nanosphere system. The preparation of SLN-mangosteen peel extract based on MAG-DAG-rich fat from coconut stearin and stearic acid effectively provided encapsulated bioactive compounds of mangosteen extract with good physicochemical properties.

Introduction

Mangosteen peel (*Garcinia mangostana L.*) is a by-product of mangosteen fruit often wasted despite containing various bioactive compounds, specifically phenolic compounds that act as antioxidants including xanthones, anthocyanins, tannins, flavonoids, and phenolic acids (Indiarto et al., 2023; E. T. de V. Silva et al., 2024). These compounds are semipolar, which contributes to the extract's antioxidant, anti-inflammatory, and antimicrobial properties. Bioactive compounds in mangosteen peel can be effectively extracted with the ultrasonic-assisted extraction (UAE) method (Bonfiglia et al., 2017) using ethyl acetate which is a low-toxicity and semi-polar solvent (Akbar et al., 2021; Rocha et al., 2023).

Mangosteen peel extract is unstable to temperature, light, oxygen,

and other environmental factors (Kusmayadi et al., 2019; Sriwidodo et al., 2022). This may cause limitations to the proper absorption of bioactive compounds from food products when consumed. Therefore, encapsulation technology such as solid lipid nanoparticles (SLN) is needed to protect bioactive compounds and control their release (Alsaad et al., 2020; Mirchandani et al., 2021; Mishra et al., 2018; Subroto et al., 2023). Phenolic compounds in the mangosteen peel extract act as bioactive compounds, which are the core ingredients encapsulated by a solid lipid matrix known as SLN-mangosteen peel extract. SLN is applied as a good delivery system for active compounds using lipid matrix and surfactants with a diameter of 40–1000 nm and a spherical shape (Duan, Dhar, Patel, Khimani, Neogi, Sharma, Kumar, et al., 2020; Nemati et al., 2024).

SLN can be synthesized with a solid lipid matrix, including palmitic

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acid or stearic acid (Öztürk et al., 2019), which stabilizes active compounds and slows down the release of active ingredients (Shylaja and Mathew, 2016). However, palmitic acid and stearic acid are non-health-beneficial saturated fatty acids, leading to the need for substitution with other better lipids such as monoacylglycerol (MAG) and diacylglycerol (DAG). MAG and DAG can improve emulsification during SLN fabrication, so that the entrapment efficiency and loading capacity increased (Feltes et al., 2013; Subroto et al., 2022). Furthermore, both MAG and DAG commonly obtained from coconut stearin rich in laurate (a medium-chain fatty acid) have antimicrobial properties and act as immune modulators. These are nonionic surfactants capable of improving lipid profile in SLN due to the ability to prevent body fat accumulation and reduce low-density lipoprotein (LDL) (Anikisetty et al., 2018; Dhara et al., 2013; Subroto and Indiarto, 2020). MAG-oleic acid was reported that it has strong anti-atherosclerotic, antioxidant, and protein glycation inhibitory activities (Cho et al., 2010), while DAG-rich rice bran and sunflower oils can modulate lipid profile and cardiovascular risk factors in Wistar rats (Anikisetty et al., 2018).

Encapsulation of hydrophilic compounds such as mangosteen peel extract using a solid lipid matrix in SLN is generally difficult, leading to the application of solvents with the inverse mini emulsion method but organic solvents can cause toxic residues. Fabrication of solvent-free SLN using the principle of melt dispersion and double emulsion ($W_1/O/W_2$) is safer. This method is more effective for encapsulating hydrophilic compounds while requiring lipophilic and hydrophilic emulsifiers (Luo and Wei, 2023; Peres et al., 2016).

The selection of lipid type and percentage greatly affects the ability to bind compounds, as well as SLN size and dispersion (Peres et al., 2016). The concentration of active compounds contributes to the entrapment efficiency (EE) and other characteristics of SLN. Therefore, this study aimed to determine the physicochemical properties of SLN-mangosteen peel extract produced using the double emulsion method based on MAG-DAG-rich fat from coconut stearin and stearic acid.

Materials and methods

Materials

Mangosteen peel, ethyl acetate (70 %), MAG-DAG rich fat resulting from glycerolysis of coconut stearin containing MAG of 55.79 %; DAG of 34.30 %; and TAG of 9.92 %, stearic acid, Tween 80, aquadest, and other chemicals with analytical grade specifications.

Mangosteen peel extraction

UAE was used for mangosteen peel extraction according to the procedure described by (Plaza et al., 2021). Mangosteen peel was boiled at 100 °C for 4 min to inactivate polyphenol oxidase, then soaked in cold water for 3 min and dried with a cabinet drier at 50 °C for 48 h. 100 g of dried mangosteen peel was reduced in size to obtain a 60 mesh powder extracted using 500 ml of ethyl acetate with a concentration of 70 % at a ratio of 1:5 (w/v), assisted by probe ultrasonication (Sonicator SVC-3000NA) with an amplitude of 65 % for 45 min. The remaining solvent was evaporated using a rotary evaporator (R-300, BUCHI, Switzerland), and then the obtained mangosteen peel extract was stored in a refrigerator (3–4 °C) until used.

Preparation of SLN-Mangosteen peel extract

SLN-Mangosteen peel extract was prepared using the double emulsion and melt dispersion method (Peres et al., 2016). During this process, 6 g of solid fat comprising stearic acid and MAG-DAG-rich fat (emulsion capacity of 94.52 % and the emulsion stability of 99.90 %) was stirred and heated at the temperature ± 70 °C, and then 2 mL of mangosteen peel extract was added. The mixture was homogenized at

13,000 rpm for 1 min at 60 °C, followed by ultrasonication for 2 min to form the first emulsion (W_1/O), and 60 mL of Tween 80 was added. This combination was homogenized again, then ultrasonication was performed for 5 min until the double emulsion ($W_1/O/W_2$) was formed. The double emulsion was poured into 500 mL of cold water (5–10 °C) and stirred for 1 min to enhance SLN solidification. The result was ultrasonicated at 45 % amplitude (500 W) for 3 min to obtain dispersed SLN that was frozen and lyophilized using a freeze dryer at –50 °C for 68 h, with Table 1 presenting the preparation formulation.

Determination of total phenolic compounds

The total phenolic compounds were determined according to the procedure described by (Siddhuraju and Becker, 2007). A test tube was filled with 0.5 mL mangosteen peel extract, followed by 2.5 mL of Folin Ciocalteu 10 %, 2 mL of Na₂CO₃ 7.5 %, and distilled water before incubating for 30 min. A spectrophotometer (UV-9200) at a wavelength of 765 nm was used to measure absorbance by applying gallic acid as a standard.

Determination of total flavonoid

The determination of total flavonoid was carried out following the procedure described by (Chang et al., 2002). Mangosteen peel extract solution (0.5 mL) was combined with methanol (3 mL), aluminium chloride 10 % (0.2 mL), and potassium acetate 1 M (0.2 mL), then incubated for 30 min in a dark room. Absorbance was measured at a wavelength of 415 nm with a spectrophotometer (UV-9200) applying quercetin as standard, and total flavonoid was expressed in the form of mg QE/g.

Determination of antioxidant activity

Antioxidant activity was determined according to the procedure described by Indiarto et al. using the DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical scavenging activity, expressed in IC₅₀ values (Indiarto et al., 2023). Approximately 2.5 mL of stock solution sample (100 ppm) was mixed with 0.5 mL of DPPH, then incubated for 30 min and the absorbance was measured at 517 nm by a UV-Vis spectrophotometer.

Determination of particle size and polydispersity index (PI)

The particle size and PI were determined using a HORIBA SZ-100 particle size analyzer, according to the method described by (Sepeliev and Reineccius, 2018). 1 mL sample was taken and diluted 200,000-fold in distilled water, then the sample was analyzed using HORIBA SZ-100 at a scattering angle of 90°, and the polydispersity index was expressed as a representation of the Scattering Light Intensity.

Determination of entrapment efficiency (EE) and loading capacity

EE was determined according to the procedure described in the study performed by (Cilek et al., 2012). Meanwhile, loading capacity was estimated following the calculations performed by (Muhamad Sahlan Adam Muhamad Fadhan, 2019). These were based on total and surface phenolic content measured with a UV spectrophotometer (UV-9200), and EE value was calculated using Eq. (1).

$$EE (\%) = \frac{EPC}{TPC} = \frac{TPC - SPC}{TPC} \times 100 \quad (1)$$

Loading capacity (LC) was also determined by analyzing the total phenolic content in the lyophilized SLN using a freeze dryer. LC was determined by measuring the ratio of total phenolic compounds trapped to the dry weight of solid lipid nanoparticles. Phenolic content was measured using a UV-Vis spectrophotometer (UV-9200) at a wavelength

Table 1
SLN-mangosteen peel extract formulas.

Formula	Solid lipid MAG-DAG-rich fat (%w/w)	Stearic acid (% w/w)	Surfactant Tween 80 (% w/w)	Drug Mangosteen peel extract (%w/w)
A1	20	80	20	15
A2	30	70	20	15
A3	40	60	20	15
A4	40	60	20	5
A5	40	60	20	25
A6 (Control)	40	60	20	0

of 725 nm, and the value was calculated with Eq. (2).

$$LC (\%) = \frac{TPC - SPC}{Dry weight of SLN} \times 100 \quad (2)$$

Determination of SLN morphology and particle structure

The morphology of nanoparticles was analyzed with a TM3000 Tabletop Microscope (M. P. Silva et al., 2019), during which SLN-mangosteen peel extract was positioned on carbon tapes and mounted on an aluminium rod. Subsequently, micrographs were captured at a magnification level of 3000 and a voltage of 15 kV. SLN structure was analyzed using a TEM model HT7700. 1 drop of diluted SLN was placed on a copper grating. The samples were stained with uranyl acetate solution 5 % (w/v) to enhance contrast microscopy and coating with a carbon film. Subsequently, micrographs were captured at a magnification level of 10,000, 20,000, and 50,000.

Analysis of polymorphism

The determination of polymorphism was carried out using the X-ray diffraction method (SmartLab, Australia). In this context, SLN sample was placed on a serrated glass plate and supplied with X-rays in the degree (2θ) range of 3 – 30, Kα filter voltage of 40 kV, and electric current of 30 mA (Le Révérend et al., 2010).

Analysis of functional groups

Functional groups were determined using FTIR-ATR (Nicolet iS10 FTIR) according to the procedure described by (Nurulhidayah et al., 2013). During this process, SLN sample was positioned on an ATR crystal at a controlled temperature of 25 °C. The FTIR spectra were scanned 50 times in the mid-infrared region at a wave number of 400–4000 cm⁻¹ with a resolution of 4 cm⁻¹, and the analysis results were presented in the form of transmittance spectra.

Analysis of thermal properties

Thermal properties were determined using a differential scanning calorimeter (Shimadzu DSC-60 Plus, Japan) according to the method by (Tomaszewska-Gras, 2013). SLN sample (10 mg) was positioned in a tightly closed aluminum pan, then the analysis was performed by heating the pan from –30 °C to 80 °C at a rate of 5 °C/min.

Statistical analysis

The data were statistically analyzed by one-way ANOVA using PASW Statistics 18. Duncan's test was then applied to investigate the significant differences at a level of $p < 0.05$.

Results and discussion

Characteristics of mangosteen peel extract

Table 2 shows that mangosteen peel extract is thick and has a water

Table 2
Characteristics of mangosteen peel extract isolated by ethyl acetate 70 %.

Characteristics	Value
Water content	28.66 ± 1.27 %
Total phenolic content	529.40 ± 4.07 mg GAE/g
Total flavonoid content	30.02 ± 0.29 mg QE/g
Antioxidant activity IC ₅₀	10.20 ± 0.34 ppm

content of 28.66 ± 1.27 %, along with a quite high total phenolic content of 529.40 ± 4.07 mg GAE/g. This phenolic content can be influenced by the variety and maturity level of mangosteen, post-harvest method, storage conditions, drying method, extraction method, types of solvents, and other factors (Netravati et al., 2024). Additionally, blanching can inactivate the polyphenol oxidase enzyme, which oxidizes phenolic compounds. The ethyl acetate solvent used is semipolar and capable of extracting xanthones (the highest polyphenols in mangosteen peel) more effectively than ethanol [32]. UAE applied is better than maceration (Bonfiglia et al., 2017), with controllable amplitude and frequency, as well as faster speed, and higher purity (Marhamati et al., 2020; D.-P. Xu et al., 2017).

Extract flavonoid content was 30.02 ± 0.29 mg QE/g, which was relatively high due to the ripe mangosteen peel (Suttirak and Manurakchinakorn, 2014). This value was higher than the flavonoid content of mangosteen peel extract by ethanol 70 %, namely 17.66 mg QE/g (Widowati et al., 2020). The ethyl acetate solvent used for the extraction process could also maximally attract flavonoid compounds with low polarity due to the large number of methoxy groups (M. Xu et al., 2019). The high phenolic and flavonoid content of mangosteen peel extract was accompanied by a very strong antioxidant activity (IC₅₀) of 10.20 ± 0.34 ppm. These two compounds are suitable as an alternative source of antioxidants because of their similarity with Vitamin C (IC₅₀ = 10.47 ppm) (Ihsanpuro et al., 2022). Flavonoids function as antioxidants mainly by donating hydrogen atoms from hydroxyl groups (OH) and chelating metal ions.

Characteristics of SLN-mangosteen peel extract

Particle size, polydispersity index, and entrapment efficiency

SLN formulas A1, A2, and A3 had varying percentages of MAG-DAG-rich fat, while A4, A5, and A6 comprised different percentages of mangosteen peel extract. EE, particle size, and PI of SLN-mangosteen peel extract are presented in Fig. 1 and Table 3.

The use of solid lipids in the form of stearic acid and MAG-DAG-rich fat combination at various percentages significantly affected ($p < 0.05$) the particle size by producing a small-sized SLN. This was due to the presence of MAG-DAG-rich fat with lower melting points and crystallinity index compared to stearic acid (Shah et al., 2021). According to Fig. 1 and Table 3, the particle size of SLN-mangosteen peel extract increased significantly ($p < 0.05$) with the increasing stearic acid used. This was attributed to the melting point of stearic acid (± 69.6 °C) being higher than MAG-DAG-rich fat (43.3 - 45.2 °C), thereby reducing the homogenization process effectiveness and generating a larger particle size (Hatefi and Farhadian, 2020; Kumar et al., 2017). The particle size in formula A3 was smaller than A2 and A1 despite using MAG-DAG-rich

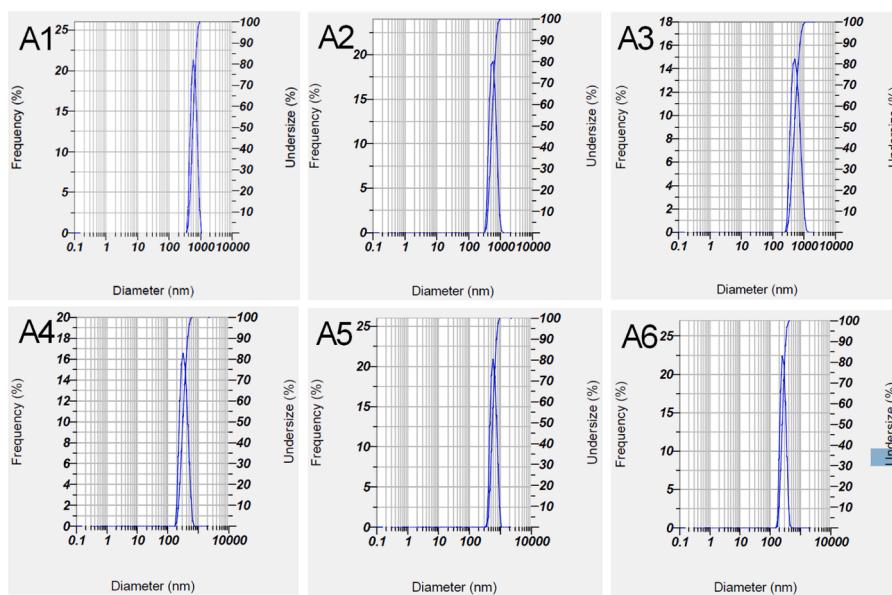


Fig. 1. Particle size distribution of SLN-mangosteen peel extract.

Table 3

Entrapment efficiency, particle size, and polydispersity index of SLN-mangosteen peel extract.

Formula	Particle size (nm)	Polydispersity Index (PI)	Entrapment Efficiency (EE) (%)
A1	450.80 ± 20.40 ^d	2.12 ± 0.11 ^d	81.04 ± 0.49 ^a
A2	380.30 ± 18.80 ^{bc}	1.69 ± 0.09 ^c	96.40 ± 0.37 ^b
A3	373.00 ± 20.30 ^b	1.52 ± 0.08 ^b	97.73 ± 0.33 ^c
A4	316.70 ± 48.50 ^b	1.44 ± 0.08 ^b	98.47 ± 1.14 ^c
A5	414.80 ± 20.80 ^c	2.01 ± 0.10 ^d	96.87 ± 0.32 ^b
A6 (Control)	257.20 ± 16.40 ^a	0.84 ± 0.05 ^a	—

Different letters in the same column indicated significant differences at the 5 % level, according to Duncan's test.

fat with the highest percentage of 40 % w/w in A3. This showed the role of MAG-DAG-rich fat as an excellent emulsifier in homogenizing the emulsion system in SLN. Increasing the percentage of MAG-DAG-rich fat reduced the surface tension of the liquid lipid and water phases to achieve a more homogeneous and stable mixture (Karthik et al., 2016).

SLN size changed with the increase in the percentage of mangosteen peel extract, corresponding with (Dawre et al., 2021), who reported that increasing rifampicin concentration expanded the particle size. In this context, the use of 20 mg produced a particle size of 458 nm, while 40 mg generated 584 nm. Based on Table 3, SLN in all formulas still had a suitable particle size ranging from 257.2 - 450.8 nm. Additionally, the fairly large size could be affected by the double emulsion method, which tended to produce larger particles than primary emulsions (Duan, Dhar, Patel, Khimani, Neogi, Sharma, Siva Kumar, et al., 2020). The particle size of SLN still followed the excellent range between 50–1000 nm (Nemati et al., 2024), but it varied as shown by a high PI, which could be caused by agglomeration. MAG-DAG-rich fat and Tween 80 were used as nonionic surfactants to produce uncharged SLN that experienced attractive forces between other fat particles, leading to agglomeration and larger particle sizes.

Table 3 shows that EE of formulas A1, A2, and A3 increased significantly ($p < 0.05$) with an increasing percentage of MAG-DAG-rich fat. MAG-DAG-rich fat improved encapsulation efficiency of SLN through mechanistic, namely MAG and DAG act as co-emulsifiers and modify the crystalline structure of the solid lipid core, so that their presence disrupts the highly ordered crystalline arrangement of pure triglycerides, reducing the likelihood of drug expulsion and enhancing drug loading. This disordered structure provided more space for drug molecules, leading to higher encapsulation efficiency (Alfutaimani et al., 2024; Shi et al.,

2019). The combination of stearic acid and MAG-DAG-rich fat enhanced the amorphous nature of the solid lipid matrix, thereby reducing the general crystallinity and expanding the space for drug or active compound entrapment. The combination of solid fat comprising different stearic acid chain structures (C18:0) with MAG-DAG-rich fat dominated by lauric acid (C12:0) and oleic acid (C18:1) will form imperfect crystals that have bigger space to accommodate more mangosteen peel extract.

The percentage of MAG-DAG-rich fat (40 % w/w) in A3 produced the highest EE, reaching 97.73 %. Additionally, the use of mangosteen peel extract at various concentrations (A3, A4, A5) affected EE value, where higher extract generated lower EE value. The difficulty in using the coating material to entrap bioactive compounds was amplified with the increasing number of core materials or active compounds. However, SLN formulas A3, A4, and A5 produced good EE, among which A3 comprising 40 % MAG-DAG rich fat and 15 % mangosteen peel extract, was selected as the best choice based on considerations of particle size characteristics, PI, and EE value. A3 was studied for its physicochemical characteristics, including particle morphology and structure, polymorphism, functional groups, and thermal properties.

Morphological characteristics and particle structure

SLN surface morphology was characterized with a scanning electron microscope (SEM) using the formulation of 0 % extract as a control and 15 % extract as the best treatment. The surface morphology and the structure of SLN-mangosteen peel extract are presented in Fig. 2 and Fig. 3.

According to Fig. 3, SLN surface morphology was not significantly different where the particles appear small in the form of spherulites. These results showed that the incorporation of 15 % extract into the nanoparticles was compatible with the application and did not affect the

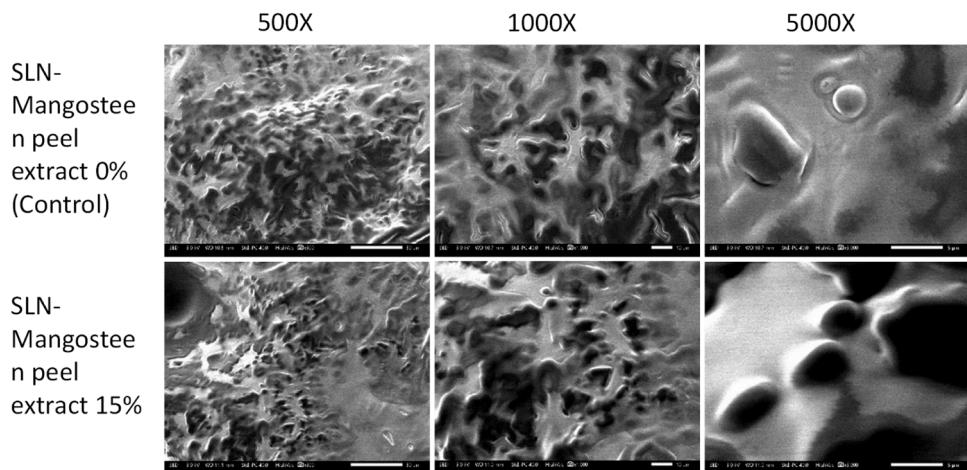


Fig. 2. SLN morphology with 500x, 1000X, and 5000X magnification using SEM.

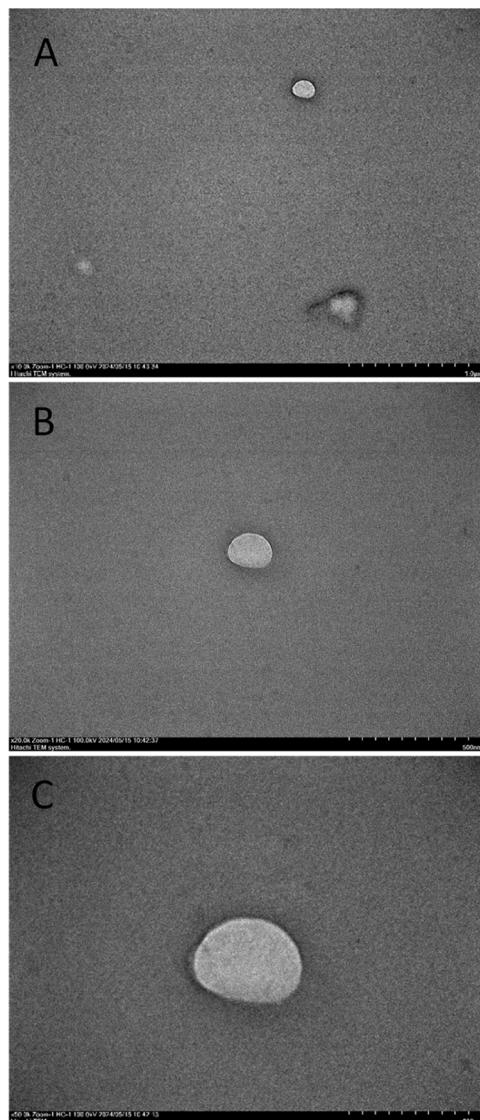


Fig. 3. Structure of SLN-mangosteen peel extract with magnification (A) 10000X, (B) 20000X, (C) 50000X using TEM.

formation of fat crystals in SLN. However, agglomeration might occur in SLN when performing lyophilization with a freeze dryer. This was also confirmed by the high polydispersity index data ranging from 0.84 to 2.12 (Table 3). Agglomeration can be caused by the use of MAG-DAG-rich fat and Tween 80, which are nonionic surfactants that can produce uncharged SLN that leads to aggregation during freeze-drying. During this process, the water phase would sublime to generate a precipitate or combined SLN compared to forming separate particles (Peres et al., 2016; Subroto et al., 2022).

SLN structure is presented in Fig. 3, while Fig. 3A shows a nearly identical spherical shape <500 nm. The results of TEM analysis were significantly smaller than particle size analysis (PSA) because PSA could be biased in cases when a single particle appeared as a group (Mahajan et al., 2018). The presence of compounds/substances detected in TEM analysis was darker due to the staining by uranyl acetate, which absorbed more in heavier masses. Black spots inside the particles in Fig. 3B showed that mangosteen peel extract was trapped in the lipid matrix of SLN. Scattered black spots denoted even distribution of the trapped mangosteen peel extract to form a nanosphere system in the W/O/W emulsion (Martien et al., 2012; Subroto et al., 2022). This result confirmed that despite the fairly high PI value, each particle formed nanospheres appearing smaller than SLN. Fig. 3C shows a bright light contrast pattern on the outer layer of the nanoparticles, suggesting the presence of a surfactant layer.

Polymorphism

SLN diffractogram containing 0 % mangosteen peel extract (control) and 15 % mangosteen peel extract (the best treatment) is presented in Fig. 4. The diffractogram shows an insignificantly different polymorphic pattern, namely in the form of low crystalline towards amorphous or semicrystalline. Semicrystalline structures of SLN have the advantage that they offer an optimal balance between drug loading, where imperfections and amorphous regions create more space for drug molecules to be incorporated. In addition, semicrystalline structures allow for a slower and more controlled release profile by restricting drug diffusion within the lipid core (Akombaetwa et al., 2023; Viegas et al., 2023). However, semicrystalline structures have disadvantages, namely semicrystalline SLNs may have less structural rigidity, making them more prone to deformation, aggregation, or instability over time. Semicrystalline structures can still undergo polymorphic transitions, leading to gradual drug leakage, and decreased long-term drug stability (Bertoni et al., 2021; Makoni et al., 2019). The amorphous form was not stable to storage temperature compared to the more stable crystalline which had difficulty dissolving active compounds (Sarabu et al., 2020), thereby affecting the loading capacity (Wardhana, 2017). The polymorphic pattern was not significantly different, implying that the incorporation

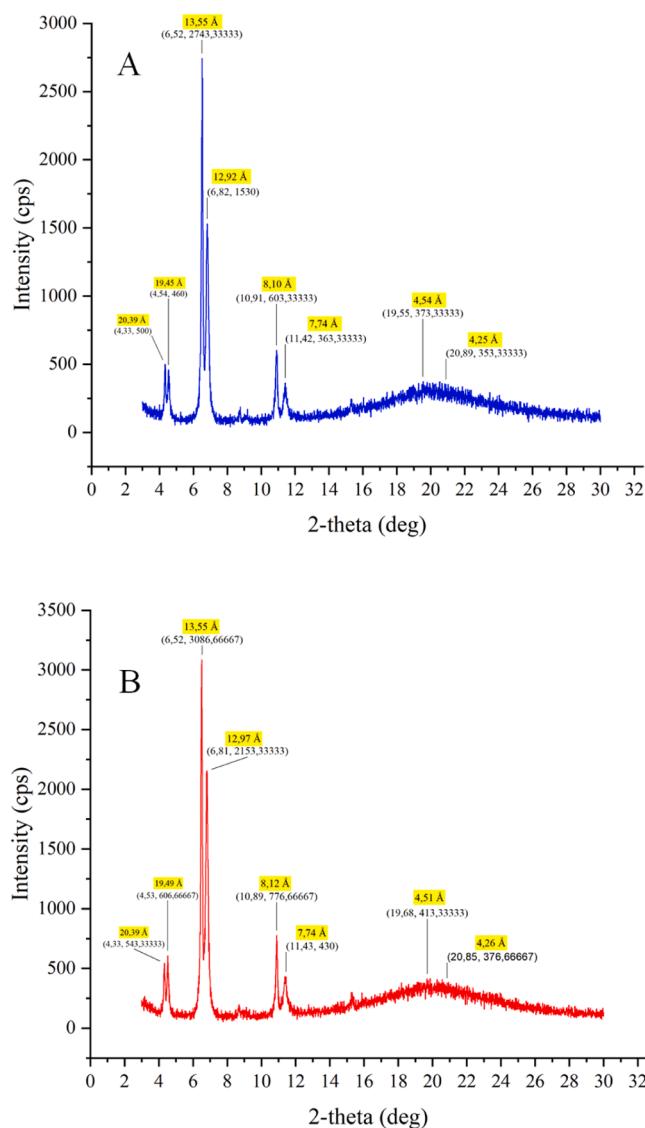


Fig. 4. Diffractogram of SLN-mangosteen peel extract 0 % (control) (A) and SLN-mangosteen peel extract 15 % (B).

of 15 % mangosteen peel extract failed to disrupt the entire SLN structure, as well as change the lipid polymorphic form and general properties of the nanoparticles. Additionally, the short spacing (d value) showed the presence of β and β' crystals in both SLN types because the β crystal had a d value = $\pm 4.58 \text{ \AA}$ and β' had a d value = $3.80 - 4.20 \text{ \AA}$. The crystal form was affected by the composition of stearic acid which comprised polymorphic β (Rahmawan et al., 2012). Meanwhile, MAG and DAG contained a mixed polymorphic form of β and β' crystals, with some tending to change when cooled to a more stable β (Basso et al., 2010; Saberi et al., 2012; Y. Xu et al., 2016).

Functional groups

FTIR spectra of SLN-Mangosteen peel extract 0 % (Control) and 15 % presented in Fig. 5 show similar peaks and wave numbers. This implied that no chemical interaction was formed between mangosteen peel extract and lipid matrix. Functional group interactions can affect the antioxidant activity of SLN-Mangosteen peel extract. These interactions determine the ability of a molecule to donate electrons or hydrogen atoms, chelate metal ions, and stabilize free radicals. These interactions occur within the antioxidant molecules or with their surrounding environment, such as lipid matrices (Doktorovová et al., 2014). In addition,

the difference in polarity between mangosteen peel extract and lipid matrices can also affect the interaction of functional groups and antioxidant activity of SLN. FTIR spectra showed fatty acid compounds (stearic acid) due to the presence of C=O groups ($1350 - 1375 \text{ cm}^{-1}$), O—H ($3750 - 3000 \text{ cm}^{-1}$), C—H ($3000 - 2700 \text{ cm}^{-1}$), -CH₂ bending (1465 cm^{-1}), and -CH₃ bending (1375 cm^{-1}) (Jayasheela et al., 2020). Additionally, the two SLN types contained MAG-DAG compounds characterized by the presence of O—H, C—H, C=O, and -CH₂ bending groups. In 15 % SLN, there was a spectral peak at 951.17 cm^{-1} , signifying the presence of a phenol group as a component of the bioactive compounds of mangosteen peel extract. The phenol was characterized based on the O—H group, reinforced by the presence of an aliphatic C—H group with absorbance at wave numbers 1370 cm^{-1} and a cyclic C—OH group at wave numbers $990 - 1060 \text{ cm}^{-1}$ (Fong Sim et al., 2012).

Thermal properties

According to Fig. 6 and Table 4, the two SLN types had different thermal properties at peaks 1 and 2, namely at T_{onset} , T_{peak} , and T_{endset} . MAG-DAG-rich fat that melted first at peak 1 was a group of shorter-chain and less saturated fatty acids containing laurate, myristate, and oleate, while stearic acid melted at peak 2 comprised a group of long-chain and saturated fatty acids. The longer chain of fatty acids needed energy to break bonds or initiate interactions between more particles. Furthermore, saturated fatty acids use Van der Waals forces to form crystal molecules requiring high energy to be melted (Siram et al., 2019). The addition of mangosteen peel extract increased the melting temperature of MAG-DAG (peak 1) and decreased the melting temperature of stearic acid (peak 2) due to the amplification of hydrogen bond interactions by extract, leading to the need for more energy. This phenomenon was attributed to the hydrophilic ability of mangosteen peel extract, which reduced the interaction of lipophilic groups of stearic acid and MAG-DAG-rich fat by increasing the wetting ability of the lipid matrix group to decrease the melting temperature (Anton et al., 2012).

Characteristics of SLN-mangosteen peel extract (after lyophilization)

The best SLN formula comprising 40 % MAG-DAG-rich fat and 15 % mangosteen peel extract was lyophilized using a freeze dryer, and then the chemical properties were characterized (Table 5). SLN had a fairly low loading capacity (LC) of 0.02 %, implying that each particle contained 0.02 % phenolic compounds. These results could be affected by the solubility of drugs in lipids, the matrix chemical and physical properties, and lipid polymer characteristics (L. Xu et al., 2022). The solubility of mangosteen peel extract tended to be hydrophilic, leading to being less soluble in a lipophilic solid matrix. Additionally, polymorphic stearic acid in the β -crystalline form caused drugs to come out of the lipid matrix, thereby necessitating the addition of other fats, such as MAG and DAG to increase drug loading (Deshpande et al., 2017). The matrices lipid containing MAG and DAG in SLN can enhance the retention of bioactive compounds of mangosteen peel extract by providing a protective, controlled-release system that improves bioavailability, stability, and targeted delivery. SLNs provide a solid lipid matrix that shields bioactive compounds from degradation, extending their shelf life and preserving activity (Ashfaq et al., 2023; Pandey et al., 2022).

Lyophilized SLN-mangosteen peel extract had a phenolic content of $5.62 \pm 0.31 \text{ mg GAE/g}$, which decreased from the total phenolic extract of $529.40 \pm 4.07 \text{ mg GAE/g}$ (Table 2). Lyophilized SLN also had a flavonoid content of $3.19 \pm 0.29 \text{ mg QE/g}$, which decreased from the total flavonoid extract of $30.02 \pm 0.29 \text{ mg QE/g}$ (Table 2). The decrease in phenolic and flavonoid content in SLN was almost the same as the study by (Shahab-Navaei and Asoodeh, 2023), which reported that phenolic content in SLN propolis extract decreased from 264.048 mg GAE/g to 238.810 mg GAE/g and flavonoid content in SLN propolis extract decreased from 44.806 mg QE/g to 32.667 mg QE/g . This decrease originated from the presence of lipid matrix-trapping bioactive

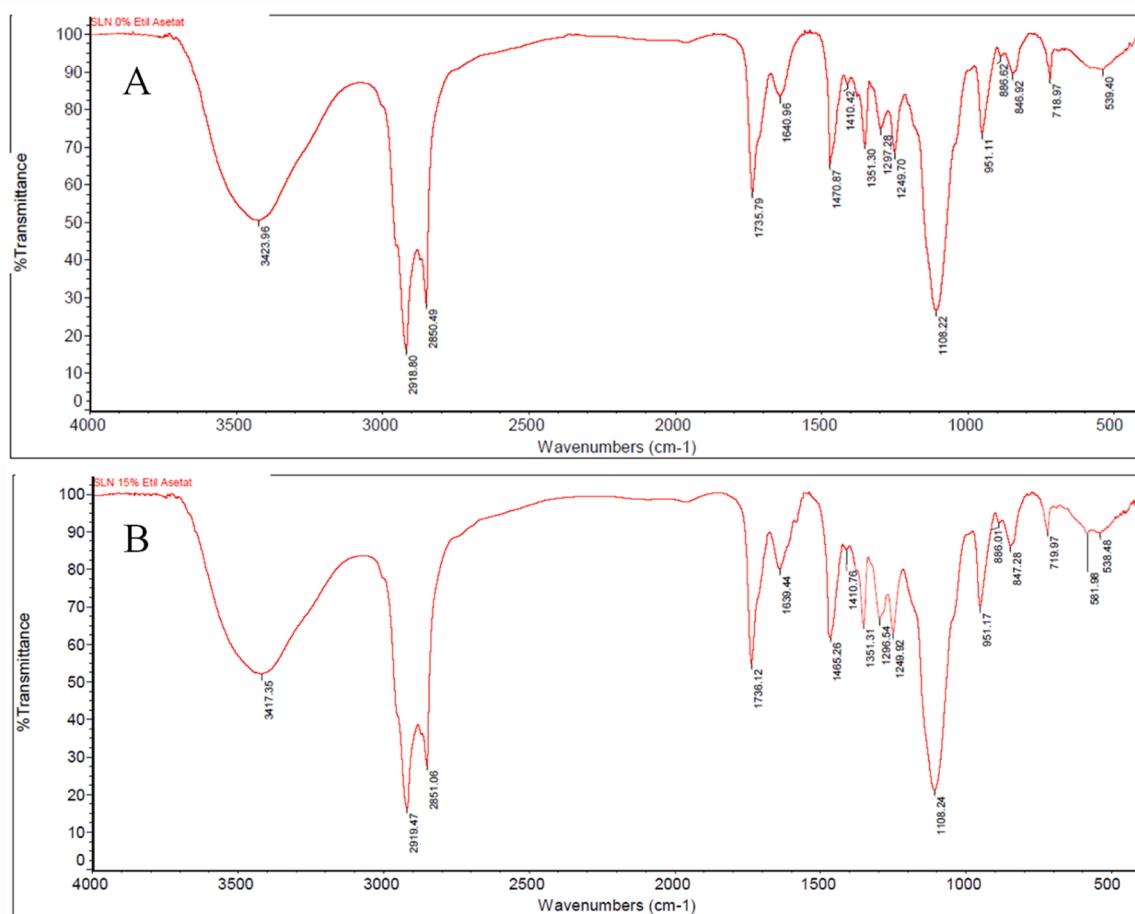


Fig. 5. FTIR spectra of SLN-mangosteen peel extract 0 % (control) (A) and SLN-mangosteen peel extract 15 % (B).

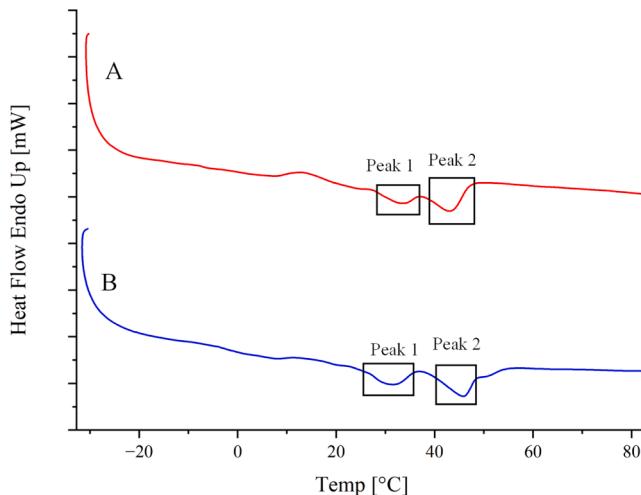


Fig. 6. Thermogram of SLN-mangosteen peel extract 0 % (control) (A) and SLN-mangosteen peel extract 15 % (B).

compounds, thereby reducing the total phenolic and flavonoid concentration (Keck et al., 2021). In addition, the fairly high SLN fabrication temperature of 65–70 °C could reduce phenolics and flavonoids (Gao et al., 2022; Ioannou et al., 2020). The antioxidant activity (IC_{50}) value of lyophilized SLN-mangosteen peel extract (235.12 ± 2.93 ppm) was lower than mangosteen peel extract and included under the weak group (Table 5), corresponding with the low phenolic and flavonoid content in

Table 4
Thermal properties of SLN-mangosteen peel extract.

Thermal properties	SLN-Mangosteen peel extract 0 % (Control)		SLN-Mangosteen peel extract 15 %	
	Peak 1	Peak 2	Peak 1	Peak 2
T _{onset} (°C)	25.37	39.18	27.90	38.35
T _{peak} (°C)	31.53	45.83	33.65	42.99
T _{endset} (°C)	35.73	48.25	36.20	46.79
Heat (J/g)	-5.95	-6.17	-2.21	-5.03

Table 5
Characteristics of SLN-mangosteen peel extract (after lyophilization).

Characteristics	Value
Loading capacity (LC)	0.02 ± 0.01 %
Total phenolic content	5.62 ± 0.31 mg GAE/g
Total flavonoid content	3.19 ± 0.29 mg QE/g
Antioxidant activity (IC_{50})	235.12 ± 2.93 ppm

SLN. The decrease in antioxidant activity was caused by using a large lipid matrix, which was consistent with the small loading capacity results. Moreover, the fat content of the SLN lipid matrix can inhibit bioactive compounds due to the difference in polarity and solubility between lipids and phenolic compounds (Plaskova and Mlcek, 2023). The lipid could interfere with free radical scavenging because the component hydrogen atoms bind to the DPPH hydroxyl radicals, leading to inhibition of the DPPH reduction process.

SLN-mangosteen peel extract had the advantage of high entrapment efficiency and good protection of antioxidant compounds because it had a stable lipid matrix structure and the ability of MAG and DAG to act as

emulsifiers and form stable β crystals. (Ramesh and Mandal, 2019) also reported the synthesis of SLN-Epigallocatechin-3-gallate (EGCG) using MAG in the form of glycerol monostearate as a lipid matrix, showing that SLN was able to improve the bioavailability and stability of EGCG. However, SLN had low loading capacity, total phenolics, and antioxidant activity. The decrease in phenolics and antioxidant activity of mangosteen peel extract during the nanoencapsulation process was also reported (Ningsih et al., 2017), which stated that the antioxidant activity of mangosteen extract nanoparticles decreased from 10.20 AEAC mg/mL to 4.56 AEAC mg/mL, while total phenolics decreased from 2711 mg GAE/mL to 2.71 mg GAE/mL.

Conclusion

In conclusion, the results showed that the characteristics of SLN-mangosteen peel extract were influenced by the application of MAG-DAG-rich fat and the concentration of mangosteen peel extract. The best treatment was using MAG-DAG-rich fat of 40 % w/w and mangosteen peel extract of 15 % w/w. This produced SLN with EE of $97.73 \pm 0.33\%$, particle size of 373.00 ± 20.30 nm, loading capacity of $0.02 \pm 0.01\%$, total flavonoid of 3.19 ± 0.29 mg QE/g, and antioxidant activity (IC_{50}) of 235.12 ± 2.93 ppm. SLN had a spherulitic morphology that trapped extract in a lipid matrix to form a W/O/W emulsion with a mixed polymorphic β and β' crystal structure, leading to an increased melting temperature for the nanoparticles. However, further research is needed, especially to improve the loading capacity, for example, by modifying the SLN fabrication method or lipid matrices. Therefore, SLN fabrication using the double emulsion method based on MAG-DAG-rich fat and stearic acid effectively encapsulated mangosteen peel extract with good physicochemical properties, but improvements are needed, especially in the loading capacity.

CRediT authorship contribution statement

Edy Subroto: Methodology, Writing – original draft, Funding acquisition, Conceptualization. **Tania Nurul Afifah:** Investigation, Project administration, Data curation. **Putri Widayanti Harlina:** Writing – review & editing, Validation. **Rossi Indiarto:** Visualization, Writing – review & editing, Validation. **Aldila Din Pangawikan:** Writing – review & editing, Validation, Software. **Syamsul Huda:** Data curation, Writing – review & editing. **Bangkit Wiguna:** Writing – review & editing, Validation. **Fang Geng:** Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical statement - studies in humans and animals

No humans or animals were subjected to the research.

Data availability

Data will be made available on request.

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