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FORMULATION, AND CHARACTERIZATION OF NANOSTRUCTURED LIPID CARRIER (NLC) CONTAINING QUERCETIN

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ABSTRACT

Quercetin, like triterpenoids, decreases blood glucose levels. Quercetin has several limitations including low solubility, low percutaneous permeability, and low bioavailability. The formulation of quercetin preparations in a Nanostructured Lipid Carrier (NLC) system is one solution to increase its solubility. The quercetin NLC system was successfully formulated by the high shear homogenization method at a speed of 6000 rpm. The solid lipid glyceryl monostearate and sunflower oil play important roles in the formation of NLC. The physicochemical characteristics examined in this study included the particle size, dispersion, viscosity, pH, and entrapment efficiency. The particle size of NLC quercetin ranges from 22.98 ± 0.008 nm to 41.04 ± 0.082 nm, with p-values < 0.05. The dispersion power of quercetin NLC ranges from 5.12 ± 0.11 cm to 7.01 ± 0.28 cm, p values < 0.05. The resulting pH range is 7.3 ± 0.01 to 7.4 ± 0.01, and the resulting viscosity is 223.7 ± 9.8 cps to 492.0 ± 0.0 cps. Entrapment efficiency range of (62.20 ± 0.245)% to (86.17 ± 0.287)% (p < 0.05). The ratio of solid lipid concentration to liquid lipid concentration in NLC quercetin has a significant effect on particle size, dispersion, and entrapment efficiency.

Keywords: Nanostructured Lipid Carrier, Quercetin, Lipid, Glyceryl Monosterate, Sunflower Oil

INTRODUCTION

Diabetes mellitus (DM) is a global health problem that must be addressed. Based on Riskedas predictions for 2030, it is estimated that there are 21.3 million people with diabetes mellitus in Indonesia. Changes in socio-culture, diet, and physical activity are among the problems that cause DM (Ogurtsova et al., 2022). New modalities derived from natural materials are needed to prevent and cure DM (Rianoor, 2022). Currently, the bioactive compound quercetin is being widely developed because it has great potential for lowering glucose in the blood. Quercetin is a flavonoid with anticancer, antioxidant, anti-inflammatory, and antidiabetic properties (Rianoor, 2022). Currently, the bioactive compound quercetin is being widely developed because of its great potential for lowering glucose levels in the blood. Quercetin is a flavonoid with anticancer, antioxidant, anti-inflammatory, and antidiabetic properties (Pinheiro et al., 2020). In their use, NLC systems have the advantage of improving the physicochemical stability of active ingredients, which can improve the bioavailability of active ingredients (Mallya & Patil, 2021)

NLC are the development of a Solid Lipid Nanoparticle (SLN) system by adding liquid fat to solid fat. The addition of these solid lipids changes the crystal lattice

arrangement of solid lipids from ordered to unordered so that there is more room for the active ingredients, in addition to minimizing the repulsion of the active ingredients during storage. This leads to increased stability of the active ingredient and can regulate its release of the active ingredient. One component that affects the effectiveness of NLC as a conductor of active ingredients is the lipid composition (Manzoor et al., 2021).

The lipid composition of the NLC system affects its characteristics, which further affects the effectiveness of the system as a conductor of active ingredients. Research conducted by Rahayu et al. (2022) states that the composition of the formula glyceryl monostearate, tween 80, shows optimal results on the characteristics of the resulting NLC, including particle size, zeta sizer, viscosity, and stability of the active ingredient (Rahayu et al., 2022). In this study, sunflower oil was added as a liquid lipid to increase the amount of active ingredients that could be encapsulated in the system and prevent the repulsion of active ingredients during storage. Sunflower oil was chosen because it can increase system penetration because it has properties as an enhancer as well as emollient properties so that it can support functions in cosmetic preparations (Khursheed et al., 2022). In this study, the formulation and optimization of quercetin NLC were carried out using the Full Factorial Design model to obtain the optimum formula with independent variables of solid lipid composition of Glyceryl Monostearate and Sunflower Oil liquid lipids, and Tween 80 surfactant with variables depending on homogeneity, particle size, dispersion, pH, viscosity, and entrapment efficiency.

RESEARCH METHODS

A full factorial design was used in this study. In this method, two factors were evaluated to obtain the optimal formula. The optimization and formulation in this research design were glyceryl monostearate (GMS) concentration (A) and sunflower oil liquid lipid (B); see **Table I**. Optimization of this formula aims to obtain optimal results for bound variables (X), namely particle size (X1), dispersion power (X2), and entrapment efficiency (X3). A full-factor design model was used to create the quercetin NLC formulation.

Table I. Optimization of NLC Quercetin Using Full Factorial Design Model

Independent Variables	**% (b/v) Concentratior**		***Coded Values***	
	Low	**High**	**Low**	**High**
A = Concentration Solid Lipid Glyceryl Monostearate	6	10	-1	+1
B = Sunflower Liquid Lipid Concentration Oil	1	3	-1	+1

Table II displays the composition of NLC Quercetin, which includes quercetin as the active ingredient, glyceryl monostearate as the solid lipid, sunflower oil as the liquid lipid, tween 80 as the surfactant, propilenglikol as the ko surfactant, and buffer phosphate as the solvent.

Table II. Formulation of NLC Quercetin

Materials	**Concentration (%)**			
	I	**II**	**III**	**IV**
Quercetin	0,24	0,24	0,24	0,24
Glyceryl Monostearate	6	6	10	10

Sunflower Oil	1	3	1	3
Propilenglicol	2	2	2	2
Tween 80	16	16	16	16
Phosphate Buffer pH 7,4±0,05	ad 100	ad 100	ad 100	ad 100

Equipment and Materials

The instruments and tools used in this research were the Shimadzu UV-Vis Spectrophotometer type UV-1280, Ultra Turrax Homogenizer, Ohaus Analytical Balance, BIOBASE Nano Particle Size Analyzer, Spreadability Tester, L-AQUA pH Meter, and NDJ-8S Type Viscometer.

The materials used in this study were quercetin p.a (Sigma Aldrich), glyceryl monostearate p.a (Sinopharm Chemical), sunflower oil p.a (Sinopharm Chemical), Tween 80 (Solvay Chemicals International), KH_2PO_4 p.a (Merck), and NaOH p.a (Merck).

Research Procedure

Manufacturing of NLC Quercetin

NLC quercetin is prepared by melting solid lipids and liquid lipids at 60 ± 5 °C on a hot plate. The lipid mixture was homogenized at 6000 rpm with an Ultra-turax homogenizer for 15 min at 60 ± 5 °C.Quercetin was dissolved using propylene glycol solvent, then added to the lipid phase and stirred at 6000 rpm for 15 min at 60 ± 5 °C until completely dissolved. Tween 80 and phosphate dapar were heated at 60 ± 5 °C, then added to the oil phase and homogenized with an Ultra-turax homogenizer at 6000 rpm for 15 minutes. Stirring is continued with an Ultra-turax homogenizer at 8000 rpm for 10 minutes until the preparation reaches room temperature (30 °C) (Zhao et al., 2022)

Particle Size Test

The particle size, particle size distribution, and zeta potential were tested using a BIOBASE Nano Particle Size Analyzer. A total of 1 gram of the preparation is added with ethanol-water up to 10 ml in a beaker glass, then put into a cuvette of about 1.5 mL. Tests conducted at 25ºC (Ferreira et al., 2023).

Viscosity Test

Viscosity measurements were carried out using an NDJ-8S Viscometer. NLC preparations are inserted in beaker glass, and then the tool is turned on using rotor 2 at a speed of 60 rpm. The viscosity value appeared automatically on a digital display (Hussain et al., 2020).

Spreadability Test

The preparation weighed 0.5 grams, was then placed on a spread-power test glass plate with a duration of 1 minute, and the diameter of the spread was measured using a caliper with 3x replication (Slamet et al., 2023)

pH Test

pH measurement is carried out using the L-AQUA pH meter to determine the pH changes of NLC preparations during storage time (Sukarjati et al., 2023)

Entrapment Efficiency (EE) Test

Entrapment efficiency was determined by centrifugation, and absorbance was measured using UV-Vis spectrophotometers. NLC preparations weighed as much as 1 gram dispersed in ethanol p.a. The suspension was centrifuged at 2500 rpm for 45 minutes. Then 3 mL of sample absorbance measurement was taken by spectrophotometry at a wavelength of 373.6 nm. The entrapment efficiency requirement of the NLC system formulation is close to 100% (Pivetta et al., 2019). The concentration of free drug in the aqueous phase was

obtained by entering the absorbance into the standard curve regression equation. The entrapment efficiency was calculated using the following formula:

$$EE = \frac{\text{Actual drug concentration}}{\text{Theoretical drug concentration}} x\ 100\% \quad \ldots (1)$$

Data Analysis

Statistical analysis was carried out using the Design of Experiment (DOE) Full Factorial Design with Minitab software version 16.

RESULTS AND DISCUSSION

Quercetin NLC preparations are formulated in four formulas with different concentrations of solid lipids and liquid lipids. The solid lipid used in this study was glyceryl monostearate (GMS). The reason for choosing GMS is that polymorphs are stable and have low potential to change shape from one form to another. Solid lipids were combined with the liquid lipids. Sunflower oil was used as the liquid lipid in combination with the NLC lipid matrix. The use of sunflower oil as a liquid lipid plays an important role in reducing crystallization and is a major factor affecting the release rate of active ingredients and entrapment efficiency in NLC systems (Ezzati et al., 2020)

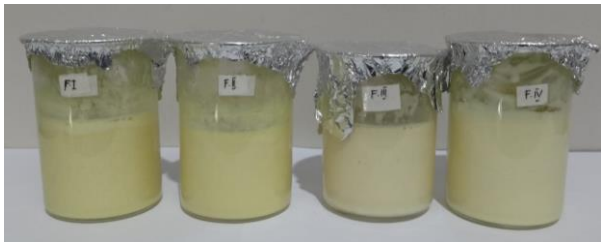

Figure 1. Quercetin NLC preparations

Table III. Results of Physicochemical Characteristics of NLC Quercetin

Formula	Particle Size ± SD(nm)	Viscosity ± SD (cps)	Spreadability SD (cm)	pH ± SD	Entrapment Efficiency (%)
F I	22,98 ± 0,008	223,7 ± 9,8	5,12 ± 0,11	7,4 ± 0,01	62,20 ± 0,245
F II	27,41 ± 0,019	415,0 ± 2,2	6,82 ± 0,07	7,3 ± 0,01	81,87 ± 0,125
F III	32,66 ± 0,028	355,3 ± 7,7	7,01 ± 0,28	7,4 ± 0,01	66,33 ± 0,309
F IV	41,04 ± 0,082	492,0 ± 0,0	6,01 ± 0,09	7,3 ± 0,01	86,17 ± 0,287

The particle size of NLC quercetin ranges from 22.98 ± 0.023 nm to 41.04 ± 0.044 nm, as shown in **Table III**. Based on **Figure 2** (main effects plot and contour plot of particle size), it is seen that A and B have a significant effect on particle size with p-values of 0.000 ($p < 0.05$). The linear regression equation using the full factorial design method is shown in equation 1.

X_1 (nm) = 31,0 + 5,83A + 3,20B …… (1)

Based on statistical analysis, it can be concluded that the ratio of liquid lipids to solid lipids affects particle size parameters. NLC have a particle size of 10–1000 nm (Pimentel-Moral et al., 2019). The addition of liquid lipids to the formula plays a role in reducing its size. The NLC particle size was reduced by increasing the concentration of the liquid lipids. Similarly, it is also reported that the addition of liquid lipids to solid lipids tends to promote the formation of small particles, which may be due to increased mobility of the lipid phase matrix after the addition of liquid lipids (George et al., 2019).

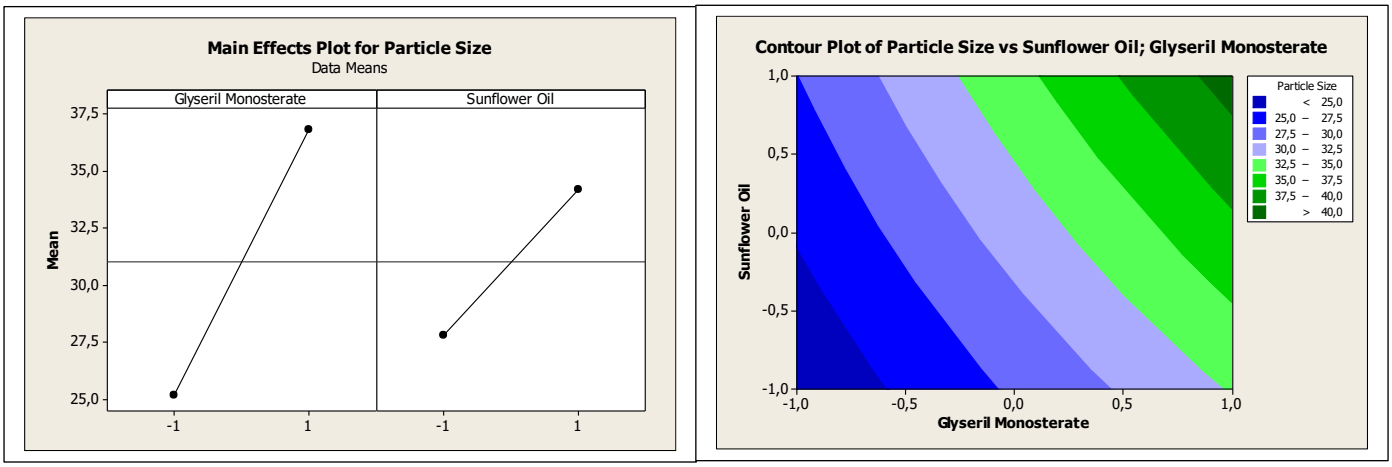

Figure 2. Main Effects Plot dan Countour Plot of Particle Size NLC Quercetin

The dispersion power of quercetin NLC ranges from 4.8 ± 0.1 cm to 7.2 ± 0.1 cm, as shown in **Table III**. Based on **Figure 2** (main effects plot and contour plot of dispersion), it can be observed that A and B have a significant effect on dispersion with sig. 0.000 ($p < 0.05$). The linear regression equation using the full factorial design method is shown in Equation 2.

X_2 (cm) = 6,22 + 0,242A + 0,147B …… (2)

Based on statistical analysis, it can be concluded that the polymer-to-surfactant ratio has a significant effect on the dispersion value. The purpose of the dispersion test is to measure the spread of NLC on the skin. The good NLC dispersion was 5-7 cm. If the diffusibility is too low, the formulation is relatively difficult to spread when applied to the skin (Wei et al., 2021; Patil & Killedar, 2021).

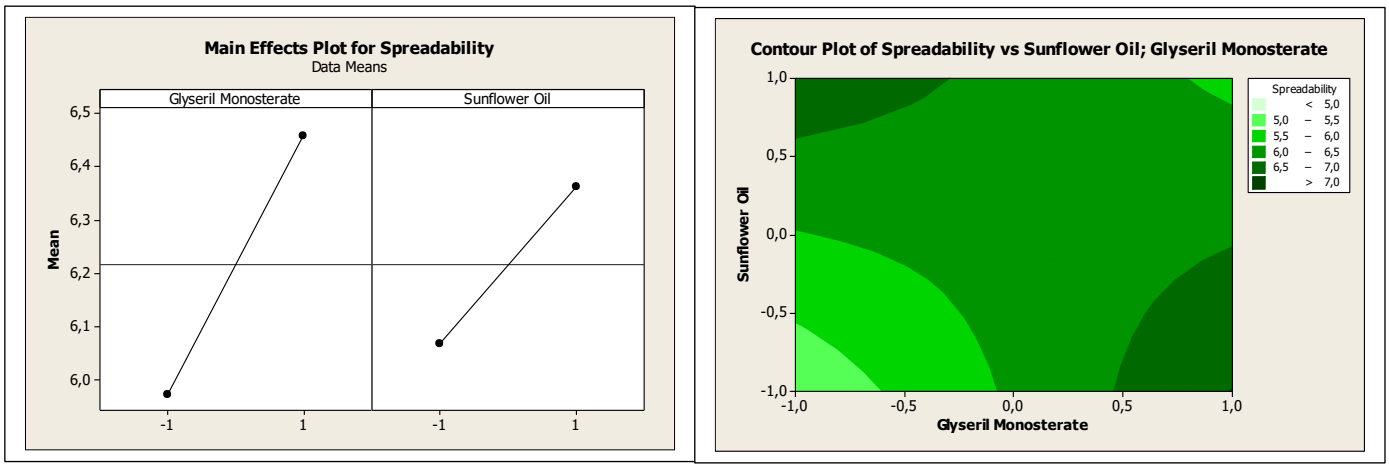

Figure 3. Main effects plot dan *Countour Plot* Spreadability NLC Quercetin

Entrapment Efficiency

The entrapment efficiency of quercetin NLC ranges from 62.20 ± 0.245% to 86.17 ± 0.287%, as shown in **Table III**. Based on

Figure 3 (main effects plot and contour plot of entrapment efficiency), it can be seen that A and B have a significant effect on the efficiency of quercetin NLC entanglement with sig. 0.000 ($p < 0.05$). The linear regression equation using the full factorial design method is shown in equation 3.

X_3 (%) = 74,4 + 2,36A + 10,1B …… (3)

The greater the percentage of entrapment efficiency produced, close to 100%, it can be said that the better the Quercetin NLC preparation because many active ingredients are trapped in NLC preparations (Natesan et al., 2017). Based on the analysis of research results on the four formulas, FIV has the highest entrapment efficiency because it has a composition of solid lipids and liquid lipids with the largest composition, namely, GMS (10 %) and sunflower oil (3 %) (Aditya et al., 2014; Liu et al., 2022). This can be caused by sunflower oil, which functions as a liquid lipid and can reduce the regularity of the glyceryl monostearate crystal lattice, so that it can contain more medicinal materials. Furthermore, the entrapment efficiency data will be analyzed using Minitab 16.0 Responce Surface Method software.

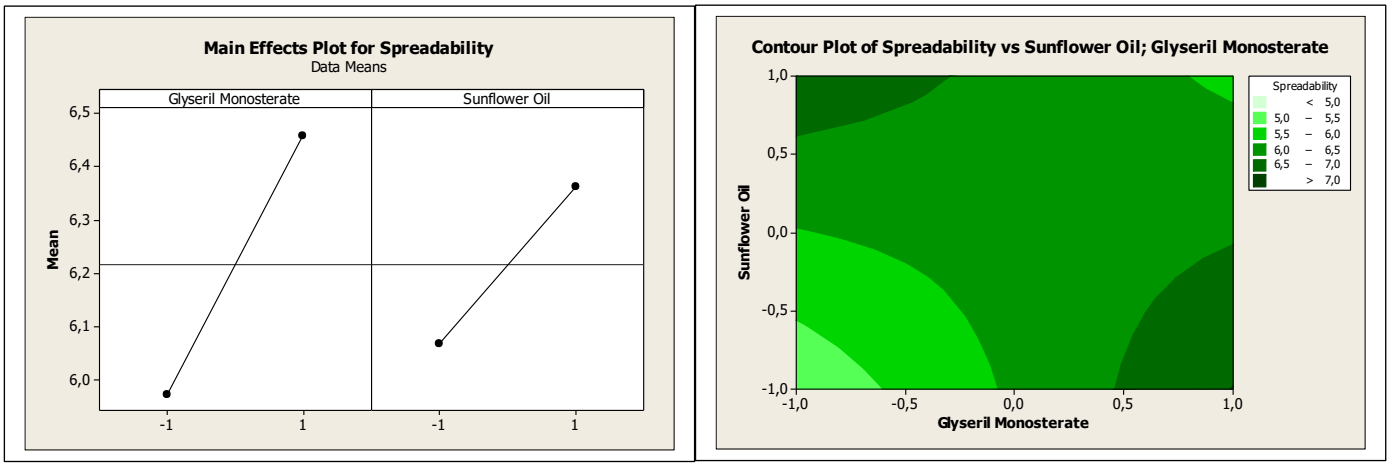

Figure 4. Main effects plot and Countour Plot EE of Quercetin NLC

The purpose of pH measurement is to determine the acidity and alkalinity of formulations, particularly topical formulations. Ideally, topical formulations should meet the specifications for skin pH. Formulations with excessive acidity levels have been shown to induce skin irritation, whereas formulations with excessive alkalinity levels have been associated with dryness and itchiness of the skin (Mallya & Patil, 2021). The composition of nanostructured lipid carrier (NLC) materials has different pH values, such as phosphate dapar with the largest concentration in the system having a pH of 7.4 for the lipid phase, GMS having a pH range of 8–10, sunflower oil having a pH of 7.38, tween 80 surfactant having a pH of 5-7, and surfactant Span 80 having a pH of 6–8. Therefore, the difference in concentration in the formulation of the nanostructured lipid carrier (NLC) system showed a value that was not significantly impacted. Based on the results of pH measurements, the pH range obtained was 7.3 ± 0.01 to 7.4 ± 0.01 (George et al., 2019).

Viscosity measurements were performed to determine the viscosity of the nanostructured lipid carrier system. The viscosity of the nanostructured lipid carrier system formulation ranges from 32.5-2499.5 cPs. The viscosity of NLC is influenced by the concentration of NLC constituents, especially the concentrations of solid and liquid lipids,

and the tools used in the evaluation process (Talarico et al., 2021). An increase in lipid concentration leads to an increase in the interaction between particles, resulting in a more rigid structure. Viscosity measurement results are listed 223.7 ± 9.8 to 492.0 ± 0.0 cps as shown in **Table III**. The higher the concentration of solid lipids in the formula, the higher the viscosity of the NLC.

CONCLUSION

Quercetin NLC has been successfully formulated as a combination of solid lipids (glyceryl monostearate) and liquid lipids derived from sunflower oil using a full factorial design model. The ratio of solid lipid concentration to liquid lipid concentration has a significant effect on particle size, dispersion, and entrapment efficiency. The results of this Quercetin NLC research are expected to be carried out through activity testing in vitro and in vivo.

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