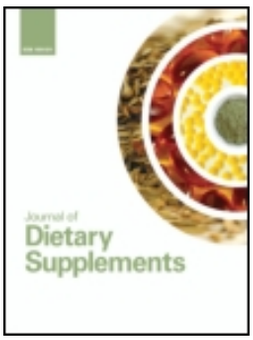

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A Randomized, Double-Blind, Crossover Study on the Pharmacokinetics of a Novel Formulation of CoQ_{10} With Pyridoxal 5′-Phosphate and Phosphatidyl Choline

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ABSTRACT. The pharmacokinetics of a single 30-mg dose of a novel enteric-coated coenzyme Q10 (CoQ_{10}) formulation with pyridoxal 5′-phosphate and phosphatidyl choline (CoQ_{10}-P5P-PC) was investigated against two comparators CoQ_{10} (NPN 02176955) and CoQ_{10} (DIN 02231736) in 21 healthy volunteers, with screening CoQ_{10} levels of 0.8 ± 0.2 mg/L. A randomized, double-blind, crossover study was designed with a washout period of 2 weeks between each formulation and blood sampled at 2, 4, 5, 6, 8, 12, 24, 48 and 72 hr postdose. Significantly, higher plasma concentrations were demonstrated for the CoQ_{10} (NPN 02176955) formulation at 6 and 8 hr postdose ($p = .010$ and $p = .042$, respectively). There were no significant differences between formulations with respect to the area under the curve, $AUC_{(0–72\ hr)}$, or the maximum plasma concentration (C_{max}). Total CoQ_{10} (T_{max}) reached maximum plasma concentrations at 6.4 ± 2.5 hr after supplementation with CoQ_{10} (NPN 02176955), 8.0 ± 9.8 hr with CoQ_{10}-P5P-PC, and 9.5 ± 9.3 hr with CoQ_{10} (DIN 02231736). The estimated elimination half-life ($t_{1/2}$) was 92.3 hr after a single oral dose of CoQ_{10}-P5P-PC, 38.2 hr with CoQ_{10} (NPN 02176955), and 80.7 hr with CoQ_{10} (DIN 02231736). The results suggest that CoQ_{10} is available for a longer time in subjects' administered with CoQ_{10}-P5P-PC in comparison with the other two formulations studied. There were no significant differences in adverse events, by severity, causality, or organ system. The CoQ_{10}-P5P-PC formulation was found to be superior in the $t_{1/2}$, and it may be suggested that fewer doses are required to maintain healthy circulatory CoQ_{10} levels.

KEYWORDS. CoQ_{10}, pyridoxal 5′-phosphate, phosphatidyl choline, half-life, pharmacokinetics

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INTRODUCTION

Clinical and experimental studies indicate that coenzyme Q10 (CoQ_{10}) deficiency may be associated with hypertension, hyperlipidemia, coronary artery disease, and congestive heart failure (Greenberg & Frishman, 1990; Wajda, Zirkel, & Schaffer, 2007). Evidence from human trials suggests CoQ_{10} supplementation to be of benefit for individuals taking β-blockers and statins, both of which have been found to reduce plasma CoQ_{10} levels by up to 40% (Ghirlanda et al., 1993; Greenberg & Frishman, 1990; Kishi, Watanabe, & Folkers, 1977; Mortensen, Leth, Agner, & Rohde, 1997). Supplementation with CoQ_{10} has also been investigated in individuals with neurological disorders, cancer, diabetes, migraine, asthma, and other clinical conditions (Miles et al., 2006).

CoQ_{10} is the most common coenzyme Q in human mitochondria (Ernster & Dallner, 1995) and is a component of the electron transport chain generating 95% of the energy required in the form of adenosine triphosphate (Mitchell, 1991). Therefore, organs with the highest energy requirements, such as the heart, liver, and brain, are reported to have the highest CoQ_{10} concentrations (Dutton et al., 2000). CoQ_{10} is an endogenously produced cofactor in oxidative respiration in the Krebs cycle and the electron transport chain (Bhagavan & Chopra, 2006). In the blood, CoQ_{10} is associated primarily with low-density lipoprotein (LDL) (Alleva, Tomasetti, Bompadre, & Littarru, 1997). The reduced form of CoQ_{10} ($CoQ_{10}H_2$) functions as an antioxidant to reduce oxidative stress on LDL. Early work suggested that CoQ_{10} levels were modified with age, disease (cardiovascular and neuromuscular diseases), medications (statins), and impaired synthesis (Wajda et al., 2007).

Absorption of CoQ_{10} in the gastrointestinal (GI) tract is enhanced in the presence of lipids that induce the release of bile. This in turn promotes emulsification that helps in CoQ_{10} absorption (Ostlund, Spilburg, & Stenson, 1999). Thus, oil-suspended or oil-solubilized CoQ_{10} may increase bioavailability of CoQ_{10} because of its fat solubility (Weis et al., 1994). Nonlinear CoQ_{10} absorption has been suggested from a few human studies (Miles, 2007), and information from animal models suggests that CoQ_{10} is taken up by all tissues following oral administration (Bhagavan & Chopra, 2006). Peak levels of CoQ_{10} occur at 5–10 hr following administration, with a half-life of 34 hr (Bhagavan & Chopra, 2006; Greenberg & Frishman, 1990; Tomono, Hasegawa, Seki, Motegi, & Morishita, 1986). A second peak may occur at approximately 24 hr, probably due to enterohepatic recirculation (Miles, 2007).

The pharmacokinetics of a novel formulation of CoQ_{10} with pyridoxal 5′-phosphate and phosphatidyl choline (CoQ_{10}-P5P-PC) was investigated in this study. The active form of vitamin B6, pyridoxal 5′-phosphate, also known as PLP and P5P, has been reported to be deficient in individuals with low plasma CoQ_{10} (Willis, Anthony, Sun, Honse, & Qiao, 1999). Phosphatidyl choline or lecithin is a naturally occurring emulsifier and has been demonstrated to significantly increase the bioavailability of a phytosterol compound, sitostanol (Ostlund et al., 1999). It was hypothesized that a CoQ_{10} supplement formulated with P5P and lecithin (>35% phosphatidyl choline) may increase bioavailability of CoQ_{10} over currently marketed forms of CoQ_{10}, which have CoQ_{10} as the sole active ingredient. Furthermore, this formulation uses an enteric coating process (cellulose acetate phthalate), which may enhance the delivery of the active ingredient, CoQ_{10}, to the small intestine, bypassing the digestion process of the stomach.

The objective of this trial was to compare the area under the concentration curve (AUC), the maximum concentration (C_{max}), the time of maximum concentration (T_{max}),

and the estimated elimination half-life ($t_{1/2}$) of a single 30-mg dose of CoQ_{10}-P5P-PC with that of two commercial CoQ_{10} preparations, in healthy adults.

METHODS

Materials

CoQ_{10}-P5P-PC was provided by Enerex Botanicals Ltd., Burnaby, BC, Canada, and manufactured by Canadian Phytopharmaceuticals Corp., Richmond, BC, Canada. Each caplet consisted of CoQ_{10} (30 mg), vitamin B6 (as P5P, 10 mg), lecithin (>35% phosphatidyl choline, 250 mg), and nonmedicinal filling of dicalcium phosphate, magnesium stearate, microcrystalline cellulose, silicon dioxide, vegetable stearin, and cellulose acetate phthalate. The product was manufactured under the quality control regulations of good manufacturing practice.

CoQ_{10}-P5P-PC was tested against two comparator products, 30-mg CoQ_{10} (DIN 02231736, WN Pharmaceuticals Ltd., Coquitlam, BC, Canada) and 30-mg CoQ_{10} (NPN 02176955, Jamieson Laboratories Ltd., Windsor, ON, Canada). Each capsule of CoQ_{10} (DIN 02231736) contained 30-mg CoQ_{10} (ubidecarenone) with nonmedicinal ingredients, cellulose and gelatin capsule. Each capsule of CoQ_{10} (NPN 02176955) contained 30-mg CoQ_{10} (ubiquinone) with black iron oxide, gelatin, glycerin, red iron oxide, soy lecithin, soybean oil, yellow iron oxide, and yellow beeswax, as the nonmedicinal ingredients.

Subjects

This study was conducted in accordance with good clinical practice guidelines and the ethical principles of the Declaration of Helsinki (2000). The study protocol was approved by an Institutional Review Board (IRB Services, Aurora, ON, Canada). The study was reviewed by Health Canada's Natural Health Products Directorate (NHPD) and was conducted in accordance with NHPD regulations. Informed consent was obtained from each subject prior to participation.

Twenty-one healthy subjects were recruited from the patient database and by advertisement. Inclusion required that subjects should have a screening CoQ_{10} level of 0.8 ± 0.2 mg/L, body mass index between 18 kg/m^2 and 30 kg/m^2, be 18 years or older, and be nonsmokers. Exclusion criteria included pregnancy, breastfeeding, alcohol, or drug abuse, as well as the presence of food restrictions, allergies or intolerances, unstable medical conditions, use of Coumadin (warfarin), supplements containing CoQ_{10}, or other natural health products within 2 weeks of randomization and use of any acute medication within 72 hr of the study.

Randomization and Blinding

Subjects were randomized using a computer-generated randomization table and assigned to one of three treatment sequences in blocks of three. To protect blinding, envelopes containing product were labeled with individual unique randomization numbers and a treatment (1, 2, or 3) labeled according to the order to be received. Individual sealed envelopes containing treatment assignment were maintained for each

subject. Subjects, investigators, and clinic coordinators were blinded to test product and sequence. In the event that an adverse event was considered serious and related to the product under investigation, the blind would be broken for that individual. Personnel related to analysis, statistics, and report writing remained blinded.

Study Design

This study was a randomized, double-blind, crossover, 72 hr, bioavailability study conducted at a single site in London, ON, Canada. CoQ_{10} formulations were administered as single oral dose in the morning, with a 2-week washout period between the three CoQ_{10} formulations. At screening medical/medication history including concomitant medications was reviewed, and anthropologic measurements and routine blood tests were conducted. Fasting blood samples were taken predose for CoQ_{10} determination. Subjects were given one capsule of the test product at time 0 with 125 mL of water and provided with breakfast. Blood samples were taken from subjects at 2, 4, 5, 6, 8, 12, 24, 48 and 72 hr postdose. Subjects were provided with a meal after the 4- and 8-hr blood sampling and were allowed to leave the clinic after the 12-hr sampling. Identical meals were supplied to all subjects on each test day. Subjects returned to the clinic for the 24-, 48-, and 72-hr blood sampling. Concomitant therapies and inclusion/exclusion criteria were reviewed at each visit. Adverse events were discussed with subjects at each visit in order to determine if the subject experienced any events since the last visit. Any changes in medications and/or health status were recorded. All adverse events reported were assessed by the medical investigator for relatedness to the study product, and severity, frequency/duration, and outcome of event were recorded.

Analytical Procedures

Laboratory tests (routine hematology and clinical chemistry) were conducted at LifeLabs Medical Laboratory Services, London, ON, Canada. The plasma concentrations of total CoQ_{10} were analyzed by high performance liquid chromatography with ultraviolet detection (HPLC-UV) by KGK Synergize Laboratory, London, ON, Canada. Data entry and verification were executed according to KGK Synergizes' Standard Operating Procedures.

Determination of Plasma Concentration of CoQ_{10}

The concentrations of CoQ_{10} in plasma were quantified by high-performance liquid chromatography (HPLC) described previously (Mosca, Fattorini, Bompadre, & Littarru, 2002). In brief, 200 μL of plasma sample were mixed with 50 μL of 1,4-benzoquinone (2 mg/mL in ethanol, prepared fresh daily) and vortex mixed for 10 s. After a 10-min incubation at room temperature, 0.5 mL of n-propanol was added to the mixture. The solution was vortexed vigorously for 10 s and was centrifuged at 10,000 rpm for 2 min. Further, 200 μL of the clear supernatant were transferred to a HPLC vial with glass insert and 50 μL injected into the HPLC system. The HPLC system is composed of Varian solvent delivery module 210, Varian Autosampler model 410, Varian 335 Photodiode Array Detector for detection, and Microsoft workstation software 6.4.1 for data acquisition. Reverse-phase isocratic HPLC analysis was performed on a

Nova-Pak C18 Column (3.9 × 150 mm, 5 μm, Waters, Mississauga, ON, Canada); guard column was Pursuit C18 (2 mm, 3 μm, Varian, Santa Clara, CA, USA). The flow rate was kept at 1 mL/min, and CoQ_{10} was detected at 275 nm, using HPLC grade methanol:ethanol (35:65, Fisher Scientific, Ottawa, ON, Canada) as the mobile phase. An external standard graph was prepared by spiking pooled plasma sample with CoQ_{10} (Sigma-Aldrich, Oakville, ON, Canada) at the following concentrations: 150 ηg/μL, 75 ηg/μL, 37.5 ηg/μL, 18.75 ηg/μL, 9.38 ηg/μL, 4.7 ηg/μL, 2.3 ηg/μL, 1.2 ηg/μL, 0.59 ηg/μL, and 0.29 ηg/μL. All standards were run in duplicate. Plasma samples spiked with CoQ_{10} were used for quality control runs. The best-fitted graph was linear with a R^2 value of 0.9999. The intra-assay and interassay coefficient of variance was less than 4.74% and 2.02%, respectively.

Pharmacokinetic Analysis

The C_{max} and T_{max} were determined from the actual data. The area under the plasma concentration-time curve from 0 to 72 hr (AUC_{0-t}) was calculated using the linear trapezoidal rule.

Group mean concentrations were used in the calculation of $t_{1/2}$. The log of the concentrations was calculated, and curves were examined to determine the log-linear phase and were based on the first 24 hr postdose. A linear regression was used to determine the slope, and the elimination rate was determined for the calculation of $t_{1/2}$.

Statistical Analysis

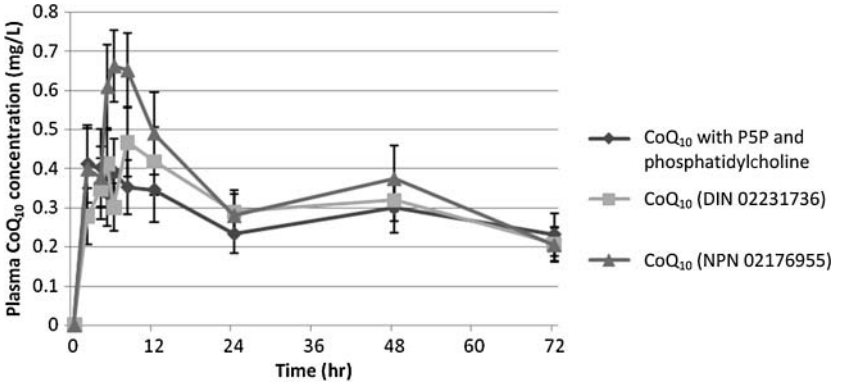
Descriptive statistics for the plasma CoQ_{10} concentrations and AUC, T_{max} and C_{max}, were provided, and between-treatment comparisons were made using a repeated-measures analysis of variance. For CoQ_{10}, AUC, T_{max}, and C_{max}, were calculated for concentrations between predose and 72 hr. In order to calculate individual subject AUC_{0-t}, data were corrected to their respective baselines. Estimated $t_{1/2}$ was calculated from the group mean curve and not on individual data, and standard deviations were not calculated. Data were log transformed prior to statistical analysis, using repeated-measures one-way analysis of variance followed by the Holm–Sidak analysis to determine statistically significant differences between groups. Because of some negative values (decreases), analyses of log-transformed concentrations or areas under the curve were not performed. Statistical comparisons were based on their nontransformed values. Probability values less than .05 were considered statistically significant. SAS version 9.1 was used to perform the statistical analysis.

RESULTS

Twenty-one healthy subjects, 14 females and 7 males, aged 41.6 ± 15.9 years (range, 21–75 years) were enrolled in the study. All subjects were in good health, as assessed by laboratory results, medical history, and physical examination. There were no withdrawals, and all subjects completed the study with 100% compliance.

The mean plasma concentration-time curves for three CoQ_{10} formulations were similar (Figure 1). The plasma total CoQ_{10} concentration demonstrated a significant difference in treatments at 6 and 8 hr after dosing with CoQ_{10} (NPN 02176955), demonstrating

FIGURE 1. Mean total plasma CoQ_{10} concentration time profiles of subjects after a single (30-mg) oral administration of three CQ_{10} formulations. Each point represents the mean ± standard error of mean for 21 healthy subjects.



the highest plasma CoQ_{10} levels ($p = .010$ and $p = .042$, respectively). The 72-hr AUC_{0-t}, C_{max} of CoQ_{10}, and T_{max} of CoQ_{10} occurring in the plasma after dosage, when adjusted for baseline, did not show any significant differences between the formulations (Table 1). Total CoQ_{10} reached maximum plasma concentrations 8.0 hr postdose with CoQ_{10}-P5P-PC, 6.4 hr with CoQ_{10} (NPN 02176955), and 9.5 hr with CoQ_{10} (DIN 02231736). The $t_{1/2}$ was 92.3 hr with CoQ_{10}-P5P-PC, 38.2 hr with CoQ_{10} (NPN 02176955), and 80.7 hr with CoQ_{10} (DIN 02231736) (Table 1). The estimated $t_{1/2}$ was not calculated on each individual subject, as some subjects did not have a sufficient number of data points on the declining part of the absorption profile.

Overall, there were seven adverse events experienced by six subjects, but there were no events assessed as having a possible relationship to the test formulations as determined by the medical investigator. There were no significant differences between formulations for adverse events by severity, causality, or organ system.

DISCUSSION

The purpose of the present study was to examine plasma CoQ_{10} response to orally ingested CoQ_{10} formulations as an indicator of CoQ_{10} bioavailability. Two CoQ_{10} comparator supplements were compared with a novel CoQ_{10} formulation with pyridoxal 5′-phosphate and phosphatidyl choline. The active form of vitamin B6, pyridoxal 5′-phosphate, also known as PLP and P5P, is essential to the internal synthesis of CoQ_{10} (Willis et al., 1999). In the current study, the two comparators, CoQ_{10} (DIN 02231736) and CoQ_{10} (NPN 02176955), were offered as gelatin capsules. CoQ_{10} with P5P and lecithin (>35% phosphatidyl choline) was offered as a caplet with an enteric coating of cellulose acetate phthalate, which was thought to enhance the delivery of the active ingredient, CoQ_{10} to the small intestine, bypassing the digestion process in the stomach.

The absorptive properties of the three different CoQ_{10} preparations were studied in the current randomized, single-dose, crossover study. Twenty-one subjects were given a 30-mg dose of CoQ_{10} and plasma CoQ_{10} measured over a 72-hr period. The mean age of the participants was 41.6 ± 15.9 years, and mean body mass index was 25.4 ± 2.9 kg/m^2. Total CoQ_{10} plasma levels at screening were 0.7 ± 0.1 mg/L, indicating a

TABLE 1. Pharmacokinetic Parameters for Plasma Total CoQ_{10} After a Single 30-mg Oral Dose of One of Three CoQ_{10} Formulations in Healthy Subjects

	Study Groups			*p* value		
	CoQ_{10}-P5P-PC	CoQ_{10} (NPN 02176955)	CoQ_{10} (DIN 02231736)			
Parameter	(*N*) Mean ± *SD* Median (Min., Max.)	(*N*) Mean ± *SD* Median (Min., Max.)	(*N*) Mean ± *SD* Median (Min., Max.)	Sequence	Treatment[a]	Period
$AUC_{(0–72\ hr)}$ (mg/L·hr)	(21) 20.3 ± 14.5 20.3 (−0.0, 60.3)	(21) 25.3 ± 15.5 23.1 (1.8, 60.4)	(21) 22.1 ± 10.6 21.2 (−0.2, 36.4)	.355	.415	.092
C_{max} (maximum concentration) (mg/L)	(21) 0.9 ± 0.4 0.8 (0.4, 1.7)	(21) 1.1 ± 0.3 1.1 (0.2, 1.8)	(21) 0.9 ± 0.3 0.9 (0.4, 1.5)	.974	.113	.030
T_{max} (time of maximum concentration) (hr)	(21) 8.0 ± 9.8 6.0 (2.0, 48.0)	(21) 6.4 ± 2.5 6.0 (2.0,12.0)	(21) 9.5 ± 9.3 8.0 (2.0,48.0)	.995	.267	.608

Note: Statistical analysis was conducted using a repeated-measures analysis of variance on nontransformed data.
[a]*p* values < .05 demonstrate statistically significant between differences treatment (group).

healthy population group as confirmed by the results from Grossi et al. (1992) who reported total CoQ_{10} plasma levels of 0.80 ± 0.20 mg/L in healthy subjects.

Previous clinical studies have demonstrated the importance of monitoring plasma levels of CoQ_{10} to verify absorption and compliance when assessing differing formulations of products (Ferrante et al., 2005; Kaikkonen, Tuomainen, Nyyssonen, & Salonen, 2002; Miles et al., 2006; Permanetter et al., 1992; Strijks, Kremer, & Horstink, 1997). The AUC_{0-t} is used for calculating the relative efficiency of investigational products and has a number of important applications in toxicology, biopharmaceutics, and pharmacokinetics. Systemic bioavailability is best described by the measurement of the relative amount of an administered dose that reaches the general circulation (AUC), the maximum concentration achieved (C_{max}), and the time (T_{max}) at which this occurs (Wiela-Hojeńska & Orzechowska-Juzwenko, 2003). For a supplement or drug to be convenient for a person to self-administer, it is best available in an oral form, and for it to be effective, it must be readily absorbed from the GI tract. As nutrients pass through the liver before reaching the general circulatory system (the *first-pass*) and to be effective, the product should also show some resistance to metabolism by the liver. Bioavailability is described as the ability of a supplement or drug to successfully pass from the GI tract to the plasma.

Plasma CoQ_{10} has a biphasic profile following oral dosing with an initial peak in plasma concentration at 5–6 hr and a second peak between 12 and 24 hr from baseline (Constantinescu et al., 2007). The second peak reflects tissue redistribution (from the liver) and release into the circulation. Pharmacokinetic studies have shown that after oral administration, CoQ_{10} plasma levels begin to increase above baseline levels within 1–2 hr if taken prior to consumption of a meal (Miles et al., 2002; Tomono et al., 1986). The present study confirmed these results, as subjects were provided with breakfast immediately after predose blood sampling, resulting in an increase in plasma CoQ_{10} levels within 1–2 hr from the baseline (predose).

Following oral ingestion, the uptake and distribution of CoQ_{10} depend on its biochemical characteristics. Because of its lipophilic 10-carbon chain and lipid characteristics (Miles, 2007), CoQ_{10} is insoluble in aqueous solutions, and thus, the first step in the uptake of exogenous CoQ10 is incorporation into chylomicrons in the small intestine for transport into the lymph and to the peripheral blood, to be finally taken up by the liver cells (Reahal & Wrigglesworth, 1992; Scalori, Alessandri, Giovannini, & Bertelli, 1990). The distribution phase occurs during the 6–12-hr period after the C_{max}. In the liver, CoQ_{10} is incorporated into lipoproteins and released into the blood, and plasma CoQ_{10} is associated with lipoproteins and shows affinity for very-low-density lipoprotein (VLDL) and LDL-cholesterol (Elmberger, Kalen, Brunk, & Dallner, 1989; Kaikkonen et al., 2002). Previous studies have shown a secondary plasma peak at approximately 24 hr following CoQ_{10} administration (Miles et al., 2002; Tomono et al., 1986; Weis et al., 1994). This peak is most likely a result of enterohepatic recirculation, where CoQ_{10} is released along with bile via the biliary tract and partially reabsorbed during a second pass through the small intestine. In the present study, this recirculation peak was seen at 48 hr following CoQ_{10} administration.

In the present study, after oral supplementation with three CoQ_{10} formulations 72 hr postsupplementation, no significant differences between groups with respect to $AUC_{(0-72\ hr)}$ were demonstrated. The C_{max} of CoQ_{10} in the plasma after supplementation of each test product did not show significant differences between groups with respect to the maximum concentration achieved. It was observed that total CoQ_{10} reached maximum plasma concentrations (T_{max}) at 8.0 hr after supplementation with CoQ_{10}-P5P-PC,

6.4 hr with CoQ_{10} (NPN 02176955), and 9.5 hr with CoQ_{10} (DIN 02231736). This difference was not significant between groups. The profile of the plasma response curve was similar to the three treatment groups. The plasma total CoQ_{10} concentration after supplementation of the three CoQ_{10} formulations showed that there was a significant difference in treatments 6 and 8 hr after dosing with CoQ_{10} (NPN 02176955), demonstrating the highest plasma CoQ_{10} levels ($p < .05$).

The prolonged elimination phase in the CoQ_{10} pharmacokinetics curve shows the redistribution of CoQ_{10} from peripheral tissues into plasma. The biological half-life or the estimated half-life of a substance is the time it takes for the product to lose half of its pharmacologic, physiologic, or radiologic activity. This may also be a reflection of the tissue redistribution and the subsequent release back into the circulation of the test product. Previous studies in healthy subjects reported a prolonged termination half-life of approximately 33 hr following a single dose of CoQ_{10}, and approximately 5–6 days were required for plasma CoQ_{10} levels to return to baseline (Miles et al., 2002; Tomono et al., 1986; Weis et al., 1994). In the present study, the $t_{1/2}$ was 92.3 hr after supplementation with CoQ_{10}-P5P-PC, 38.2 hr with CoQ_{10} (NPN 02176955), and 80.7 hr with CoQ_{10} (DIN 02231736). These results suggest that CoQ_{10} remains in the blood stream and is available for a longer time in subjects taking CoQ_{10}-P5P-PC in comparison with the other two formulations studied. Depending upon the presence of CoQ10 in the circulation for a longer time after single-dose supplementation, fewer doses may be required to maintain healthy circulatory CoQ_{10} levels and that the time to pharmacological steady state is fairly prolonged (1–2 weeks). Further, this study demonstrated similar predose CoQ_{10} levels in the subjects demonstrating that 2 weeks was sufficient for CoQ_{10} levels to return to baseline.

Previous studies have indicated the importance of product formulation (Bhagavan & Chopra, 2006). Using lipid formulations and taking CoQ_{10} with food are reported to increase absorption. The presence of lipids in product formulations has been indicated as promoting better absorption of CoQ_{10}. In a previous bioavailability study, it was found that the increase per 100 mg of reduced CoQ_{10} formulation was remarkably high when offered with oil (Evans, Baisley, Barss, & Guthrie, 2009). CoQ_{10} absorption is enhanced in the presence of lipids by inducing the release of bile in turn promoting emulsification and hence absorption (Ostlund et al., 1999). Phosphatidyl choline from soybean lecithin, a naturally occurring emulsifier, has been demonstrated to increase the absorption of lycopene, another fat-soluble compound (Nishimukai & Hara, 2004). Significantly, higher plasma CoQ_{10} levels after 6 and 8 hr of dosing with CoQ_{10} (NPN 02176955) ($p < .05$) suggest that specific formulation with soy lecithin, soybean oil, and beeswax may have contributed toward higher bioavailability of this product.

In this study, CoQ_{10} with P5P and lecithin (>35% phosphatidyl choline) was offered as a caplet with an enteric coating of cellulose acetate phthalate. The administration of the caplet was followed with the provision of a meal to the subjects. As enteric coating of cellulose acetate phthalate is involved in enhancing the delivery of the active ingredient to the small intestine, bypassing the digestion process in the stomach, administration of this product on an empty stomach, without the consumption of a meal may contribute to better bioavailability in comparison with the other two products which were nonenteric coated. The competitor formulations were required to be taken with a meal, and it is noteworthy that the CoQ_{10} with P5P and lecithin demonstrated an increased $t_{1/2}$ as compared with the comparator products.

In conclusion, CoQ_{10}-P5P-PC though showing similar AUC, T_{max}, and C_{max} to the comparators demonstrated a better $t_{1/2}$, suggesting the product is available in blood for

a longer period of time. It may be suggested that fewer doses of CoQ_{10}-P5P-PC need to be consumed in order to maintain healthy circulatory levels.

Declaration of Interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

Alleva R, Tomasetti M, Bompadre S, Littarru P. Oxidation of LDL and their subfractions: kinetic aspects and CoQ10 content. Mol Aspects Med. 1997;18:s105–s112.

Bhagavan HN, Chopra RK. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. Free Rad Res. 2006;40:455–453.

Constantinescu R, McDermott MP, DiCenzo R, Elisabeth A, de Blieck EA, Christopher H, Beal MF, Bednarczyk EM. A randomized study of the bioavailability of different formulations of coenzyme Q_{10} (ubiquinone). J Clin Pharmacol. 2007;47:1580–1586.

Dutton PL, Ohnishi T, Darrouzet E, Leonard, MA, Sharp RE, Cibney BR, Daldal F, Moser CC. 4 coenzyme Q oxidation reduction reactions in mitochondrial electron transport. In: VE Kagan and PJ Quinn (Eds.), Coenzyme Q: Molecular mechanisms in health and disease, pp. 65–82. Boca Raton, FL: CRC Press, 2000.

Elmberger PG, Kalen A, Brunk UT, Dallner G. Discharge of newly-synthesized dolichol and ubiquinone with lipoproteins to rat liver perfusate and to the bile. Lipids 1989;24:919–930.

Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta. 1995;1271:195–204.

Evans M, Baisley J, Barss S, Guthrie N. A randomized, double-blind trial on the bioavailability of two Q_{10} formulations. J Funct. Foods 2009;1:65–73.

Ferrante KL, Shefner J, Zhang H, Betensky R, O'Brien M, Yu H, Fantasia M, Taft J, Beal MF, Traynor B, Newhall K, Donofrio P, Caress J, Ashburn C, Freiberg B, O'Neill C, Paladenech C, Walker T, Pestronk A, Abrams B, Florence J, Renna R, Schierbecker J, Malkus B, Cudkowicz M. Tolerance of high-dose (3,000 mg/day) coenzyme Q_{10} in ALS. Neurology 2005;65:1834–1836.

Ghirlanda G, Oradei A, Manto A, Lippa S, Uccioli L, Caputo S, Greco A, Littarru G. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. J Clin Pharmacol. 1993;33(3):226–229.

Greenberg S, Frishman WH. Co-enzyme Q10: a new drug for cardiovascular disease. J Clin Pharmacol. 1990;30:596–608.

Grossi G, Bargossi AM, Fiorella PL, Piazzi S, Battino M, Bianchi GP. Improved high-performance liquid chromatographic method for the determination of coenzyme Q_{10} in plasma. J Chromatogr. 1992;593:217–226.

Kaikkonen J, Tuomainen TP, Nyyssonen K, Salonen JT. Coenzyme Q_{10}: absorption, antioxidative properties, determinants, and plasma levels. Free Radic Res. 2002;36:389–397.

Kishi T, Watanabe T, Folkers K. Bioenergetics in clinical medicine XV. Inhibition of coenzyme Q10-enzymes by clinically used adrenergic blockers of beta-receptors. Res Commun Chem Pathol Pharmacol. 1977;17(1):157–164.

Miles MV. The uptake and distribution of coenzyme Q10. Mitochondrion 2007;7(Suppl. 1): S72–S77.

Miles MV, Horn P, Miles L, Tang P, Steele P, DeGrauw T. Bioequivalence of coenzyme Q_{10} from OTC supplements. Nutr Res. 2002;22:919–929.

Miles MV, Patterson BJ, Schapiro MB, Hickey FJ, Chalifonte-Evans M, Horn PS, Hotze SL. Coenzyme Q10 absorption and tolerance in children with Downs' syndrome: a dose-ranging trial. Ped Neurol. 2006;35:30–37.

Mitchell P. The vital protomotive role of coenzyme Q. In: K Folkers, Y Yamamura, GP Littarru (Eds.). *Biomedical and clinical aspects of coenzyme Q* (Vol 6), (pp. 3–10). Amsterdam, the Netherlands: Elsevier, 1991.

Mortensen SA, Leth A, Agner E, Rohde M. Dose-related decrease of coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. Mol Aspects Med. 1997;18(Suppl.):137–144.

Mosca F, Fattorini D, Bompadre S, Littarru GP. Assay of coenzyme Q_{10} in plasma by a single dilution step. Anal Biochem. 2002;305:49–54.

Nishimukai M, Hara H. Enteral administration of soybean phosphatidylcholine enhances the lymphatic absorption of lycopene, but reduces that of alpha-tocopherol in rats. J Nutr. 2004;134(8):1862–1866.

Ostlund RE, Jr., Spilburg CA, Stenson WF. Sitostanol administered in lecithin micelles potently reduces cholesterol absorption in humans. Am J Clin Nutr. 1999;70(5):826–831.

Permanetter B, Rossy W, Klein G, Weingartner F, Seidl KF, Blomer H. Ubiquinone (coenzyme Q_{10}) in the long term treatment of idiopathic dilated cardiomyopathy. Eur Heart J. 1992;13:1528–1533.

Reahal S, Wrigglesworth J. Tissue concentrations of coenzyme Q_{10} in the rat following its oral and intraperitoneal administration. Drug Metab Dispos. 1992;20:423–427.

Scalori V, Alessandri MG, Giovannini L, Bertelli A. Plasma and tissue concentrations of coenzyme Q_{10} in the rat after intravenous, oral and topical administrations. Int J Tissue React. 1990;12:149–154.

Strijks E, Kremer HP, Horstink MW. Q_{10} therapy in patients with idiopathic Parkinson's disease. Mol Aspects Med. 1997;18(Suppl.):S237–S240.

Tomono Y, Hasegawa J, Seki T, Motegi K, Morishita N. Pharmacokinetic study of deuterium-labelled coenzyme Q10 in man. Int J Clin Pharmacol Ther Toxicol. 1986;24:536–541.

Wajda R., Zirkel J, Schaffer T. Increase of bioavailability of coenzyme Q10 and vitamin E. J Med Food 2007;10:731–734.

Weis M, Mortensen SA, Rassing MR, Moller-Sonnergaard J, Poulsen G, Rasmussen SN. Bioavailability of four oral coenzyme Q10 formulations in healthy volunteers. Mol Aspects Med. 1994;(15 Suppl.):s273–s280.

Wiela-Hojeńska A, Orzechowska-Juzwenko K. Bioavailability and its significance in pharmacotherapy. Pol Merkur Lekarski. 2003;14(79):89–93.

Willis R, Anthony M, Sun L, Honse Y, Qiao G. Clinical implications of the correlation between coenzyme Q10 and vitamin B6 status. Biofactors 1999;9(2–4):359–363.