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Design and Optimization of Nanostructured Lipid Carriers for Quercetin in Skin Lightening Applications

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Abstract

Background*: Quercetin, a potential skin-lightening agent, reduces intracellular and fungal tyrosinase activities. However, its poor water solubility and limited skin permeability hinder its applications. Nanostructured lipid carriers (NLCs), which are composed of biocompatible and biodegradable lipids, enhance drug stability and skin penetration. The lipid type, surfactant concentration, and formulation parameters influence NLC stability.* ***Objective:*** *This study aimed to optimize NLC formulations for quercetin delivery by evaluating their organoleptic properties, particle size, polydispersity index (PDI), and pH.* ***Methods:*** *NLCs were prepared using 10% total lipids (4% solid and 6% liquid lipids) and surfactant mixtures at varying concentrations via High Shear Homogenization. Initial formulations using myristic acid and castor oil were unstable and underwent phase separation within five days.* ***Results:*** *Substituting the solid lipid with a 1:3 combination of beeswax and cocoa butter produced a stable formulation during storage at room temperature. The lipid and surfactant compositions significantly influenced the particle size and PDI. While the pH remained stable, statistical analysis revealed significant changes in particle size and PDI across the formulations.* ***Conclusion:*** *Optimized NLC formulations for quercetin delivery demonstrated improved stability and potential for effective skin lightening. Further research is warranted to evaluate the in vivo efficacy and scalability of this approach.*

Keywords*: cosmetic delivery system, formula optimization, NLC, quercetin, skin lightening*

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INTRODUCTION

Melanin levels, which determine skin color, vary due to genetic factors and environmental influences, such as sun exposure. While melanin protects against skin damage, excessive accumulation can lead to hyperpigmentation, causing aesthetic concerns. Conditions such as melasma, freckles, and age spots often result from prolonged UV exposure, which increases reactive oxygen species (ROS) and triggers inflammatory responses (Choi & Shin, 2016).

Quercetin, a naturally occurring flavonoid found in fruits and vegetables, exhibits potent anti-tyrosinase and antioxidant properties, making it a promising candidate for skin-lightening applications. Compared to conventional agents such as kojic acid and arbutin, quercetin exhibits superior anti-tyrosinase activity (IC50 1.59 ± 0.38 µg/mL vs. 98.14 ± 1.45 µg/mL for arbutin); however, it suffers from poor water solubility and limited skin penetration (Hatahet et al., 2016; Lu et al., 2019). These limitations necessitate the development of advanced delivery systems to improve their stability, bioavailability, and efficacy.

Nanostructured Lipid Carriers (NLCs) offer a promising solution, leveraging biocompatible and biodegradable lipids to enhance drug stability and penetration through the skin. The stability of NLCs depends on formulation parameters, such as lipid type, surfactant concentration, and particle size distribution. Smaller, uniformly distributed particles (<0.5 PDI) are associated with enhanced stability and reduced aggregation (de Barros et al., 2022). However, physical instability, including creaming, phase separation, and sedimentation, remains a challenge. Factors such as viscosity, lipid crystallization, and storage conditions significantly impact NLC performance and require careful optimization (Sakellari et al. 2021).

Myristic acid, a solid lipid, has a high melting point and excellent crystal properties, which can provide stability to the NLC system. However, the use of myristic acid is limited by its retention and release capabilities of active ingredients. Research has shown that myristic acid can reduce molecular diffusion but is not always optimal for increasing the encapsulation efficiency of bioactive compounds. This can cause physical instability if not balanced with the appropriate liquid lipids (Husnawiyah et al., 2023).

Beeswax and oleum cacao are intriguing substitutes for solid lipids in NLC formulations. This combination not only provides better stability but also improves the emollient properties of the final product. Beeswax can form a beneficial film on the skin surface, while oleum cacao is known for its moisturizing properties. This combination can improve the retention of active ingredients and reduce the risk of creaming or phase separation during storage (Khasanah & Rochman 2022). The physical stability of NLC using a beeswax-oleum cacao combination was superior to that using myristic acid. Research has shown that this solid lipid replacement can reduce the particle size and improve the particle distribution in the system. A smaller particle size contributes to increased stability because it reduces the potential for aggregation. In addition, beeswax can help stabilize the interface between solid and liquid lipids, thereby preventing recrystallization (Husnawiyah et al., 2023).

This study aimed to optimize NLC formulations for quercetin delivery by evaluating key parameters, including organoleptic properties, particle size, polydispersity index (PDI), and pH. These findings contribute to the development of stable and effective delivery systems for skin-lightening applications.

MATERIALS AND METHODS

Material

Quercetin (Sigma-Aldrich, Germany), beeswax (Sigma-Aldrich, China), Cocoa Butter (PT Darjeeling Sembrani Aroma, Indonesia), Myristic Acid (Sisco Research Laboratories Pvt. LTD, India), Castor Oil (Sigma-Aldrich, China), Tween 80 (Sigma-Aldrich, Germany), Span 80 (Sigma-Aldrich, Germany), Propylene Glycol (Supelco, Germany), phenoxyethanol (Raja Kimia, Indonesia), Potassium Dihydrogen Phosphate (Merck, Germany), and Potassium Hydroxide (Merck, Germany).

Method

Procedure for making NLC

NLC Quercetin was produced by amalgamating the aqueous and lipid phases utilizing a high-speed stirrer. An Ultra Turrax IKA ® T25 Digital High Shear Homogenizer was employed in this study. The oil phase was created by melting myristic acid or beeswax-cocoa butter, castor oil, and Span 80 at approximately 70°C using a hotplate stirrer. The aqueous phase consisted of Tween 80, propylene glycol, phenoxyethanol, and phosphate buffer (pH 5). After mixing the two ingredients in a single beaker until they were completely blended, the mixture was heated to 70°C. After the oil phase was prepared, the water phase was added slowly. The mixture was stirred for 10 min using an Ultra Turrax IKA® T25 Digital High Shear Homogenizer at a speed of 5000 rpm.

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Table 1. Optimization of NLC formula composition (% w/w)

Composition	Function	F1	F2	F3	F4	F5	F6
Myristic Acid	Solid lipids	4	4	6	6	-	-
Beeswax	Solid lipids	-	-	-	-	1	1
Oleum Cacao	Solid lipids	-	-	-	-	3	3
Castor Oil	Liquid lipids	6	6	4	4	6	6
Span 80	Surfactants	2.02	2.02	2.47	2.47	5.05	6.73
Tween 80	Surfactants	9.98	9.98	9.53	9.53	9.95	13.27
Propylene glycol	Co-Surfactants	3.5	10	3.5	10	5.0	5,0
Phenoxyethanol	Preservatives	0.5	0.5	0.5	0.5	0.5	0.5
Phosphate buffer pH 5 ad	Aqueous phase	100	100	100	100	100	100

The velocity was then increased to 16,000 rpm and the mixture was stirred for 2 min. Stirring was continued with a hotplate stirrer at a speed of 500 rpm until the hotplate stirrer reached approximately 25°C (Mayangsari et al., 2021).

Physical characteristics testing procedure

Organoleptic

Organoleptic evaluation employs the five senses to evaluate the color, aroma, texture, and potential phase separation (Mayangsari et al., 2021).

Particle size and polydispersity index (IP)

The preliminary stage involved the dilution of the formulation. Next, 50 mg of the sample was weighed using an analytical balance, and distilled water was added to reach a final volume of 50.0 mL. A magnetic stirrer mixed the solution at 500 rpm for 10 min. Subsequently, 2.0 mL of the solution was taken, and 8 mL of distilled water was added. The mixture was stirred again for 10 min at 100 rpm. The next step involved using a DelsaTM nano submicron particle size analyzer to evaluate the particle size and polydispersity index (Mayangsari et al., 2021).

pH

The pH meter was calibrated using a standard solution of pH 7.0 before assessing the sample's pH value, and the electrode was then cleaned and dried. The subsequent stage involved diluting the sample with distilled water at a 1:9 ratio. The pH was measured using an SI Analytics pH Meter Lab 855 (Mayangsari et al., 2021).

Real time test

This investigation involved a real-time physical stability assessment of preparations stored in an air-conditioned room at a temperature of 20 ± 1°C, with a relative humidity of 65% and shielded from sunlight. The examination was administered over three months (90 days). The stability test evaluated the organoleptic properties, particle size, polydispersity index (PDI), and pH value. Assessment was performed on days 0, 30, 60, and 90 (Mayangsari et al. 2021).

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, can be employed.

RESULTS AND DISCUSSION

Organoleptic

Table 2 illustrates that the organoleptic assessments of the formulations (F1-F4) indicated that the NLC had a white hue, possessed a distinct odor, and presented a semi-solid consistency with a soft texture. Creaming, oil phase separation, and sedimentation of high-density components are examples of physical instability in emulsion-based carrier systems. Table 2 illustrates the phase separation occurring during storage, with a distinct layer at the bottom signifying system instability on the fifth day. Creaming in NLC systems refers to the phenomenon in which lipid particles in suspension ascend and create a creamy layer above the dispersion system. Inadequate surfactant levels necessary for sustaining the NLC system during storage may result in phase separation (Suyuti et al., 2023). The lipid-to-surfactant ratio significantly affects system stability, highlighting the crucial role of surfactants in stabilizing the NLC system. Surfactants can rapidly decrease surface tension, inhibit particle aggregation, and prevent the recrystallization of the drug. Additional research has indicated that the concentration and type of surfactant can influence the stability of the NLC system. The surfactant-to-oil ratio and specific type of oil can influence the stability of the colloidal dispersion system.

This can establish macroscopic carrier systems at lipid-to-surfactant ratios above 1:2; however, the process of NLC formation also influences this. Elevated surfactant concentrations facilitate the formulation of lipid-based carriers. Low-density lipids can influence

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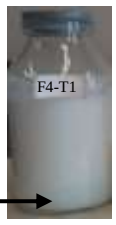
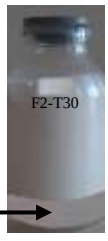
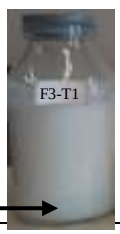
the system stability, leading to creaming, flocculation, and coalescence (Rohmah et al. 2019).

The calculated HLB ratios for the formulas (F1-F2) were 13.20, (F3-F4) were 12.8, and (F5-F6) were 11.40. The difference in HLB values was mainly due to the difference in the composition of the solid lipids of myristic acid (HLB = 12) used. In F1-F4, the ratio of solid lipids to liquid lipids (4:6) in formulas (F1-F2) and (6:4) in formulas (F3-F4). In formulas (F5-F6), the researchers replaced the type of solid lipids used with beeswax (HLB = 12) and cocoa butter (HLB = 6) at a ratio of solid lipids to liquid lipids (4:6). The HLB value affects the interfacial tension between the oil and water. The correct HLB value reduces the interfacial tension, thereby increasing the stability of the emulsion. Conversely, an inappropriate HLB value increases the interfacial tension, thereby accelerating coalescence and the formation of cream droplets (Smejkal et al., 2024). Solid lipids, such as cacao butter or myristic acid, have different crystal forms that affect the physical properties and stability of NLCs. More stable crystal forms (such as beta cacao butter) ensure that the particles are stable and prevent their coalescence or agglomeration. Oleum cacao has polymorphic forms that result in high entrapment but are less stable during storage. Although beeswax has a more regular crystal lattice than cacao butter, the combination of cacao butter and beeswax produces smaller particles than when the two lipids are used separately. Oleum cacao and beeswax were used in a ratio of 75:25 because it produced a low crystallinity index, as opposed to the combinations of 25:75 and 50:50. This increases the stability of NLCs (Munandar Erawati et al., 2023). Fluctuations in the co-surfactant concentration and composition can markedly influence the stability of NLC. Research indicates that fluctuations in co-surfactant concentration and composition significantly influence the stability of NLC by diminishing the surface tension between the oil and water phases, thereby decreasing the likelihood of particle aggregation and recrystallization. Elevated quantities of co-surfactants can enhance stability by preserving the surface equilibrium of the emulsifying particles (Rahmi et al., 2013).

Table 2 illustrates that the organoleptic assessment of the formulas (F5-F6) revealed that the NLC was white, had a distinct odor, exhibited a semi-solid consistency, had a soft texture, and demonstrated no phase separation after storage. The crystallinity index denotes the regularity and density of the crystalline structure of the material. Solid lipids with a high crystallinity index in NLC exhibit a more uniform and stable crystalline architecture, enhancing the physical stability of the particles. A denser crystalline structure inhibits lipid diffusion and migration, thereby enhancing system stability (Dragicevic & Maibach, 2016).

Table 2. Results of NLC-0 observations during storage (F1-F6)

Day	1	5	30	Day	1	5	30
F1				F4			
F2				F5			
F3				F6			

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Solid lipids, such as cacao butter and myristic acid, have different crystalline structures that affect their physical behavior and stability as nanostructured lipid carriers (NLCs). More stable crystalline structures (such as the beta polymorph of cocoa butter) guarantee particle stability and inhibit coalescence and agglomeration. Oleum cacao exhibits a polymorphic structure that facilitates substantial trapping but demonstrates reduced stability during storage. The beeswax basis possesses a more uniform crystal lattice than oleum cacao; nonetheless, the amalgamation of oleum cacao and beeswax results in smaller particles than when the two lipids are utilized independently. Oleum cacao and beeswax were utilized in a 75:25 ratio, as this configuration yielded a low crystallinity index, unlike the 25:75 and 50:50 combinations. This enhances the entrapment efficiency (Erawati et al., 2023). Myristic acid is a saturated fatty acid that contains 14 carbon atoms. Its crystal structure is comparatively uncomplicated compared to that of cacao butter or beeswax. Myristic acid crystals exhibited a more regular and denser structure than beeswax; however, they may be less intricate than cacao butter. Compared to beeswax, myristic acid often exhibits a greater crystallinity index; however, it may be lower than that of cacao butter, mostly due to differences in crystal morphology and the intricate lipid composition of cacao butter (Müller & Careglio, 2018).

Lipids with a high crystallinity index tend to form more stable and uniform particles in NLCs. In contrast, a more ordered crystalline structure can reduce the range of particle sizes and improve the stability of the particle sizes in formulations. Systems with a high crystallinity index typically exhibit narrower and more uniform particle size distributions. The presence of lipids with a solid crystalline structure makes NLCs more stable by lowering the chance of creaming or settling. Moreover, a solid crystalline structure diminishes the probability of particle size alterations during storage and aids in safeguarding the active ingredient from degradation during storage. The chemical stability of the active substance encapsulated in the lipid matrix can be enhanced by increasing the crystallinity index (Da Silva & Martini, 2024).

Characterization of particle size and polydispersity index (IP)

The particle measurement results showed that decreasing the amount of co-surfactant in formulations (F1–F2) and (F3–F4) resulted in smaller particle sizes. Nevertheless, increasing the quantity of solid lipids (F1-F4) can enhance the dimensions of the NLC particles (Table 3). The particle size of the overall formula (F1-F6) ranged from 153.9 to 259.5 nm, which complies with the NLC particle size specifications of 10-1000 nm (Suyuti et al., 2023). Statistical analysis using GraphPad Prism 10 (F1–F6) in the NLC system (Figure 1) showed that the particle sizes were significantly different between the formulations. The only formulas that did not show any significant differences (F1, F2), (F1, F4), (F2, F4), and (F5 and F6). The results indicated that F5-F6 yielded the smallest particle size compared to other formulations utilizing various forms of solid lipids (F1-F4).

Table 3. Characterization results of particle size and PDI of NLC-0

Formula	Replication	Particle size (nm)	Mean ± SD	PDI	Mean ± SD	pH	Mean ± SD
F1	R1	229.7	232.0 ± 2.4	0.308	0.312 ± 0.004	5.181	5.180 ± 0.001
	R2	231.8		0.315		5.180	
	R3	234.4		0.314		5.179	
F2	R1	229.7	229.4 ± 0.3	0.233	0.230 ± 0.003	5.173	5.170 ± 0.003
	R2	229.1		0.229		5.170	
	R3	229.5		0.227		5.167	
F3	R1	258.9	258.7 ± 0.9	0.383	0.386 ± 0.008	5.170	5.169 ± 0.001
	R2	259.5		0.395		5.168	
	R3	257.7		0.379		5.169	
F4	R1	239.7	240.8 ± 1.1	0.378	0.361 ± 0.019	5.178	5.177 ± 0.002
	R2	241.8		0.340		5.179	
	R3	240.8		0.365		5.175	
F5	R1	177.6	170.3 ± 7.6	0.300	0.326 ± 0.032	5.320	5.347 ± 0.055
	R2	162.5		0.317		5.410	
	R3	170.7		0.362		5.310	
F6	R1	153.9	169.1 ± 17.8	0.014	0.074 ± 0.100	5.410	5.387 ± 0.021
	R2	164.7		0.189		5.381	
	R3	188.7		0.018		5.370	

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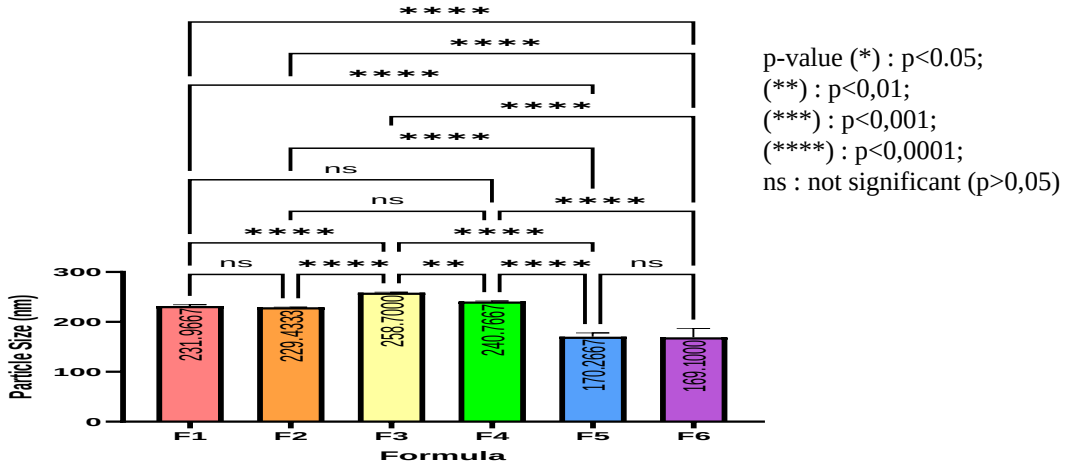

Figure 1. Particle size F1-F6 (data are the average of three replications ± SD)

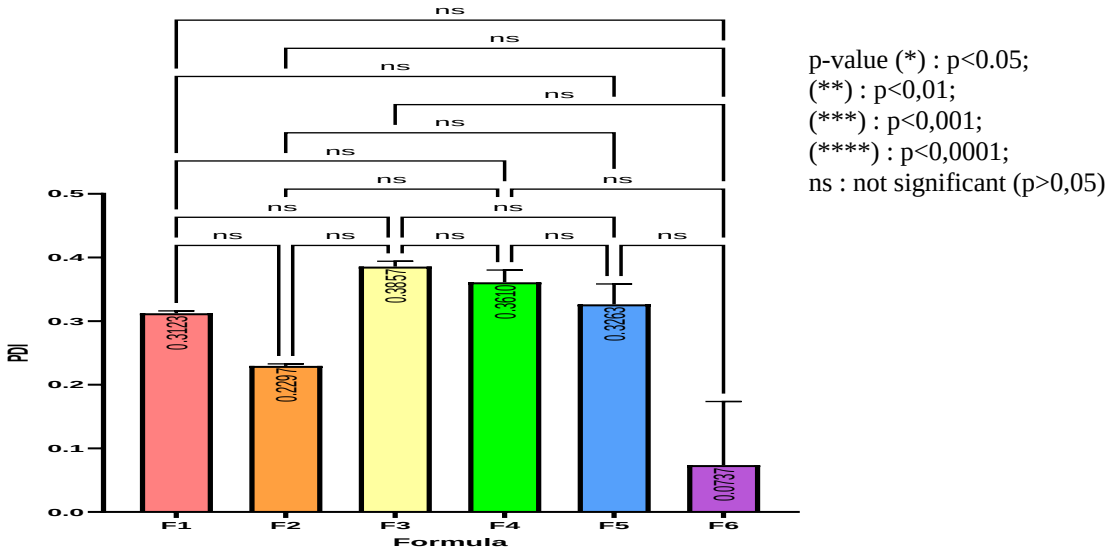

Figure 2. PDI F1-F6 (data are the average of 3 replications ± SD)

The PDI value measurements showed that an increase in the co-surfactant quantity in the formulas (F1-F2) and (F3-F4) results in a decrease in the PDI value. Nonetheless, an increase in the quantity of solid lipids (F1-F4) can elevate the PDI of the NLC (Table 3). The overall formula (F1-F6) PI values ranged from 0.014 to 0.395 (Table 3), which complies with the PI requirements (0-1), indicating a homogenous particle size distribution (Suyuti et al., 2023). The GraphPad Prism 10 statistical analysis results (F1–F6) for the NLC system (Figure 2) showed that the PDI values did not change significantly among the different formulas. The results indicated that F6 yielded the lowest PDI value compared to all other formulations utilizing various solid lipids (F1-F4).

The lipid crystallinity index influences the interaction between surfactants and the system. Highly crystallized lipids may require a greater quantity of surfactants to achieve a stable emulsion, whereas less crystallized lipids may be more readily stabilized with a basic surfactant. Co-surfactants can modify or stabilize the crystalline architecture of lipids, and lipids with high crystallization may exhibit increased sensitivity to co-surfactants (Han et al., 2008).

Surfactants diminish the interfacial tension between the lipid matrix and aqueous phase. This may influence the particle size and trajectory, leading to a stable system, during storage. Non-ionic surfactants, such as a combination of Span 80 and Tween 80, are utilized because of their lower toxicity and irritancy compared to ionic surfactants. Propylene glycol was used in the formulation as a co-surfactant to reduce the particle diameter, thereby enhancing the entrapment of drug molecules within the NLC system (Han et al., 2008).

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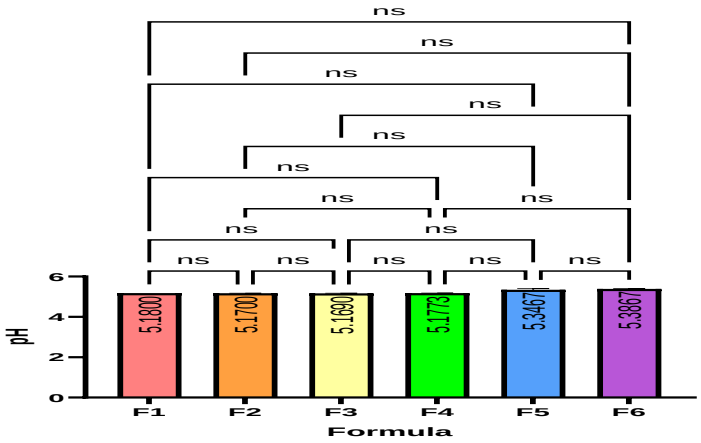

Figure 3. pH F1-F6 (data are the average of 3 replications ± SD)

Surfactants reduce the surface tension between the lipid and water phases, facilitating the production of smaller particles during homogenization. An ideal surfactant quantity can yield particles with reduced dimensions and a more homogeneous size distribution. Surfactants stabilize the produced particles by creating a protective coating around the lipid particles. Insufficient surfactant can lead to particle aggregation, resulting in increased particle size and a broader particle size dispersion. Excessive surfactant concentrations may lead to micelle formation, which can disrupt lipid particle formation and produce a broader particle size distribution (Fitriani et al., 2024).

Characterization of pH

The NLC formula was determined by evaluating the pH of formulations F1-F6 (Table 4). The pH of the NLC formulations varied between 5.17 and 5.41. This is attributable to the presence of a phosphate buffer at pH 5 as the carrier solution, which corresponds to the utilized pH buffer, that is, pH 5 ± 0.5. The purpose of applying a pH buffer is to preserve the pH stability of the active ingredients. Furthermore, pH testing is essential to prevent skin irritation and dryness. An excessively acidic pH may induce irritation and stinging, whereas an excessively alkaline pH can lead to itching and dryness; hence, the formulation must be sustained within a skin pH range of 4.0-7.0 (Dyah et al., 2023). The GraphPad Prism 10 statistical analysis results (F1–F6) for the NLC system (Figure 3) showed that the pH values did not change significantly between the formulas. The results indicate that F5-F6 yield the highest pH values compared to other formulations utilizing various solid lipids (F1-F4).

Real time test

The results of the real-time physical stability test for preparations F1-F4 show that creaming/phase separation on day 1 prevented stability testing. The stability test findings for the NLC preparation F5-F6 indicated that they could only sustain stability for 30 days.

Stability results of particle size and polydispersity index (IP)

The particle measurement data showed that as the amount of surfactant in F5 and F6 increased over time (t1–t30), the particle size increased (Figure 4), and the PDI value decreased (Figure 5). Nonetheless, the comprehensive formula (F5-F6) continued to satisfy the criteria for NLC particle size ranging from 10 to 1000 nm and a PDI of 0 to 1 (Suyuti et al., 2023). The statistical analysis results of the NLC system using GraphPad Prism 10 (F5–F6) showed no significant differences in particle size (Figure 4) or PDI (Figure 5) among the different formulas. The results indicate that F6 yielded the smallest particle size and PDI among the two formulations. Nonetheless, the F6 formula comprised a total surfactant concentration of 20%, surpassing that of F5, which was 15%. Surfactants are crucial for stabilizing the NLC system by reducing surface tension and inhibiting particle agglomeration. Research indicates that increasing the surfactant content can enhance the stability of the NLC formulation; however, excessive surfactant may adversely affect the skin (Juanita & Aryani, 2023).

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Table 4. Stability results of particle size characterization, PDI, and pH of NLC-0

Formula	Time (Days)	Particle Size (nm)	Mean ± SD	PDI	Mean ± SD	pH	Mean ± SD
F5	t1	170.3	175.0 ± 5.1	0.326	0.405 ± 0.113	5.39	5.44 ± 0.06
	t5	174.3		0.355		5.43	
	t30	180.4		0.534		5.5	
F6	t1	169.1	173.6 ± 4.9	0.074	0.203 ± 0.180	5.35	5.40 ± 0.06
	t5	173		0.127		5.4	
	t30	178.8		0.409		5.46	

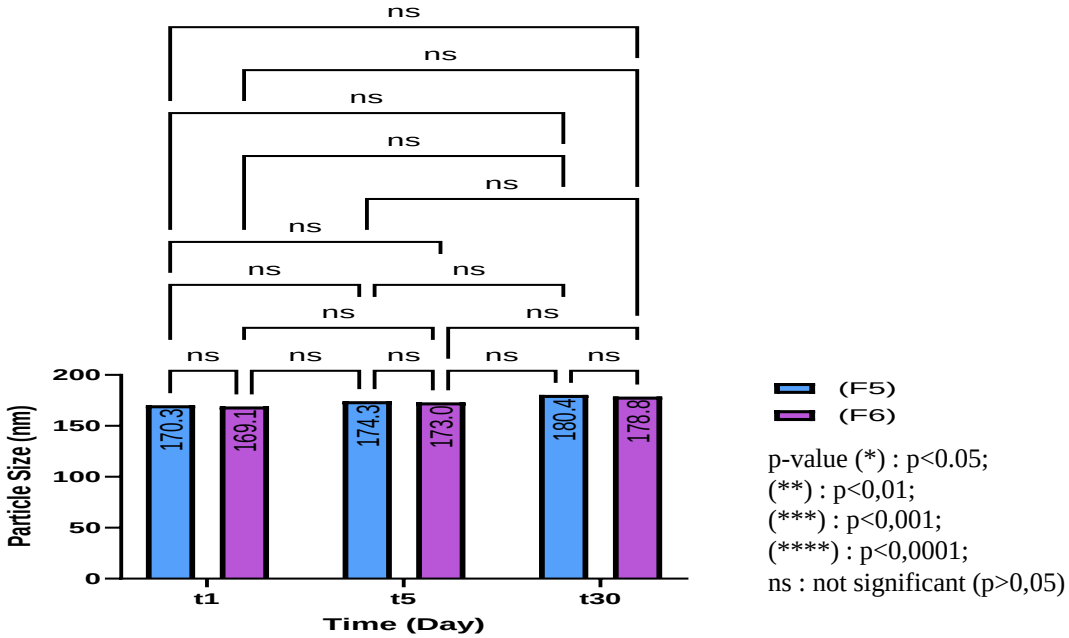

Figure 4. Graph of changes in particle size F5-F6 (data are the average of three replications ± SD)

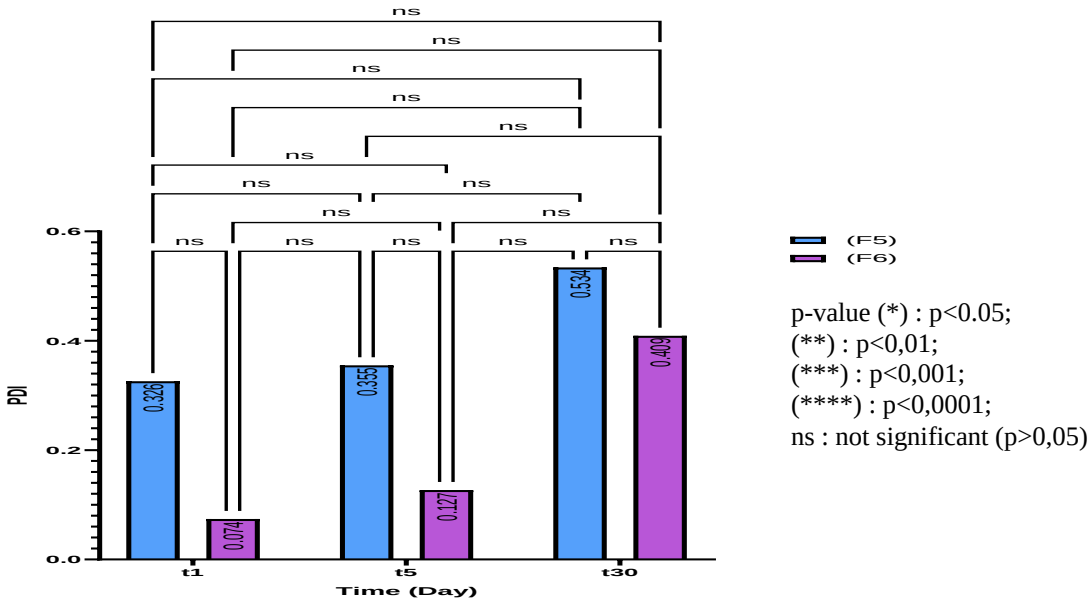

Figure 5. Graph of changes in PDI F9-F10 values (data are the average of three replications ± SD)

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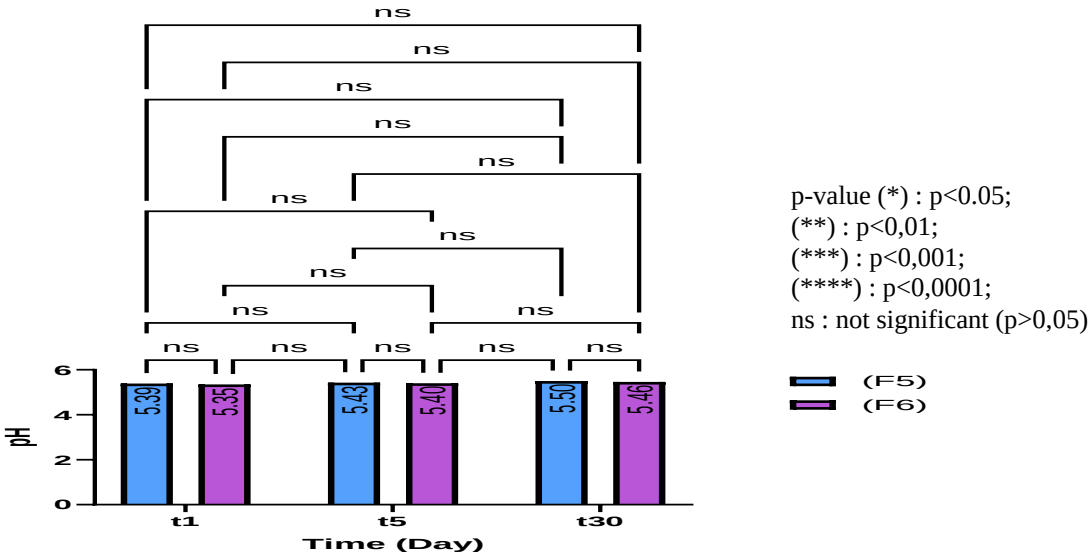

Figure 6. Graph of pH value changes F5-F6 (data are the average of three replications ± SD)

Stability results of pH

Characteristic testing was performed for pH evaluation to understand the stability of the system during storage. The results of the pH tests show that as the amount of surfactant in formulations F5 and F6 increased over time (t1–t30), the pH value decreased (Table 5). The pH of the NLC formulation varied between 5.35 and 5.50. This results from the utilization of a pH 5 phosphate buffer as the carrier solution, which corresponds to the employed pH buffer, specifically pH 5 ± 0.5. Nonetheless, the complete formula (F5-F6) remained compliant with the stipulated skin pH range of 4.0-7.0 (Dyah et al., 2023). The GraphPad Prism 10 statistical analysis results (F5–F6) for the NLC system showed that the pH values did not change significantly across the different formulas (Figure 6). The results indicated that F5 yielded the highest pH value compared to the other formulations. The incorporation of surfactants into NLC formulations frequently results in a reduction in pH levels. Surfactants can alter how lipids interact in the stratum corneum, which could affect the stability of the formulation's pH. Anionic surfactants, such as sodium lauryl sulfate (SLS), can reduce pH and enhance skin permeability; however, at elevated doses, they may induce irritation (Mukhlishah & Ningrum, 2019). The pH significantly influences the stability of topical preparations. Formulations with unstable pH may induce physical alterations, such as precipitation or color changes, potentially leading to skin discomfort (Helmidanora et al., 2023).

CONCLUSION

The NLC delivery system for quercetin was successfully optimized using the high-shear homogenization method. The optimal NLC-0 formulation consisted of 4% solid lipids (3:1 ratio of oleum cacao to beeswax), 6% castor oil as a liquid lipid, Tween 80 and Span 80 as surfactants with propylene glycol as a co-surfactant in a 4:1 ratio, 0.5% phenoxyethanol as a preservative, and distilled water. The resulting NLC-0 demonstrated a particle size range of 169.1–298.7 nm, polydispersity index (PDI) between 0.074 and 0.476, and pH range of 5.17–5.39, aligning with the skin's natural pH (4.0–7.0). Stability tests indicated that the formulation remained stable for 30 days of storage, supporting its potential as a robust carrier for quercetin delivery. These findings pave the way for the further development of NLC-based quercetin formulations for pharmaceutical and cosmetic applications.

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AUTHOR CONTRIBUTIONS

Conceptualization, R.M.; Methodology, R.M., W.S, T.E.; Software, R.M.; Validation, R.M., W.S., T.E.; Formal Analysis, R.M., W.S., T.E.; Investigation, R.M., W.S., T.E.; Resources, R.M.; Data Curration; R.M., W.S., T.E,; Writing - Original Draft, R.M., W.S., T.E.; Writing - Review & Editing, R.M., W.S., T.E.;

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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