© 2021 Journal of Pharmacy & Pharmacognosy Research, 9 (5), 573-583, 2021
ISSN 0719-4250
http://jppres.com/jppres

Original Article

Development, characterization *in vitro* and *in silico* of coenzyme Q10 loaded myristic acid with different liquid lipids nanostructured lipid carriers

[Desarrollo, caracterización *in vitro* e *in silico* de coenzima Q10 cargado de ácido mirístico con diferentes lípidos líquidos portadores de lípidos nanoestructurados]

Ni Luh Dewi Aryani[1,4], Siswandono[2], Wdji Soeratri[3]*, Dian Yulyandani Putri[4], Pingky Dwi Puspitasarini[4]

[1]Doctoral Program of Pharmaceutical Sciences, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia.
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia.
[3]Department of Pharmaceutics, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia.
[4]Department of Pharmaceutics, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia.
*E-mail: widji-s@ff.unair.ac.id

Abstract

Context: Nanostructured lipid carriers can enhance skin penetration of active substances. Coenzyme Q10 is a lipophilic antioxidant, that has poor skin penetration. This limitation is overcome by nanostructured lipid carriers.

Aims: To developed coenzyme Q10 nanostructured lipid carriers using myristic acid with various liquid lipids as lipid matrix by *in vitro* studies and *in silico* approach for explaining the interaction of coenzyme Q10-lipid at the molecular level.

Methods: The coenzyme Q10 nanostructured lipid carriers were prepared using myristic acid as solid lipid with oleic acid, isopropyl myristate, and isopropyl palmitate as liquid lipids using the high shear homogenization method. Then, they were evaluated in physicochemical characteristics by dynamic light scattering, differential scanning calorimetry, Fourier transforms infrared, scanning electron microscopy, spectrophotometry ultraviolet-visible, and pH meter. Furthermore, the *in silico* studies were conducted using AutoDock 4.2.

Results: The coenzyme Q10 nanostructured lipid carriers using myristic acid-oleic acid, myristic acid-isopropyl myristate, and myristic acid-isopropyl palmitate as lipid matrix had the mean particle size, polydispersity index, entrapment efficiency, drug loading, and pH value were less than 300 nm, less than 0.3, more than 80%, about 10%, and about 5.0, respectively. Moreover, molecular docking of coenzyme Q10 and lipid showed hydrogen and hydrophobic bonds. These results supported differential scanning calorimetry and Fourier transforms infrared results.

Conclusions: The coenzyme Q10 nanostructured lipid carriers were successfully prepared using myristic acid-oleic acid, myristic acid-isopropyl myristate, and myristic acid-isopropyl palmitate as lipid matrix as well as *in silico* study could be used for explaining of coenzyme Q10-lipid interaction.

Keywords: coenzyme Q10; *in silico*; *in vitro*; nanostructured lipid carriers.

Resumen

Contexto: Los portadores de lípidos nanoestructurados pueden mejorar la penetración cutánea de sustancias activas. La coenzima Q10 es un antioxidante lipofílico, que tiene poca penetración en la piel. Esta limitación se supera mediante portadores de lípidos nanoestructurados.

Objetivos: Desarrollar portadores de lípidos nanoestructurados de coenzima Q10 utilizando ácido mirístico con varios lípidos líquidos como matriz lipídica mediante estudios in vitro y enfoque in silico para explicar la interacción de la coenzima Q10-lípido a nivel molecular.

Métodos: Los portadores de lípidos nanoestructurados de coenzima Q10 se prepararon usando ácido mirístico como lípido sólido con ácido oleico, miristato de isopropilo y palmitato de isopropilo como lípidos líquidos usando el método de homogeneización de alto cizallamiento. Luego, fueron evaluados en características fisicoquímicas por dispersión dinámica de luz, calorimetría diferencial de barrido, transformadas de Fourier infrarrojas, microscopía electrónica de barrido, espectrofotometría ultravioleta-visible y pHmetro. Además, los estudios in silico se realizaron utilizando AutoDock 4.2.

Resultados: Los portadores de lípidos nanoestructurados de coenzima Q10 que utilizaron ácido mirístico-ácido oleico, ácido mirístico-miristato de isopropilo y ácido mirístico-palmitato de isopropilo como matriz lipídica tuvieron un tamaño medio de partícula, índice de polidispersidad, eficiencia de atrapamiento, carga de fármaco y valor de pH menores. de 300 nm, menos de 0,3, más del 80%, aproximadamente el 10% y aproximadamente 5,0, respectivamente. Además, el acoplamiento molecular de la coenzima Q10 y el lípido mostró enlaces hidrófobos y de hidrógeno. Estos resultados apoyaron la calorimetría de barrido diferencial y los resultados infrarrojos transformados de Fourier.

Conclusiones: Los portadores de lípidos nanoestructurados de coenzima Q10 se prepararon con éxito utilizando ácido mirístico-ácido oleico, miristato de ácido mirístico-isopropilo y ácido mirístico-palmitato de isopropilo como matriz lipídica, así como un estudio in silico que podría usarse para explicar la interacción coenzima Q10-lípido.

Palabras Clave: coenzima Q10; *in silico*; *in vitro*; portadores de lípidos nanoestructurados.

ARTICLE INFO
Received: February 6, 2021.
Received in revised form: March 15, 2021.
Accepted: March 16, 2021.
Available Online: April 5, 2021.

INTRODUCTION

Nanostructured lipid carrier (NLC) is the second generation of lipid nanoparticle delivery system. The first generation is solid lipid nanoparticles (SLN). SLN and NLC have different compositions of lipid matrix. SLN has a lipid matrix consisting of solid lipid, while NLC has a lipid matrix consisting of a solid lipid and liquid lipid (Garcês et al., 2018). The liquid lipid causes the ordered crystal structure of solid lipid to decrease, so that drug loading of NLC is higher than SLN (Montenegro, 2014; Chauhan et al., 2020).

Besides the drug loading of NLCs is higher than SLNs, the positive characteristics of NLCs are enhanced skin hydration, enhanced lipid barrier, and enhanced skin penetration of active substances. Therefore NLCs are many used in cosmetics formulations including skin anti-aging products (Montenegro, 2014; Montenegro et al., 2016). One anti-aging agent is coenzyme Q10 (Hseu et al., 2019). Coenzyme Q10 (2,3-dimethoxy-5 methyl-6-decaprenyl-benzoquinone) is an antioxidant. Due to the 10 units of the isoprenoid side chain, the nature of coenzyme Q10 is a lipophilic antioxidant (Casagrande et al., 2018; Martelli et al., 2020). Because of its lipophilic property, coenzyme Q10 tends to deposit in the stratum corneum, so that the penetration into the deeper layers of the skin is low (Montenegro, 2014). Hence, the development of coenzyme Q10 NLCs is more reasonable than coenzyme Q10 SLNs, because NLCs enhance skin penetration and have a higher drug loading than SLNs.

In recent research, the coenzyme Q10 NLCs were developed using myristic acid as a solid lipid, whereas oleic acid, isopropyl myristate, and isopropyl palmitate were used as liquid lipids. The previous studies revealed that myristic acid, oleic acid, isopropyl myristate, and isopropyl palmitate capable of penetration enhancers in transdermal delivery systems (Touitou et al., 2002; Guo et al., 2006; Ibrahim and Li, 2010; Eichner et al., 2017). Moreover, the liquid lipids used in this study have different lipophilicity. The lipid matrix of NLCs influences the physicochemical characteristics of the lipid nanoparticle delivery system (Fang et al., 2012).

Further, the coenzyme Q10 NLCs were characterized *in vitro* by dynamic light scattering (DLS) for particle size, polydispersity index (PDI), potential zeta, by differential scanning calorimetry (DSC) for crystallinity behaviors, by Fourier transforms infrared (FTIR) for FTIR spectra, by scanning electron microscopy (SEM) for surface morphology, by spectrophotometry ultraviolet (UV) for entrapment efficiency and drug loading, as well as by pH meter for pH value. Additionally, molecular modeling *in silico* was performed by molecular docking to predict and explain the results of the experimental study (Akyüz et al., 2017). In this research, it was used to predict and explain the interaction between coenzyme Q10 and the lipids at the molecular level.

MATERIAL AND METHODS

Materials

Coenzyme Q10 was purchased from Kangcare Bioindustry Co., ltd. (Nanjing, China. myristic acid, isopropyl myristate, and isopropyl palmitate, Tween 80, and propylene glycol were purchased from Bratachem (Surabaya, Indonesia). Span 80, oleic acid, phenoxyethanol were purchased from Universal Pharma Chemical (Surabaya, Indonesia). Ethanol 96% p.a, NaH_2PO_4 p.a, Na_2HPO_4 p.a, were purchased from E. Merck (Darmstadt, Germany). All of the study materials were pharmaceutical quality unless otherwise indicated.

Preparation of coenzyme Q10 nanostructured lipid carrier (NLC)

The coenzyme Q10 NLCs were produced using various concentrations of lipid matrix and surfactants (HLB 14) to obtain an optimal formula, as shown in Table 1. Firstly, myristic acid and liquid lipid were melted at 70°C and agitated at 3400 rpm by Ultra Turrax until homogeneous for approximately 1 min. Coenzyme Q10 (1%) was put into the lipid mixture and agitated until dissolved for approximately 2 min. Separately, Span 80 and

Table 1. The lipid matrix and surfactants concentrations of the coenzyme Q10 NLCs for optimization (concentration in %).

Formula	20% Surfactants									10% Surfactants		
	Lipid 8%						Lipid 10%			Lipid 8%		
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Myristic acid	5.6	5.6	5.6	6.4	6.4	6.4	7	7	7	5.6	5.6	5.6
Oleic acid	2.4	-	-	1.4	-	-	3	-	-	2.4	-	-
Isopropyl myristate	-	2.4	-	-	1.4	-	-	3	-	-	2.4	-
Isopropyl palmitate	-	-	2.4	-	-	1.4	-	-	3	-	-	2.4
Tween 80	18	18	18	18	18	18	18	18	18	9	9	9
Span 80	2	2	2	2	2	2	2	2	2	1	1	1

Tween 80 were heated to 70°C. They were added to the lipid phase sequentially and agitated until homogeneous for approximately 1 min. The phosphate buffer and 10% propylene glycol were heated independently of the lipid phase at 70°C. The mixture was added slowly to the lipid phase and agitated until it was homogeneous for approximately one min. The mixture was then agitated at 24 000 rpm for 3 min. The agitating speed was changed then to 3400 rpm and 0.6% phenoxyethanol was added to the mixture at 40°C and agitated until ambient temperature.

Selection of the coenzyme Q10 NLC formulas

The coenzyme Q10 NLCs were observed visually for 10 days at ambient temperature to obtain physically stable NLCs. Following this, the phase separation of the NLCs was assessed by the centrifugation method at 3500 rpm for 20 min using a centrifuge Hettich Rotofix 32A to select the optimal formulas (Loo et al., 2013; Restu et al., 2015).

Particle size, polydispersity index (PDI), and zeta potential

The particle size, PDI, and zeta potential were measured by a nanoparticle analyzer (Nanotrac Wave, Microtrac W3717). The samples were diluted with appropriate demineralized water previously.

The surface morphology

The samples were spread on an object-glass and dried by a hot plate at 40-50°C and coated in gold. Then, the samples were observed the surface morphology by Scanning Electron Microscope (SEM, ZEISS) with magnifications of 25 000×.

Differential scanning calorimetry (DSC)

DSC was used to analyze the melting point, enthalpy (ΔH), and crystallinity behaviors of coenzyme Q10, myristic acid, and coenzyme Q10 NLCs. The approximately 4 mg sample was put into an aluminum pan. Then it was heated by a calorimeter (DSC model 1/500, Mettler Toledo) from 30 to 100°C at the heating rate of 10°C/min. The crystallinity index (CI) is calculated according to the equation [1] (Chauhan et al., 2020).

$$\% \text{ CI} = \frac{(\Delta H) \text{ coenzyme Q10 NLC}}{(\Delta H) \text{ myristic acid} \times \text{concentration lipid phase}} \times 100 \quad [1]$$

Fourier transform infrared (FT-IR)

The samples were put into KBr powder and compressed to obtain a transparent plate by a hydraulic press. The plate then was scanned at the wavenumber of 400-4000 cm^{-1} by an FT-IR spectrophotometer (Jasco FT-IR 5300).

The pH value

The pH values of the coenzyme Q10 NLCs were measured using a calibrated pH meter (SI analytic Lab 850). The approximately 20 g sample was put in a beaker glass and the electrode of the pH meter was dipped into the sample.

Entrapment efficiency (EE) and drug loading (DL)

The entrapment efficiency and drug loading of coenzyme Q10 NLCs were determined by indirect methods. The coenzyme Q10 NLCs were diluted quantitatively using demineralized water. They were then placed into Amicon® Ultra-15 tubes with 30 kDa molecular weight cut-offs (Merck Millipore) and centrifuged for 30 min at 10 000 rpm. The UV spectrophotometer (UV 1800 Shimadzu) was used to measure the filtrate absorbance at a wavelength of 275 nm. The UV spectrophotometry method was used base on the previous study (Xia and Wang, 2010) with modifications. The calibration curves were established using least-squares linear regression analysis in the range between 10-50 ng/mL. The linearity, accuracy, precision, and specificity were determined. The correlation coefficients (r)>0.9000, %recovery = 90-110%, relative standard deviation (RSD) ≤2%) were considered for meeting method validation requirements. The entrapment efficiency and drug loading were calculated according to equations [2] and [3] (Chauhan et al., 2020), respectively.

$$\% \text{ EE} = \frac{(\text{the initial concentration of Q10 in NLC} - \text{free Q10 concentration in the filtrate})}{\text{the initial concentration of Q10 in NLC}} \times 100 \quad [2]$$

$$\% \text{ DL} = \frac{\text{the initial amount of Q10 in NLC} - \text{free Q10 amount in the filtrate}}{\text{lipid amount in Q10 NLC}} \times 100 \quad [3]$$

Molecular docking

The three-dimensional (3D) chemical structure of coenzyme Q10, oleic acid, isopropyl myristate, and isopropyl palmitate were obtained using MarvinSketch version 19.20. The structures were then conducted optimized energy minimization by the same program. The two-dimensional (2D) chemical structures of the molecules were generated using PubChem®, previously. Molecular docking of Q10 and various lipids were performed using AutoDock 4.2 (The Scripps Research Institute). Spacing (Armstrong) was selected at 0.375, and a grid box was set to cover all the molecules. Molecular docking was run 100 times. The results of molecular docking were visualized by Discovery Studio Visualizer (Dassault Systemes BIOVIA).

Statistical analysis

The data were reported as a mean ± standard deviation (SD) from three replicate measurements. The one-way ANOVA statistical method was used and followed by the Tuckey Honestly test for analyzing the differences among means. There was a statistically significant difference at $p<0.05$. The statistic program used SPPS version 23.

RESULTS AND DISCUSSION

Selection of the coenzyme Q10 NLC formulas

The physical stability of the coenzyme Q10 NLCs after 10 days of storage at ambient temperature and centrifugation were presented in Table 2. The centrifugation at 3500 rpm for 20 min could be equivalent for gravity ± 1 year (Restu et al., 2015).

After 10 days of storage, the coenzyme Q10 NLCs with 10% of the surfactant mixture (Tween 80 and Span 80) occurred a phase separation, whereas 20% of the surfactant mixture did not occur a phase separation. This was because 10% surfactants in concentration were inadequate to stabilize the coenzyme NLCs. The concentration of Tween 80 (HLB 15) and Span 80 (HLB 4.3) respectively, were calculated to reach the HLB value of the surfactant mixture, i.e., HLB 14. The HLB value 14 was close to the required hydrophilic-lipophilic balance (rHLB) value of the lipid matrix of the coenzyme Q10 NLCs. The rHLB value of the lipid matrix of the coenzyme Q10 NLCs was calculated based on the rHLB value of blended myristic acid-oleic acid, myristic acid-isopropyl myristate, and myristic acid-isopropyl palmitate. The rHLB value of myristic acid is not available (Pasquali et al., 2009), therefore, it was assuming the same with rHLB of stearic acids (15), which have almost the same length hydrocarbon chains. The rHLB value of oleic acid is 11, whereas isopropyl myristate and isopropyl palmitate have the same rHLB values, i.e., 11.5. In addition to the surfactant concentration, the matching HLB value of the surfactants and rHLB of the lipid matrix also affects the stability of the emulsion during the production of NLCs (Severino et al., 2012).

Table 2. Physical stability, particle size, PDI, and zeta potential of the coenzyme Q10 NLCs.

Formula	Stability after 10 d	Stability after centrifugation	Particle size (nm)	PDI	Zeta potential (mv)
Coenzyme Q10 NLC (F1)	No separation	No separation	289.2 ± 20.8*	0.246 ± 0.123	-38.5 ± 0.9
Coenzyme Q10 NLC (F2)	No separation	No separation	232.1 ± 18.0**	0.268 ± 0.114	-55.6 ± 3.3
Coenzyme Q10 NLC (F3)	No separation	No separation	248.2 ± 22.7***	0.240 ± 0.073	-56.2 ± 1.0
Coenzyme Q10 NLC (F4)	No separation	No separation	368.0 ± 8.9*	0.257 ± 0.080	-27.8 ± 1.3
Coenzyme Q10 NLC (F5)	No separation	No separation	310.6 ± 27.4**	0.375 ± 0.067	-53.7 ± 1.0
Coenzyme Q10 NLC (F6)	No separation	No separation	321.8 ± 27.2***	0.227 ± 0.124	-38.0 ± 0.7
Coenzyme Q10 NLC (F7)	No separation	No separation	596 ± 14.2*	0.082 ± 0.060	-21.5 ± 0.7
Coenzyme Q10 NLC (F8)	No separation	No separation	316.3 ± 30.0**	0.248 ± 0.135	-41.4 ± 3.3
Coenzyme Q10 NLC (F9)	No separation	No separation	349 ± 11.5***	0.276 ± 0.039	-55.7 ± 0.3
Coenzyme Q10 NLC (F10)	No separation	Separation	-	-	-
Coenzyme Q10 NLC (F11)	No separation	Separation	-	-	-
Coenzyme Q10 NLC (F12)	No separation	Separation	-	-	-

Data are reported as mean ± SD, n = 3. *The particle size of F1, F4, and F7 showed significant differences ($p<0.05$). **The particle size of F2, F5, and F8 showed significant differences ($p<0.05$). ***The particle size of F3, F6, and F9 showed significant differences ($p<0.05$).

The coenzyme Q10 NLCs used the lipid matrix, which was Generally Recognized as Safe (GRAS) substances and did not use an organic solvent. It was water-based technology and easy to prepare also. Hence, the coenzyme Q10 NLCs were safe, cost-effective, and potentially intended for large-scale production. Further, the coenzyme NLCs (F1)-(F9) was evaluated in the particle size, distribution particle, and zeta potential.

Particle size, PDI, and zeta potential

The coenzyme Q10 NLCs (i.e., F1 to F9) had particle sizes from 232 to 596 nm, as shown in Table 2. The particle size of the Q10 NLCs (F1), (F2), and (F3) were less than 300 nm. While the other coenzyme Q10 NLCs (i.e., F4 to F9) had particle sizes of more than 300 nm.

The coenzyme Q10 NLC (F1), (F4), and (F7) used myristic acid-oleic acid as a lipid matrix. The coenzyme Q10 NLC (F2), (F5), and (F8) used myristic acid-isopropyl myristate as a lipid matrix. The coenzyme Q10 NLC (F3), (F6), and (F9) used myristic acid-isopropyl palmitate as a lipid matrix. The ratio of solid lipid and liquid lipid of coenzyme Q10 NLCs (F4) - (F6) were higher (80:20) than coenzyme Q10 NLCs (F1)-(F3) (70:30). The lipid matrix concentrations of coenzyme Q10 NLCs (F7) to (F9) were higher than coenzyme Q10 NLCs (F1) to (F3). Increasing the solid lipid concentration and lipid matrix concentration might cause an increase in the viscosity of the systems. Therefore, the stirrer shearing capacity decreases, then the reduction of particle size becomes difficult. Moreover, the surfactant concentration was inadequate to cover the particle surface, hence the particle size increased. A similar result also was observed in the previous studies (Shah et al., 2014).

The particle size distributions of almost all coenzyme Q10 NLCs were narrow and homogenous, except (F5). It is due to the PDI of Q10 NLCs were <0.3 (Amasya et al., 2020; Öztürk et al., 2020) as shown in Table 2. The zeta potentials of the Q10 NLCs were -21.5 to -56.2 mv, as shown in Table 2. The NLCs have good physical stability if they have a zeta potential less than -30 and more than +30 (Subramaniam et al., 2020). Almost all of the coenzyme Q10 NLCs had zeta potential less than -30 mv, except (F4) and (F7), hence, they had good physical stability, except (F4) and (F7).

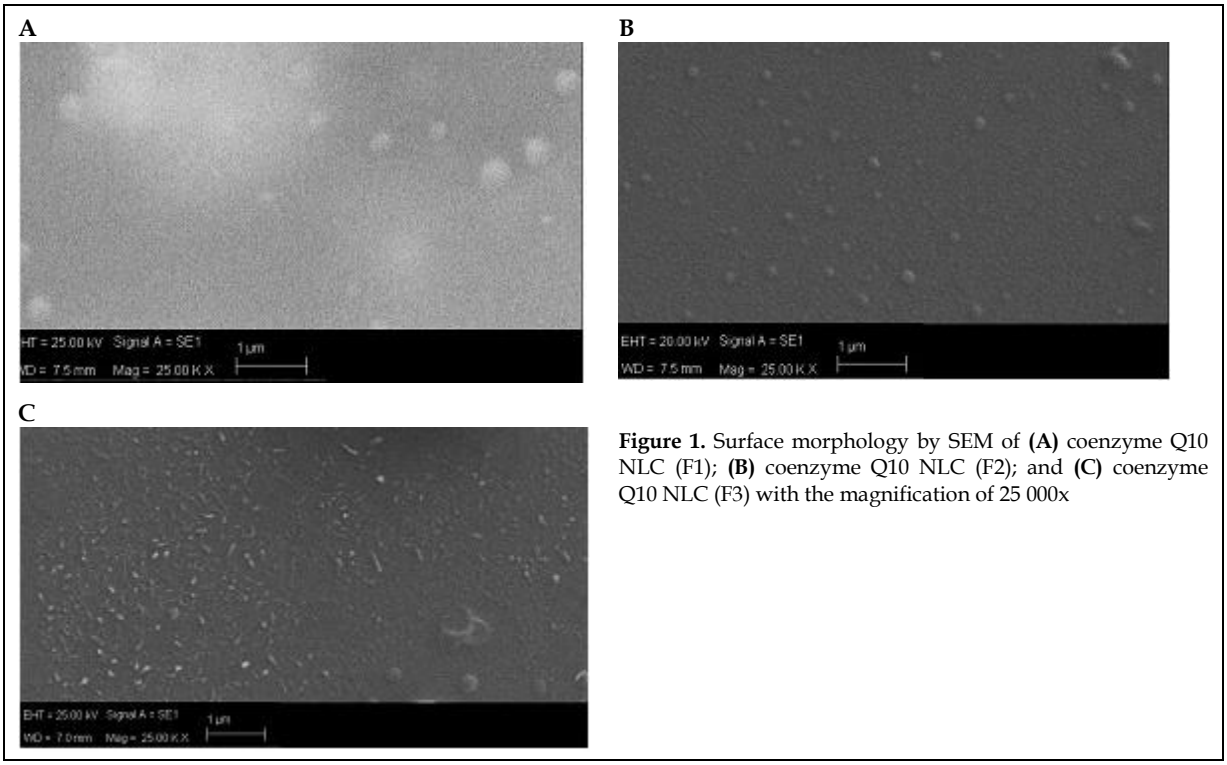

Figure 1. Surface morphology by SEM of **(A)** coenzyme Q10 NLC (F1); **(B)** coenzyme Q10 NLC (F2); and **(C)** coenzyme Q10 NLC (F3) with the magnification of 25 000x

Based on the particle size, PDI, and zeta potential data, the coenzyme Q10 NLCs (F1), (F2), and (F3) were selected as optimal formulas. This was due to that their particle sizes were less than 300 nm and the smallest of the same lipid matrix. The nanocarriers with particle sizes less than 300 nm can penetrate through the deeper skin layers, but cannot be absorbed (Danaei et al., 2018). Therefore, they are appropriate for cosmetics formulations. Further, the Q10 NLCs (F1), (F2), and (F3) were characterized physicochemically.

The surface morphology

The morphologies of the coenzyme Q10 NLCs (F1), (F2), and (F3) were spherical form and relatively smooth surfaces as presented in Fig. 1.

Differential scanning calorimetry (DSC)

The thermal and crystallinity behaviors of the samples were analyzed by DSC (Annepogu et al., 2020). The coenzyme Q10 NLCs illustrated endothermic peaks, as shown in Fig. 2. The melting points of coenzyme Q10, myristic acid, coenzyme Q10 NLC (F1), (F2), and (F3) were 51.63, 54.95, 38.61, 41.55, and 34.25°C, respectively. The melting enthalpy (ΔH) of coenzyme Q10, myristic acid, coenzyme Q10 NLC (F1), (F2), and (F3) were -153.20, -911.94, -2.42, -5.08, -5.49 J/g, respectively. The melting points and enthalpies of the coenzyme NLCs were lower than the melting points and enthalpies of coenzyme Q10 and myristic acid. It was due to that coenzyme Q10 become an amorphous phase and molecularly dispersed into the lipid matrix (Aliasgharlou et al., 2016; Bhattacharyya and Reddy, 2019; Amasya et al., 2020).

The crystallinity index of coenzyme Q10 NLC (F1), (F2), and (F3) were 3.32, 6.96, and 7.53%, respectively. The crystallinity index of myristic acid was assuming 100%. The crystallinity index of coenzyme Q10 NLC (F1), (F2), and (F3) were <10%. The addition of liquid lipid causes the ordered crystal structured of solid lipid to become less order (Averina et al., 2010; Essaghraoui et al., 2019), hence the crystallinity indexes of the coenzyme Q10 NLCs were lower than myristic acid. It caused left enough space for the entrapment of coenzyme Q10 (Averina et al., 2010; Essaghraoui et al., 2019). The lipid crystallinity influences the en-

trapment efficiency and drug loading of NLCs (Diniz et al., 2018; Subramaniam et al., 2020).

Fourier transform infrared (FT-IR)

The FT-IR spectra of coenzyme Q10, coenzyme Q10 NLCs, and the lipids in the region of 4000–400 cm^{-1} are shown in Fig 3.

The FT-IR spectra of coenzyme Q10 exhibited peaks at 2962.13 cm^{-1} for C-H stretching, 1732.73 cm^{-1} for C=O stretching, 1645.95 cm^{-1} for C=C stretching, and 1200.47 cm^{-1} for C-O stretching. The coenzyme Q10 NLCs FT-IR spectra showed no new peaks, moreover, there was not significantly shifting of wavenumber compared to FTIR spectra of coenzyme Q10 and the lipids. It was caused by the absence of chemical interactions leading to the creation of new functional groups in the coenzyme Q10 NLCs (Üner et al., 2014).

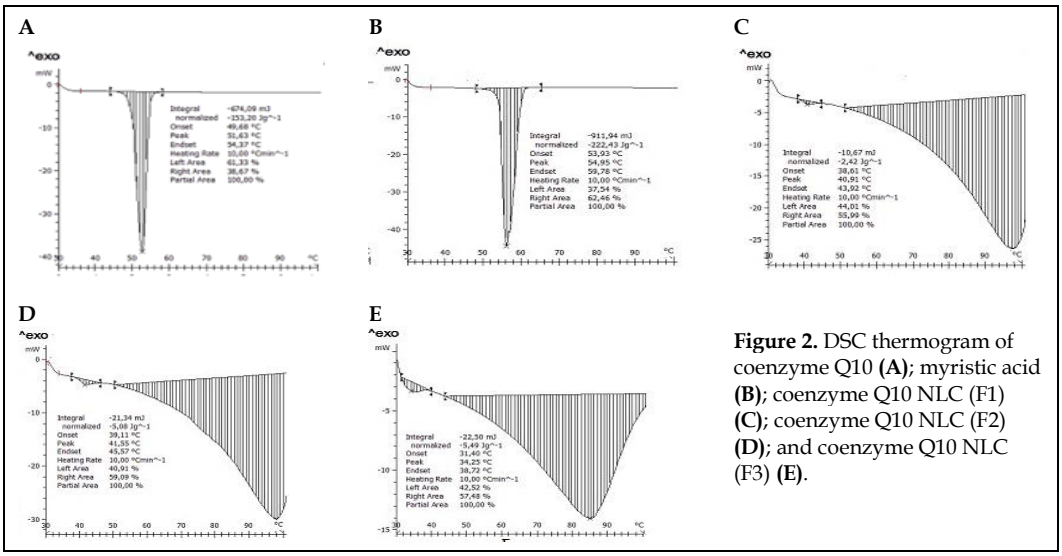

Figure 2. DSC thermogram of coenzyme Q10 **(A)**; myristic acid **(B)**; coenzyme Q10 NLC (F1) **(C)**; coenzyme Q10 NLC (F2) **(D)**; and coenzyme Q10 NLC (F3) **(E)**.

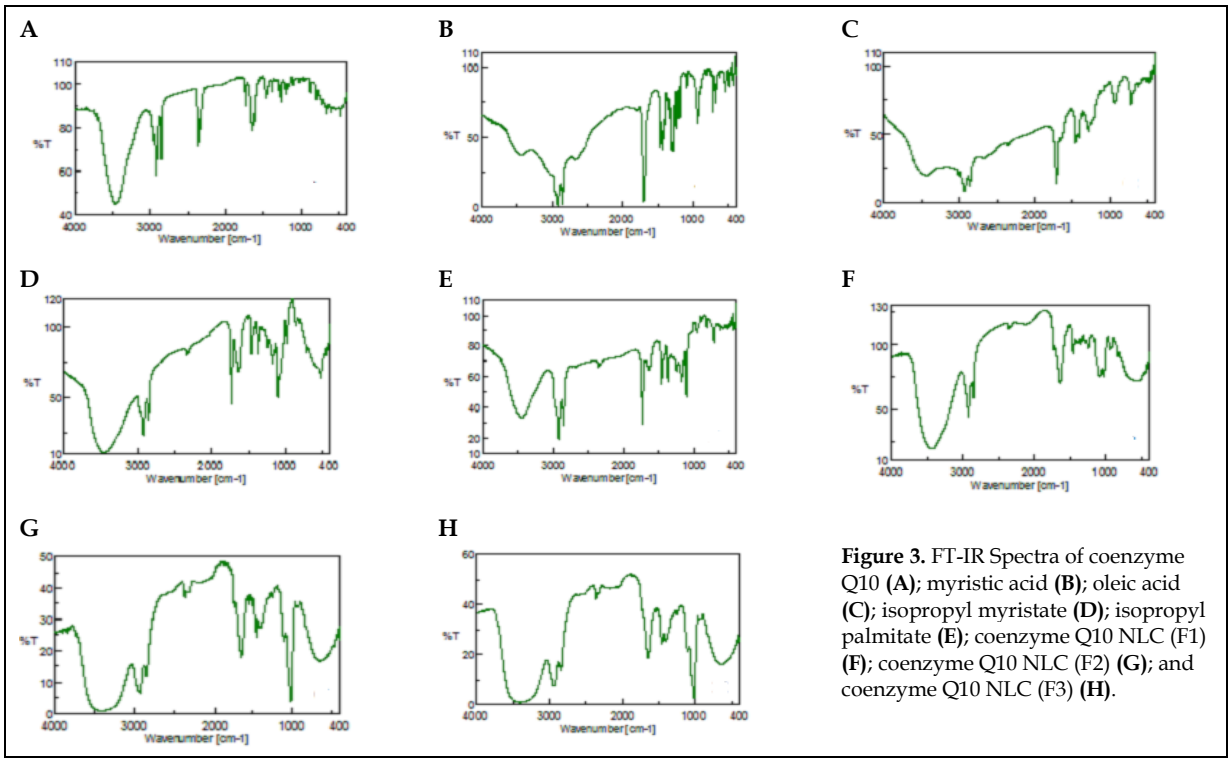

Figure 3. FT-IR Spectra of coenzyme Q10 **(A)**; myristic acid **(B)**; oleic acid **(C)**; isopropyl myristate **(D)**; isopropyl palmitate **(E)**; coenzyme Q10 NLC (F1) **(F)**; coenzyme Q10 NLC (F2) **(G)**; and coenzyme Q10 NLC (F3) **(H)**.

Table 3. The pH values, entrapment efficiency, and drug loading of the coenzyme Q10 NLCs.

Formula	pH	Entrapment efficiency (%)	Drug loading (%)
Q10 NLC (F1)	5.47 ± 0.02*	81.39 ± 0.21**	10.17 ± 0.03***
Q10 NLC (F2)	5.52 ± 0.01*	82.50 ± 0.44**	10.31 ± 0.05***
Q10 NLC (F3)	5.52 ± 0.01*	85.49 ± 0.07**	10.69 ± 0.01***

Data are reported as (mean±SD, n=3). *The pH values of F1, F2, and F3 did not show significant differences ($p<0.05$). **The **entrapment efficiency** (%) of F1, F2, and F3 showed significant differences ($p<0.05$). ***The **drug loading** (%) of F1, F2, and F3 showed significant differences ($p<0.05$).

The pH value

The pH values of the coenzyme Q10 NLC (F1), (F2), and (F3) were about 5. The pH value of the normal skin surface is in the range of 4 to 6.5 (Kuo et al., 2020). The pH values of coenzyme Q10 NLC (F1), (F2), and (F3 met the pH value of the normal skin. The pH values of the coenzyme Q10 NLC(F1), (F2), and (F3) are presented in Table 3.

Entrapment efficiency (EE) and drug loading (DL)

The analytical method used for determining the entrapment efficiency and the drug loading met the requirements of method validation, i.e., linear in the range 10-50 µg/mL ($r>0.9000$), %recovery = 90-110%, RSD<2%, and no interference of absorbance of excipients used in the NLCs. The entrapment efficiency and the drug loading of the coenzyme Q10 NLCs were more than 80% and about 10%, respectively, as shown in Table 3. the entrapment efficiency and the drug loading of the coenzyme Q10 NLC (F3) were the highest among the others. It is due to that isopropyl palmitate has the highest lipophilic property compared to oleic acid and isopropyl myristate. The lipophilicity of the lipid matrix affects entrapment efficiency and drug loading of NLCs, besides the crystallinity (Haider et al., 2020).

Molecular docking

The molecular docking method is used for analyzing the affinity of the drug and excipient by determining free binding energy (ΔG). The lower the ΔG, the higher the affinity of the drug-excipient (Hathout and Metwally, 2016; Firdaus and Maarof, 2017; Hathout et al., 2020). The ΔG *in silico* of coenzyme Q10-oleic acid, coenzyme Q10-isopropyl myristate, and coenzyme Q10- isopropyl palmitate were -1.30, -1.37, and -1.38 kcal/mol, respectively. The ΔG *in silico* of coenzyme Q10-isopropyl palmitate was the lowest. This indicated that isopropyl palmitate had the highest affinity for coenzyme Q10. The affinity of coenzyme Q10-lipids influenced the entrapment efficiency and the drug loading of the coenzyme Q10 NLCs.

The graphs of the ΔG *in silico,* the entrapment efficiency, and the drug loading of the coenzyme Q10 NLCs were presented in Fig 4. The graphs show that the lower the ΔG *in silico*, the higher the entrapment efficiency and the drug loading of the coenzyme Q10 NLCs. The interaction between the molecule of coenzyme Q10 and the molecule of lipid could occur as the ΔG *in silico* was negative. It was a spontaneous reaction (Tou et al., 2019).

Intermolecular interactions consist of ionic, ion-dipole, and dipole-dipole, hydrogen, van der Waals and hydrophobic bonds (Prema et al., 2013). The 3-D visualization of molecular docking of coenzyme Q10 and liquid lipids using Discovery Studio Visualizer showed hydrogen and hydrophobic bonds, as shown in Fig. 5. The previous studies of molecular docking of Q10 with omega 3 fatty acids also showed hydrogen and hydrophobic bonds (Zulfakar et al., 2018; Tou et al., 2019).

The 3D visualization of coenzyme Q10-oleic acid interaction showed the hydrogen bond between atom O1 and O4 of coenzyme Q10 with atom H34 of oleic acid with distances of 2.05 and 2.72 Å, respectively, as well as the hydrophobic bond between atom C24 and C57 of coenzyme Q10 with atom C17 of oleic acid with distances of 4.41 and 3.82 Å, respectively. The 3D visualization of coenzyme Q10-isopropyl myristate showed the hydro-

phobic bond between atom C56 of coenzyme Q10 with atom C1 of isopropyl myristate with a distance of 4.27 Å. The 3D visualization of coenzyme Q10-isopropyl palmitate showed the hydrogen bond between atom H4 and H7 of coenzyme Q10 with atom O_2 of isopropyl palmitate with distances of 2.58 and 2.56 Å, respectively, as well as the hydrophobic bond between atom C57 of coenzyme Q10 with atom C18 of isopropyl palmitate with a distance of 3.41 Å. The 3D visualization of coenzyme Q10-lipid demonstrated that functional groups of coenzymes Q10 still exist in the interaction of coenzyme Q10-lipid. These results supported the results of the DSC and FTIR studies. The DSC and FTIR studies revealed that there was no chemical interaction between coenzyme Q10 and the lipid, which created new peaks or shifted the wavenumber.

CONCLUSIONS

The coenzyme Q10 NLCs were successfully prepared using myristic acid-oleic acid, myristic acid-isopropyl myristate, and myristic acid-isopropyl palmitate as the lipid matrices. The DSC and FTIR studies indicated that coenzyme Q10 was entrapped and molecularly dispersed in the lipid matrix. The crystallinity index of the coenzyme Q10 NLCs was low. It caused left enough space to entrap coenzyme Q10 in the lipid matrix, resulting in high entrapment efficiency and high drug loading of the coenzyme Q10 NLCs.

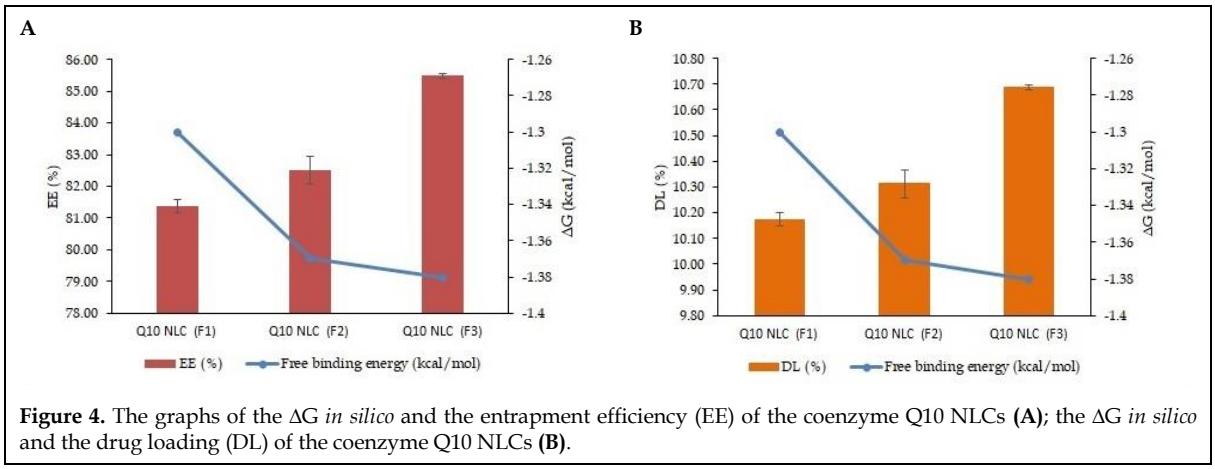

Figure 4. The graphs of the ΔG *in silico* and the entrapment efficiency (EE) of the coenzyme Q10 NLCs **(A)**; the ΔG *in silico* and the drug loading (DL) of the coenzyme Q10 NLCs **(B)**.

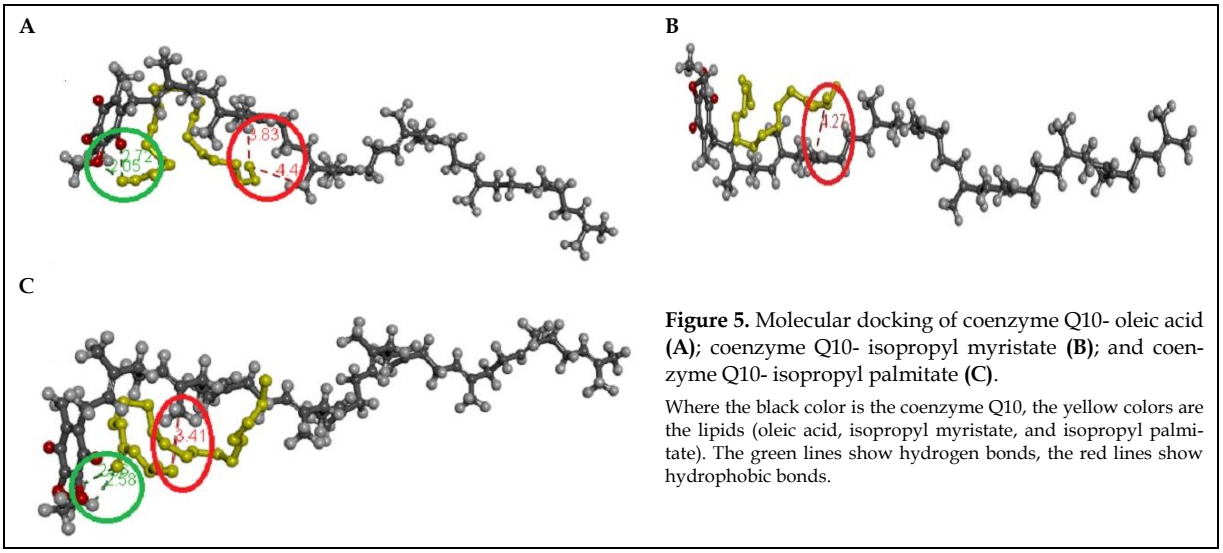

Figure 5. Molecular docking of coenzyme Q10- oleic acid **(A)**; coenzyme Q10- isopropyl myristate **(B)**; and coenzyme Q10- isopropyl palmitate **(C)**.

Where the black color is the coenzyme Q10, the yellow colors are the lipids (oleic acid, isopropyl myristate, and isopropyl palmitate). The green lines show hydrogen bonds, the red lines show hydrophobic bonds.

Furthermore, the results of *in silico* studies by molecular docking supported and could explain the result of the DSC and FTIR studies. The ΔG *in silico* of coenzyme Q10-lipid decreased with increased entrapment efficiency and drug loading of the coenzyme Q10 NLCs. Hence, it could be inferred that the *in silico* study could be used to explain the results and to design the development of coenzyme Q10 NLCs.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

ACKNOWLEDGMENTS

The authors would like to thank the University of Surabaya, Surabaya, Indonesia for financially supporting this research.

REFERENCES

Akyüz L, Duman F, Kaya M (2017) Encapsulation of flurbiprofen by chitosan using a spray-drying method with *in vitro* drug releasing and molecular docking. Turkish J Pharm Sci 14: 34–39.

Aliasgharlou L, Ghanbarzadeh S, Azimi H, Zarrintan MH, Hamishehkar H (2016) Nanostructured lipid carrier for topical application of N-acetyl glucosamine. Adv Pharm Bull 6: 581–587.

Amasya G, Türk CTŞ, Badilli U, Tarimci N (2020) Development and statistical optimization of solid lipid nanoparticle formulations of fluticasone propionate. Turkish J Pharm Sci 17: 359–366.

Annepogu H, Ahad HA, Nayakanti D (2020) Determining the best poloxamer carrier for thiocolchicoside solid dispersions. Turkish J Pharm Sci 17: 372–380.

Averina ES, Seewald G, Müller RH, Radnaeva LD, Popov DV (2010) Nanostructured lipid carriers (NLC) on the basis of Siberian pine (*Pinus sibirica*) seed oil. Pharmazie 65: 25–31.

Bhattacharyya S, Reddy P (2019) Effect of surfactant on azithromycin dihydrate loaded stearic acid solid lipid nanoparticles. Turkish J Pharm Sci 16: 425–431.

Casagrande D, Waib PH, Jordão Júnior AA (2018) Mechanisms of action and effects of the administration of coenzyme Q10 on metabolic syndrome. J Nutr Intermed Metab 13: 26–32

Chauhan I, Mohd Y, Madhu V, Singh Pratap A (2020) Nanostructured lipid carriers: a groundbreaking approach for transdermal drug delivery. Adv Pharm Bull 10: 150–65.

Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, Khorasani S, Mozafari MR (2018) Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics 10(2): 57.

Diniz F, Marques C, Barbosa TC, Martins D, Nalone L, Costa S, Chaud MV, Silva CF da, Souto EB, Barbosa R de M, Severino P (2018) Polymorphism, crystallinity and hydrophilic-lipophilic balance (HLB) of cetearyl alcohol and cetyl alcohol as raw materials for solid lipid nanoparticles (SLN). Aspects Nanotechnol 1(1): 52–60.

Eichner A, Stahlberg S, Sonnenberger S, Lange S, Dobner B, Ostermann A, Schrader TE, Hauß T, Schroeter A, Huster D, Neubert RHH (2017) Influence of the penetration enhancer isopropyl myristate on stratum corneum lipid model membranes revealed by neutron diffraction and 2H NMR experiments. Bioch Biophys Acta 1859(5): 745–755.

Essaghraoui A, Belfkira A, Hamdaoui B, Nunes C, Costa Lima SA, Reis S (2019) Improved dermal delivery of cyclosporine a loaded in solid lipid nanoparticles. Nanomaterials 9: 1204–1217

Fang CL, Al-Suwayeh SA, Fang JY (2012) Nanostructured lipid carriers (NLCs) for drug delivery and targeting. Recent Pat Nanotechnol 7: 41–55.

Firdaus MA, Maarof H (2017) Multiple docking of α -, β -, and γ-cyclodextrin with vinpocetine chiral complexes. EProceedings Chem 2: 12–17.

Garcês A, Amaral MH, Sousa Lobo JM, Silva AC (2018) Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cutaneous use: A review. Eur J Pharm Sci 112: 159–167.

Guo H, Liu Z, Li J, Nie S, Pan W (2006) Effects of isopropyl palmitate on the skin permeation of drugs. Biol Pharm Bull 29(11): 2324–2326.

Haider M, Abdin SM, Kamal L, Orive G (2020) Nanostructured lipid carriers for delivery of chemotherapeutics: A review. Pharmaceutics 12: 288–313.

Hathout RM, Metwally AA (2016) Towards better modelling of drug-loading in solid lipid nanoparticles: Molecular dynamics, docking experiments and Gaussian processes machine learning. Eur J Pharm Biopharm 108: 262–268.

Hathout RM, Metwally AA, Woodman TJ, Hardy JG (2020) Prediction of drug loading in the gelatin matrix using computational methods. ACS Omega 5: 1549–1556.

Hseu YC, Ho YG, Mathew DC, Yen HR, Chen XZ, Yang HL (2019) The *in vitro* and *in vivo* depigmenting activity of coenzyme Q10 through the down-regulation of α-MSH signaling pathways and induction of Nrf2/ARE-mediated antioxidant genes in UVA-irradiated skin keratinocytes. Biochem Pharmacol 164: 299–310.

Ibrahim SA, Li SK (2010) Efficiency of fatty acids as chemical penetration enhancers: mechanisms and structure enhancement relationship. Pharm Res 27(1): 115–125.

Kuo S, Shen C, Shen C (2020) Role of pH value in clinically relevant diagnosis. Diagnostics 10: 107–123.

Loo CH, Basri M, Ismail R, Lau HLN, Tejo BA, Kanthimathi MS, Hassan HA, Choo YM (2013) Effect of compositions in nanostructured lipid carriers (NLC) on skin hydration and occlusion. Int J Nanomed 8: 13–22.

Martelli A, Testai, L, Colletti A, Cicero AFG (2020) Coenzyme Q10: Clinical applications in cardiovascular diseases. Antioxidants 9: 341–366.

Montenegro L (2014) Nanocarriers for skin delivery of cosmetic antioxidants. J Pharm Pharmacogn Res 2: 73–92.

Montenegro L, Lai F, Offerta A, Sarpietro MG, Micicchè L, Maccioni AM, Valenti D, Fadda AM (2016) From nanoemulsions to nanostructured lipid carriers: A relevant development in dermal delivery of drugs and cosmetics. J Drug Deliv Sci Technol 32: 100–112.

Öztürk N, Kara A, Vural İ (2020) Formulation and *in vitro* evaluation of telmisartan nanoparticles prepared by emulsion-solvent evaporation technique. Turkish J Pharm Sci 17: 492–499.

Pasquali RC, Bregni C, Taurozzi MP (2009) New values of the required hydrophilic-lipophilic balance for oil in water emulsions of solid fatty acids and alcohols obtained from solubility parameter and dielectric constant values. J Dispers Sci Technol 30(3): 328–331.

Prema S, Saraswathi A, Chitra K, Gopal V (2013) A review on supramolecular chemistry in drug design and formulation research. Indones J Pharm 214: 131–150.

Restu WK, Sampora Y, Meliana Y, Haryono A (2015) Effect of accelerated stability test on characteristics of emulsion systems with chitosan as a stabilizer. Procedia Chem 16: 171–176.

Severino P, Andreani T, Macedo AS, Fangueiro JF, Santana MHA, Silva AM, Souto EB (2012) Current state-of-art and new trends on lipid nanoparticles (SLN and NLC) for oral drug delivery. J Drug Deliv 2012: 750891.

Shah R, Eldridge D, Palombo E, Harding I (2014) Optimisation and stability assessment of solid lipid nanoparticles using particle size and zeta potential. J Phys Sci 25: 59–75.

Subramaniam B, Siddik ZH, Nagoor NH (2020) Optimization of nanostructured lipid carriers: understanding the types, designs, and parameters in the process of formulations. J Nanopart Res 22: 141–169.

Tou KAS, Rehman K, Ishak WMW, Zulfakar MH (2019) Influence of omega fatty acids on skin permeation of a coenzyme Q10 nanoemulsion cream formulation: characterization, *in silico* and *ex vivo* determination. Drug Dev Ind Pharm 45: 1451–1458.

Touitou E, Godin B, Karl Y, Bujanover S, Becker Y (2002) Oleic acid, a skin penetration enhancer, affects Langerhans cells and corneocytes. J Control Release 80: 1–7.

Üner M, Karaman EF, Aydoğmuş Z (2014) Solid lipid nanoparticles and nanostructured lipid carriers of loratadine for topical application: Physicochemical stability and drug penetration through rat skin. Trop J Pharm Res 13: 653–660.

Xia Q, Wang H (2010) Preparation and characterization of coenzyme q10-loaded nanostructured lipid carries as delivery systems for cosmetic component. NSTI-Nanotech 3: 498–501.

Zulfakar MH, Chan LM, Rehman K, Wai LK, Heard CM (2018) Coenzyme Q10-loaded fish oil-based bigel system: probing the delivery across porcine skin and possible interaction with fish oil fatty acids. AAPS PharmSciTech 19: 1116–1123.

AUTHOR CONTRIBUTION:

Contribution	Aryani NLD	Siswandono	Soeratri W	Putri DY	Pingky DP
Concepts or ideas	x	x	x		
Design	x	x	x		
Definition of intellectual content	x	x	x	x	x
Literature search	x	x	x	x	x
Experimental studies	x			x	x
Data acquisition	x			x	x
Data analysis	x	x	x	x	x
Statistical analysis	x	x	x	x	x
Manuscript preparation	x	x	x		
Manuscript editing	x	x	x		
Manuscript review	x	x	x	x	x

Citation Format: Aryani NLD, Siswandono, Soeratri W, Putri DY, Pingky DP (2021) Development, characterization *in vitro* and *in silico* of coenzyme Q10 loaded myristic acid with different liquid lipids nanostructured lipid carriers. J Pharm Pharmacogn Res 9(5): 573–583.

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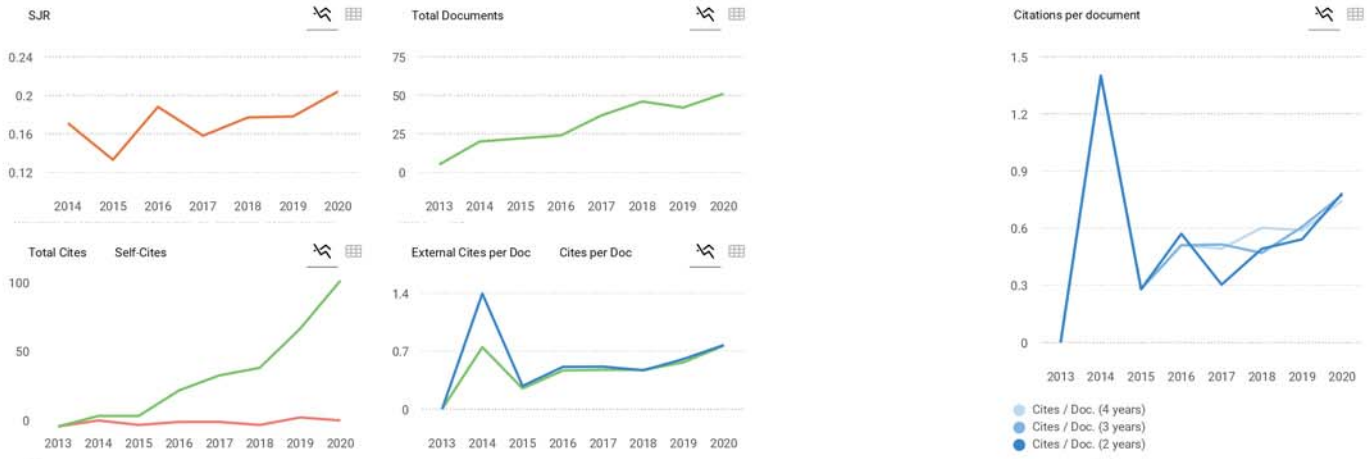

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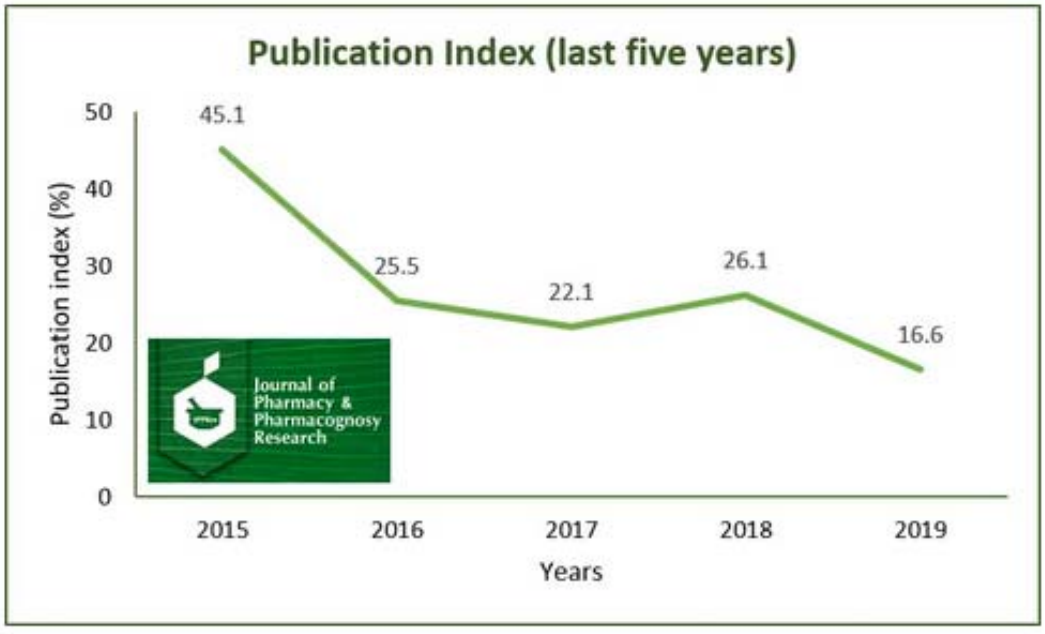

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