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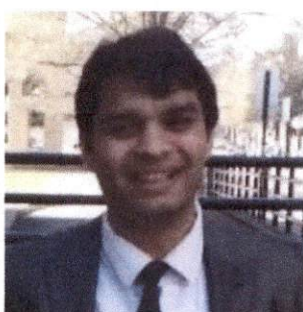
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Skin Penetration of Coenzyme Q10 in Nanostructure Lipid Carriers Using Olive Oil and Cetyl Palmitate

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ABSTRACT

Penetration is an absolute requirement for active ingredient to produce an effect in deep of the skin. First obstacle for active ingredient to penetrate through the skin is stratum corneum. Nanotechnology that has nano size particles, is the answer to make it's penetrate through the skin. In this research the skin penetration of Coenzyme Q10 was loaded in the lipid nanoparticles that is nanostructure lipid carrier (NLC) was compared with it was dissolved in olive oil. The research result known that Coenzyme Q10 was loaded in NLC has deeper penetration ($639.34 \pm 17.69 \mu\text{m}$) in the mice skin than it was dissolved in olive oil as control ($33.00 \pm 1.71 \mu\text{m}$), its just least penetrated into the skin after 6 hours sample application.

Keywords: Cetyl palmitate, Coenzyme Q10, NLC, Olive oil, Skin penetration.

INTRODUCTION

Stratum corneum is the main barrier that obstruct of active ingredient to penetrate through the skin. Nanotechnology, one of most popular delivery system that has nano size particles, came to solve this problem¹. There are many type of nanotechnology such as nanoemulsion, nanostructure lipid carrier (NLC), liposome, noisome, and others. Nanoemulsion is an emulsion of oil in water or water in oil with the droplet size between 50 - 1000 nm. The small droplet of nanoemulsion make it has the big surface area so make it possible as an effective delivery system². In the resent research nanoemulsion was used as delivery system of insoluble materials but the system tends to be unstable after 2 month^{3,4}. So that in these research Coenzyme Q10 was loaded in nanostructure lipid carriers (NLC). Nanostructure lipid carriers (NLC) is the second generation of lipid nanoparticles that contain of solid and liquid lipid and stabilize by surfactant with the particle size 40 - 1000 nm^{5,6}. The mixture of solid and liquid lipid was decreased the formation of crystal in lipid so can increase entrapment efficiency of active ingredient⁷.

Coenzyme Q10 is a lipid soluble material in mitochondria membrane of every cell of the body that has activity as antioxidant. It can prevent of lipid per-oxidation⁷, so can prevent collagen and elastine damage and help to avoid wrinkle of the skin⁸. Coenzyme Q10 has low solubility in water (0.193 $\mu\text{g/ml}$ in water), large molecule weight (863.36 g/mol), and has high lipophilicity (log P>10), so it makes low penetration^{8,9}.

In this research the skin penetration of Coenzyme Q10 that was loaded in the nanostructure lipid carrier (NLC) was compared with it was dissolved in olive oil.

MATERIALS AND METHODS

Research Material

Coenzyme Q10 (Kangcare), olive oil, cetyl palmitate, Tween 80 (Sigma Aldrich), Span 80 (Sigma Aldrich), Ethanol 96% (E.Merck), Acetic acid p.a (E.Merck), sodium acetate (E.Merck) p.a.

Research Instrument

Thermo shaker, Viscometer cone and plate, Transmission Electron Microscope (TEM) JEOL JEM 1400, Delsa™ Nano Submicron Particle Size and Zeta Potential Dynamic Light Scattering, Microscope Olympus FX-100, differential scanning calorimetric (DSC), FTIR Spectrophotometer (Jasco FT-IR 5300), UV Spectrophotometer.

Coenzyme Q10 in NLC Preparation

Solid lipid, liquid lipid, and Coenzyme Q10 melted at 60°C. Besides that, the surfactants also warmed at 60°C. After the solid lipid melted, the mixture of surfaktans was added to the lipid mixture, than was mixed using Ultra-Thurrax High Shear Homogenizer at 5000 rpm of speeds. After that the mixture of co-surfactant and acetate buffer was added slowly, and then the stirred speeds was straised up at 16.000 rpm for 3 minutes. The Coenzyme Q10 NLC formula was presented in Table 1.

Coenzyme Q10 in NLC Characterization

Characterization of Coenzyme Q10 in NLC including the melting point using Differential Scanning Calorimetric (DSC), the spectrogram using FTIR Spectrophotometer (Jasco FT-IR 5300), the pH value using pH-meter, the viscosity using Viscometer cone and plate, the particle morphology by Transmission Electron Microscope (TEM) JEOL JEM 1400, the particle size and polydispersity index by Delsa™ Nano Submicron Particle Size and Zeta Potential Dynamic Light Scattering.

Determination of Entrapment Efficiency

NLC coenzyme Q10 (100.0 mg) was dissolved in ethanol up to 10.0 ml and was centrifuged (2,500 rpm, 15 minutes).

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Table 1: Formula of Coenzyme Q10 in NLC.

Function	Materials	Concentration (%w/w)
Active ingredient	Coenzyme Q10	1
Oil phase / liquid lipid	Olive oil	1,8
Solid lipid	Cetyl palmitate	4,8
Surfactant	Tween 80	18,5
Surfactant	Span 80	2
Co-surfactant	Ethanol 96%	3,5
Water Phase	Acetate buffer pH 4,2 ± 0,2	Ad 50

Table 2: Physical characterization of Coenzyme Q10 in NLC.

Particle Size (nm)	Polydispersity Index	pH value	Entrapment Efficiency (%)
69.73 ± 0.93	0.348 ± 0.050	4.454 ± 0.006	74.33 ± 0.87

And then 1.0 ml of the filtrat was added with ethanol up to 10.0 ml. The mixture was measured by UV spectrophotometer with 3 wavelengths (at 261 nm, 271 nm, and 281 nm). Entrapment efficiency was calculated using the following equations:

$$EE (\%) = \frac{W_{initial\ drug} - W_{free\ drug}}{W_{initial\ drug}} \times 100\%$$

In vivo Skin Penetration

Skin penetration was evaluated in vivo using male *Mus musculus* mice wight has body weight between 30 – 40 gram. Under anaesthetized with ketamine via intraperitoneal, the hair of skin back mice was shaved approximately 2x2cm. After that the sample that was mixed with rhodamine as fluorescent label was spreaded on mice hairless skin. The mice were divided by 3 groups; group 1 was sacrificed by cervick dislocation at 2 hours after sample application, group 2 sacrificed at 4 hours after sample application and group 3 sacrificed at 6 hours after sample application. And than the mice skin was made histological preparation using frozen-cryotome and the

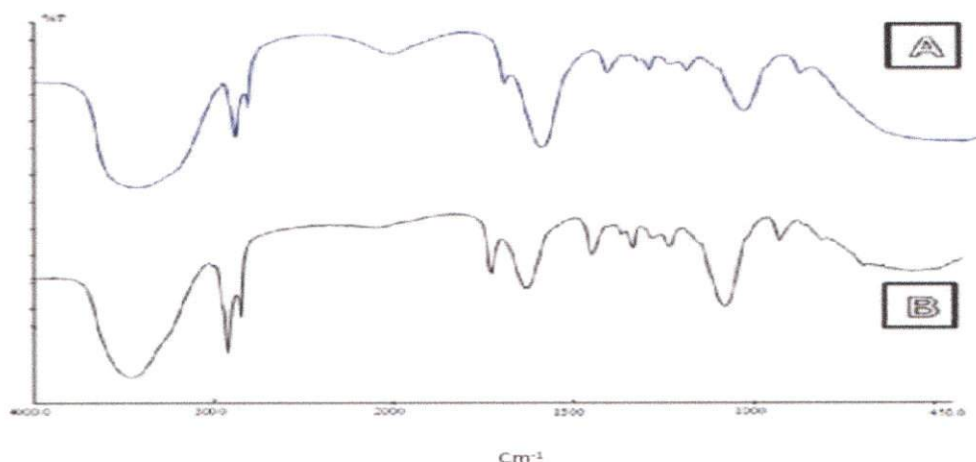


Figure 1: Spectrum FTIR of blank NLC (A) and NLC Coenzyme Q10 (B).

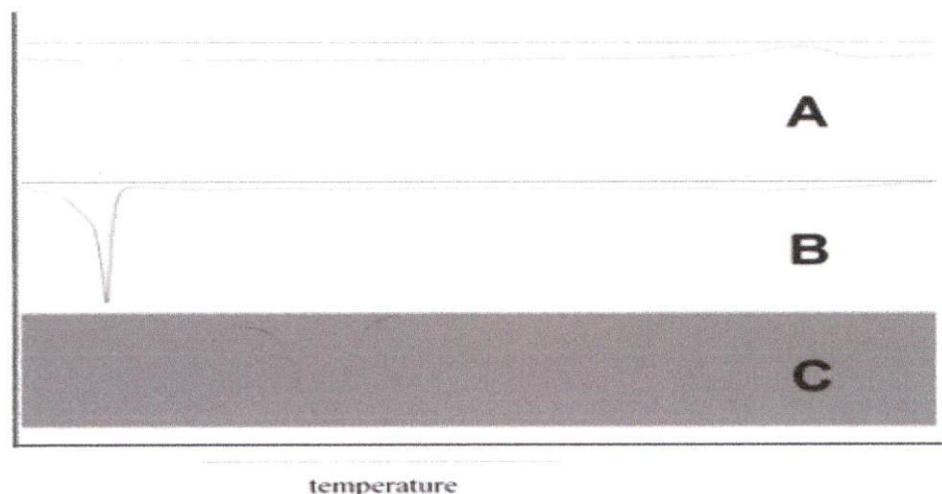


Figure 2: Thermogram of Coenzyme Q10 (A) was 52.73°C; Cetyl Palmitate (B) was 53.11°C, and NLC Coenzyme Q10 (C) was 109.42°C by differential scanning calorimetric (DSC).

Table 3: Skin penetration depth of Coenzyme Q10 in NLC (A), and in olive oil (B) into mice back skin at three different times (2, 4 and 6 hours after sample application) using Olympus FX-100 microscope in 42x zoom.

Formula		Depths of Penetration (µm)			Average ± SD (µm)
		I	II	II	
A	2 Hours	423.86	439.86	421.00	428.24 ± 10.16
	4 Hours	555.70	554.64	553.49	554.61 ± 01.10
	6 Hours	635.89	658.50	623.62	639.34 ± 17.69
B	2 Hours	0	0	0	0
	4 Hours	0	0	0	0
	6 Hours	34.07	33.90	31.03	33.00 ± 1.71

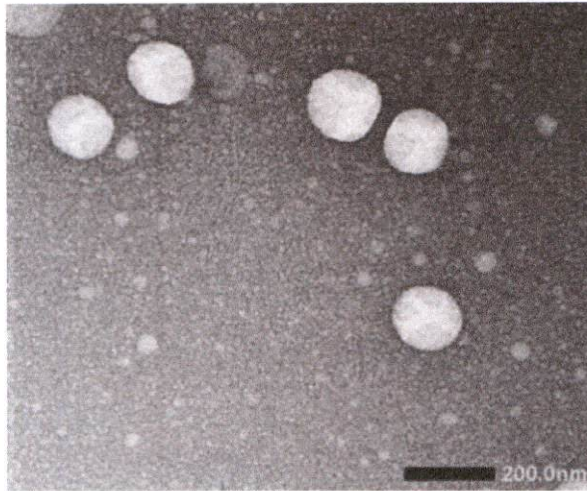


Figure 3: Particle morphology of NLC Coenzyme Q10 by Transmission Electron Microscope (TEM) JEOL JEM 1400.

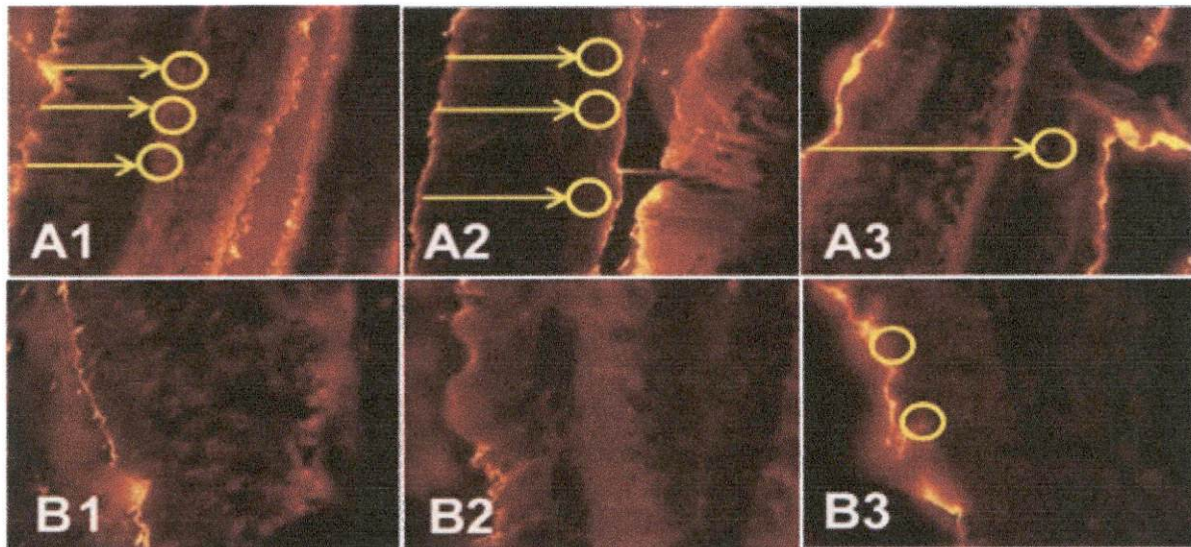


Figure 4: Histological preparation of skin penetration of Coenzyme Q10 in NLC at 2 hours (A1), at 4 hours (A2) at 6 hours (A3) after sample application and in olive oil at 2 hours (B1), at 4 hours (B2) at 6 hours (B3) after sample application was determined by Microscope Olympus FX-100 42x zoom.

depth penetration was measured by fluorescent microscope.

RESULT AND DISCUSSION

The observation of FTIR spectra (Figure 1) as there are no new peak at NLC Coenzyme Q10, it means that there was no chemical interaction between Coenzyme Q10 with constituents of the NLC

From figure 2 was known that NLC coenzyme Q10 (109.42°C) has higher melting point than Coenzyme Q10 (52.73 °C), and cetyl palmitate (53.11 °C). It can be indicating there was a new bond, but it not appeared in FTIR spectrum because it was no covalent bond. It may be a hydrophobic bond which can form from some hydrophobic material¹⁰. To break hydrophobic bond need more energy so it can increase the melting point.

From Table 2, was known NLC Coenzyme Q10 has small particle size (69.73 ± 0.93 nm), small particle can penetrate easily to the skin. Polydispersity Index of NLC Coenzyme Q10 particles size was 0.348 ± 0.050 , it was indicates the NLC Coenzyme Q10 has good homogeneity of particle size distribution. NLC Coenzyme Q10 pH value was 4.454 ± 0.006 it in the skin pH range and has high entrapment efficiency $74.33 \pm 0.87\%$ ($>70\%$). From figure 3, was known that morphology of NLC Coenzyme Q10 particle was spherical.

The result of in vivo skin penetration tests at three different times (2, 4 and 6 Hours) was known that panetration depth of Coenzyme Q10 in NLC were 428.24 ± 10.16 ; 554.61 ± 01.10 and 554.61 ± 17.69 μm , respectively. And Coenzyme Q10 which is dissolved in olive oil up to 4 hours after sample application cannot penetrate the stratum corneum. It just penetrated 6 hours after sample application with only near penetration was 33.00 ± 1.71 μm . It shows that Coenzyme Q10 really needs a delivery system to penetrate to the skin.

CONCLUSION

The research result known that Coenzyme Q10 was loaded in NLC has deeper penetration (639.34 ± 17.69 μm) in the mice skin than it was dissolved in olive oil as control (33.00 ± 1.71 μm), its just least penetrated into the skin after 6 hours sample application.

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