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Original Article

The Performance of Nanostructured Lipid Carrier (NLC) Incorporated Transdermal Patch Coenzym Q10 : Effect of Lipid Ratio as Drug Reservoir and HPMC 606 as Rate Controlling Membrane

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ABSTRACT

Coenzyme Q10 is a strong antioxidant. Coenzyme Q10 can improve cellular dynamics in human body and play an effective role in preventing skin aging, keratinization and DNA oxidative. Coenzyme Q10 NLC system with different lipid ratio 70:30 (cetyl palmitate and alpha tocopheryl acetate) used as drug reservoir dan hydroxypropyl methylcellulose 606 (HPMC 606) as rate controlling membrane. NLC coenzyme Q10 as drug reservoir were prepared using high shear homogenization method. Transdermal patch was using membrane type with HPMC 606 as rate controlling membrane. This research was investigate the effect of concentration of HPMC 10%, 15% and 20% on the characteristics coenzyme Q10 transdermal patch. The prepared transdermal patches were evaluated for thickness, weight variation, moisture content, drug content and drug homogenity which were found to 1.98 ± 0.003 mm, 1.422 ± 0.003 g, 8.441 ± 0.077 %, 96.90± 0.92 and 97.75 ± 1.78 %, respectively. All independent variables had no significant effect on the dependent variables (p-values >0.05) using one way ANOVA, except the weight and moisture content patches.

Key words: Coenzyme Q10, Hydroxypropyl methyl cellulose606, Nanostructured lipid carrier, Characteristic of transdermal patch

1. INTRODUCTION

Coenzyme Q10 has functions of providing and preventing the skin. Reactive oxygen species can be restrained and the peroxidation form of lipid would be slowed and protected by coenzyme Q10. However, coenzyme Q10 has limited due to

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solubility in water is very low (4 ng/ml), causing low bioavailability and permeability of the oral administration[1].

NLCs were developed as improvements over Solid Lipid Nanoparticles (SLNs). SLNs are composed of a solid lipid, whereas the NLC lipid phase contains both solid and liquid lipids. NLC increases the amount of liquid lipid such that the nanoparticles form a non-standard shape and stack, resulting in a non-perfect lattice and forming an amorphous structure. As increasing the liquid lipid can enhance the solubility of active substances, and active substances can help with better encapsulation NLCs lipid material shows more application potential. NLCs augment drug stability and loading capacity, and reduce drug leakage during storage[2]. NLC can penetrate the skin and pass through the barrier of the stratum corneum by intercellular mechanisms, they move according to the osmotic gradient to a deep hydrated layer. Solid lipid in NLC system have been widely used as drug reservoir for the controlled release of active agents [3, 4].

Transdermal patches offer an attractive route of administration for patients who are unable to swallow oral medications and to avoid the need for pain or risks associated with intravenous administration[5]. Patches may also allow for less frequent dosing and improved disadvantages 'drug expulsions' of NLC. Permeation enhancement is primarily due to small size and swelling of stratum corneum by an increase in skin hydration caused by the occlusive film of NLC[2]. Enhancement of transdermal drug permeation of coenzyme Q10 using NLC have been reported, studied that coenzyme Q10 using solid lipid cetyl palmitate and alpha tocopherol acetate ratio 70:30 (% w/w) showed good characteristics, higher % EE, good penetration, controlled release, and stable during 90 days storage[6].

The aim of this study was to formulate coenzyme Q10 NLC system with different lipid ratio 70:30 (cetyl palmitate and alpha tocopheryl acetate) used as drug reservoir and HPMC 606 as rate controlling membrane and evaluate the characteristics coenzyme Q10 patch to enhance skin penetration.

2. MATERIALS AND METHODS

Materials

Coenzyme Q10 was obtained from Xi'an Future Biotechnology, Co., Ltd., cetyl palmitate Cutina®CP (Cognis Chemical Care), alpha tocopherol acetate (Xinchang pharma), propylene glycol (Dow Chemical Pacific), Tween 80 (KAO.,Ltd), HPMC 606 (hydroxy propyl methyl cellulose606) (Wuhan Senwayer Century Chemical Co., Ltd), Cetostearyl alcohol and menthol (Bratachem.,Ltd), Ethanol pro analysis, NaOH (sodium hydroxide) and NaH2PO4 (natrium dihydrogen phosphate) pro analysis (Merck). Aqua demineralized (Bratachem.,Ltd), Backing layer was gifted by Pharmaceutic laboratory of Airlangga University. All other chemicals were of analytical grade.

Preparation Coenzyme Q10 NLC System

Coenzyme Q10- NLC was produced by hot High Pressure Homogenization (HPH). Briefly, after melting the lipid phase (cetyl palmitate : alpha tocopheryl acetate) ratio 70:30, at a temperature 65°C, coenzyme Q10-NLC was added until thoroughly dissolved and the mixture was immediately dispersed in a hot surfactant solution using an Ultra-Turrax High Shear Homogenizer IKA T-25 at 20.000 rpm for 8 minutes. The pre emulsion was further processed by high pressure homogenizer at 65°C[6]. The obtained nanoemulsions were cooled to room temperature to crystallize the lipid and finally formed the active-loaded NLC.

The composition of coenzyme Q10 NLC system with different lipid ratio 70:30 can be seen in table 1. There prepared NLC was evaluated particle size and polydispersity index (PI) which were measured with Delsa Nano^{TM} particle size analyzer. PI ilustrates the variation on the sample. The small value of PI (<0.3) indicates that the sample is monodisperse[7].

Table 1: Composition of coenzyme Q10 NLC system

Formulation	Coenzyme Q10 (%b/b)	Cetyl palmitate (%b/b)	Alpha tocopherol acetate (%b/b)	Tween 80 (%b/b)	Propyleneglycol (%b/b)
Coenzyme Q10 NLC(70:30)	2.4	70	30	20	11

NLC: Nanostructured Lipid Carrier

Preparation of transdermal patches

Coenzyme Q10 NLC system with different lipid ratio 70:30 (cetyl palmitate and alpha tocopherol acetate) used as drug reservoir. HPMC 606 as rate controlling membrane was prepared by dissolving the polymer (10%, 15%, 20%) in aqua demineralized. Menthol was dissolved in ethanol were added into HPMC 606, cetostearyl alcohol was dissolved in ethanol were added into the mixture. The resultant dispersion was placed into circular patches diameter 3.5 cm and placed in desiccator for 24hour. The composition of coenzyme Q10 transdermal patches with can be seen in table 3.

Evaluation of transdermal patches

Thickness [8]

The thickness of patches was measured using Digital Vernier calipers at three different locations, and mean value was calculated.

Weight variation [8]

Weigt variation was studied by individually weighing three randomly selected patches. The determination was performed for each formulation and mean value was calculated.

Moisture content (MC) [8]

Moisture content was measured using weigher and stored patch in the desiccator for 24 hours**.**

Drug content

A prepared patch was added to 200-mL absolute ethanol and stirred vigorously for 2 hours. The contents were filtered,

and Coenzyme Q10 was estimated spectrophotometrically at wavelength of 273 nm.

Drug homogeneity

To calculate drug drug homogenity, pacth equivalent a quarter part were accurately weighed, then was dissolved into ethanol and stirred for 2 hours. This resulting solution was then filtered through Whatmann filter paper then was determined by Spectrophotometric analysis at a wavelength of 273 nm.

Scanning Electron Microscopy (SEM)[9]

Surface morphology and shape of patch was studied using Scanning Electron Microscopy (SEM), Model Carl Zeiss MA10, USA at suitable magnification in room temperature. The microphotographs were observed for morphological characteristics and to confirm morphology of patch.

3. RESULT AND DISCUSSION

Evaluation of the prepared NLC

From the result of prepared NLC was evaluated particle size and polydispersity index which were measured with Delsa Nano^{TM} particle size analyzer which were found to 153.766 ± 1.220 nm and 0.198± 0.014, can be seen in table 2.

Table 2: Evaluation particle size and polydispersity index

Formulation	Replicate	Evaluation	
		Particle size (nm)	Polydispersity index
Coenzyme Q10 NLC (70:30)	1	153.50	0.214
	2	155.10	0.187
	3	152.70	0.194
Mean ± SD		153.766 ± 1.220	0.198 ± 0.014

From the results of particle size, it was found that all prepared coenzyme Q10 NLC have a particle size less than 0.2 µm, and as such are effective for transdermal applications. It was noticed that the small particle size impacted to the occlusivity increased due to surface of skin's contact area increased. Increasing the occlusive impacted to the hydration of stratum corneum which would be impacted to the drug released profile and flux[10, 11].Coenzyme Q10 NLC have a particle size less than 3 µm, and as such are effective for transdermal applications[3]. The Polydispersity Index is dimensionless and scaled such that values smaller than 0.05 are rarely seen other than with highly monodisperse standards. Values greater than 0.7 indicate that the sample has a very broad size distribution and is probably not suitable for the dynamic light scattering (DLS) technique[12].As shown in the table 2, polydispersity index meet the specification (PI < 0.3), so coenzyme Q10 NLC system lipid ratio 70:30 had monodisperse of particle size[7].

Preparation of transdermal patches

Transdermal patch containing Coenzyme Q10 were prepared as per table 3.

Table 3:Compotition of coenzyme Q10 transdermal patches

Formulation code	Coenzyme Q10 NLC (70:30)	HPMC 606 (10%)	HPMC 606 (15%)	HPMC 606 (20%)	Menthol	Cetostearyl alcohol
F1	1.604 mg	1 ml	-	-	1%	350 mg
F2	1.604 mg	-	1 ml	-	1%	350 mg
F3	1.604 mg	-	-	1 ml	1%	350 mg

NLC: Nanostructured Lipid Carrier, HPMC: Hydroxy Propyl Methyl Cellulose

Organoleptic evaluation of transdermal patches

As shown in table 4, all of formulas indicated orange color, round shape, dry and slightly stiff, smooth surface texture, and menthol odor. Patch F1 and F2 have smooth surface better than F3 due to concentration of HPMC 606 as rate controlling membrane has more than other formulas, so there were more particles entrapped.

Table 4: Organoleptic observation of coenzyme Q10 transdermal patches

Formulation code	Shape	Colour	Odor
F1	Round, dry and slightly stiff, smooth surface texture	Orange	Menthol
F2	Round, dry and slightly stiff smooth surface texture	Orange	Menthol
F3	Round, dry and slightly stiff rough surface texture	Orange	Menthol

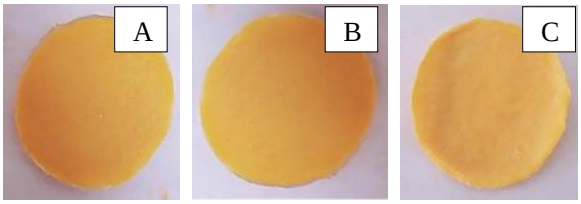


Fig 1: Organoleptic of coenzyme Q10 transdermal patches. F1 (fig. A), F2 (fig. B), and F3 (fig. C).

Evaluation of transdermal patches

Thickness

This test was carried out to ensure the uniformity of thickness of each patch. The thickness was affected by the technique of pouring into the mold. Patch thickness was measured at 3 different points using the calipers. The results of the Coenzyme Q10 patch thickness test can be seen in table 5. The thickness range were (1.92 ± 0.003 to 1.98 ± 0.003 mm). This thickness value showed good characteristics of the patch[13].

The results showed that the thickness F1 <F2 <F3, due to HPMC 606 has swelling so it would expand when dissolved to solvent. The higher the concentration of HPMC 606 increased, the thickness of the patch also increased. Thickness of the patch affected to the drug released and flux. Thickness increased impacted to the duration of release, the time of action more longer. Based on one way ANOVA test (0.068 > 0.05) there was no significant difference in the thickness value of the patch of each formula.

Table 5: Thickness test of coenzyme Q10 transdermal patches

Formulation code	Thickness of patch(mm)			Mean± SD
	1	2	3	
F1	1.90	1.90	1.95	1.92 ± 0.003
F2	1.95	1.95	2.00	1.97 ± 0.003
F3	2.00	2.00	1.95	1.98 ± 0.003

Weight variation

Coenzyme Q10 patch with various concentration of HPMC 606 as the controlling membrane rate can be seen in table 6. If the weight of the patch decreases from the specified weight, then there was likely that one ingredient that has a reduced weight. If one of the reduced ingredients was the active ingredient, it would affect the amount of active ingredient in the penetration testing, therefore the weight was considered.

The test results showed F1 <F2 <F3, due to concentration of HPMC 606 increased, so the weight of the patch also increased. The weight range from 1.235 ± 0.006 to 1.422 ± 0.003 g. Based on the one way ANOVA test there were significant differences (0.00 < 0.05) in the weight parameter.

Table 6: Weight variation test of coenzyme Q10 transdermal patches

Formulation code	Weight of patch (g)			Mean ± SD
	1	2	3	
F1	1.235	1.229	1.241	1.235±0.006
F2	1.315	1.307	1.309	1.310±0.004
F3	1.419	1.424	1.422	1.422±0.003

Moisture content (MC)

The moisture content (MC) range of 8.441 ± 0.077 for F3 to 9.514 ± 0.073% for F1, % MC value decreased as the HPMC 606 polymer increased. Low moisture content could maintain the stability of the preparation. MC requirement for patch preparation was<10%[14]. All formulas were meet the requirements.The moisture content result were shown in table 7.

Based on one way ANOVA test, there weresignificant differences in the moisture content value of each formulas (0.00 < 0.05). Prepared patch was expected low moisture content in order to increase stability and reduced wrinkles in storage for a long time[15].

Table 7: Moisture content test of coenzyme Q10 transdermal patches

Formulation code	Moisture content (%)			Mean ± SD
	1	2	3	
F1	10.040	9.927	9.659	9.875± 0.196
F2	9.430	9.564	9.549	9.514 ± 0.073
F3	8.457	8.357	8.509	8.441 ± 0.077

Drug content and Drug homogeneity

The drug content and drug homogeneity result were shown in table 8 and table 9. This test aim to ensure that the amount of coenzyme Q10 contained in the patch was at the right amount or in the specified range. Measurement of drug content in the patch matrix to obtain coenzyme Q10 levels using a optimun wavelength of 273 nm. The standard curve equation obtained is y = 0.00406x + 0.00797 with the coefficient of determination (R^2) of 0.99954. Measurement of drug content and drug homogeneity was carried out on the optimal formula with replication 3 times. The results of drug content ranged from 96.90% to 97.21% while drug homogeneity ranged from 97.18% to 98.03%.The calculation of patch homogeneity shows the % CV value is less than 2%, so it can be said that coenzyme Q10 is spread evenly on patch preparation[15].Based on the results of the one way ANOVA test (0.889> 0.05 and 0.779 > 0.05) there were no significant differences of drug content and drug homogeneity of each formula.

Table 8: Drug content of coenzyme Q10 transdermal patches (data shows mean [n=3]±SD)

Evaluation	Formulations code		
	F1	F2	F3
Drug content (%)	97.21±1.90	97.20±0.53	96.90±0.92
CV (%)	1.95	0.55	0.95

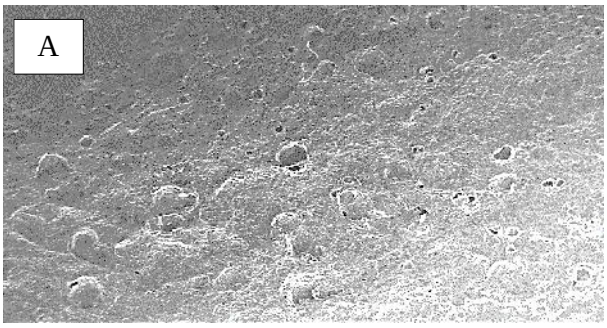
Table 9: Drug homogeneity of coenzyme Q10 transdermal patches (data shows mean [n=3]±SD)

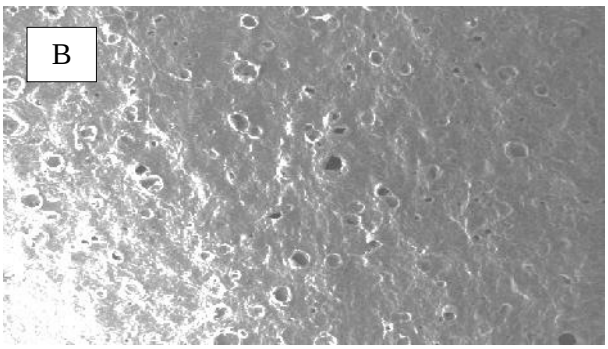
Evaluation	Formulations code		
	F1	F2	F3
Drug homogeneity (%)	98.03±0.50	97.18±1.78	97.75±1.78
CV (%)	0.51	1.83	1.82

Scanning Electron Microscopy (SEM)

SEM photographs of the matrix patch was taken, surface morphology and drug distribution pattern of the transdermal patches sould be studied from SEM model Carl Zeiss MA10, USA with 56x magnification (Fig 2).

Scanning Electron Microscopy (SEM) images showed the upper surface of the patches in F1, F2 and F3. The greater of HPMC 606 concentration used, the greater the pore formed in the prepared patch, due to the swelling of HPMC 606 during Coenzyme Q10 patch preparation[16]. The pores on the patch are useful in the drug released from the matrix, the large pores allow the drug escape more easily. Penetration enhancement is an improving system that leads to the increase in the count of drugs through skin because of possessing different features like natural origin, favorable penetration enhancement and partitioning action in the skin by the oils[17].





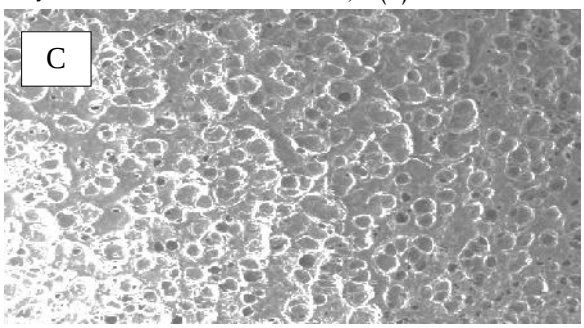


Fig 2: Photograph of Coenzyme Q10 patches surface with various levels of HPMC 606 using SEM with 56x magnification. F1 (fig. A), F2 (fig. B), dan F3 (fig. C).

4. CONCLUSION

Transdermal patch coenzyme Q10 preparations using NLC coenzyme Q10 as a drug reservoir and HPMC 606 (10%, 15%, and 20%) as the rate controlling membrane, all provide good characteristics. Based on the results of the one way ANOVA test(p-values > 0.05)there were no significant differences of evaluated for thickness, drug content and drug homogenity, except on the weight and moisture content of patch gives significant results.

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