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ORIGINAL ARTICLE

Formulation and evaluation of ubidecarenone transdermal delivery systems

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Abstract

Purpose: This study is aimed to examine the feasibility of developing ubidecarenone (coenzyme Q_{10}, CoQ_{10}) transdermal delivery systems (TDS). *Method*: *In vitro* permeation study using solution formulation and pressure-sensitive adhesive (PSA) TDS and *in vivo* pharmacokinetic study were conducted. *Results*: When using solution formulations, isopropyl alcohol (103.39 ± 1.61), ethyl alcohol (81.55 ± 7.27), and the mixture of diethylene glycol monoethyl ether (DGME)/propylene glycol monolaurate (PGML) at the ratio of 60:40 (91.08 ± 26.07) showed high flux (μg/cm^2/hour). The addition of fatty acids to DGME-PGML failed to show profound enhancing effects; only unsaturated fatty acids such as linoleic acid and oleic acid at 3% and caprylic acid at 3% and 10% slightly increased permeation flux. CoQ_{10} from the acrylic PSA TDS showed biphasic permeation profile that was permeated very rapidly up to the first 12 hours, and after that, permeation rate became slower. Overall, 6% fatty acids showed high permeation rates and the highest maximum flux of 9.3 μg/cm^2/hour was obtained with a formulation containing 6% lauric acid in DGME-PGML (60:40). The *in vivo* pharmacokinetic study using TDS with 6% fatty acids in DGME-PGML (60:40) showed that the absorption of CoQ_{10} decreased in the following order: TDS containing linoleic acid > oral dosage form > TDS with oleic acid > TDS with lauric acid > TDS with caprylic acid > TDS with capric acid. TDS containing oleic acid showed preferable pharmacokinetic profile with respect to lower C_{max}, comparable AUC, and prolonged $t_{1/2}$ and T_{max} compared to oral administration of drug. *Conclusions*: For effective transdermal delivery system of CoQ_{10}, 6% linoleic acid or oleic acid in DGME-PGML (60:40) could be employed.

Key words: *Percutaneous absorption; pharmacokinetic profile; pressure-sensitive adhesives; ubidecarenone; vehicles*

Introduction

Ubidecarenone (coenzyme Q_{10}, CoQ_{10}) is a natural compound that exists in the inner membrane of mitochondria. CoQ_{10} works as a cofactor in the mitochondrial electron transport chain and is, therefore, essential for the production of ATP[1]. Tissues with high-energy requirements or metabolic activity such as the heart, kidney, liver, and muscle contain relatively high concentrations of CoQ_{10}[2].

CoQ_{10} in its reduced form as the hydroquinone (ubiquinol) is a potent lipophilic antioxidant and is capable of recycling and regenerating other antioxidants such as tocopherol and ascorbate[1,3]. Attention has been paid to the effect of CoQ_{10} supplementation on cardiovascular, neurodegenerative, and neuromuscular disease[4–7]. CoQ_{10}'s therapeutic benefit is attributed to its antioxidant properties as well as its enhancement of cellular bioenergy capacity[6]. CoQ_{10} is available as a dietary supplement in strengths ranging from 10 to 100 mg. In cardiovascular diseased patients, CoQ_{10} dosages are generally 100–200 mg a day[8], whereas a dosage of up to 1200 mg a day was employed in the Parkinson's disease trial[9].

CoQ_{10} is practically insoluble in aqueous solutions because of its lipophilic 10-carbon chain[10]. Because of its hydrophobicity and large molecular weight of 863.36, the oral absorption of CoQ_{10} is very slow and limited. It

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has been reported that the absorption of CoQ_{10} is dependent on the nature of the formulation such as solubilized formulations and the ingestion of fatty meal[11–13]. To improve bioavailability and reduce the variability of absorption among products or individuals, an alternative route of administration is required; transdermal delivery systems (TDS) could be such a choice. Although CoQ_{10} has been studied for the topical application in cosmetic field[14,15], only few studies have been performed for its systemic effect. The objective of this article was, thus, to examine the feasibility of developing CoQ_{10} TDS by performing the in vitro permeation study and the in vivo pharmacokinetic experiment.

Materials and methods

Animals

Male hairless mice aged 6–8 weeks and male Sprague Dawley (SD) rats weighing 280–320 g were purchased from Orient Bio Inc. (Gapyeong, Kyunggido, Korea).

Materials

CoQ_{10} and CoQ_9 (internal standard, IS) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Propylene glycol monolaurate (PGML), propylene glycol laurate (PGL), propylene glycol monocaprylate (PGMC), oleoyl macrogol-6 glycerides (LBF 1944), polyethylene glycol-8 glyceryl linoleate (LBF 2609), diethylene glycol monoethyl ether (DGME) (Gattefossé, Gennevilliers Cedex, France), polyethylene glycol 400 (PEG 400), propylene glycol (PG), ethyl alcohol (EA), iso-propyl alcohol (IPA), iso-propyl myristate (IPM), *n*-octanol, chloroform, sodium acetate, and glacial acetic acid (Duksan Pure Chem. Co. Ltd., Ansan, Gyunggido, Korea) were used. Methanol and *n*-hexane were of high-performance liquid chromatography HPLC grade and other reagents used were of analytical grade. Acrylic pressure-sensitive adhesive (PSA) solution Duro-Tak® 87-2510 (copolymer: acrylate, functional group: –OH, 40.5% solution of noncrosslinking acrylic copolymer, 4500 cps, solubility parameter 16) was obtained from National Starch and Chemical Company (Bridgewater, NJ, USA).

Analysis

The HPLC system consisted of a pump (Waters 510; Waters, Milford, MA, USA) with an electrochemical detector (ECD, ESA CouloChem III detector; ESA Biosciences, Chelmsford, MA, USA). The system consisted of two cells (pre- and postcolumn) and an analytical cell. One carbon filter was placed before the precolumn cell and another between the analytical column and the postcolumn cell. Both pre- and postcolumn cells were coulometric electrodes (ESA Model 5020; ESA Biosciences). A schematic diagram of this HPLC-ECD system is well described by Tang et al.[16] The analytical cell (ESA Model 5010; ESA Biosciences) consisted of a series of two coulometric electrodes and was connected in series to the postcolumn cell; the first electrode was for reduction of CoQ_{10} and the second electrode was for the detection of $CoQ_{10}H_2$.

The analytical column was a reversed-phase Microsorb-MV 100-5 C18 column (5 μm, 4.6 mm × 15 cm, Varian, Palo Alto, CA, USA) equipped with radial-pak insert column (C18; Waters). CoQ_{10} was eluted with a mixture of sodium acetate trihydrate:glacial acetic acid: IPA:methanol:*n*-hexane (6.8:15:15:695:275, w/v/v/v/v) at a flow rate of 1.0 mL/min. The two analytical cell potentials were set at –0.75 and +0.45 V, respectively.

Solubility determination

An excess amount of CoQ_{10} was added to the various pure solvents and shaken at 37°C for 48 hours. The solutions were then centrifuged at 7500 rpm for 5 minutes, and the supernatant was assayed by HPLC after appropriate dilution.

Partition coefficient determination

Lipophilic (*n*-octanol, IPM, chloroform) and hydrophilic (water) phases were saturated with each other before the experiment. CoQ_{10} solution (50 μg/mL) was prepared with lipophilic phase saturated with hydrophilic phase. One milliliter of this solution was then transferred to 10-mL centrifuge tube containing 1-mL of hydrophilic phase saturated with lipophilic phase. The tube was vortexed for 10 minutes and centrifuged at 3000 × *g* for 5 minutes, and the drug concentrations in both phases were determined by HPLC.

Preparation of CoQ_{10} transdermal delivery systems

Forty milligram of CoQ_{10} was dissolved in 2 mL of DGME–PGML (60:40) with fatty acids and then mixed with 5.3 g of acrylic adhesive solution, Duro-Tak® 87-2510. The fatty acids used for in vitro study were 3%, 6%, and 10% caprylic acid, capric acid, lauric acid, oleic acid, and linoleic acid. CoQ_{10} PSA TDS were prepared by casting the above solutions on a polyester release liner coated with silicone (Gelroflex ALU-PET 100 μ-2S DR; 3M, St. Paul, MN, USA) using a casting knife. The area of the cast solutions was 10 cm × 20 cm per 7.3 g solution. They were set at room temperature for 10 minutes to evaporate the solvents, and then dried for 20 minutes in an oven set at 37°C. The dried film was transferred onto a backing film (Scotchpak 1109; 3M).

Procedure for skin permeation from solution formulations and PSA transdermal delivery systems

After killing with ether, the dorsal skin of each hairless mouse was excised. One milliliter of CoQ_{10} solution formulation (5 mg/mL) or PSA TDS of an appropriate size was applied to the epidermal side of the skin and mounted on a Franz Cell permeation system (Diffusion Cell Drive System, Labfine, Anyang, Kyunggido, Korea). The dermal side was in contact with the receptor compartment. The surface area of the receiver cell opening was 1.766 cm^2, and the cell volume was 12 mL. The theoretical amount of drug loaded to the epidermal side from PSA TDS was about 176.6 μg. Receptor compartment cells were filled with IPA to maintain the sink condition, and the media were stirred by a Teflon-coated magnetic bar to keep them well mixed. The permeation media were maintained at 37°C. At predetermined time intervals, 1 mL of receptor solutions was withdrawn, and the amount of CoQ_{10} permeated was determined by HPLC.

Animal studies

SD rats were divided into seven groups, each group comprised of six rats. Group 1 was administered oral dosage form while groups 2–7 were on TDS 1, 2, 3, 4, 5, and 6, respectively. The oral dose consisted of CoQ_{10} (5 mg), microcrystalline cellulose (110 mg), hydroxypropyl cellulose (5 mg), and corn starch (q.s.). The compositions of TDS 1, 2, 3, 4, 5, and 6 were 6% caprylic acid, capric acid, lauric acid, oleic acid, and linoleic acid in DGME–PGML (60:40) and neat DGME–PGML (60:40), respectively. The animals were fasted overnight and the fasting continued for the first 6 hours of the experiment, but they were allowed water ad libitum. For the administration of TDS, the hair of the abdomen was shaved carefully so that the stratum corneum remained intact. The size of formulated CoQ_{10} TDS applied to the shaved site of the rat was 4 cm × 5 cm, which contains a theoretical CoQ_{10} dose of 5 mg. Blood samples were collected by periorbital puncture at predetermined time interval and analyzed by HPLC. The pharmacokinetic studies of CoQ_{10} TDS were carried out according to the *Principles for Biomedical Research Involving Animals* developed by the Council for International Organizations of Medical Sciences.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed using WinNonlin (Version 1.1; Scientific Consulting Inc., Cary, NC, USA). The drug concentration–time curves were fitted to a one-compartment model with a first-order absorption. The area under the plasma concentration–time profile (AUC) was calculated using the log-linear trapezoidal method.

Statistical analysis

All the values are expressed as the mean ± SD. The pharmacokinetic variables of all dosage forms were compared by Kruskal-Wallis, which was followed by a posterior test with the use of the Bonferroni correction. A *P*-value of less than 0.05 was considered significant.

Results and discussion

As shown in Table 1, CoQ_{10} had higher solubilities in ester-type vehicles compared to those in alcohol-type vehicles; the highest solubility of 26.41 mg/mL was achieved with PGML among vehicles used in this study. To formulate CoQ_{10} TDS, vehicles that have a solubility of at least 10 mg/mL are required considering that the daily dose is 10–100 mg. Therefore, ester-type vehicle was considered as a good candidate vehicle for CoQ_{10} TDS formulations.

The partition coefficient (P_c) is defined as the ratio of the concentrations of a solute in two immiscible mutually saturated phases in contact. It would give insight into the ability of the drugs to pass through the cellular membranes of stratum corneum[17], which is known to have an excellent barrier property against skin penetration. The P_c between oil phase (IPM, *n*-octanol, and chloroform) and water were 26.74 ± 7.29, 34.10 ± 4.91, and 174.4 ± 13.60, respectively. The log P_c with *n*-octanol, which is known to have a similar polarity to that of the lipids of skin[18], has been used to predict skin permeability coefficient of a drug, along with molecular weight[19]. Based on the algorithm proposed by Flynn[19], CoQ_{10} was not a good candidate for TDS because of its high molecular weight and moderate P_c with *n*-octanol.

Table 1. Permeation parameters of CoQ_{10} from solution formulations using excised hairless mouse skins.

Vehicles	J_s (μg/cm^2/hour)	T_L (hours)	Solubility (mg/mL)
LBF 1944	29.23 ± 11.60	4.96 ± 0.51	22.52 ± 2.76
LBF 2609	29.10 ± 8.01	14.39 ± 3.81	16.11 ± 3.12
IPM	44.44 ± 13.02	7.13 ± 0.83	22.98 ± 1.98
PGL	23.60 ± 6.98	9.56 ± 0.54	18.32 ± 2.32
PGMC	32.78 ± 3.67	9.58 ± 0.32	19.50 ± 1.98
PGML	24.66 ± 3.78	10.42 ± 0.38	26.41 ± 1.12
DGME	77.07 ± 1.64	4.93 ± 0.70	2.15 ± 0.76
EA	81.55 ± 7.27	6.27 ± 0.91	0.28 ± 0.10
IPA	103.39 ± 1.61	4.35 ± 0.28	2.04 ± 1.03
PG	10.86 ± 4.54	15.48 ± 8.94	0.001 ± 0.0002
PEG 400	24.93 ± 3.92	18.53 ± 1.04	0.15 ± 0.03

Data were expressed as the mean ± SD (n = 3). LBF 1944, oleoyl macrogol-6 glycerides; LBF 2609, polyethylene glycol-8 glyceryl linoleate; IPM, iso-propyl myristate; PGL, propylene glycol laurate; PGMC, propylene glycol monocaprylate; PGML, propylene glycol monolaurate; DGME, diethylene glycol monoethyl ether; EA, ethyl alcohol; IPA, iso-propyl alcohol; PG, propylene glycol; PEG 400, polyethylene glycol 400.

Even though CoQ_{10} itself is not an excellent agent for developing a TDS, transdermal delivery could be enhanced by using appropriate vehicles and penetration enhancers. Table 1 shows the permeation flux and lag time from solution formulations. Among pure vehicles, alcohol- and ether-type vehicles such as IPA and EA, and DGME, respectively, showed high flux compared to ester-type vehicles. This was thought to be the increased thermodynamic activity due to the low solubility, where thermodynamic activity is approximately proportional to the ratio of concentration to the solubility of the drug in the vehicle. The increased thermodynamic activity is known to promote the interfacial drug transfer into the stratum corneum[20].

Figure 1 shows the permeation flux of CoQ_{10} from the cosolvents containing DGME and either PGMC or PGML. The addition of DGME to PGMC increased permeation flux although higher permeation rate was not achieved with the cosolvents compared to DGME only. On the contrary, in case of PGML, the addition of DGME at concentration of 60% revealed the highest permeation flux (91.08 ± 26.97 μg/cm^2/hour). The addition of DGME to PGMC or PGML enhanced permeation rate compared to PGMC or PGML only regardless of DGME concentration. It has been suggested that DGME itself may not have a profound effect on the structural integrity of the skin and that it just eases the partition of a compound by increasing the solubility of the compound in the skin[20]. Our previous studies have reported that the addition of DGME to the ester-type vehicles such as PGL, PGMC, and PGML considerably increased the permeation flux of many drugs including melatonin, ondansetron, ketorolac, and tenoxicam[21–24].

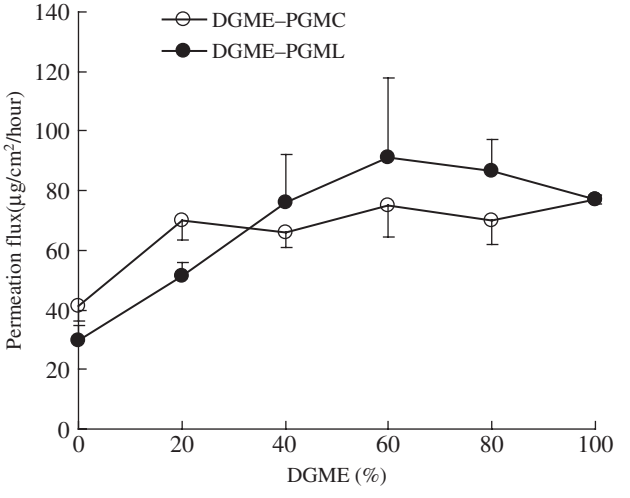

Figure 1. Effect of diethylene glycol monoethyl ether at various concentrations in propylene glycol monolaurate or propylene glycol monocaprylate on the permeation of CoQ_{10} from solution formulations (mean ± SD, $n = 3$).

We investigated the effects of five fatty acids on the CoQ_{10} permeation when they are added to DGME–PGML (60:40) cosolvents; three were saturated fatty acids—C_8 (caprylic acid), C_{10} (capric acid), and C_{12} (lauric acid)—and the other two were unsaturated fatty acids—C_{18} with one double bond (oleic acid) and C_{18} with two double bonds (linoleic acid). Figure 2 shows the steady-state permeation flux and lag time obtained from CoQ_{10} solutions containing DGME–PGML (60:40) with various fatty acids for 36 hours. The addition of fatty acids to DGME–PGML (60:40) failed to show profound enhancing effects compared to DGME–PGML (91.08 ± 26.97 μg/cm^2/hour). Linoleic acid and oleic acid at 3%, and caprylic acid at 3% and 10% slightly increased permeation flux, which were 115.9 ± 22.13, 109.8 ± 19.42, 108.7 ± 5.95, and 100.2 ± 27.71 μg/cm^2/hour, respectively.

The lag time of CoQ_{10} from pure solvents was very long, which ranged between 4.35 and 18.53 hours as tabulated in Table 1. The lag time was 9.95–15.70 hours from cosolvents containing DGME–PGMC or DGME–PGML. The addition of fatty acids to cosolvents shortened the lag time to 2.90–6.34 hours as depicted in Figure 2B, indicating that skin diffusivity increased by barrier disruption with the addition of fatty acids. Many studies reported that the penetration enhancement mechanism by fatty acids appear to involve disruption

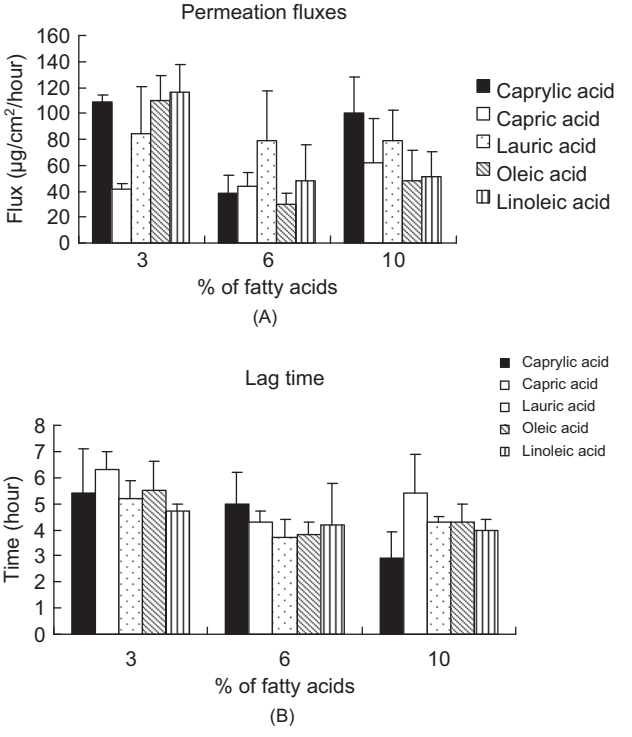

Figure 2. The permeation flux (A) and lag time (B) of CoQ_{10} from solution formulations containing various concentrations of fatty acids in propylene glycol (mean ± SD, $n = 3$).

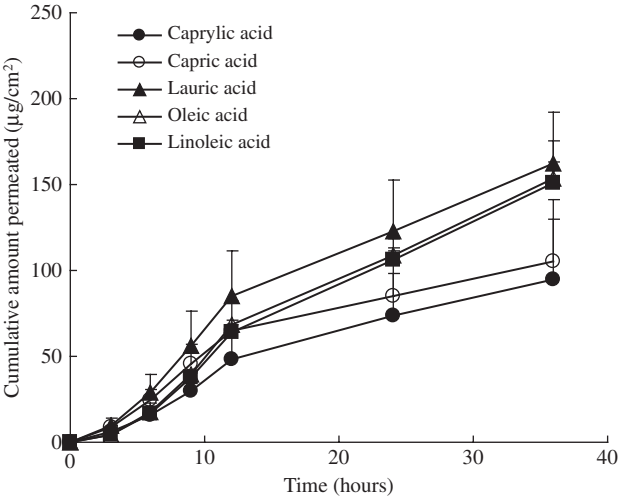

Figure 3. Effect of fatty acids at various concentrations in diethylene glycol monoethyl ether–propylene glycol monolaurate (60:40) on the permeation of CoQ_{10} from formulated transdermal delivery systems (mean ± SD, $n = 3$).

of the densely packed lipids that fill the extracellular spaces of the stratum corneum[25–27].

As shown in Figure 3, CoQ_{10} from the PSA TDS containing 6% fatty acids in DGME–PGML (60:40) showed biphasic permeation profile that was permeated very rapidly up to the first 12 hours, and after that, permeation rate became slower. The maximum permeation flux for the first 12 hours and steady-state flux after 12 hours are described in Table 2. One of the explanations of the biphasic phenomenon was possibly because dissolution was rate-limiting for permeation; the concentration of solubilized drug in PSA TDS decreased in the later phase, and the dissolution rate of undissolved drug particles was slower than the permeation rate of the drug, resulting in the decrease in the driving force. The decrease in permeation rate with time was also attributable to the rapid reduction in driving force, by rapid drop in CoQ_{10} concentration in the TDS. The initial rapid permeation was attributable to the short lag time.

The effects of fatty acid concentrations on the permeation of CoQ_{10} from PSA TDS were quite different from solution formulations; overall, 6% fatty acids showed high permeation rates from PSA TDS while permeation flux was very low in solution formulations at that concentration. The difference was possibly thought to be because of the solubility or diffusivity change by mixing with PSA.

Based on the in vitro results, the pharmacokinetic study was conducted using PSA TDS in the presence and absence of 6% fatty acids in DGME–PGML (60:40). Table 3 shows the pharmacokinetic profiles of CoQ_{10} oral dosage form and the formulated TDS. No quantitable absorption occurred with the formulation of neat DGME–PGML (60:40). It was found that there were statistically significant differences in all the evaluated parameters ($P < 0.0001$).

Table 2. Permeation fluxes of CoQ_{10} from pressure-sensitive adhesive transdermal delivery systems containing various concentrations of fatty acids in diethylene glycol monoethyl ether–propylene glycol monolaurate (60:40) using excised hairless mouse skins.

Fatty acid concentration (%)	$J_{s(maximum)}$ (μg/cm²/hour)	$J_{s(steady\ state)}$ (μg/cm²/hour)
Caprylic acid		
3	5.77 ± 0.86	2.86 ± 0.51
6	5.37 ± 1.49	1.93 ± 0.82
10	4.63 ± 2.16	2.07 ± 0.79
Capric acid		
3	3.21 ± 0.47	0.91 ± 0.24
6	6.60 ± 2.02	1.71 ± 0.73
10	3.22 ± 1.02	1.43 ± 0.28
Lauric acid		
3	0.41 ± 0.15	0.41 ± 0.15
6	9.31 ± 2.66	3.22 ± 0.16
10	6.83 ± 3.19	2.41 ± 0.58
Oleic acid		
3	6.48 ± 2.73	2.39 ± 0.14
6	8.47 ± 0.37	3.54 ± 0.80
10	6.97 ± 0.86	2.48 ± 0.77
Linoleic acid		
3	8.48 ± 0.30	3.48 ± 0.46
6	7.91 ± 0.53	3.63 ± 0.32
10	9.20 ± 1.27	2.68 ± 0.35

Data were expressed as the mean ± SD ($n = 3$).

Even though there was no statistically significant difference, TDS containing 6% linoleic acid in DGME–PGML (60:40) showed higher bioavailability, compared to oral dosage form (Figure 4 and Table 3). Based on AUC, the formulation could be ranked in the order of TDS containing linoleic acid > oral dosage form > TDS with oleic acid > TDS with lauric acid > TDS with caprylic acid > TDS with capric acid (Table 3). This result was consistent with steady-state permeation flux across the hairless mouse skin using PSA TDS as shown in Table 2. In our previous study of ketorolac TDS[23], a linear relationship between in vitro steady-state flux and in vivo absorption was found. Therefore, it was speculated that the in vivo absorption of some drugs could be predicted from the in vitro steady-state flux from PSA TDS. All the formulated TDS prolonged the $t_{1/2}$, compared to oral dosage form, significantly. TDS containing oleic acid showed preferable pharmacokinetic profile with respect to lower C_{max}, comparable AUC, and prolonged $t_{1/2}$ and T_{max} compared to oral administration of drug.

This study showed the feasibility of developing CoQ_{10} TDS. Formulations containing 6% linoleic acid or oleic acid in 2 mL DGME–PGML (60:40) mixed with 5.3 g Duro-Tak® 87-2510 could be a good candidate for developing a new CoQ_{10} TDS that achieves bioavilability comparable to oral delivery but with prolonged effect.

Table 3. Pharmacokinetic parameters of CoQ_{10} oral dosage form and formulated transdermal delivery systems containing 6% fatty acids in DGME–PGML (60:40) after administration to rats.

	Oral	TDS 1	TDS 2	TDS 3	TDS 4	TDS 5
C_{max} (ng/mL)	40.5 ± 7.7	21.3 ± 3.9[a*]	9.8 ± 2.4[a*,b]	21.6 ± 5.4[a,c]	22.5 ± 4.3[a,c]	36.5 ± 8.6[b,c*,d,e]
T_{max} (hours)	48.0	48.0	48.0	52.0	72.0[a*,b*,c*,d*]	48.0[e*]
AUC (μg·hour/mL)	3.2 ± 0.5	1.8 ± 0.3[a*]	0.9 ± 0.2[a*]	2.2 ± 0.5[a,c]	2.8 ± 0.3[b,c*]	3.6 ± 0.5[b*,c*,d*]
$t_{1/2}$ (hours)	26.5 ± 1.8	29.5 ± 1.7[a*]	28.5 ± 1.6[a,b]	28.9 ± 2.5[a*]	39.1 ± 3.9[a*,b*,c*,d*]	34.8 ± 7.4[a*,b,c*,d*]
Cl/F/kg (L/hour)	1.6 ± 0.3	2.8 ± 0.5[a*]	5.7 ± 1.5[a*]	2.3 ± 0.8[a,c]	1.8 ± 0.5[b,c*]	1.4 ± 0.2[b*,c*,d*]
Vz/F/kg (L)	62.3 ± 10.3	120.8 ± 22.7[a*]	231.9 ± 63.3[a*]	96.8 ± 19.8[a,c]	99.9 ± 14.9[a,c]	72.6 ± 22.5[b,c*]

Data were expressed as the mean ± SD (n = 6). TDS 1, caprylic acid; TDS 2, capric acid; TDS 3, lauric acid; TDS 4, oleic acid; TDS 5, linoleic acid. [a]$P < 0.05$ versus oral. [b]$P < 0.05$ versus TDS 1. [c]$P < 0.05$ versus TDS 2. [d]$P < 0.05$ versus TDS 3. [e]$P < 0.05$ versus TDS 4. [*]$P < 0.0001$.

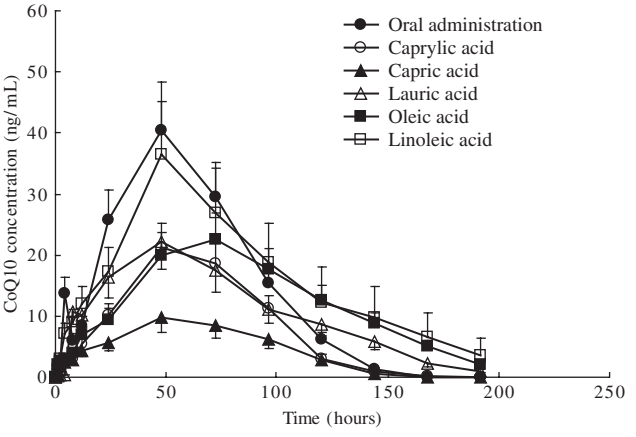

Figure 4. CoQ_{10} plasma concentrations after administration by oral and transdermal delivery systems containing 6% fatty acids in DGME–PGML (60:40) (mean ± SD, n = 3).

Declaration of interest: The authors report no conflicts of interest.

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