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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 activity. However, its poor water solubility and limited skin permeability hinder its application. Nanostructured lipid carriers (NLCs), composed of biocompatible and biodegradable lipids, enhance drug stability and skin penetration. Lipid type, surfactant concentration, and formulation parameters influence NLC stability.* ***Objective:*** *This study aimed to optimize NLC formulations for quercetin delivery by evaluating organoleptic properties, particle size, polydispersity index (PDI), and pH.* ***Method:*** *NLCs was 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, undergoing 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. The lipid and surfactant composition significantly influenced particle size and PDI. While pH remained stable, statistical analysis revealed significant changes in particle size and PDI across formulations.* ***Conclusion:*** *Optimized NLC formulations for quercetin delivery demonstrated improved stability and potential for effective skin-lightening applications. Further research is warranted to evaluate in vivo efficacy and scalability.*

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

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INTRODUCTION

Melanin levels, which determine skin color, vary due to genetic factors and environmental influences like sun exposure. While melanin protects against skin damage, its excessive accumulation can lead to hyperpigmentation, causing aesthetic concerns. Conditions like 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 in fruits and vegetables, has demonstrated potent anti-tyrosinase and antioxidant properties, making it a promising candidate for skin-lightening applications. Compared to conventional agents like 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) but suffers from poor water solubility and limited skin penetration (Hatahet et al., 2016; Lu et al., 2019). These limitations necessitate advanced delivery systems to improve its 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, or 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, as a solid lipid, has a fairly high melting point and excellent crystal properties, so it can provide stability to the NLC system. However, the use of myristic acid also has limitations related to the retention and release capabilities of active ingredients. Research shows that myristic acid can reduce the process of molecular diffusion but is not always optimal in increasing the encapsulation efficiency of bioactive compounds. This can cause physical instability if not balanced with appropriate liquid lipids (Husnawiyah et al., 2023).

Beeswax and oleum cacao present an intriguing substitute for solid lipids in NLC formulations. This combination not only provides better stability but also improves the emollient properties of the final product. Beeswax has the ability to 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 tends to be superior compared to the use of myristic acid. Research shows that this solid lipid replacement can reduce particle size and improve particle distribution in the system. 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 aims to optimize NLC formulations for quercetin delivery by evaluating key parameters, including organoleptic properties, particle size, polydispersity index (PDI), and pH. The findings will 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. This study employed the Ultra Turrax IKA®T25 Digital High Shear Homogenizer. The oil phase was created by melting myristic acid or beeswax-cocoa butter, castor oil, and Spaan 80, at approximately 70°C using a hotplate stirrer. The aqueous phase consisted of Tween 80, propylene glycol, phenoxyethanol, and phosphate buffer at pH 5. After mixing the two ingredients in a single beaker until they completely blended, the mixture was heated to 70°C. After the oil phase was ready, the water phase was added slowly. The mixture was stirred for 10 minutes using an Ultra Turrax IKA® T25 Digital High Shear Homogeniser 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 stirred for 2 minutes. 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 color, aroma, texture, and potential phase separation (Mayangsari et al., 2021).

Particle size and polydispersity index (IP)

The preliminary stage entails the dilution of the formulation. Weigh 50 mg of the sample using an analytical balance and subsequently add distilled water to reach a final volume of 50.0 mL. A magnetic stirrer mixes the solution at 500 revolutions per minute for 10 minutes. Subsequently, take 2.0 mL of the solution and include 8 mL of distilled water. Stir the mixture again for 10 minutes at a velocity of 100 revolutions per minute. The next step involves using the DelsaTM nano submicron particle size analyzer to evaluate the particle size and polydispersity index (Mayangsari et al., 2021).

pH.

Calibrate the pH meter using a standard solution of pH 7.0 before assessing the sample's pH value and then clean and dry the electrode. The subsequent stage involves diluting the sample with distilled water at a ratio of 1:9. The pH is measured via the 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°C ± 1°C, with a relative humidity of 65% and shielded from sunlight. The examination was administered over a duration of three months (90 days). The stability test evaluated organoleptic properties, particle size, polydispersity index (PDI), and pH value. The assessment was performed on days 0, 30, 60, and 90 (Mayangsari et al., 2021).

Statistical analysis

The data use the one-way analysis of variance (ANOVA) method to statistically evaluate physical characteristic parameters. This strategy is employed when the data are homogeneous and regularly distributed. Alternatively, you can employ non-parametric statistical tests, specifically the Kruskal-Wallis test with a post hoc test.

RESULTS AND DISCUSSION

Organoleptic

Table 2 illustrates that organoleptic assessments of the formulations (F1-F4) indicated that 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 all 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 where lipid particles in suspension ascend and create a creamy layer above the dispersion system. Inadequate surfactant levels necessary for sustaining the NLC system during the storage duration may result in phase separation (Suyuti et al., 2023). The lipid-to-surfactant ratio significantly impacts the stability of the system, highlighting the crucial role of surfactants in stabilizing the NLC system. Surfactants can rapidly decrease surface tension, inhibit particle aggregation, and prevent recrystallization. Additional research has indicated that the concentration and type of surfactants can influence the stability of the NLC system. The surfactant-to-oil ratio and the 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, but the process for NLC formation also influences this. Elevated surfactant concentrations facilitate the formulation of lipid-based carrier systems. Low-density lipids can influence

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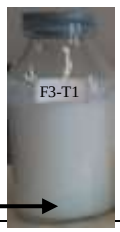
system stability, leading to creaming, flocculation, and coalescence (Rohmah et al., 2019).

The calculated HLB ratio for formulas (F1-F2) was 13.20; (F3-F4) was 12.8; and formulas (F5-F6) were 11.40. The difference in HLB values was mainly due to the difference in the composition of solid lipids of myristic acid (HLB = 12) used. In F1-F4, the ratio of the amount of solid lipids: liquid lipids (4:6) in formulas (F1-F2) and (6:4) in formulas (F3-F4). While in formulas (F5-F6), researchers replaced the type of solid lipids used with beeswax (HLB = 12) and cocoa butter (HLB = 6) with a ratio of the amount of solid lipids: liquid lipids (4:6). The HLB value affects the interfacial tension between oil and water. The right 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, which 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 coalescence or agglomeration. Oleum cacao has polymorphic forms that result in high entrapment but are less stable on storage. While beeswax base has a more regular crystal lattice than oleum cacao, the combination of oleum cacao and beeswax produces smaller particles than when the two lipids are used separately. Oleum cacao and beeswax are used in a ratio of 75:25 because it produces a low crystallinity index, as opposed to the combinations of 25:75 and 50:50. This will increase the stability of NLCs (Munandar Erawati et al., 2023). Fluctuations in cosurfactant concentration and composition can markedly influence the stability of NLC. Research indicates that fluctuations in cosurfactant concentration and composition significantly influence the stability of NLC by diminishing the surface tension between the oil and water phases, hence decreasing the likelihood of particle aggregation and recrystallization. Elevated quantities of cosurfactants can enhance stability by preserving the surface equilibrium of the emulsifying particles (Rahmi et al., 2013).

Table 2 illustrates that the organoleptic assessment of 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 within 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. The denser crystalline structure inhibits lipid diffusion and migration, hence 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 how they behave physically and how stable they are as nanostructured lipid carriers (NLCs). More stable crystalline structures (such as the beta polymorph of cocoa butter) guarantee particle stability and inhibit coalescence or agglomeration. Oleum cacao exhibits a polymorphic structure that facilitates substantial trapping yet demonstrates reduced stability during storage. The beeswax basis possesses a more uniform crystal lattice compared to 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 are utilized in a 75:25 ratio, as this configuration yields a low crystallinity index, unlike the 25:75 and 50:50 combinations. This will enhance the entrapment efficiency (Munandar Erawati et al., 2023). Myristic acid is a saturated fatty acid including 14 carbon atoms. Its crystal structure is comparatively uncomplicated in relation to cacao butter or beeswax. Myristic acid crystals exhibit a more regular and denser structure compared to beeswax; however, they may be less intricate than cacao butter. In comparison 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 make particles in NLCs that are more stable and uniform. On the other hand, a more ordered crystalline structure can reduce the range of particle sizes and improve the stability of particle sizes in formulations. Systems exhibiting a high crystallinity index typically possess narrower and more uniform particle size distributions. Having lipids with a solid crystalline structure makes NLCs more stable by lowering the chance of them 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. The chemical stability of the active substance encapsulated in the lipid matrix can be enhanced by an increased crystallinity index (Da Silva & Martini, 2024).

Characterization of particle size and polydispersity index (IP)

The particle measurement results show that decreasing the amount of cosurfactant in formulations (F1–F2) and (F3–F4) makes the particle sizes smaller. Nevertheless, augmenting the quantity of solid lipids (F1-F4) can enhance the dimensions of NLC particles (Table 3). The particle size of the overall formula (F1-F6) ranges from 153.9 to 259.5 nm, which complies with the NLC particle size specifications of 10-1000 nm (Suyuti et al., 2023). The statistical analysis using GraphPad Prism 10 (F1–F6) in the NLC system (Figure 1) showed that particle sizes very different between the formulas. The only formulas that didn't show any significant differences (F1 and F2), (F1 and F4), (F2 and F4), and (F5 and F6). The results indicated that F5-F6 yielded the lowest 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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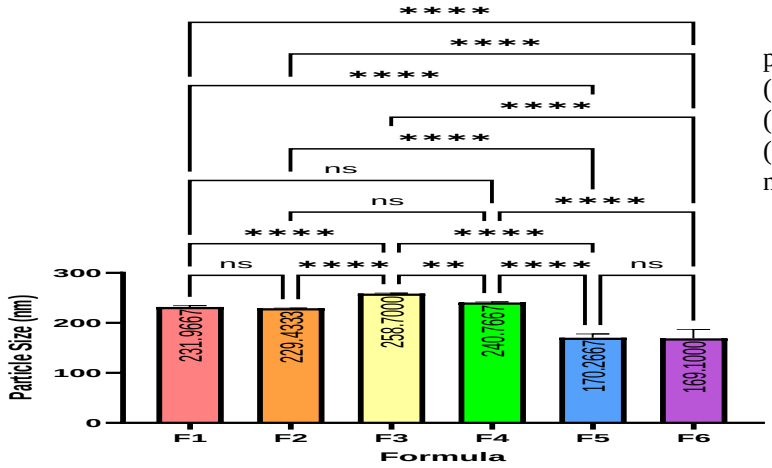

Figure 1. Particle size F1-F6 (data are the average of three replications ± SD)

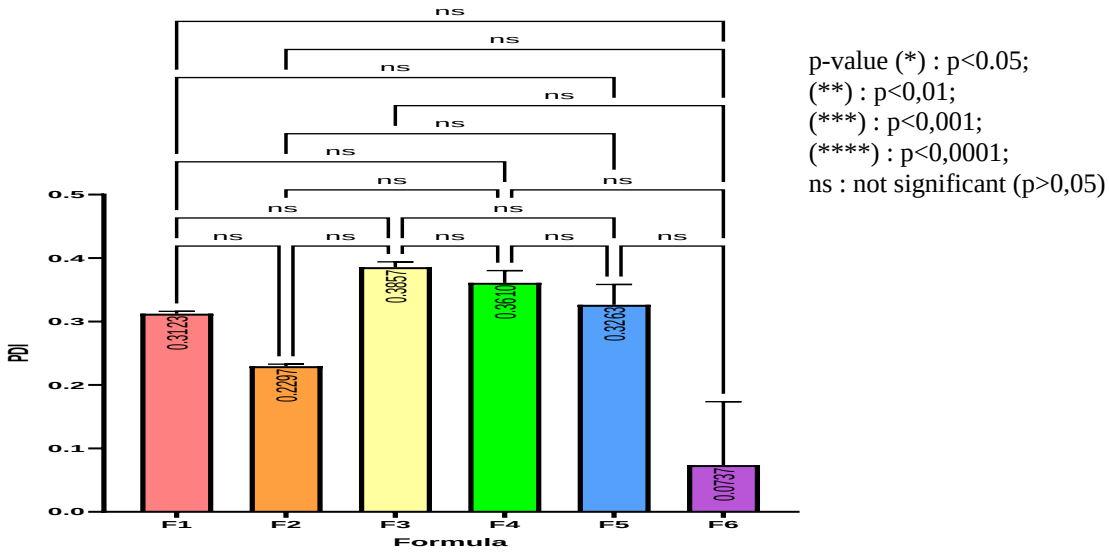

Figure 2. PDI F1-F6 (data are the average of 3 replications ± SD)

The results of PDI value measurements show that an increase in cosurfactant quantity in 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 NLC (Table 3). The overall formula (F1-F6) PI value ranges 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) in the NLC system (Figure 2) showed that the PDI values did not change significantly between the different formulas. The results indicate that F6 yields the lowest PDI value compared to all formulations utilizing various solid lipids (F1-F4).

The lipid crystallinity index influences the interaction of surfactants with the system. Highly crystallized lipids may necessitate a greater quantity of surfactant 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 will diminish the interfacial tension between the lipid matrix and the aqueous phase. This may influence the particle size and trajectory, leading to a stable system during storage. Non-ionic surfactants, such as the combination of Span 80 and Tween 80, are utilized because of their lower toxicity and irritancy compared to ionic surfactants. Propylene glycol is used in the formulation as a cosurfactant to diminish the particle diameter, hence enhancing the entrapment of drug molecules within the NLC system (Han et al., 2008).

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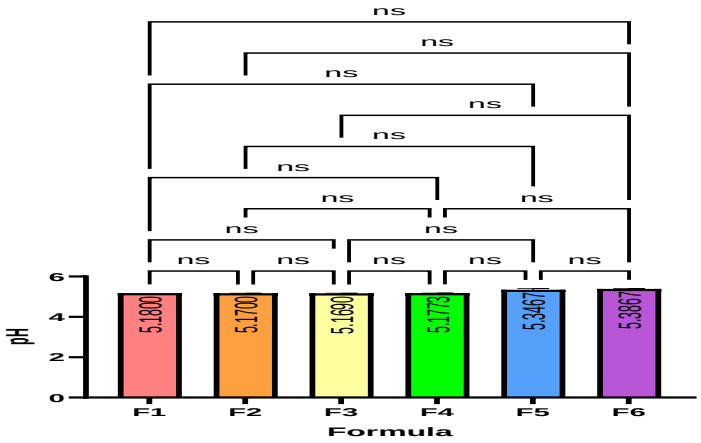

Figure 3. pH F1-F6 (data are the average of 3 replications ± SD)

Surfactants reduce the surface tension between the lipid and water phases, facilitating the production of smaller particles during homogenization. The ideal quantity of surfactant can yield particles of reduced dimensions and a more homogeneous size distribution. Surfactants function to stabilize the produced particles by creating a protective coating surrounding the lipid particles. Insufficient surfactant can lead to particle aggregation, resulting in increased particle sizes and a broader particle size dispersion. Excessive surfactant concentration 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 carried out by evaluating the pH of formulations F1-F6 (Table 4). The pH of the NLC formulation 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, namely pH 5 ± 0.5. The purpose of applying a pH buffer is to preserve the pH stability of the active ingredient. Furthermore, pH testing is essential to avert skin irritation and dryness. An excessively acidic pH may induce irritation and stinging, whilst a too 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) in 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 the creaming/phase separation on day 1 prevented stability testing. The stability test findings for the NLC preparation F5-F6 indicated that it could only sustain stability for 30 days.

Stability results of particle size and polydispersity index (IP)

The particle measurement data show that as the amount of surfactant in formulas F5 and F6 increased over time (t1–t30), the particle size grew (Figure 4) and the PDI value went down (Figure 5). Nonetheless, the comprehensive formula (F5-F6) continues 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 GraphPad Prism 10 (F5–F6) statistical analysis results in the NLC system showed that there no significant differences in particle size (Figure 4) or PDI (Figure 5) between the different formulas. The results indicate that F6 is the formulation yielding the least particle size and PDI among the two formulations. Nonetheless, the F6 formula comprises a total surfactant concentration of 20%, surpassing that of F5, which is 15%. Surfactants are crucial in stabilizing the NLC system by diminishing surface tension and inhibiting particle agglomeration. Research indicates that elevating 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	

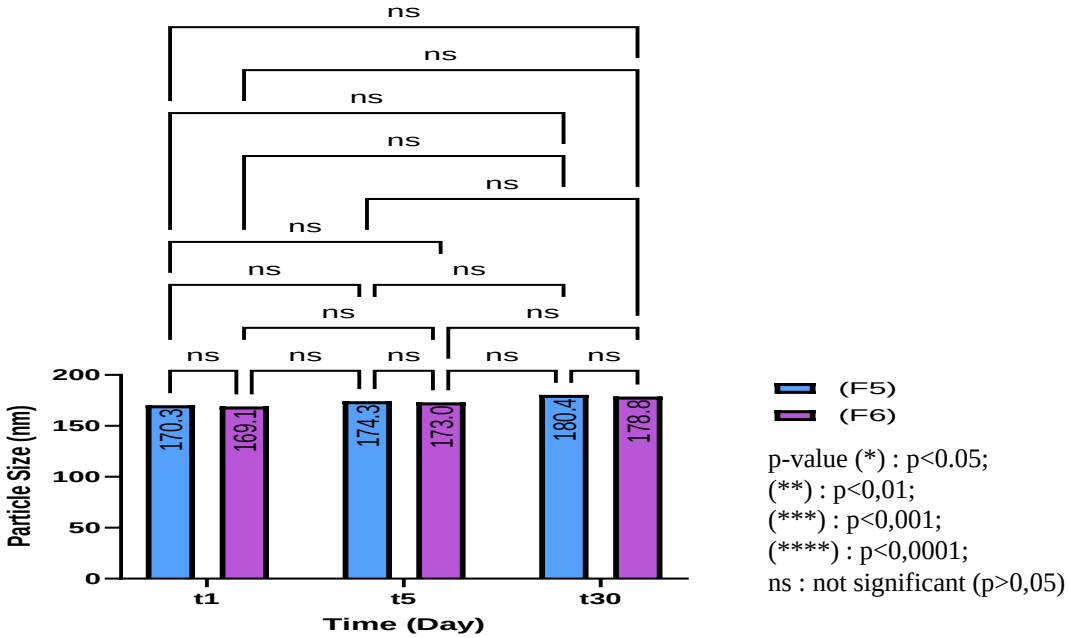

Figure 4. Graph of changes in particle size F5-F6 (data are the average of three replications ± SD)

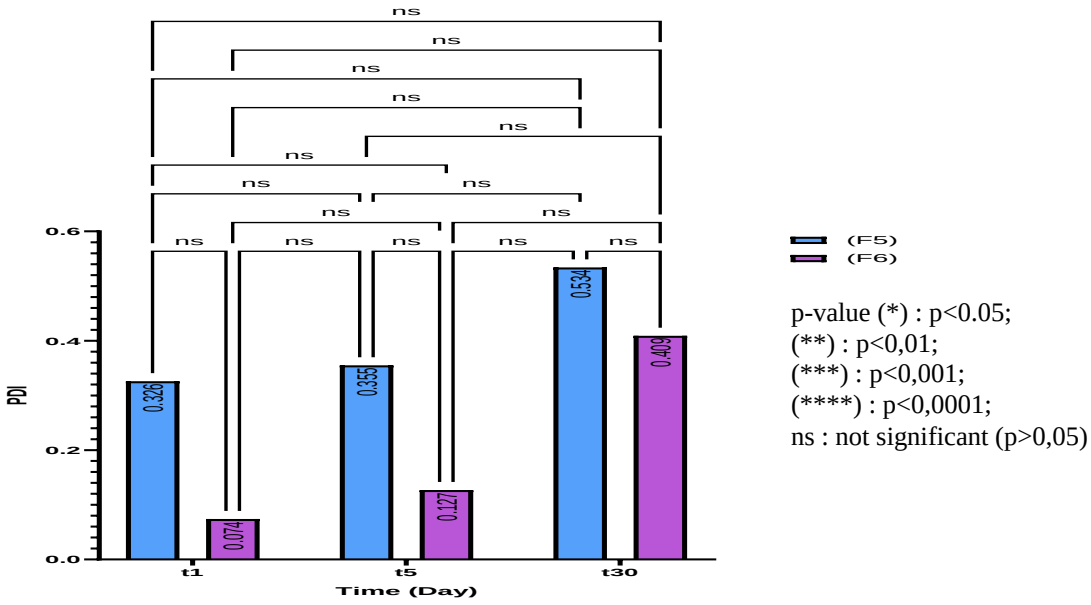

Figure 5. Graph of changes in PDI F9-F10 values (data are the average of three replications ± SD)

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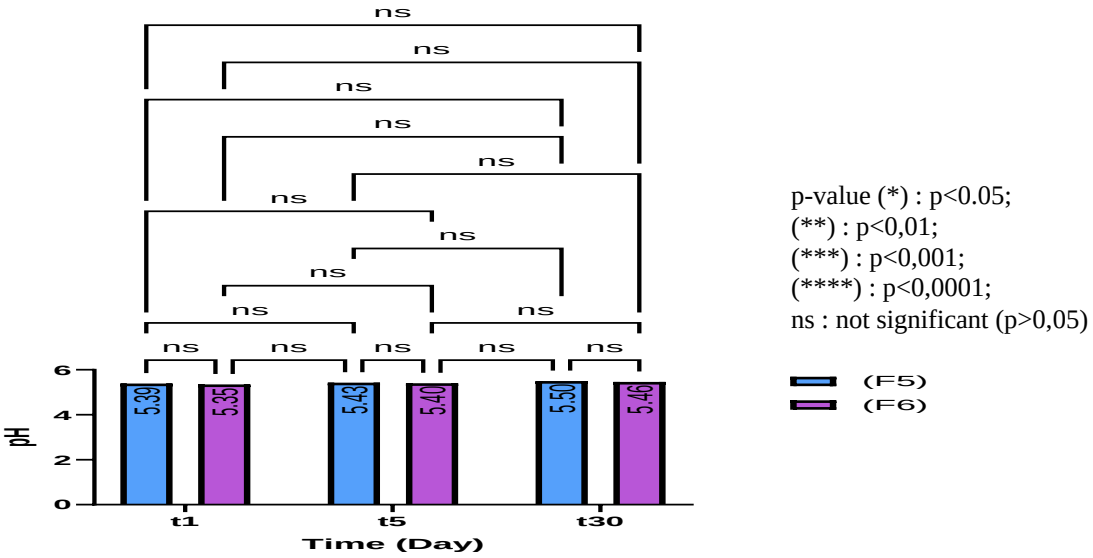

Figure 6. Graph of pH value changes F5-F6 (data are the average of three replications ± SD)

Stability results of pH

Characteristic testing was performed on 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 rises over time (t1–t30), the pH value falls (table 5). The pH value of the NLC formulation varies 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) remains 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) in 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 greatest pH value compared to the other formula. The incorporation of surfactants in NLC formulations frequently results in a reduction of pH levels. Surfactants can change how lipids interact in the stratum corneum, which could affect how stable the formulation's pH is. Anionic surfactants, such as sodium lauryl sulfate (SLS), can reduce pH and enhance skin permeability, but, at elevated doses, they may induce irritation (Mukhlishah & Ningrum, 2019). The pH value 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 optimization of the NLC delivery system for quercetin was successfully achieved using the high shear homogenization method. The optimal NLC-0 formulation consists of 4% solid lipids (a 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 cosurfactant 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, a polydispersity index (PDI) between 0.074 and 0.476, and a 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 under 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 in 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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