Synthesis of Solid Lipid Nanoparticles Containing CoenzymeQ10 and Vitamin E through Hot Homogenization Process

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***Abstract*—The aim of present work was to develop a new formulation of Solid Lipid Nanoparticles (SLNs) containing Coenzyme Q10 (CoQ10) and Vitamin E (VitE) for transdermal drug delivery application using hot homogenization process. Three different conditions without drug loading were modified for optimization. The optimum condition was further used to prepare VitE-loaded SLNs and CoQ10&VitE-loaded SLNs. All drug-free and drug-loaded nanoparticles were in a diameter size range of 100 to 200 nm. The mean diameter of drug-free SLNs, SLNs containing VitE, SLNs containing CoQ10&VitE were 135 ± 39, 141 ± 37 and 162 ± 46 nm, respectively. Monodispersed SLNs were successful prepared with Polydispersity Index (PDI) value (below 0.5). Zeta potential value was around 40 mV for all prepared particles providing a good physical stability. Except that of CoQ10&VitE-loaded particles, their zeta potential was around -60 mV. By UV-vis spectrophotometer, the encapsulation efficiency of VitE-loaded and CoQ10&VitE-loaded SLNs were nearly 100%. XRD analysis results showed amorphousness (broad peak) of the prepared nanoparticles (NPs).**

***Index Terms*—solid lipid nanoparticles, coenzyme Q10, vitamin E, hot homogenization**

I. Introduction

Vitamin E (VitE) is a well-known antioxidant. It has been used for dermal therapy more than 50 years [1]. It is the most abundant biological compound that can fight free radicals. The other important antioxidant is coenzyme Q10 (CoQ10) [2]. It is widely known as an antioxidant with effective anti-aging and anti-wrinkle properties. Rabe et al, 2006 found that CoQ10 can significantly reduce wrinkles in six months [3], [4]. Both CoQ10 and VitE are non-toxic and present in food. They are enormously interested by cosmetic production industry. Obviously, they are usually formulated in a form for topical administration. Moreover, the results from the study of Kagan *et al.*, 2000 showed that an efficient recycling of the VitE can be obtained from an interaction between VitE and CoQ10 [5]. Therefore, a product contained both CoQ10 and VitE might have higher potency than that contained only one of them. However, their fat-solubility are barriers for transporting through skin [6], [7]. They both are also sensitive to light, high temperature and moisture. These limitations can reduce their efficacy [6], [7]. To overcome these boundaries, lipid-based nanocarriers have been introduced as a reservoir to deliver VitE and CoQ10. SLN is an alternative colloidal carrier system which was developed to overcome the limitations of other colloidal carrier system such as liposomes and polymeric nanoparticles. The advantages of SLN are small size, controlling drug release, high bioavailability and avoidance of organic solvent. It has low toxicity in vitro [8]. It also increases occlusive effect which promotes the drug penetration through skin [9]. Moreover, chemically unstable compounds can be encapsulated by SLN to avoid undesired reactions caused from photolysis, oxidation and hydrolysis [6]. Size of particles is one of major factors affecting skin penetration. NPs with the size of 100-200 nm was considered to be the suitable size range for transdermal permeation [10].

This study aims to develop a new formulation of SLN which is suitable to deliver CoQ10 together with VitE through skin in order to enhance antioxidant activities. Therefore, different formulations will be performed. The characterizations of synthesized SLNs were also evaluated in terms of size, encapsulation efficiency, stability and crystallographic structure.

II. Materials and Methods

A. Materials

Dichloromethane (DCM) was purchased from CARLO ERBA reagent. Sorbitan Esters 80 (Span® 80),

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polysorbate 80 (Tween® 80), α-Tocopherol (VitE), coenzyme Q10 (CoQ10) and steric acid were purchased from SIGMA-ALDRICH.

B. CoQ10&VitE-Loaded SLNs Synthesis

The SLNs were prepared according to a hot high homogenization method modified from the study of Kelidari *et al.*, 2015 and Liu *et al.*, 2011 [11], [12]. Firstly, three different conditions (condition A, B, C) with different parameter setting (referred to Table I) were performed for the optimization (Condition A was modified to condition B and condition B was modified to condition C). The SLNs synthesis was started with dissolving span 80, and steric acid (referred to Table I for amounts) in 20 ml dichloromethane (DCM) under an ultrasonication for 7 min (organic phase). Tween 80 was dissolved with 100 ml of distilled water (aqueous phase) under homogenization at 5,200 rpm by using high-shear homogenizer (IKA® T25 digital ULTRA TURRAX®). The 2/3 of the aqueous phase was separated and maintained in an ice bath. The remaining 1/3 of aqueous phase was heated at 70-90ºC (depending on each condition). The organic phase was slowly poured into 1/3 of the pre-heated aqueous phase along with mechanical stirring speed at speed number 3 (IKA® C-MAG HS7 hot magnetic stirrer) or an ultrasonic water bath (Elma ultrasonic cleaner bath). The mixture was dispersed into the 2/3 of the water phase maintained in an ice bath and homogenized by high shear-homogenizer (IKA® T25 digital ULTRA TURRAX®). The solution was filtered (pore size: 0.45µm). DCM was then evaporated by mechanical stirring for overnight (18-24 h). The only best condition (condition C) was further used to prepare for drug loaded SLNs under the two formulations shown in Table II.

TABLE I. THREE CONDITIONS WITH DIFFERENT PARAMETERS WHICH WERE SET FOR SYNTHESIS OF DRUG-FREE SLNS

Parameters	[a]Condition A	Condition B	Condition C
Steric acid	0.05 g	0.05 g	0.05 g
Span 80	0.25 g	0.25 g	0.3 g
Tween 80	0.5 g	1 g	1.2 g
DCM	20 ml	20 ml	20 ml
Temperature in an ultrasonic bath or on hot magnetic stirrer	79-80 ºC[a]	86-88 ºC	90-93 ºC
Homogenization speed	13,000 rpm	13,000 rpm	16,400 rpm
Homogenization time	7 min	15 min	7 min
Overall heating time (including heating up, pouring and stirring)	10-15 min	10-15 min	10-15 min
Filtered by 0.45 µm filter right after synthesis	No	No	Yes
Volume of solution containing suspensions were left with stirring overnight	100 ml	100 ml	100 ml

[a]An ultrasonication bath was used only in condition A. The rest were using hot magnetic stirrer.

TABLE II. AMOUNT OF SUBSTANCES USED IN SYNTHESIS OF SLNS WITH CONDITION C

Formulation	Stearic acid (mg)	Span 80 (mg)	Tween 80 (mg)	VitE (mg)	CoQ10 (mg)
1	0.0500	0.300	1.200	0.0125	-
2	0.0500	0.300	1.200	0.0125	0.0125

C. Particle Characterization

To investigate size of the particles, Polydispersity Index (PDI) and Zeta Potential (ZP), nanoparticle analyzer (HORIBA scientific nano particle sz-100) was used. Crystalline structure was investigated using X-ray Diffractometer (XRD).

D. Encapsulation Efficiency

The percentage of encapsulation efficiency was calculated using indirect method. The optimization of particles was centrifuged using a refrigerator centrifuge (Hettich Centrifuge Universal 320R) with centrifuge filters (Amicon® Ultra Centrifugal Concentrators). The supernatant was filtered (pore size: 0.22µm) and used for the determination of the unencapsulated VitE&CoQ10 concentration with using UV-Visible spectrophotometer. The encapsulation efficiency of SLNs was calculated by using the equation below.

$$\%EE = [(C_{(initial\ drug)}-C_{(free\ drug)})/C_{(initial\ drug)}]\times 100 \quad (1)$$

where, %EE is the percentage of encapsulation efficiency. $C_{(initial\ drug)}$ is the total concentration of VitE&CoQ10, which was put in the dispersion solution (mg/ml). $C_{(free\ drug)}$ is the total concentration of VitE&CoQ10, which was left in the supernatant (mg/ml).

III. RESULTS AND DISCUSSION

A. Particle Size of Drug-Free SLNs

The particle size of drug-free SLNs from each condition was measured by dynamic light scattering and showed in Fig. 1. Parameters were modified based on the previous studies from condition A to B and to C in order to optimize particle's size within the range of 100-200 nm. Condition A and B showed several peaks, indicating that they were having various sizes of particles. The highest peak of condition A showed the unacceptable range of particle size. Therefore, condition A was modified into condition B by increasing the amount of Tween 80 and homogenization time. Unfortunately, condition B also showed the unacceptable range of particle size (above 200 nm). It can be clearly seen that particles obtained from condition B was 2-3 times larger than that from condition A. This was probably due to particle precipitation. According to the study of Rosdi *et al.*, 2016, it showed that exceeding one particular value can affect stability of colloid particles and prolonging the high shearing can induce a droplet collision [13]. Therefore, larger particles would form in the Condition B. Thus, Condition B was modified to condition C.

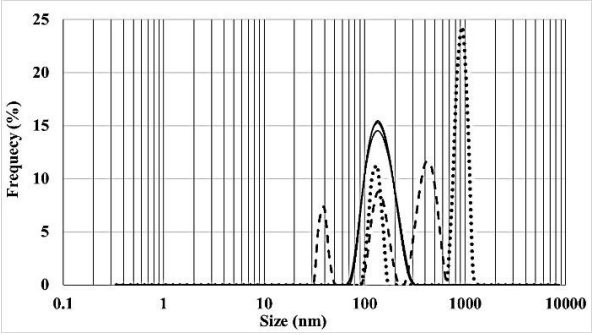

Figure 1. Comparison between drug-free SLNs obtained from condition A (- -) (N=1), condition B (· ·) (N=1) and Condition C (−) (N=3).

Condition C was done in triplicate. Each batch of condition C had only one peak which was in expected size range (100-200 nm). This was probably because the samples were filtered by 0.45 µm filter after synthesis. Therefore, there were less contaminates and surface contamination in samples. Filtration would help to avoid an increase in surface charge level from contaminates, which could increase particle sizes [14]. The size of particles obtained from condition C was about seven times smaller than that from condition B. It was probably because of an increase in homogenization speed from 13,000 rpm to 16,400 rpm and an increase in temperature from 86-88ºC to 90-93ºC. This could be deduced that the homogenization speed and temperature had an effect on particle size [15], [16]. In the study of Mulia *et al.*, 2019 showed that an increase in homogenization speed can reduce particle size [16]. Moreover, rising in temperature could induce an explosive nucleation, which might lead to small particles during reaction [17]. The condition C presented small particle size within an acceptable range (100-200 nm). Therefore, condition C was further investigated in drug loaded (VitE and CoQ10) SLNs.

B. Particle Size of VitE-Loaded SLNs and CoQ10&VitE-Loaded SLNs

The particle sizes of VitE-loaded and CoQ10&VitE-loaded were measured and compared as shown in Fig. 2. They were all in an acceptable size range (100-200 nm). However, the particle size of CoQ10&VitE-loaded SLNs was about 20 nm larger than VitE-loaded SLNs. This can be concluded that addition of CoQ10 could affect nanoparticle size. This also occurred in the study of Uchiyama *et al.*, 2019 [18]. As CoQ10 is highly hydrophilic, it could highly solubilize in VitE. It probably affected recrystallization process therefore particle size was increased.

C. Zeta Potential and Polydispersity Index (PDI)

The Polydispersity Index (PDI) is an indication of size distribution. Low PDI can indicate the narrow size distribution and vice versa. Although, FDA did not mention the criteria of acceptable PDI, the value with higher than 0.7 was not suitable for analysis using the Dynamic Light Scattering (DSL) [19]. Table III. shows that all conditions had PDI which were lower than 0.5. The value of PDI slightly decreased along with an increase in temperature. It might be-cause of that high temperature could help in reducing size distribution of particles and consequently affect PDI [15]. All conditions had negative charge surface (Table III). This was probably the result of nonionic surfactant (Tween80 and Span80). Nonionic surfactant can influence hydroxyl ions (OH-) on the surface of particles [20]. All formulation had zeta potentials with higher -40 mV. In the study of Riddick *et al.*, 1968, it was defined that the particles with zeta potentials ranged from -31 up to -100 are stable [21]. It can be implied that all conditions could provide stable particles. With the addition of CoQ10, the zeta potential negatively in-creased to more than -60 mV, which was similar to the study of Zhou *et al.*, 2013 who prepared lecithin nano-capsules with a load of CoQ10 [22]. This can be deducted that adding CoQ10 can negatively increase charge surface of CoQ10&VitE-loaded SLNs particles.

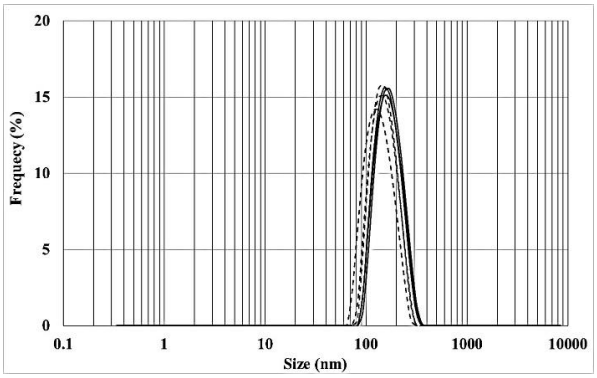

Figure 2. Comparison between particle sizes of drug-loaded SLNs obtained from condition C with VitE-loaded SLN (- -) (N=3) and CoQ10&VitE-loaded SLN (−) (N=3).

TABLE III. PROPERTIES OF SYNTHESIZED SLNS

	Condition A	Condition B	Condition C[b]		
Drug loaded	**Non**	**Non**	**Non**	**VitE**	**VitE& CoQ10**
Mean particle size ± SD (nm)	397.5 ±74.5 [a]	866.9 ±102.6 [a]	134.7 ±39.2	141.1 ±37.4	162.5 ±46.0
PDI± SD	0.471	0.425	0.413 ±0.025	0.412 ±0.090	0.399 ±0.007
ZP± SD (mV)	-45.4	-40.2	-42.86 ±1.38	42.80 ±1.31	-62.20 ±1.35

[a]The mean particle size ± SD was only from the highest peak as shown in Fig. 1.
[b]The mean particle size ± SD, polydispersity index, zeta potential was averaged from three batches.

D. The XRD Data

XRD patterns of drug-free, VitE-loaded, CoQ10&VitE -loaded SLNs were presented in Fig. 3. The highest two peak (at 2θ range of between 21º and 23º) of drug-free SLNs can be attributed to stearic acid, which were similar to the XRD pattern of pure stearic acid in the study of Yan Chen *et al.*, 2017 [23]. While the broad peaks (at 2θ of between 9º and 15º) of the prepared particles reflected

the amorphous structure, this broad peak was not affected by loading VitE and CoQ10 [24]. The amorphousness may probably help in releasing VitE and CoQ10 due to irregular structure. However, the reduction of peak was observed be-tween 21º and 23º (2θ) in VitE-loaded SLNs. This supported that the particles were less crystalline and VitE was encapsulated inside the particles, which was similar to the study of Calvaho *et al.*, 2013 [25]. High intensities of peaks were seen when CoQ10 was introduced to nanoparticles (at 2θ range of between 21º and 23º). When it was compared to the XRD pattern of CoQ10 powder from the study of Piao *et al.*, 2011 [26], a shift to lower 2θ region was noticed. This might be attributed to the interaction between CoQ10 and VitE. Therefore, the intensity of peaks was probably supported by the shifted peaks of CoQ10. Moreover, the comparison with pure CoQ10 also showed a noticeable reduction of peaks at 2θ range of between 27º and 32º (after shifting). This result indicated that CoQ10 was encapsulated inside nanoparticles.

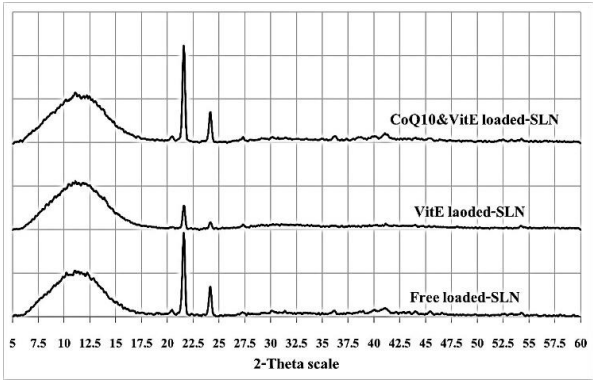

Figure 3. XRD patterns of drug-free, VitE-loaded, CoQ10&VitE-loaded SLN.

E. Percentage of Encapsulation Efficiency (EE%)

In Table IV, encapsulation values of VitE-loaded and CoQ10&VitE-loaded SLNs were close to 100% (98-99%). This might due to the high lipophilicity of both active drug and their high solubility in oil [27]. Due to amorphous structure of SLNs as shown in Fig. 3, providing large space for incorporation with the active drugs. There was a very small decease (less than 1%) in EE% of VitE when CoQ10 was added. Encapsulation values of VitE and CoQ10 were very similar when they were together introduced into particles. This was probably because CoQ10 and VitE had similar lipophilic property.

TABLE IV. ENCAPSULATION EFFICIENCY OF VITE-LOADED SLNS AND COQ10&VITE-LOADED

Condition C	EE% of VitE	EE% of CoQ10
VitE-loaded SLN (N=3)	99.15± 0.47%	-
CoQ10&VitE-loaded SLN (N=3)	98.56 ± 1.55%	98.99 ± 0.88%

IV. CONCLUSION

Hot homogenization technique was used to prepare solid lipid nanoparticles containing VitE and CoQ10. The CoQ10&VitE-loaded SLNs with a diameter range of 100 to 200 nm were successfully synthesized using the modified condition (condition C). The size distributions were in an acceptable range (lower than 0.7) to be analyzed by Dynamic Light Scattering (DSL). The zeta potential value (around -40 to -60 mV) indicated good physical stability of prepared particles in the aqueous solution. The prepared particles have an amorphousness (broad peak of XRD spectra) and high encapsulation efficiency (close to 100%). Loading VitE and CoQ10 did not affect the amorphous structure that would increase released VitE and CoQ10 from the particle structure. Interestingly, loading CoQ10 did not hinder the %EE of VitE. However, particle size and zeta potential were significantly affected by the addition of CoQ10. This might be the result of high hydrophilicity of CoQ10. Therefore, it highly solubilized in VitE affecting recrystallization process.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Sirapatsorn Chaiprateep conducted the research and wrote the paper. Parichart Naruphontjirakul conducted the research and analyzed the data. Parichart Naruphontjirakul was the corresponding author of the paper; all authors had approved the final version.

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