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Research Article

Optimization and characterization of solid lipid nanoparticles carrier ethanol extracts of *Parkia speciosa* pod

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ABSTRACT

Parkia speciosa (Petai) contains phenolic and flavonoid components as an antioxidant. This function is not optimal because the biological membrane is lipophilic while the compounds is hydrophilic. The objective of this study was to prepare the ethanol extract of *Parkia speciosa* into Solid Lipid Nanoparticles (SLN) as an effort to overcome the difficulty of penetration of active compounds through biological membranes. The optimum formula was designed using factorial design 2^3. Surfactant concentration, preparation temperature, and stirring speed were independent variable that act as factors. The influence of these factors on characteristics of SLN was analyzed by using Design Expert®10 (Stat-Ease Inc.) software. The test results showed that the optimum formula was obtained at a tween-80 concentration of 0.704 mL, a preparation temperature of 60°C and a stirring speed of 1000 rpm. The optimum formula characteristic was % EE 88.81±0.06%, particle size of 393.8 nm, polydispersity index (PDI) of 0,421 and zeta potential of -1.7 mV, respectively. The percentage of diffused SLN was better (9.83±0.011%) than the percentage of diffused extract (4.48±0.022%). The results showed that the ability of SLN to penetrate membrane was greater than the extract but SLN showed instability due to the formation of aggregates in storage. The compartmental analysis with WinSAAM™ software revealed the optimum formula following the compartment lag model with a p-value <0.05.

Keywords: *Petai*, solid lipid nanoparticles, surfactant, temperature

INTRODUCTION

Parkia speciosa (Petai) is a plant species classified under the *Fabaceae* family and is found almost everywhere in Indonesia, Malaysia and The Philippines (Kamisah *et al.,* 2013). The phenolic and flavonoids compounds of *P. speciosa* are the major ingredients that make them function as antioxidants (Zaini and Mustaffa, 2017). The total phenolic content in petai pod extract is 7.2-255.55 mg GAE / gDW and has an antioxidant activity 105-357 ± 27 TE / g DW (Zaini and Mustaffa, 2017). The antioxidant properties of petai pod can be used as an antioxidant in topical preparations. The challenge of the extract formulation for topical preparations is limitation of drug penetration to the barrier of stratum corneum layer. In the last few decades, approach to overcome the skin barrier for the use of drug delivery systems like nanoparticles and lipid-based delivery systems is studied. Solid Lipid Nanoparticle (SLN) has been successfully utilized for skin delivery (Jain *et al.,* 2016). SLN has advantages over other drug delivery systems because its' good biocompatibility, biodegradable, nontoxic and it can be used to deliver hydrophilic and hydrophobic drugs (Arana *et al.,* 2015; Nikam *et al.,* 2014; Soma *et al.,* 2017). Additionally, it also has the capability of penetrating the stratum corneum barrier and makes it effective to be used topically (Londhe and Save, 2017).

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Petai pod ethanol extract contains active flavonoid compounds as antibacterial and antioxidant (Kamisah, 2013). This pharmacological activity causes the extract to be potentially developed as a topical preparation. The problem is that flavonoid compounds are polar, so their penetration into the stratum corneum layer is not maximum. By incorporating the extracts into SLN form, this problem can be overcome.

Hence, the objectives of this study were to modify the ethanol extract of petai (EP) into SLN dosage form thereby improve its drug penetrating ability and also to determine the optimum formula through the use of design expert. Surfactant is a substantial part of SLN which functions as a stabilizer (Kim *et al.,* 2014). Adequate temperature and stirring speed are required in the preparation process of SLN. This study was designed to find out of the influence of the concentration of the surfactant, the preparation temperature and the stirring speed on the characteristics of SLN. The optimum formula was decided through factorial design method 2^3 in Design Expert®10 software (Stat-Ease Inc. USA).

MATERIALS AND METHODS

The materials used in this research study include: petai pod, ethanol, Tween80, propylene glycol, and cetyl alcohol. Petai Pod was collected in Muara Lakitan districts, South Sumatra. Samples were collected in November 2018.

Preparation of extract

Extract of parkia was prepared by maceration method. Before extracting, fresh Petai pod was dried under the sunlight and ground into powder. The extraction process of 500 mg powder of petai pod was carried out three times for 48 hours with ethanol solvent 96% (3L). The filtrate was evaporated by using rotary evaporator (Yamato®) at 70°C (Kamisah *et al.,* 2013).

Table 1: The composition of the independent variable factor level

Independent Variable	Minimum level	Maximum level
Tween 80 (% $^{v}/_{v}$)	5	10
Making temperature (°C)	60	75
Stirring Speed (rpm)	1000	1500

Preparation of SLN

Surfactant concentration, manufacturing temperature and stirring speed were the three independent variables used in this study. The extract concentration used was 4%. The levels of each of these variables are shown in Table 1. The SLN of petai Extract (SLN EP) formula is determined by the factorial design method 2^3. The composition of the formulas are shown in Table 2.

SLN EP preparation was started by melting of cetyl alcohol at temperature of 75°C for 5 minutes until it changes into a liquid. Then, the petai pod's extract was dissolved in 1 mL ethanol 70% and added into the oil phase. The aqueous phase was made by dissolving tween 80 and propylene glycol into distilled water at 75°C. The aquaeous phase was dispersed into the oil phase drop by drop on a magnetic stirrer (IKA® C-MAG HS 4) for 5 hours at 1000 rpm. The chocolate flavor was added to it. Suspension was homogenized by using a bath sonicator (GT SONIC®VGT-1620QTD 50 Hz) for 15 minutes to produce a homogeneous SLN dispersion. The results were stored in a closed container and away from any light at room temperature (Nikam *et al.,* 2014; Priya and Jeevitha, 2016).

Table 2: The formula design of SLN for optimization using Design Expert®10

Component	Formula							
	F1	F2	F3	F4	F5	F6	F7	F8
Extract (%)	4	4	4	4	4	4	4	4
Cetyl alcohol (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Tween 80 (%)	5	10	5	10	5	10	5	10
Propylene glycol (mL)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Making Temperature (°C)	60	60	75	75	60	60	75	75
Stirring Speed (rpm)	1000	1000	1000	1000	1500	1500	1500	1500
Chocolate Aroma (drops)	2	2.	2	2	2	2	2.	2.

Characterization of SLN

Entrapment efficiency (% EE)

The SLN EP was centrifuged at a speed of 10,000 rpm for 60 minutes (DLAB©: D2012 PLUS) until 2 phases formed. The entrapment efficiency was carried out at the supernatant phase spectrometrically (Biobase®BK-UV1900PC), by using flavonoids level as the marker (Badawi *et al.,* 2018; Priya and Jeevitha, 2016). The total content of extracts encapsulated in SLN was calculated using the Equation 1 below.

$$\% \text{ EE} = \frac{\Sigma C_a - \Sigma C_b}{\Sigma C_a} \text{ X } 100\% \quad \ldots. (1)$$

Notes:
C_a = amount of extract added
C_b = amount of extract free in the supernatant

Physical stability test

The test for the physical stability was done by heating-cooling cycle method as carried out by (Sugiyati and Djajadisastra, 2015) with slight modification. The formulas of SLN EP were stored at two different temperatures of 4°C (24 hours) and 40°C (24 hours) in one cycle and observations were made for six cycles. The measurement of the flavonoids content was done at the beginning and end of the cycle. The calculation of the decrease content was using the equation 2 as:

$$\% \text{ decreased levels} = \frac{\text{Initial flavonoid levels} - \text{Final flavonoid levels}}{\text{Initial flavonoid levels}} \text{X } 100\% \ldots. (2)$$

pH determination

The pH was checked using pH meter (Lutron® pH Electrode PE-03). The preparation was tested three times (triplo) to ascertain its stability.

Optimum formula determination

Optimization is a method that involves the application of available resources to achieve best results to be implemented in designing and developing dosage forms (Badawi *et al.,* 2018). In this experiment, design factorial was used to optimize SLN EP formula based on maximum criteria of entrapment efficiency, stability and specified pH range. This analysis was conducted to measure the significance level with the use of ANOVA factorial design. Optimum formula analysis including particle morphology, stability test, interaction of lipids base and extract by FTIR and *in vitro* diffusion test.

Analysis of particle characteristic

The analysis of particle size, its distribution, zeta potential and the poly-dispersion index were carried out through the use of a particle size analyzer (Horiba Scientific®SZ-100). The test was done through the dispersion of the SLN in aquadest at a ratio of 1:10 (v/v) at 25ºC (Londhe and Save, 2017). The particle morphology was examined using a TEM device (Jeol®JEM 1400).

***In vitro* diffusion test**

The experiment was done according to the test carried out on the *Pomegranate extract*-loaded solid lipid nanoparticles (Acharya *et al.,* 2016). Since the flavonoid are active compounds of extract, it was used as an indicator in the in vitro tests. The flavonoids content were measured with a UV spectrophotometer (Biobase® BK-UV 1900PC) at a wavelength of 273 nm.

Data analysis

The data was analyzed based on the factorial design calculation method to determine the influence of surfactant concentration, preparation temperature, and stirring speed on the solution (Equation 3). The correlation analysis of response results was done by using the SPSS®.

$$Y = b_0 + b_A X_A + b_B X_B + b_C X_C + b_{AB} X_A X_B + b_{AC} X_A X_C + b_{BC} X_B X_C + b_{ABC} X_A X_B X_C \quad \ldots (3)$$

Notes:
Y = response of the observed results
X_A = surfactant concentration
X_B = Preparation temperature
X_C = stirring speed
X_{ABC} = surfactant concentration, Preparation temperature, stirring speed
b_0, b_A, b_B, b_C = coefficient

The compartment analysis of diffusion test results was done by using the WinSAAM ™ and SPSS®16 programs (Ikasari *et al.,* 2015). Prediction data from DX®10 and research data were analyzed with one sample t-test (SPSS version 16.0). $\alpha < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

The yield of the extract obtained was 25.72 g. Preparation of SLN of ethanol extract of *Parkia* pod (SLN EP) was carried out by using ultrasonication technique with hot homogenization method to get a homogeneous matrix model type of SLN (Nikam *et al.,* 2014). The characterization of SLN are shown in Table 3.

Table 3: The characteristic of SLN EP (n =3)

Formula	EE (%)	pH	Decrease content (%)
F1	96.95±0.014	5.02±0.005	5.93±0.074
F2	82.03±0.058	5.28±0.010	8.59±2.206
F3	96.37±0.022	5.15±0.015	9.89±0.995
F4	76.13±0.058	5.24±0.020	13.19±3.755
F5	96.68±0.022	5.13±0.020	11.81±1.236
F6	80.06±0.089	5.17±0.015	15.85±3.144
F7	97.12±0.022	5.16±0.010	13.53±1.358
F8	78.93±0.058	5.19±0.005	32.41±4.944

The results of the analysis using DX®10 for all responses produce equations 4-6:

$$Y = +68.0470 + 79.679A + 0.682B + 0.024C - 1.712AB - 0.066AC - 3.660x10^{-4}BC + 1.002x10^{-4}ABC \quad ... (4)$$

$$Y = +0.826 + 5.346A + 0.055B - 2.760x10^{-3}C - 0.066AB - 3.506x10^{-3}AC - 3.555x10^{-5}BC + 4.444x10^{-5}ABC \quad ...(5)$$

$$Y = -150.723 + 222.103A + 2.416B + 0.140C - 3.705AB - 0.221AC - 2.193x10^{-3}BC + 3.788x10^{-3}ABC \quad ...(6)$$

Notes:
Y = EE percentage (equation 5), pH (equation 6) and stability (equation 7)
X_4 = the proportion of tween-80 concentration
X_5 = the proportion of Preparation temperature
X_6 = the proportion of stirring speed

Equation 4-6 revealed that the concentration of tween-80, as a non-ionic surfactant, had a significant influence on the percentage of EE and the stability. Because it has the ability of reducing the surface tension and maintain the physical stability of the preparation. As a result, it can increase the efficiency of encapsulation (Ali Attia Shafie, 2013). It can be concluded that tween-8, preparation temperature, and stirring speed had a significant influence on improving the stability of the nano suspension.

Optimum formula for SLN EP was tested by using the DX®10 software by Stat-Ease Inc. The desirability value produced by the optimum formula was 0.750. Based on the results of the EE percentage response evaluation, stability and pH, the optimum formula was obtained with the proportion 0.740 mL of tween-80, preparation temperature 60°C and stirring speed of 1000 rpm.

The analysis of SLN optimized

The results of the EE percentage, stability, and pH optimum formula for SLN EP were shown in Table 4. The comparative analysis of one sample t-test was carried out onDX®10 prediction test data and research data by using SPSS®16. This test was carried out to find out the average difference between the research data and the predictive data.

Table 4: The results of comparative analysis between predictive and research data

Response	Prediction	Data obtained (n=3)	%RSE	*p-value*
%EE	90.867	88.808±0.058	2.2659	0.000
Stability	7.019	11.027±0,098	36.347	0.000
pH	5.130	5.123±0.015	0.1364	0.529

The p-value for EE percentage and stability was found to be <0.05. This showed that there was a significant difference between the research data and predictive data for these two variables. There was no significant difference for pH. A high percentage residual standard error (RSE) of stability indicates instability of the preparation. The higher the % RSE value, the more inaccurate is the predictive value (Loong *et al.,* 2014).

Determination of optimum formula of SLN characteristic

The determination of optimum formula of SLN characteristic were particle size, particle distribution, potential zeta, particle morphology, stability, FT-IR analysis and in vitro diffusion test. PSA analysis showed that Diameter of Particle was 393.8 nm, Zeta Potencial was -1.700 nV and PDI was 0.421. Nano-vesicles with a diameter of 10-600 nm was able to deliver the drug into the material on transdermal dosage form (Danaei *et al.,* 2018). It can be concluded from the results obtained that SLN EP could be applied on topical preparations because the resulting particle size was 393.8 nm. The ideal PDI value for SLN preparations is ≤ 3 but a value of < 5 is also acceptable (Rohan Shah, 2014). The SLN EP PDI value of 0.421

indicates that the dispersion formula of the optimum SLN EP is quite homogeneous (Priya and Jeevitha, 2016; Shah *et al.,* 2014). Potential zeta is a parameter used in predicting colloidal suspense stability during storage. Its value, which was found to be greater than ±30 mV, could ensure good physical stability (López-García and Ganem-Rondero, 2015). In this study, the value was found at -1.7 mV and this reveals the problem of physical stability during storage.

Particle morphology

The test using TEM (Jeol®JEM 1400) was conducted to investigate the morphology of SLN EP. Our investigation revealed SLNEP had a spherical shape but were not sufficiently distributed (Figure 1). Particles with spherical shape are known to increase uptake or absorption into the cells in comparison to particles with rod-like shapes (Chithrani and Chan, 2007).

The results of the analysis showed the aggregation of SLN EP preparations. This was due to the occurrence of an attractive tensile force between the particles in the colloid. In addition, it can occur due to unpredictable changes and irreversible gelation phenomena which can cause an increase in particle size and agglomeration (Jain *et al.,* 2016). The SLN EP particle shape was almost as spherical as SLN Green Tea extract particle (SLN GTE) (Arana *et al.,* 2015) but the SLN EP particle size was bigger (393.8 nm) compared to SLN GTE particle size (100-200 nm). This was related to the extract incorporated into SLN. SLN EP used 4% extract while SLN GTE used only 0.1% and 0.17% extract. GTE SLN particles were distributed more homogeneously with a PDI value of 0.2 while the PD SLN EP value was 4.21. PDI value was related to the possibility of aggregation. The higher the PDI value, the bigger the possibility of aggregate formation resulting its stability to decrease (Arana *et al.,* 2015).

Stability test

The result of the test showed a decreasing in drug content of SLN EP after it was stored in each cycle (Figure 2). This might be as the result of a higher temperature factor (40°C) that reduced the viscosity of the emulsion and induced the destabilization of the system. The higher temperatures also increase the kinetic energy of SLN which is enough to overpower electrostatic repulsion to form agglomerates (Shah *et al.,* 2014).

A high potential zeta value is needed to guarantee the stability of the SLN. If the system has a high potential zeta value, aggregation will be difficult to occur and the emulsion will be more stable (Tan-May *et al.,* 2017). This was shown

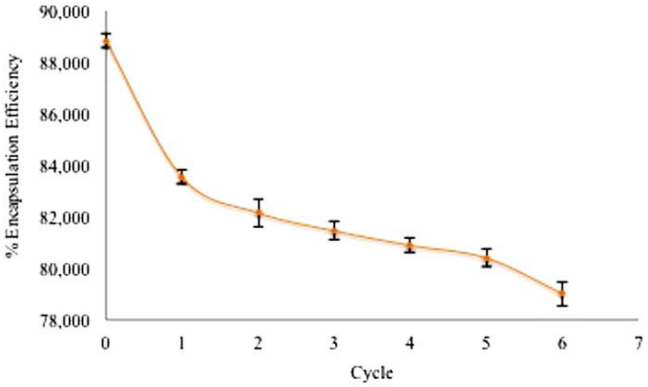
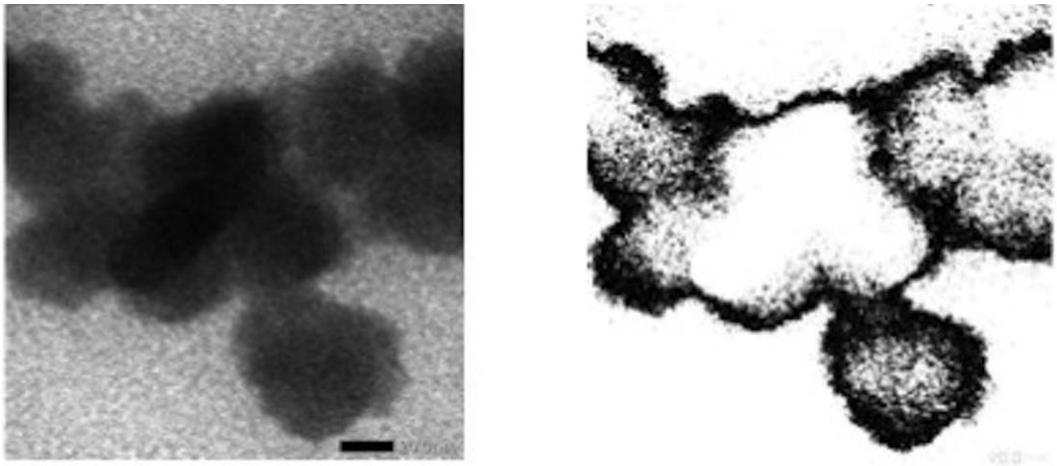


Figure 2: The profile of EE optimum formula percentage decrease (n=3)

Figure 1: (a) TEM with magnification by 80.000 times and (b) TEM after setting the contrast using ImageJ®



in *Dracocephalum moldavica* extract SLN (SLN TFDM) which has a potential zeta value of -28.7 ± 1.94 mV was efficient in stabilizing in the system. This was different from SLN EP with a potential zeta value of -1.7mV thus the particles were more easily aggregated. Temperature factors also affect the stability of SLN. *Kaempferia Parviflora* extract loaded with solid lipid nanoparticles (SLN KP) showed very good stability even when in storage for up to 60 days, but the tests were carried out at room temperature (Suttanaut *et al.,* 2009). While SLN EP was stored at 40°C thus increasing the system destabilization.

The FTIR analysis

The FTIR analysis was carried out for the purpose of discovering the interaction between the lipid excipients and extracts (drugs) in the optimum SLN EP formula. Figure 3 shows the IR spectrum of SLN, extracts and excipients (placebo). Spectra showed that there was no additional dominant shifts and no loss of functional peaks of the extract, lipid and SLN EP. This indicated that there was no interaction exists between the drug and lipid.

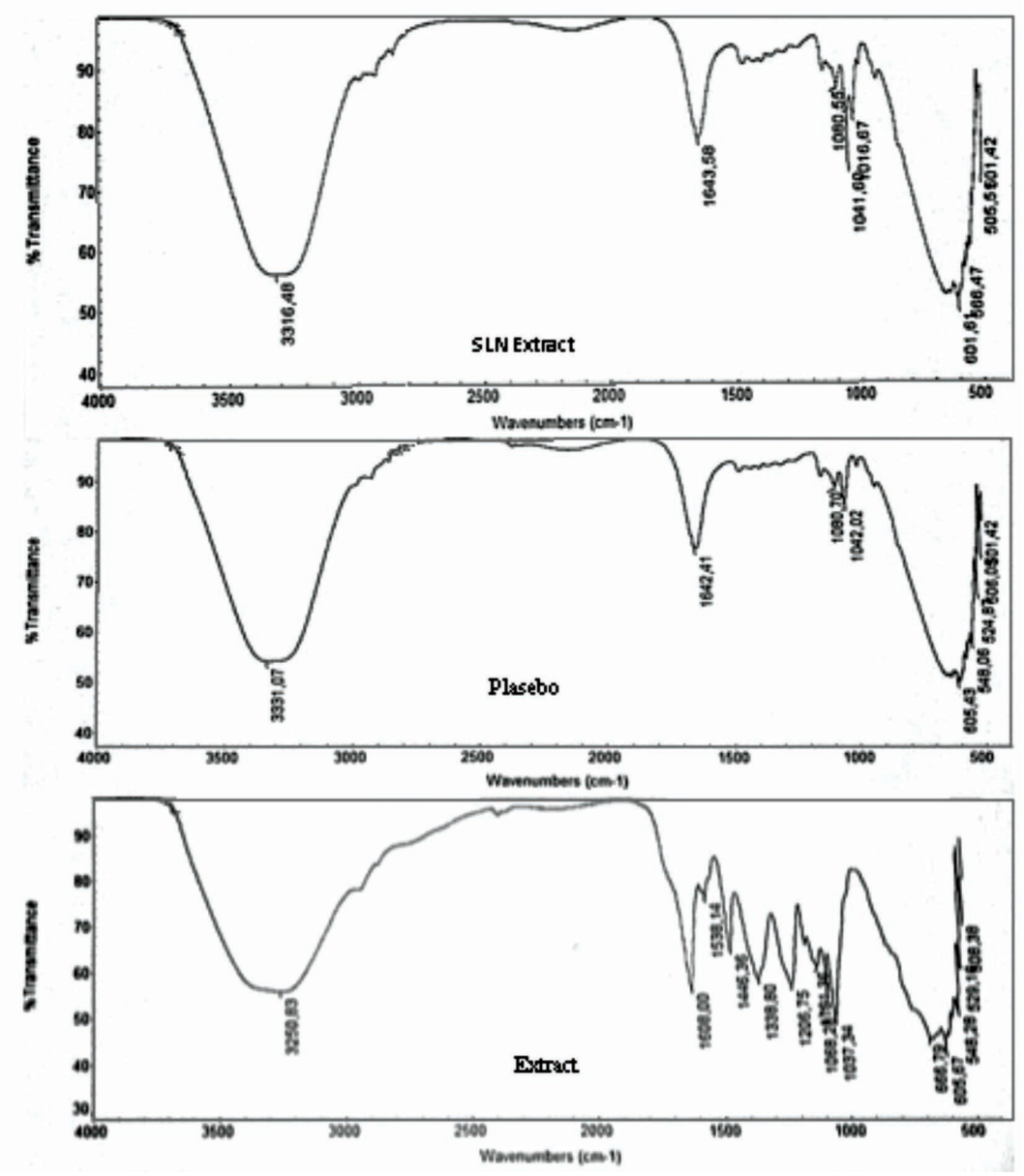


Figure 3: The Comparison of IR spectrum: SLN, pure extract and placebo

In vitro diffusion test

Diffusion test was carried out through the use of Franz diffusion cell. This test was to compare the ability of diffusion for flavonoid compounds from the extracts and SLN EP. The flavonoids content were measured by spectrophotometer. Figure 4 reveals the differences in profiles of diffusion between SLN EP and extract. The percentage of diffusion in SLN EP was greater than the extract. The average percentage of diffusion by the optimum formula of SLN EP was 9.83 ± 0.01% while the pure extract was 4.48 ± 0.03%. This shows that SLN EP diffusion is better than that of the extract.

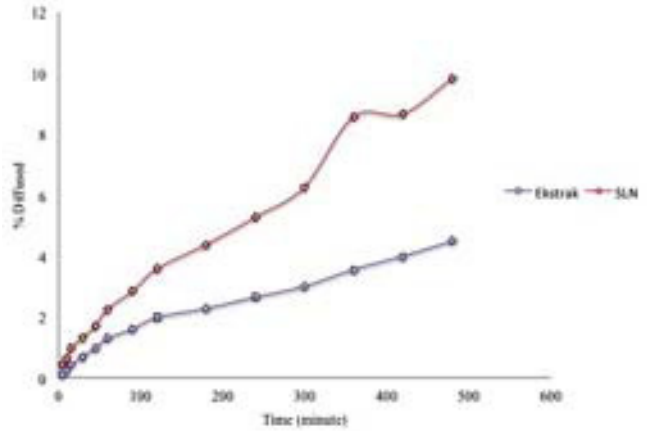


Figure 4: The Profile of percent diffuses of SLN EP and pure extract (n=3)

Similar to the results of *Dracocephalum moldavica* SLN research (SLN TFDM) that the cumulative percentage of drugs released from TFDM SLN was higher (96.23%) than pure extracts (86.51%) in same time period (Tan-May *et al.,* 2017). Drug released from SLN occurred in two stages where the initial stage was rapid release followed by a slower release stage (Soma *et al.,* 2017).

The ethanol extract of petai pods is difficult to penetrate the cellophane membrane because the components of the extract are hydrophilic compounds and while the cellophane membrane is lipophilic. The extracts which has been covered by a lipid matrix are more easily penetrate into the cellophane membrane because of their lipophilic properties.

The results of the analysis through the use of two-way ANOVA revealed a p-value was <0.05. This means that there was significant difference between the percentage of flavonoid diffusion from extract and SLN EP.

The compartmental analysis of diffusion

Compartmental analysis was performed to determine the influence of lag time on the rate of molecules that were penetrating the membrane. WinSAAM™ is a suitable method that can be used to explain the pharmacokinetics of the compartment system (Ikasari *et al.,* 2015). The results showed that SLN EP had a lag time in absorption of drug. This was because of the time it took the solvent to diffuse into the preparation matrix. This affected the diffusion speed of flavonoid compounds from SLN preparations through the cellophane membrane.

The rate of absorption for SLN EP optimum formula from the processing of WinSAAM™ software was found to be 1.6 x 10^{-6}µg / minute with a distribution volume of 0.92 L while the comparison value of the rate of absorption for pure extract of petai pod was found to be 1 x 10^{-7} µg / min with a distribution volume of 0.018 L.This proves that SLN diffusion is better than pure extract.

The results of the Submicro Poly Particle (Lactic-co-Glycolic Acid) (PLGA) Betamethasone Valerate Carrier showed that the compartmental analysis of the submicro diffusion results of PLGA particles of dexamethasone valerate carrier showed 3 compartment model (Mardianto *et al.,* 2018). This means that the drug needed time to be released from the polymer before it penetrates the membrane. The lag time on SLN EP was due to the fact that flavonoid compounds need time to be released from the SLN matrix.

CONCLUSION

The optimum formula of SLN EP was obtained with the proportion of tween -80 at 0.704 mL, preparation temperature at 60°C, and stirring speed at 1000 rpm. This proportion indicating a percentage of diffusion which was better than the pure extract. SLN EP had a spherical shape with a particle size of 393.8 nm, PDI of 0.421, zeta potential of -1.7700 and % entrapment efficiency of 88.808 ± 0.058%. No chemical interactions existed between drug and lipids but SLN EP showed instability during storage. The SLN EP had a percentage of diffusion better than the pure extract and had a lag time in drug absorption.

CONFLICT OF INTEREST

Authors declare : No conflict of interest.

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