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DESIGN AND OPTIMIZATION OF VCO AND OLEIC ACID FOR NLC QUERCETIN USING SIMPLE LATTICE DESIGN

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ABSTRACT

Quercetin is a flavonoid compound that exhibits skin-brightening activity by inhibiting tyrosinase. However, its topical application is limited because of its low solubility. A Nanostructured Lipid Carrier (NLC) was selected as the delivery system to enhance the stability and topical efficacy of quercetin. This study aimed to optimize the combination ratio of oleic acid and Virgin Coconut Oil (VCO) as the liquid lipid phase in the NLC Blank Formulation using the Simplex Lattice Design (SLD) method. Eight blank NLC formulations were prepared using the high-shear homogenization method and were evaluated based on organoleptic properties, particle size, polydispersity index (PDI), pH, and real-time stability over 30 days. Eight blank NLC Blank Formulations showed that a balanced VCO to oleic acid ratio (5.5:4.5) produced small particle sizes (<160 nm), low polydispersity index (PDI <0.25), and good physical stability. Blank Formulations dominated by either VCO or oleic acid tended to have larger particles and lower stability, indicating that the liquid lipid ratio influenced the NLC characteristics. Optimization using the Simplex Lattice Design (SLD) method identified three optimal lipid ratios: B1 (4.86:5.31), B2 (2:8), and B3 (9:1), each with desirability values near 1. The model was validated by comparing the predicted (dry lab) and experimental (wet lab) data, which showed no significant differences in key parameters ($p > 0.05$), confirming the reliability of the SLD model. This approach effectively optimized quercetin-loaded NLC Blank Formulations, and the three selected Blank Formulas serve as a strong basis for developing topical quercetin NLC products.

Keywords: Quersetin, Nanostructured Lipid Carrier (NLC), Virgin Coconut Oil, Asam Oleat, Simplex Lattice Design

INTRODUCTION

Quercetin exhibits anti-melanogenesis activity by inhibiting the enzyme tyrosinase, thereby reducing melanin production (Choi & Shin, 2016). Although quercetin has potential as a skin brightening agent, it faces challenges related to its physicochemical properties, such as low solubility with a log P of 1.82 and classification as a Biopharmaceutics Classification System (BCS) class II compound (Salvioni *et al.*, 2021). Poor solubility limits the development of topical Blank Formulations, necessitating Blank Formulation technologies that can improve quercetin's solubility and stability (Huang *et al.*, 2017). Due to its poor water solubility and instability, quercetin requires encapsulation in a well-designed lipid matrix supported by suitable surfactants. Surfactants are critical for stabilizing the NLC system and influencing particle size and enhancing skin penetration, which is particularly beneficial for poorly soluble compounds such as quercetin (Gorle *et al.*, 2023).

NLC are colloidal dispersions composed of a mixture of solid and liquid lipids that form an imperfect lipid matrix stabilized by surfactants (Chen-yu *et al.*, 2012). Their small particle size (40–1000 nm) enhances solubility and entrapment efficiency and provides controlled release and long-term stability for active compounds (Pamudji *et al.*, 2016; Wadhwa *et al.*, 2022). NLC are significantly influenced by several Blank Formulation factors. First, the selection of an appropriate surfactant is crucial for reducing the interfacial tension

between the lipid and aqueous phases, thereby producing a stable system (Elmowafy & Al-Sanea, 2021). Co-surfactants also contribute to enhancing the flexibility of the interfacial layer, assisting surfactants in maintaining the structure during cooling and recrystallization processes (Akbar *et al*., 2022). Another important factor is the type and ratio of the lipids used. The combination of solid and liquid lipids forms an imperfect crystal structure, which prevents the expulsion of the active ingredient from the matrix and allows for a higher entrapment efficiency of the active compound (Chauhan *et al*., 2020).

In this study, two types of liquid lipids were selected: oleic acid and virgin coconut oil (VCO). Oleic acid is an unsaturated fatty acid abundant in vegetable oils, particularly olive oil (55–80%), and it functions as a penetration enhancer and an effective solvent for quercetin. However, its unsaturated structure renders it prone to oxidation (Soeratri *et al*., 2019). VCO is a mixture of medium-chain saturated fatty acids, mainly lauric acid (~54%), which confers greater thermal stability and the ability to produce smaller particle sizes in NLC systems (Baskara *et al*., 2020). Additionally, the lauric acid content of VCO provides beneficial emollient effects on the skin. In the study *"Empty nano and micro-structured lipid carriers of virgin coconut oil for skin moisturisation"* the entrapment efficiency (EE) of VCO in solid lipid particles (SLP) ranged from 98% to 99% at different sonication intensities (60%–90%). However, EE decreased from 94.36% to 88.74% as the particle size increased, indicating that smaller particles tend to retain more lipid content (Ghani *et al*., 2018).

Despite the promising potential of quercetin-loaded NLCs, few studies have investigated the combination of virgin coconut oil and oleic acid as liquid lipid phases. Furthermore, the application of Simplex Lattice Design (SLD) as a systematic optimization method for lipid combinations in quercetin-NLC systems remains underexplored. This study addresses this gap by formulating and optimizing quercetin-loaded NLCs using different ratios of VCO and oleic acid, followed by experimental validation of their physicochemical properties and stability.

This study was conducted using an experimental laboratory approach to optimize the combination ratio of oleic acid and VCO as liquid lipids in the Blank Formulation of quercetin-loaded NLCs by evaluating the effect of the lipid combination ratio on the characteristics and stability of the system. Blank Formulation optimization was performed using the Design of Experiments (DoE) method, specifically the Simplex Lattice Design (SLD) for quercetin NLCs, and validated experimentally (wet lab) (Dwiputri *et al*., 2022). Characterization included organoleptic tests, pH, particle size, and polydispersity index (PDI) to evaluate the physicochemical properties and stability of the system.

RESEARCH METHODS

Equipment and Materials

The equipment used in this study included an analytical balance (KERN-ABS 220-4), Design Expert® software version 13, Digital Ultra Turrax T-25 (IKA Labortechnik), Thermo Scientific Cimarec+, Delsa™ Nano Particle Analyzer (Beckman Coulter®), and a pH meter (OneMed). The materials used in this study were cetyl palmitate (BASF, Germany), virgin coconut oil (Universal Pharma Chemical, Surabaya, Indonesia), oleic acid (Brataco Ltd., Indonesia), Tween 80 (Universal Pharma Chemical, Surabaya, Indonesia), Span 80 (Universal Pharma Chemical, Surabaya, Indonesia), propylene glycol (Dow Chemical, Singapore), and phosphate buffer (pH 6 ± 0.22).

Research Procedure

1. Preparation of Blank NLC Blank Formulations

   Based on Table I, which was generated using the Simplex Lattice Design method in Design Expert® software version 13.0, eight Blank Formulations were obtained with varying concentration combinations of VCO and oleic acid. To optimize the mixture ratios of oleic acid and VCO, this study employed the Simplex Lattice Design (SLD), a statistical mixture design method that enables the evaluation of various combinations of two or more components in a Blank Formulation. The SLD is particularly useful in

mixture experiments, where the response depends not on the absolute quantity of components but on their relative proportions. This design provides a structured and efficient approach to investigate the influence of each lipid and their interactions on key Blank Formulation parameters, such as particle size, polydispersity index (PDI), pH, and physical stability.

Table I. Combination of VCO and Oleic Acid Concentrations

Materials	Function	Concentration							
		F1	F2	F3	F4	F5	F6	F7	F8
VCO	Liquid lipid	7.25	5.5	2	5.5	2	3.75	9	9
Asam Oleat	Liquid lipid	2.75	4.5	8	4.5	8	6.25	1	1

2. Preparation and optimation of blank NLC

The NLC system was prepared using the High Shear Homogenization (HPH) method (Soeratri *et al*., 2019). Table II presents the blank NLC formulations. The preparation method involved weighing all the required ingredients. Cetyl palmitate was first melted at 60°C. Separately, VCO, oleic acid, a mixture of Tween 80 and Span 80, and an aqueous phase containing phosphate buffer (pH 6) were heated in another container to the same temperature (60°C). Once the cetyl palmitate was completely melted, a mixture of VCO, oleic acid, Tween 80, and Span 80 was added to the melted cetyl palmitate. The mixture was heated at 60°C. The aqueous phase was then added dropwise to the oil phase while stirring using an Ultra Turrax at 5000 rpm for 10 minutes. The speed was then increased to 16,000 rpm for 2 minutes, followed by a 1-minute pause. Homogenization was continued at 16,000 rpm for 2 minutes. The emulsion was then cooled to 25°C using a magnetic stirrer at 500 rpm.

Table II. Optimization of Blank NLC Composition (%w/w)

Materials	Function	Formulation (%W/W)							
		F1	F2	F3	F4	F5	F6	F7	F8
Cetil Palmitat	Solid Lipids	15	15	15	15	15	15	15	15
VCO	Liquid Lipid	7.25	5.5	2	5.5	2	3.75	9	9
Asam Oleat	Liquid Lipid	2.75	4.5	8	4.5	8	6.25	1	1
Tween 80	Surfactants	10.2	10.7	14.4	11.5	5.7	7	8.6	8.6
Span 80	Surfactants	9.75	5.7	5.5	8.4	14.4	12	11.3	11.3
Propilen Glikol	Co-Surfactants	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Dapar Phosphate (pH 6±0.22)	Aqueous Phase	100	100	100	100	100	100	100	100

3. Physical Characteristics Testing Procedure

a. Organoleptic

The physical appearance (color, odor, and texture) of a product is used as an early indicator of instability, such as oxidation or degradation, which is critical for topical product acceptance (Anwar *et al*., 2020).

b. Particle Size and Polydispersity Index (IP)

Determines the efficiency of the drug delivery. Smaller particles enhance skin penetration, solubility, and stability of the NLC system and indicate particle size uniformity. Weigh 50 mg of the sample using an analytical balance and add distilled water to reach a final volume of 50.0 mL. A magnetic stirrer mixed the solution at 500 rpm for 10 minutes. Subsequently, 2.0 mL of the solution was taken and 8 mL of distilled water was added. The mixture was stirred for another 10 minutes at 100 rpm. The next step involved using the DelsaTM nano submicron particle size analyzer to evaluate the particle size and polydispersity index (Bahari

& Hamishehkar, 2016).

c. pH

It ensures skin compatibility and prevents irritation. Topical products should have a pH close to that of the skin (4.5–6.5) to maintain barrier integrity and active stability. The pH meter was calibrated using a standard solution of pH 7.0 before assessing the sample's pH value, and the electrode was cleaned and dried. The samples were then diluted with distilled water at a ratio of 1:9. The pH was measured using an SI Analytics pH Meter Lab 855 (Erawati *et al*., 2023).

4. Real Time

Assesses changes in particle size, pH, and organoleptic properties over time to ensure Blank Formulation robustness under storage conditions. Test This investigation involved a real-time physical stability assessment of preparations stored in an air conditioned room at a temperature of 20°C ± 1°C, with a relative humidity of 65% and shielded from sunlight. The exam was administered over a duration of 1 month (30 days). The stability test evaluated the organoleptic properties, particle size, polydispersity index (PDI), and pH. Assessment was performed on days 0 and 30 (Erawati *et al*., 2023).

Data Analysis

Statistical Analysis One-way analysis of variance (ANOVA) was used to statistically evaluate the physical characteristic parameters. This strategy is employed when the data are homogeneous and regularly distributed. Alternatively, non-parametric statistical tests, specifically the Kruskal-Wallis test with a post-hoc test, were employed.

RESULTS AND DISCUSSION

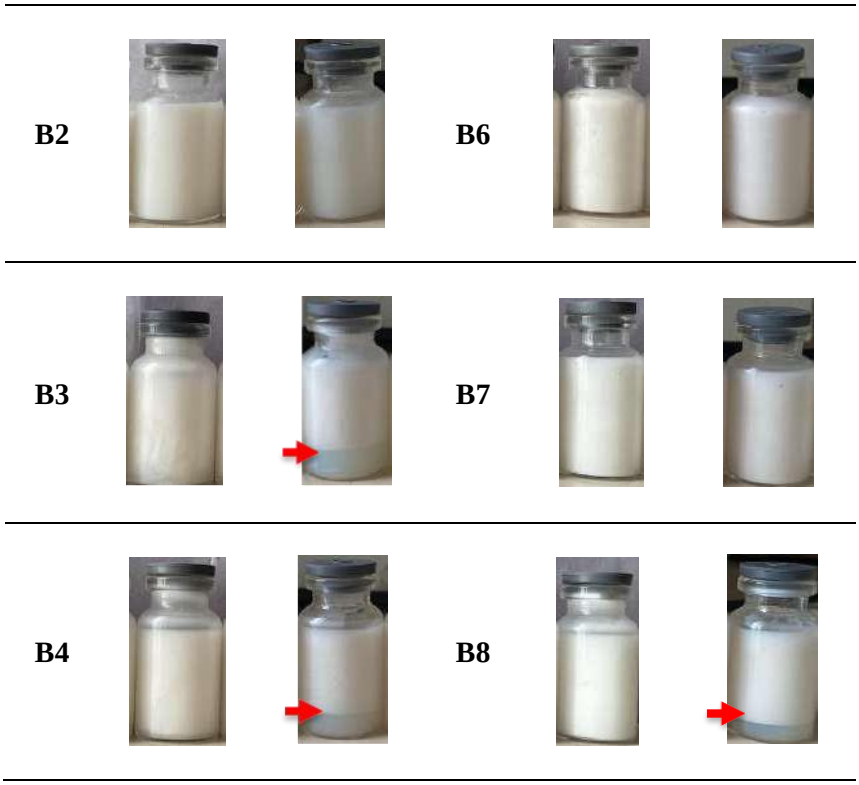
1. Evaluasi Physical Characteristics NLC Testing

a. Organoleptic

Table III presents the organoleptic evaluation results of Blank Formulations B1–B8, indicating that the NLCs exhibited a white color, characteristic odor, and semi-solid consistency with a smooth texture. However, some Blank Formulations displayed physical instability, such as clumping and phase separation. Phase separation was clearly observed on day 30, particularly in Blank Formulations B3, B4, and B8, as indicated by the formation of a distinct layer at the bottom of the dispersion system. Phase separation in NLC systems reflects the tendency of lipid particles to rise to the surface, forming a creamy layer owing to differences in density and phase incompatibility (Imran *et al*., 2020). This instability may be attributed to insufficient surfactant content to maintain system stability during storage (Barros *et al*., 2022). The lipid-to-surfactant ratio plays a crucial role in determining the physical stability of the system, highlighting the importance of using an optimal surfactant concentration to prevent phase separation and maintain homogeneity of the lipid dispersion (Suyuti *et al*., 2023).

Table III. Blank NLC day 0 & 30

Day	1	30	Day	1	30
B1			B5		



b. Particle Size

Table IV presents the particle size measurements of all Blank Formulations (B1–B8) on day 0, ranging from 128.9 to 388.9 nm, and after 30 days of storage, ranging from 159.0 to 384.8 nm. Although a slight increase in particle size was observed over time, the values remained within the acceptable NLC size range of 10–1000 nm (Suyuti *et al.*, 2023). Variations in the VCO and oleic acid ratios in B1–B8 showed that a balanced ratio (1.2:1) in B2 and B4 resulted in better physical stability and smaller particle sizes. In contrast, the high VCO ratio (9:1) in B7 and B8 led to larger particle sizes (≥ 374 nm), likely due to the higher viscosity of VCO, attributed to its medium-chain fatty acid (MCFA) content, especially lauric acid (53.70–54.06%), which promotes the formation of larger droplets during emulsification (Ghani *et al.*, 2018). Meanwhile, Blank Formulations dominated by oleic acid (B3, B5, and B6) also produced larger particle sizes and showed lower stability after 30 days. This can be attributed to the physicochemical properties of oleic acid, a monounsaturated fatty acid with a kinked molecular structure that impedes tight packing in the lipid matrix and disrupts particle stability (Berman *et al.*, 2015). A similar trend was reported by Yiyin et al. (2016), where NLCs containing Brucea javanica oil showed a slight increase in particle size from 181.5 nm to 195 nm after 30 days due to aggregation during storage (Yiyin *et al.*, 2016).

Table IV. Particle Size Test of Blank NLC

Blank Formula	NLC day-0 Particle size (nm)	NLC day-30 Particle size (nm)	Value Interpretation
B1	219.7	364.9	<400 nm
B2	128.9	159.0	
B3	222.2	228.2	
B4	231.8	237.4	
B5	253.5	291.6	
B6	292.4	367.0	

B7	374.7	376.2
B8	388.9	384.8
Mean ± SD	**264.0 ± 86.0**	**301.1 ± 85.1**

There was a statistically significant increase in particle size from day-0 (264.0 ± 86.0 nm) to day-30 (301.1 ± 85.1 nm), with a p-value of 0.038 (*paired t-test*), indicating potential minor instability during storage. Particle size of blank NLC formulations on day-0 (blue) and day-30 (red). All formulations showed particle sizes below 400 nm, with a slight increase observed after 30 days of storage, indicating physical stability.

c. Polydispersity Index (PDI)

A PDI value below 0.3 indicates a narrow particle size distribution and a relatively homogenous system. As shown in Table IV, blank formulas B7 and B8 with a high VCO ratio exhibited large particle sizes but maintained stable PDI values (0.26–0.28). This was attributed to the higher viscosity of the system owing to the 9% VCO content (Ghani *et al.*, 2018). The PDI values of blank formulations B3 and B5, which had a high oleic acid ratio, increased from 0.238 to 0.262 after 30 days of storage. The high oleic acid content enhances lipid matrix fluidity in the NLC system. Increased fluidity can lead to thermal and mechanical instability as lipid molecules move and interact more freely, potentially causing particle fusion or changes in the internal structure during storage (Gorle et al., 2023). In contrast, Blank Formulations with a balanced VCO:oleic acid ratio, such as B2 and B4 (5.5:4.5), demonstrated lower and more stable PDI values (0.222–0.283).

This aligns with the findings of Soeratri et al. (2019), who reported that a combination of liquid lipids, such as soybean oil and oleic acid, in resveratrol-loaded NLC Blank Formulations enhanced physical stability over 30 days of storage (Soeratri *et al.*, 2019).

Table V. PDI Test of Blank NLC

Blank Formula	NLC day-0 PDI	NLC day-30 PDI	Value Interpretation
B1	0.147	0.233	≤ 0.3
B2	0.288	0.222	
B3	0.200	0.262	
B4	0.212	0.283	
B5	0.251	0.238	
B6	0.221	0.276	
B7	0.262	0.288	
B8	0.213	0.255	
Mean ± SD	**0.224 ± 0.04**	**0.257 ± 0.02**	

The average PDI slightly increased from day-0 (0.224 ± 0.040) to day-30 (0.257 ± 0.020), indicating a minor broadening of the particle size distribution. However, all values remained below 0.3, suggesting that the formulations maintained an acceptable homogeneity. Statistical analysis revealed that the change was not significant ($p > 0.05$), indicating no substantial instability over the 30-day period. PDI values of blank NLC formulations on day-0 and day-30. All formulations exhibited PDI values ≤ 0.3, indicating acceptable particle size homogeneity.

d. pH

The pH data of the eight NLC Blank Formulations in Table VI show slight

increases and decreases during 30 days of storage, varying across Blank Formulations. These variations were closely related to the differences in the VCO and oleic acid ratios. In Blank Formulations with high VCO content (B7 and B8), the pH values remained relatively stable, with a slight increase. This can be attributed to the high content of saturated fatty acids in VCO, which are more inert and less prone to hydrolysis into free acids that would lower the pH (Ghani *et al*., 2018). In contrast, Blank Formulations dominated by oleic acid (B3, B5, and B6) exhibited a slight decrease in pH, likely due to the higher reactivity and susceptibility to oxidation and hydrolysis of oleic acid, which may generate free fatty acids that contribute to pH reduction over time (Pamudji *et al*., 2016). Blank Formulations with a balanced liquid lipid ratio showed relatively stable pH values throughout storage, suggesting a synergistic interaction between the stable saturated fatty acids in VCO and the more reactive oleic acid (Akin-Ajani *et al*., 2025). VCO acts as a lipid matrix that helps inhibit the further degradation of oleic acid by providing physicochemical protection against oxidation and hydrolysis (Dayrit, 2015).

Table VI. pH Test of Blank NLC

Blank Formula	NLC day-0 pH	NLC day-30 pH	Value Interpretation
B1	6.866	6.003	4.5 – 6.5
B2	5.930	5.594	
B3	5.309	5.022	
B4	6.356	6.145	
B5	5.273	5.244	
B6	5.442	5.407	
B7	5.415	5.590	
B8	5.311	5.577	
Mean ± SD	**5.738 ± 0.59**	**5.573 ± 0.36**	

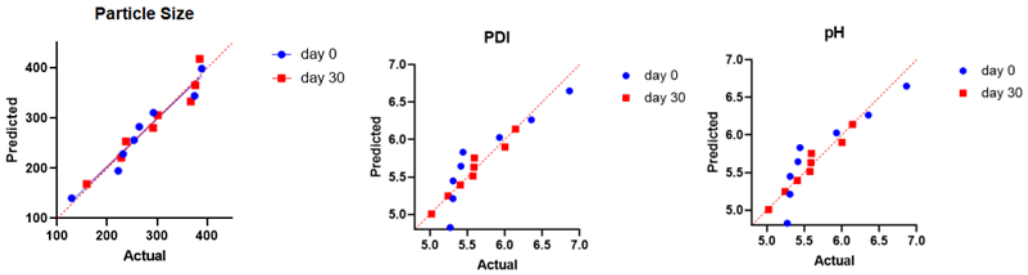
The pH of all blank NLC formulations ranged from 5.3 to 6.9 on day-0 and 5.0 to 6.1 on day-30, remaining within the acceptable topical range of 4.5 to 6.5. A slight decrease in the mean pH was observed (5.738 ± 0.59 to 5.573 ± 0.36), which was not statistically significant ($p > 0.05$), indicating acceptable chemical stability during storage. pH values of blank NLC formulations on day-0 and day-30. All formulations remained within the acceptable pH range for topical application (4.5–6.5 pH).

e. Real Time Stability

The particle size increased in all Blank Formulations after 30 days of storage, as shown in Table IV. Blank Formulation B2 demonstrated the highest stability, with only a slight increase from 128.9 nm to 159.0 nm, whereas B1 and B6 showed significant increases. The average particle size increased from 264.0 ± 86.0 nm to 301.1 ± 85.1 nm, indicating a tendency toward aggregation in some blank formulations due to imbalanced lipid ratios. As presented in Table V, all blank formulations maintained PDI values below 0.3, indicating a relatively homogenous particle distribution. The average PDI increased slightly from 0.224 ± 0.04 to 0.257 ± 0.02 after 30 days, although these changes remained within the stability thresholds. Table VI shows that the pH of all Blank Formulations slightly decreased after 30 days of storage, from an average of 5.738 ± 0.59 to 5.573 ± 0.36. The greatest pH reduction was observed in B1; however, all blank formulations remained within the safe range for topical application. These minimal pH changes indicate good chemical stability during storage.

2. Optimization of VCO and Oleic Acid Combination in NLC

The Simplex Lattice Design (SLD) method was employed to optimize Blank Formulations involving various types and proportions of ingredients (Hajrin *et al.*, 2021). This approach allows for the use of a minimal number of samples and helps reduce the time and cost by eliminating the need for repeated trial-and-error experiments (Akbar *et al.*, 2022). In this study, the concentration of liquid lipids—comprising virgin coconut oil (VCO) and oleic acid—ranged from 0–10% and was optimized using Design Expert® v13 software to obtain the most suitable NLC Blank Formulation based on particle size, polydispersity index (PDI), and pH parameters. Three optimal Blank Formulations were selected based on the optimization results.



a **b** **c**

Figure 1. Predicted vs. actual plots for (a) particle size, (b) PDI and (c) pH

Figure 1 presents the predicted vs. actual plot used to evaluate the accuracy of the model developed using the Simplex Lattice Design (SLD) method. The data points closely aligned along the diagonal line (y = x) indicate that the predicted (x) values from the model closely match the experimental (actual = y) values, demonstrating a strong predictive capability.

Table VII. Optimal Solutions Identified Using Simplex Lattice Design

Number	VCO	Oleic Acid	Particle Size (nm)	PDI	pH	Desirability	
B1	2.000	8.000	227	0.226	6.210	0.662	
B2	**4.866**	**5.134**	**261**	**0,256**	**6.173**	**0.772**	**Selected**
B3	9.000	1.000	371	0.212	6.335	0.624	

The optimization results yielded desirability values close to B2, confirming that the obtained combinations of liquid lipids (VCO and oleic acid) represented the most optimal Blank Formulations based on the defined parameters: particle size, polydispersity index (PDI), and pH. The selected optimal lipid compositions were: B2 (VCO:oleic acid = 4.86:5.31), B1 (2:8), and B3 (9:1). This supports the reliability of the model in predicting and guiding Blank Formulations with desirable NLC characteristics. The three selected Blank Formulations (dry lab) were statistically compared with the corresponding wet lab Blank Formulations using One-Way ANOVA, followed by Tukey's HSD test, to determine whether significant differences existed between the groups. The analysis results for particle size (p-value = 0.084), PDI (p-value = 0.168), and pH (p-value = 0.136) all showed p-values greater than 0.05, indicating no statistically significant differences between the predicted Blank Formulations and the experimental results. These findings confirm that the SLD model accurately predicts Blank Formulations consistent with wet lab outcomes. Therefore, the three selected Blank Formulations were suitable for the further development of quercetin-loaded NLCs.

CONCLUSION

In conclusion, this study successfully formulated and optimized the combination of Virgin Coconut Oil (VCO) and oleic acid as liquid lipids in a Nanostructured Lipid Carrier (NLC) system for quercetin using the Simplex Lattice Design (SLD) approach. The SLD method was effective in exploring and determining the optimal ratio of the two liquid lipids to produce NLC Blank Formulations with desirable physical characteristics, including small particle size, low polydispersity index (PDI), appropriate pH for topical use, and good physical stability during storage.

Three selected Blank Formulations from the SLD results met the evaluation criteria and were validated as suitable candidates for further development. The combination of VCO and oleic acid in specific proportions balanced the individual properties of each lipid, with VCO contributing to stability and biocompatibility, while oleic acid improved the solubility of quercetin and may function as a skin penetration enhancer.

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