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Effect of Different Lipid Ratios on Physicochemical Stability and Drug Release of Nanostructured Lipid Carriers Loaded Coenzyme Q10

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Abstract

Background*: For treatment or skin care via topical route, Coenzyme Q10 needs to permeate the epidermis which it is practically insoluble in water and a high molecular weight that make it difficult to penetrate the skin. Nanostructured Lipid Carriers (NLC) is chosen because of its ability to dissolve and solve the problem of low skin permeation. The type and ratio of solid and liquid lipids used in NLC affect the physicochemical characteristics, thus affecting the release profile and system stability.* ***Objective****: This study aimed to determine the effect of various ratios of Compritol 888 ATO as solid lipid and Miglyol 812 as liquid lipid on the physicochemical stability and Coenzyme Q10 release profile of NLC system.* ***Methods****: NLC was prepared using High Shear Homogenization method with three different lipid ratios. The ratio of Compritol 888 ATO : Miglyol 812 was 70:30, 80:20, and 90:10, respectively. NLC was evaluated for drug release and stability parameters including organoleptic, particle size, polydispersity index (PI), pH, viscosity, assay, and entrapment efficiency.* ***Results****: The stability test result for 90 days showed increments in the particle size and viscosity, whereas for assay and entrapment efficiency were decreased. The release test results showed no significant difference in the release parameters of the three tested formulas.* ***Conclusion****: During stability evaluation, NLC-CoQ10 systems did not significantly change pH and PI values, but statistically significantly changed particle size, viscosity, assay, and entrapment efficiency. The different in lipid ratios used in the formulas did not show significantly different results for release parameters.*

Keywords*: coenzyme Q10, NLC, stability, release*

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INTRODUCTION

Endogenous antioxidant molecules are less likely to produce as a person gets older, which reduces their ability to protect the skin. Additionally, prolonged and excessive exposure to UV light might reduce antioxidant levels in the skin layer (Andarina & Djauhari, 2017). Exogenous antioxidant supplementation can be a substitute for restoring antioxidant deficiency while protecting the skin from damage and early aging caused by excessive UV exposure.

Various types of antioxidant compounds have been commonly applied topically to the skin, such as carotenoids, coenzyme Q10, essential oils, polyphenols, and vitamins. Topical administration of drugs offers many advantages over oral administration, including avoiding first-pass metabolism, targeting active ingredients for local effects, and improving patient compliance. Especially in the case of treatment or treatment for the skin, topical drug administration is very effective because it is directly applied to the targeted area thus allowing higher drug accumulation in the target area with minimal side effects compared to oral administration (Ryu *et al.,* 2020).

One of the antioxidants that are often associated with the aging process and aging-related diseases of the skin is coenzyme Q10 (Hernández-Camacho *et al.,* 2018). As people get older, their bodies produce less CoQ10, which lowers the quantities in their tissues and plasma. Because the skin is frequently exposed to environmental stressors including UV radiation and air pollution, CoQ10 levels in the skin declining. Many studies have shown that CoQ10 supplementation can increase the antioxidant properties of the skin, reduce reactive oxygen species, prevent premature aging, and is suitable for skin photoprotection (Sguizzato *et al.,* 2020). However, for administration through the skin, CoQ10 needs to overcome the skin's stratum corneum barrier and penetrate through the epidermis. Its practically insoluble in water and relatively high molecular weight (863.3 g/mol), make CoQ10 difficult to penetrate the skin despite its beneficial effect (Ryu *et al.,* 2020). In addition, CoQ10 is easily degraded when exposed to light *(Guedes et al.,* 2021). Therefore, a special delivery system is needed that can dissolve and overcome the problem of low skin permeation while providing stability to light. Developing a Nanostructured Lipid Carrier (NLC) is one alternative.

The lipid components of the carrier system are non-irritating and non-toxic, making NLC suitable for drug delivery applications through the skin. Lipid-based carrier systems are capable of providing drug protection from degradation after loading into the system, enabling controlled release, as well as enhanced skin penetration and retention *(Nene et al.,* 2021). The selection of the type and ratio of solid lipids and liquid lipids used in NLC affects the physicochemical characteristics, thus affecting the release profile and stability of the preparation.

This study aimed to determine the effect of various ratios of solid lipid Compritol 888 ATO and Miglyol 812 liquid lipids on the physicochemical stability and drug release profile of the NLC system. The ratio of solid lipid and liquid lipid is 70:30, 80:20, and 90:10 to a total lipid of 10% of the formula. Compritol 888 ATO was chosen because it is superior in terms of drug-trapping ability compared to homogeneous glycerides (Aburahma & Badr-Eldin, 2014). Research conducted by Nayak *et al.* (2017) prepared an NLC containing the active ingredient CoQ10 and retinaldehyde to treat wrinkles which were applied topically, showing that Compritol 888 ATO can dissolve CoQ10 better than some other lipid candidates. As for the liquid lipid component, Miglyol 812 was chosen because of its ability to increase the solubility of hydrophobic materials in the NLC system, thereby increasing drug loading capacity and preventing drug expulsion during storage (Ortiz *et al.,* 2021). The formulation of the NLC system containing CoQ10 in this study was intended for topical application as an anti-aging. The preparation was made at pH 6.0 ± 0.05 according to the skin pH specification range and the stability of the active ingredients. The method used for the manufacture of NLC is the high shear homogenization method because the process is simple, fast, and relatively low cost.

MATERIALS AND METHODS

Materials

Coenzyme Q10 (Kangcare Bioindustry - China), Compritol 888 ATO (Gattefosse - France), Miglyol 812 (Sigma Aldrich - USA), Poloxamer 188 (BASF - Germany), and propylene glycol (Dow Chemical Pacific - Singapore). All of these substances were pharmaceutical grade unless otherwise noted.

Tools

High shear homogenizer (T25 Ultra-Turrax IKA®), particle size analyzer (Delsa™ Nano), pH meter (Transinstrument WalkLAB HP9010), viscometer cone and plate (Brookfield), USP dissolution test apparatus 5 (Erweka DT820), double beam spectrophotometer UV-vis (Shimadzu UH5300).

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Method

Preparation method of NLC

NLC loaded Coenzyme Q10 (NLC-CoQ10) was prepared using the High Shear Homogenization (HSH) method. The composition of the NLC-CoQ10 with various ratios of solid lipid and liquid lipid can be seen in Table 1. Using a hot plate set to 80°C, Compritol 888 ATO and Miglyol 812 were placed in a beaker glass and melted. Then put some CoQ10 into the mixture. Separately prepared surfactant solution (Poloxamer 188) in phosphate buffer solution and heated using a hot plate at 80°C. The water phase is added gradually into the oil phase. A high-speed homogenizer was then used to stir this mixture for 2 minutes at 3400 rpm. Then slowly added the mixture of propylene glycol and phosphate buffer solution which has been heated at 80°C using a hot plate. The mixture was homogenized by high shear homogenizer at 20,000 rpm for 5 minutes in three cycles with constant heating at 80°C after all the ingredients had been added. The result was cooled while stirring at 500 rpm until room temperature and the best NLC system was obtained.

Stability test

A stability test is used to predict system stability during the storage period. A stability test was performed using real-time conditions at room temperature (25 ± 2°C). The organoleptic, particle size, PDI, pH, and viscosity were evaluated on 1, 15, 30, 60, and 90 days. In addition, evaluation of assay and entrapment efficiency were also carried out at the beginning and end of storage.

Organoleptic

Organoleptic tests were carried out by visually determining the form, color, and odor of each formula.

Particle size and polydispersity index (PI) evaluation.

Measurement of particle size and PI were carried out using a Delsa™ nanoparticle size analyzer. Approximately 50 mg of the sample was added with 50 mL of distilled water. It stirred using a magnetic stirrer for 10 minutes at a speed of 500 rpm. Then put 2 mL of solution and added distilled water up to 10 mL. The sample was placed in the glass cuvette and perform a measurement.

pH evaluation

In 20 mL of distilled water, approximately 1 g of NLC system was dissolved, then immersed the electrode into the sample. A digital pH meter was used to measure the pH value of the NLC preparations, which were already calibrated using a standard buffer solution.

Viscosity test

A cone and plate viscometer was used to determine the viscosity of the samples. About 2 mL samples were poured into the plate. Between the stationary plate and the rotating cone, the sample was in a shear.

Assay

About 100 mg of NLC systems was added by 10.0 ml of ethanol and sonicated for 20 minutes. The solution was transferred to a venoject tube and centrifuged at 2500 rpm for 15 minutes. The supernatant was taken at 1.0 ml and added with ethanol up to 10.0 ml. The assay was measured at 274 nm by spectrophotometry.

Entrapment efficiency test

The centrifugation technique was used to measure drug entrapment efficiency. The amount of free drug was measured to estimated amount of drug trapped, then the entrapment efficiency was calculated using the ratio of the amount of drug trapped to the total amount of drug added. About 2 g of NLC systems were centrifuged for 60 minutes at 3000 rpm. After phase separation, the supernatant was collected and 10.0 ml of ethanol was added. About 1 ml solution was taken and added with ethanol again up to 10.0 ml. The amount of drug was measured at 274 nm by spectrophotometry.

Table 1. The composition of NLC formulas (% w/w)

Composition	Function	Formula 1 (F1)	Formula 2 (F2)	Formula 3 (F3)
Coenzyme Q10	Active ingredient	2.4	2.4	2.4
Compritol 888 ATO	Solid lipid	7	8	9
Miglyol 812	Liquid lipid	3	2	1
Poloxamer 188	Surfactant	8	8	8
Propylene glycol	Co-surfactant	8	8	8
Phosphate buffer pH 6.0	Water phase	Until 100	Until 100	Until 100

Note :
Formula F1 = concentration ratio of solid lipid and liquid lipid 70:30
Formula F2 = concentration ratio of solid lipid and liquid lipid 80:20
Formula F3 = concentration ratio of solid lipid and liquid lipid 90:10

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Drug Release test

The drug release test apparatus used was USP dissolution test apparatus 5 (paddle over disk). The apparatus consists of a paddle and vessel as used in dissolution tests, with the addition of a stainless steel disk designed as a transdermal dosage container at the bottom of the vessel. The disk form is a flat cylinder with the center space as a container which is closed with the membrane facing upwards. Due to insolubility of Q10 in water or a buffer solution, the dissolution medium was prepared with a mixture of 2.5% Tween 80 and 20% ethanol p.a in phosphate buffer pH 6.0 ± 0.05. The media was placed into a chamber and set to a temperature of 32 ± 0.5ºC. About 2,5 g samples were inserted into the disk. The membrane used (cellulose acetate) closed in such a way that there were no air bubbles between the membrane and the sample surface. The prepared disk was placed at the bottom of the chamber. The bottom edge of the paddle should be 25 ± 2 mm from the disk. At each time interval, samples were taken from the middle zone between the surface of the media and the top of the paddle, not less than 1 cm from the vessel wall (United States Pharmacopoeia, 2007).

During operation, the paddle stirrer was rotated at 100 rpm and the media volume was 500 mL. About 5 mL of sample solution was taken and replaced with 5 mL of receptor medium using an injection syringe at 0, 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 minutes. Then the sample was analyzed with UV-Vis spectrophotometer at 274 nm. The drug concentration in the sample was calculated using the standard curve regression equation. To account for the 5 mL dilution of the release medium, the measured concentrations were corrected by following equation:

$$C_{n,corr} = C_n + \frac{Vs}{Vm}\int_{i=1}^{n-1} C_i$$

where $C_{n,corr}$ is the corrected concentration at sample interval n; Cn is the measured or uncorrected concentration at sample interval n; Vm is the original media volume in the dissolution vessel; Vs is the volume of sample removed at each time interval; and Ci is the uncorrected concentration at each previous sample interval i (Salt, 2021).

Statistical analysis

To statistically analyze the drug release parameter and initial data of physicochemical characteristics, if the data were homogenously and normally distributed, a one-way Analysis of Variance (ANOVA) technique was utilized. But if the data were not homogenous or not normally distributed, statistics test was conducted with a non-parametric statistical test (Kruskal-Wallis). On the other hand, to statistically analyze the stability of each formula during storage, a repeated measure ANOVA or paired t-test technique was utilized. The stability test was not carried out by comparing between the different formulas, but a comparison between different time of measurement in each formula to find out whether there is a difference in the initial characteristics and after storage. The formula is declared stable if there is no significant difference from the measurement results after being stored. Thus repeated measure ANOVA is used if there are 5 observation days (days 1, 15, 30, 60, 90) and paired t-test if only measured on 2 observation days (days 1 and 90).

RESULTS AND DISCUSSION

Stability test result

Organoleptic

The organoleptic observation showed that the CoQ10- NLC was yellow, specific odor, and had a semisolid form and soft texture, as shown in Table 2. There was no change during storage except in Formula 3 on day 90 there was a separating layer at the bottom which indicated the presence of instability. This phase separation is probably due to the surfactant being less able to maintain the system in Formula 3 during the storage period.

Particle size and polydispersity index (PI) evaluation.

Particle size is influenced by some factors such as the type of surfactant, concentration of surfactant, manufacture method, concentration, and ratio of liquid lipids and solid lipids (Salvi & Pawar, 2019). This study found that increasing liquid lipid ratio contributed to smaller particle size (Figure 1). Statistically, at initial day (1st day) showed a significant difference at least one pair between the groups of formulas F1, F2, and F3 at α = 0.05. The results of the post hoc test using Tukey HSD showed that the significantly different groups for particle size are F1 with F3, and F2 with F3. However, the particle size values show that there was a tendency for average particle size F1 < F2 < F3. Smaller particle size was obtained when the ratio of liquid lipids in the formula was increased. Liquid lipid helps to dissolve the drugs thereby allowing the system particle size to be smaller (Apostolou *et al.*, 2021). Particle size evaluation results during storage showed significantly increased size at 60th and 90th observation days, possibly due to particle coalescence. The presence of phase separation

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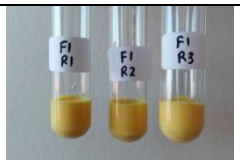
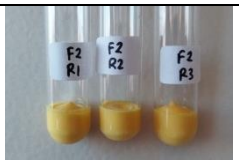
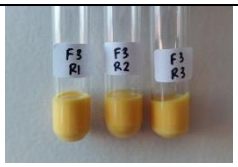
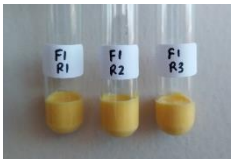
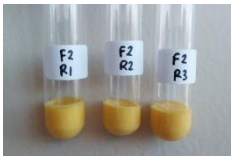
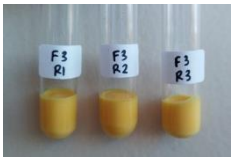
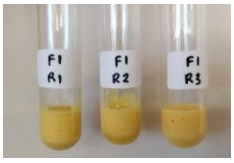
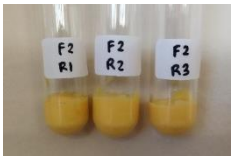
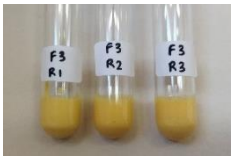
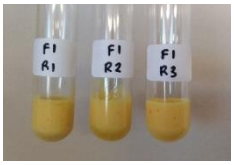
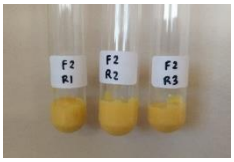
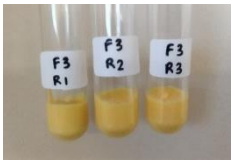
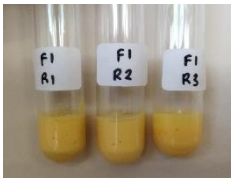
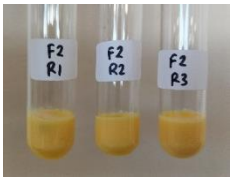
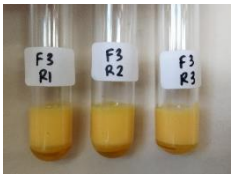
that is visually visible on the organoleptic observation of F3 also has an impact on the particle size of F3 at 90th observation day which has a greather variation between replicates. However, during 90 days of storage, especially in formulas 1 and 2, the particle size was still below 600 nm, which is still able to deliver the encapsulated material into deeper layers of the skin (Danaei *et al.*, 2018).

Table 2. Visual observation of CoQ10-NLC systems during stability test

Observation Days	Formula 1 (F1)	Formula 2 (F2)	Formula 3 (F3)
1			
15			
30			
60			
90			

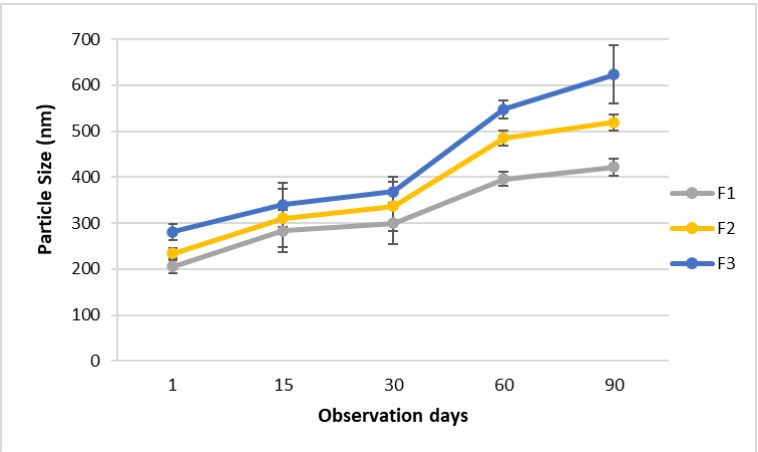


Figure 1. Stability test result for particle size during storage. Data is the mean of three replications ± SD

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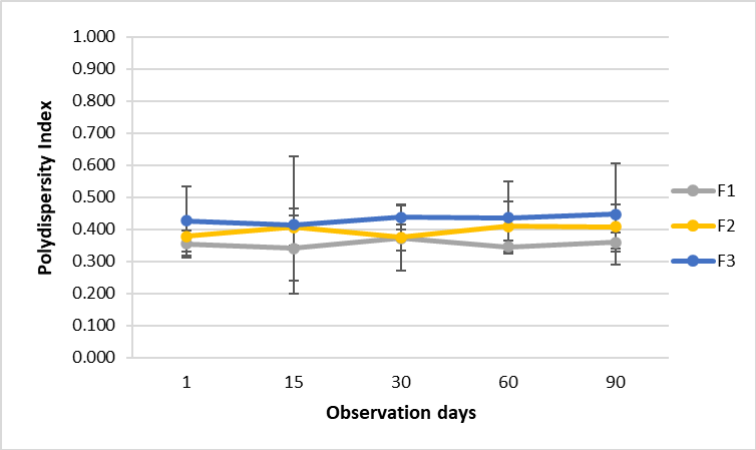

Figure 2. Stability test result for polydispersity index during storage. Data is the mean of three replications ± SD

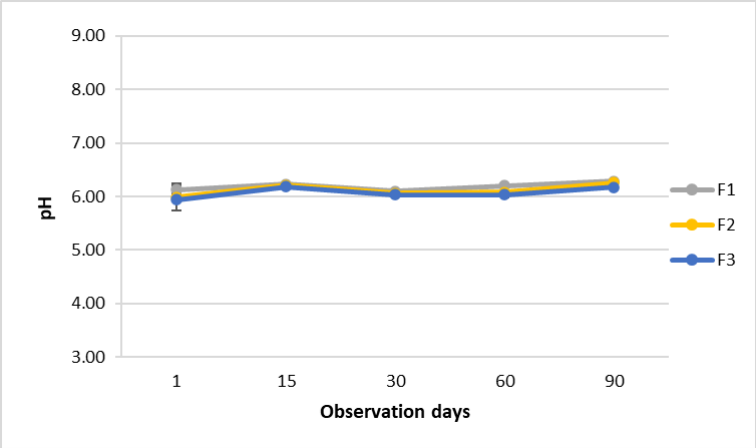

Figure 3. Stability test result for pH during storage. Data is the mean of three replications ± SD

The particle size distribution can be seen from the polydispersity index (PI). The PI indicates the uniformity of particle sizes within the sample population (Hendradi *et al.,* 2017). PI value that is lower than 0.5 indicates homogeneity and mono-dispersity formulation. If PI > 0.5 indicates a less homogeneous size variation or polydispersity in the formulation. However, the polydispersity index value < 1 is still acceptable because the colloidal carrier system is not always monodispersed (Salvi & Pawar, 2019). The polydispersity index obtained from this study shows a large variation between replicates. It was probably caused by variations in manufacture which are still perform manually. However, PI average result are < 0.5, which indicates a homogenous particle size distribution in the system (Figure 2). The statistical analysis of PI found no significant differences between all the formulas. Furthermore, there was no significant change during the storage period which indicates that all formulas remain homogeneous.

pH evaluation

The average pH of all formulas (Figure 3) was similar to the pH of the buffer solution (pH 6,00) used in the formulas. It was demonstrated that NLC systems can be used for topical administration in accordance with normal skin pH of 4 - 6 (Prakash *et al.,* 2017). The statistical analysis of pH found no significant differences between all the formulas. Furthermore, there was no significant change during the storage period which indicates that the pH of this system remains stable.

Viscosity test

The proper viscosity is required for NLC to adhere to the skin surface, thereby increasing drug penetration and residence time (Hendradi *et al.,* 2017). Viscosity can describe the ease of preparation when applied and predict the ease of moving molecules associated with drug release. Statistically, on initial day (1st day) the three groups of formulas showed significant differences in viscosity. On 1st day, the viscosity values show that there was a tendency F1 < F2 < F3 (Figure 4). Lower viscosity was obtained when the ratio of liquid lipids in the formula was higher. This is consistent with the

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theory that a higher liquid lipid ratio can reduce the viscosity and reduce particle size, consequently results in a greater release of the drug and improved penetration ability (Apostolou *et al.*, 2021). Furthermore, there was no significant change during the storage period except for 90th day of storage. At that time, the viscosity value of the entire formula increased which was probably due to the coalesence between particles in the system and evaporation of the liquid during the storage period which resulted in a higher viscosity value. At 90th day, the viscosity value of F3 being lower than F2. It was probably due to the phase separation that occurs in F3 so that the consistency becomes slightly thinner.

Assay

An assay test during stability testing was useful for predicting the shelf life of a pharmaceutical preparation. The results of the assay test can be seen in Table 3. Based on the result of t-tes statistical analysis, it showed a significant difference among all formulas both for initial day (1st day) and end of storage (90th day). At the end of the storage period, the drug level was seen to decrease. This is probably due to the system being not stable enough so that drug degradation occurred.

Entrapment efficiency test

The results of the entrapment efficiency test can be seen in Table 3. Based on the result of t-tes statistical analysis, it showed a significant difference among all formulas both for initial day (1st day) and end of storage (90th day). The entrapment was increased with an increasing liquid lipid ratio. This is consistent with the theory that an increase in the liquid lipid ratio will improve the flexibility of the NLC core by influencing the imperfections in the crystal lattice, causing numerous drugs to be trapped in the system during the solidification of the lipid phase. This increase in the flexibility of the NLC core is also useful for preventing expulsion (Apostolou *et al.*, 2021). Miglyol 812's ability to increase the solubility of CoQ10 results in increased entrapment and penetration efficiency, making it a good choice for use in NLC formulations containing CoQ10. Miglyol can give a less perfect crystal shape to produce a larger space in the crystal. The enlarged crystal space can accommodate larger drugs so that the entrapment efficiency is greater (Annisa *et al.*, 2016). At the end of the storage period, the entrapment efficiency was seen to decrease. This is probably due to the system being not stable enough so that drug expulsion occurred.

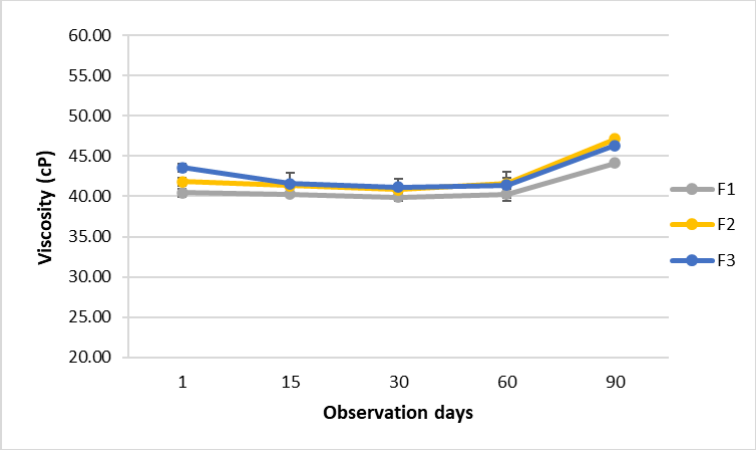

Figure 4. Stability test result for viscosity during storage. Data is the mean of three replications ± SD

Table 3. Stability test results for assay and entrapment efficiency of CoQ10-NLC systems during storage

Parameter	Formula	Before Storage (%)	After Storage (90 days) (%)
Assay	F1	92.66 ± 1.04	83.55 ± 4.40
	F2	92.35 ± 1.30	85.11 ± 4.28
	F3	91.60 ± 1.55	80.78 ± 3.18
Entrapment Efficiency	F1	92.73 ± 0.93	76.89 ± 1.03
	F2	87.90 ± 0.90	70.45 ± 1.90
	F3	84.60 ± 0.69	66.15 ± 1.41

Note: The data are represented as mean of three replicates ± SD

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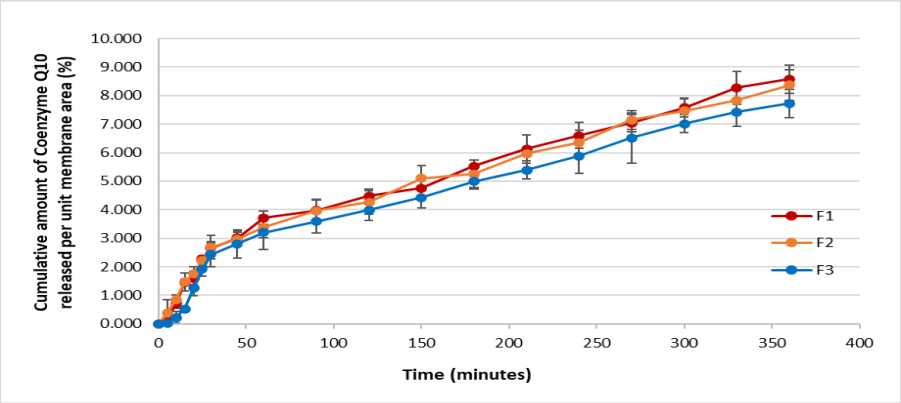

Figure 5. The relationship between the cumulative amount of Coenzyme Q10 released against time at 32°C in the dissolution medium. Data is the mean of three replications ± SD

Table 4. Regression line equations and correlation coefficient (r) of zero-order, first-order release kinetics, Higuchi model, and Korsmeyer-Peppas model

Release kinetics model		Formula 1 (F1)	Formula 2 (F2)	Formula 3 (F3)
Zero order	Regression equation	y = 0.0217x + 1.3221	y = 0.0209x + 1.3673	y = 0.0204x + 1.0108
	r	0.9705	0.9723	0.9663
First order	Regression equation	y = 0.0028x + 0.1161	y = 0.0026x + 0.1654	y = 0.0036x – 0.1194
	r	0.7833	0.8403	0.6885
Higuchi	Regression equation	y = 0.4541x – 0.3046	y = 0.4374x – 0.2001	y = 0.4268x – 0.5207
	r	0.9933	0.9953	0.9899
Korsmeyer-Peppas	Regression equation	y = 0.5480x – 0.4901	y = 0.4917x – 0.3722	y = 0.7085x – 0.9094
	r	0.8822	0.9284	0.7860

Drug release test result

This drug release test aims to determine the release kinetics and the rate of release (flux) of Coenzyme Q10 from the NLC system. The release rate (flux) is indicated by the slope value in the regression equation between the amount of Coenzyme Q10 released per unit area of the membrane against time. The relationship between the cumulative amount of Coenzyme Q10 released against time can be seen in Figure 5. Statistically, it is known that there is no significant difference between the cumulative amount of Coenzyme Q10 regardless of the formulas F1, F2, and F3 at α = 0.05.

The flux of Coenzyme Q10 from the NLC matrix was studied with various mathematical models to obtain the best model of the release kinetics of Coenzyme Q10 from the NLC matrix. Mathematical models used include zero-order kinetic models, first-order kinetic models, Higuchi models, and Korsmeyer-Peppas models. The result of regression line equations and correlation coefficient from some mathematical models can be seen in Table 4. The correlation coefficient (r) of the Higuchi model is the highest, so the release kinetics of Coenzyme Q10 from the NLC matrix follows the release kinetics of the Higuchi model.

The flux is indicated by the slope value in the regression equation between the amount of Coenzyme Q10 released per unit of time. The result of flux calculation can be seen in Table 5. From the results of the test which was carried out for 6 hours, it was found that no significant differences between all the formulas. However, there was a tendency for cumulative drug release and release rate F1 > F2 > F3. The F1 release rate tends to be the highest because it has lowest viscosity. Formula 1 contains more liquid lipids which causes a thinner viscosity and smaller particle size, which theoretically affects the ease of drug ingredients to be separated from the base. The lower viscosity value will cause the molecules to move faster and give a greater release of the drug (Apostolou *et al.*, 2021). This trend is likely to be more significantly different if the difference in the ratio is enlarged, so there will be a significant difference between the three formulas.

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Table 5. Coenzyme Q10 release rate from NLC with Higuchi model

Formula	Release rate (Flux) (µg/cm^2/minutes)
F1	0.4394 ± 0.0257
F2	0.4245 ± 0.0190
F3	0.4049 ± 0.0097

Note: The data are represented as mean of three replicates ± SD

CONCLUSION

The NLC-CoQ10 was successfully prepared using Compritol 888 ATO and Miglyol 812 as the lipid matrix. During stability evaluation, NLC-CoQ10 systems did not significantly change pH and PI values, but statistically significantly changed particle size, viscosity, assay, and entrapment efficiency. There were increments in the particle size and viscosity, which indicates the incorporation of small particles or coalescence. On the other hand, there was decrease in the assay and entrapment efficiency, which shows that the system is not stable enough so optimization is still needed to obtain the best system that has a long shelf life. From the results of the release test, it was known that NLC-CoQ10 was able to release the drug continuously but there was no statistically significant difference in the release parameters of the three tested formulas.

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