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A randomized, double-blind trial on the bioavailability of two CoQ10 formulations

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ARTICLE INFO

Article history:
Received 4 August 2008
Accepted 26 August 2008
Available online 11 October 2008

Keywords:
Coenzyme Q10
Reduced Coenzyme Q10
Bioavailability

ABSTRACT

The bioavailability of a single, 100 mg, dose of reduced Coenzyme Q10 (CoQH-CF) and Coenzyme Q10 formulation was compared in individuals of >60 years. Significantly higher ($P < 0.001$) plasma concentrations were demonstrated for the CoQH-CF formulation at 5, 6, 8, 12, 24, 48 and 72 h post-dose compared to the CoQ10 formulation. The area under the curve (AUC) of reduced and total Coenzyme Q10 was significantly higher ($P < 0.001$) in subjects administered CoQH-CF resulting in 4.3-fold higher plasma $AUC_{0-72\ h}$ (430% increase) in subjects receiving CoQH-CF compared to subjects receiving Coenzyme Q10. Oxidized Coenzyme Q10 in plasma was higher ($P < 0.001$) in subjects receiving CoQH-CF compared to subjects receiving Coenzyme Q10 resulting in a 3.3-fold higher plasma $AUC_{0-72\ h}$ (329% increase). Total CoQ10 reached maximum plasma concentrations 15.5 ± 19.6 h after supplementation with CoQH-CF and 26.5 ± 25.8 h after supplementation with Coenzyme Q10, respectively. Thus, reduced Coenzyme Q10 liquid soft gel formulation was found to be superior to the commercial formulation of Coenzyme Q10 for bioavailability.

1. Introduction

Coenzyme Q10 or ubiquinone, produced endogenously, is a ubiquitous compound vital to energy metabolism. Most metabolically active tissues, such as the heart and immune system, are found to have the highest levels of CoQ10 (Bhagavan & Chopra, 2006). Early work reported that CoQ10 levels were modified with age and disease; however, more recent work suggests that total CoQ10 may not be as important as reduced CoQ10 ($CoQ10H_2$) or the ratio of reduced CoQ10 to total CoQ10 (Anonymous, 2007; Tang et al., 2001). The reduced form of CoQ10 ($CoQ10H_2$) functions as an antioxidant to reduce oxidative stress and is thought to be lower in relation to total CoQ10 in individuals with various types of cancer, heart disease, and neuromuscular disease (Tang et al., 2001). In metabolic syndrome, levels of $CoQ10H_2$ have been found to increase as an adaptive response to oxidative stress (Miles et al., 2004a).

Research on animal models has demonstrated that CoQ10 is taken up by all tissues following oral administration and

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Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; AUC, area under the concentration–time curve; BUN, blood urea nitrogen; CBC, complete blood count; CHF, coronary heart failure; Cl, chloride; C_{max}, maximum concentration; CoQ10, Coenzyme Q10; $CoQ10H_2$, reduced Coenzyme Q10; EDTA, ethylenediaminetetraacetic acid; g, gram; GGT, gamma glutamyl transferase; IRB, Institutional Review Board; K, potassium; LDL, low density lipoprotein; mg/dL, milligrams per decilitre; ml, millilitre; mmHg, millimetre of mercury; mmol/L, millimoles per litre; Na, sodium; NHP, natural health product; NHPD, Natural Health Products Directorate; SAE, serious adverse event; SST, serum separating tube; $t_{1/2}$, half-life; T_{max}, time at maximum concentration; ULN, upper limit of normal; μg/mL, microgram per mL; μmol/L, micromole per litre

1756-4646/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.jff.2008.09.010

that tissue content of reduced CoQ10 and the ratio of reduced CoQ10 to total CoQ10 may be used as a marker of disease (Bhagavan & Chopra, 2006; Miles et al., 2005). Evidence from human trials suggests that CoQ10 supplementation may be beneficial for individuals with cardiovascular disease, chronic heart failure, and hypertension (Anonymous, 2007). CoQ10 supplementation is considered to be beneficial for individuals using statin therapy due to statin-induced reduction in plasma CoQ10. Supplemental CoQ10 has also been investigated in individuals with neurological disorders, cancer, diabetes, migraine and asthma (Alleva et al., 1997; Tang et al., 2001; Miles et al., 2004a,b, 2005, 2006; Anonymous, 2007).

Due to its clinical potential, currently, CoQ10 is a popular oral supplement. In general, CoQ10 supplements are considered to be bioavailable and to have a half-life of approximately 34 h with peak levels occurring 5–10 h following administration (Tomono et al., 1986; Greenberg & Frishman, 1990; Bhagavan & Chopra, 2006). Nonlinear CoQ10 absorption has been suggested from a few human studies (Miles, 2007).

The objective of this trial was to compare the bioavailability (AUC, $t_{1/2}$, T_{max}, and C_{max}) of a specially formulated reduced Coenzyme Q10 preparation, CoQH-CF, with that of a commercial Coenzyme Q10 preparation, in healthy adults.

2. Materials and methods

2.1. Study subjects

The study was a single-centre, double-blind, randomized two-arm crossover study conducted in London, ON, Canada. Ten subjects, eight females and two males, were recruited from KGK Synergize's clinic patient database and by advertisement. Subjects were assessed as being healthy as determined by laboratory results, medical history and physical examination. Detailed information on the study was provided to the subjects during a preliminary telephone call so that only interested and likely eligible individuals reported for screening. The study was managed by KGK Synergize Inc. and conducted at a single site at the KGK Synergize Clinic, London, ON, Canada, under the supervision of the Investigators, David Crowley, MD and Dale Wilson, MD. The study protocol was reviewed by an Institutional Review Board (IRB Services, Aurora, ON, Canada) and unconditional approval was granted on December 19, 2007. The study was reviewed by Health Canada's Natural Health Products Directorate (NHPD), and (Notice of Authorization was received on December 27, 2007) was conducted in accordance with NHPD Regulations. This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Informed consent was obtained from each subject at the screening visit prior to any study-related activities.

2.2. Inclusion and exclusion criteria

Subjects were required to meet the following criteria to be eligible for enrollment: male or female aged 60 years or older; subjects deemed healthy as determined by laboratory results, medical history and examination by a physician; BMI of 18–29.9 kg/m^2; screening CoQ10 levels of 0.2–1.0 μg/mL; and voluntary, written, informed consent to participate in the study; subjects were excluded from the study based on the following criteria: unstable medical condition; use of Coumadin Warfarin, supplements containing Coenzyme Q10, or other natural health products within 2 weeks of randomization; use of any acute medication within 72 h of the study (each test date).

2.3. Randomization and blinding

Subjects were randomized using a computer generated randomization table and assigned to one of two treatment sequences (order of treatments) in blocks of two. No formal sample size calculation was performed as this was a peak absorption study to determine bioavailability. Blinding was considered necessary for this study and was feasible. At randomization, concomitant therapies and inclusion/exclusion criteria were reviewed. Eligible subjects were randomly and blindly assigned to receive a single dose of one of two test materials, each formulated to contain 100 mg of CoQ10. No known side effects of supplements were likely to reveal patient classification. In order to protect blinding, envelopes containing product were labeled with individual unique randomization numbers and a treatment (1 or 2) labeled according to the order to be received. Envelopes were contained in a resealable plastic bag labeled "CoQH-CF (Lot: C72380780) or Coenzyme Q10 (Lot: 20062007)". Individual sealed envelopes containing treatment assignment were maintained for each subject. 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. Neither the patient, nor the investigator, nor the research staff was aware which test order the subject was assigned. Personnel related to analysis, statistics and report writing remained blinded.

2.4. Study protocol

At screening, informed consent was obtained from subjects prior to any study procedures. Medical/medication history including concomitant medications was reviewed and anthropologic measurements and routine blood tests were conducted.

Fasting blood samples were taken pre-dose for CoQ10 determination. Subjects were given one capsule of the test product at time zero with 125 mL of water, and breakfast was provided immediately after the dose. Capsules were administered as a single oral dose in the morning, with a minimum of 2 weeks between the two Coenzyme Q10 test products. In order to ensure compliance, the single dose of the test product, was taken in the clinic in the presence of the study coordinator on each testing day. Blood samples were taken from subjects at 2 and 4 h post-dose. A meal was provided following the 4-h sample. Blood sampling was repeated at 5, 6 and 8 h post-dose and a meal was provided after the 8-h sampling. Subjects were sampled next at 12 h post-dose and allowed to leave the clinic. Subjects returned to the clinic for 24, 48 and 72-h blood sampling. Previously published studies have used a similar time curve for blood testing (Constantinescu et al., 2007). Concomitant therapies, adverse events, and inclusion/exclusion criteria were reviewed at each visit. Identical meals were supplied to all

subjects on each test day. Side effects (adverse events) were discussed with subjects at each visit in order to determine if the subject experienced any adverse events since the last visit. Furthermore, any changes in medications and/or health status were recorded. All adverse events reported were assessed by the Investigators for relatedness to the study product, and severity, frequency/duration and outcome of each adverse event recorded.

2.5. *Treatment*

CoQH-CF (batch number: C72380780) was manufactured and supplied by Soft-Gel Technologies, Inc., Los Angeles, CA, USA. Ingredients for the specific batch of formulation used in this trial on a per soft gel capsule basis were: reduced Coenzyme Q10 106.25 mg, capric acid 9.37 mg, D-limonene oil 336.25 mg, α-lipoic acid 6.25 mg, and caprylic acid 21.88 mg. *Capsule structure:* gelatin 192.041 mg, water 28.620 mg and caramel liquid 8.841 mg. The ubiquinol concentration in the CoQH-CF formulation analyzed by HPLC methodology was determined to be 104 mg per capsule.

Coenzyme Q10, DIN# 02245852 (batch number: 20062007), was supplied by Nutri-Chem, ON, Canada. Ingredients for the specific batch of formulation used in this trial on a per hard capsule basis were Coenzyme Q10, 100 mg and methylcellulose to fill. Capsules were stored at room temperature, protected from heat, moisture, and direct light. Each product was manufactured under food GMP, as required by the FDA. Both study formulations were encapsulated. Coenzyme Q10 was encapsulated in a hard shell capsule, while CoQH-CF was encapsulated in a soft gel capsule. The dose of active ingredient in a single dose of the formulation was considered to be adequate to observe absorption and bioavailability, and side effects of a single dose of Coenzyme Q10 in any form were considered to be unlikely.

Table 1 – Demographics and characteristics of all randomized subjects at screening

Variable	Mean ± SD Median (minimum–maximum)
Age (years)	67 ± 5 67 (60–78)
Gender (n)	
Female	8
Male	2
Total	10
Height (cm)	163.5 ± 7.8 163.1 (155.3–182.6)
Weight (kg)	71.0 ± 8.1 72.7 (58.2–82.5)
BMI (kg/cm^2)	26.6 ± 2.9 27.9 (21.5–30.0)
Systolic blood pressure (mmHg)	128 ± 12 130 (105–148)
Diastolic blood pressure (mmHg)	78 ± 7 80 (70–86)
Heart rate (bpm)	65 ± 8 60 (56–78)

2.6. *Analytical procedures*

Laboratory tests (routine blood parameters) were conducted at LifeLabs Medical Laboratory Services, ON, Canada. The plasma concentrations of reduced and total CoQ10 were analyzed by HPLC-EC (HPLC with electrochemical detection) by ESA Laboratories, Inc., Chelmsford, MA, USA. Data entry and

Table 2 – Blood parameters of all subjects at randomization (*N* = 10)

Parameter	Mean ± SD Median (minimum–maximum)
Hemoglobin (g/L)	142 ± 6 144 (135–155)
Hematocrit	0.43 ± 0.02 0.44 (0.41–0.46)
White blood cell count (×E9/L)	6.5 ± 1.1 6.5 (4.5–8.1)
Red blood cell count (×E12/L)	4.56 ± 0.29 4.51 (4.21–5.16)
MCV (fL)	95.0 ± 3.6 94.9 (88.2–101.1)
MCH (pg/L)	31.2 ± 0.9 31.1 (30.0–32.8)
MCHC (g/L)	329 ± 7 329 (319–341)
RDW	13.3 ± 0.6 13.3 (12.2–14.5)
Platelet count (×E9/L)[a]	231 ± 127 247 (205–359)
Neutrophils (×E9/L)	3.7 ± 0.7 3.5 (2.4–5.0)
Lymphocytes (×E9/L)	2.0 ± 0.5 2.0 (1.6–3.1)
Monocytes (×E9/L)	0.6 ± 0.2 0.5 (0.4–1.1)
Eosinophils (×E9/L)	0.2 ± 0.1 0.2 (0.0–0.4)
Basophils (×E9/L)	0.0 ± 0.0 0.0 (0.0–0.1)
Fasting glucose (mmol/L)	4.7 ± 1.0 4.9 (2.2–5.8)
Sodium (mmol/L)	143 ± 2 143 (141–147)
Potassium (mmol/L)	4.69 ± 0.63 4.50 (3.8–5.7)
Chloride (mmol/L)	104 ± 2 104 (102–108)
AST (μ/L)	28 ± 8 25 (19–43)
ALT (μ/L)	27 ± 13 21 (13–52)
GGT (μ/L)	27 ± 22 16 (13–81)
Total bilirubin (μmol/L)	6 ± 3 5 (3–12)
Creatinine (mmol/L)	74 ± 8 72 (62–81)
eGFR	85 ± 13 84 (68–114)
Total CoQ10 (μg/mL)	0.2640 ± 0.0856 0.2458 (0.1851–0.4665)

a *N* = 9.

verification were executed according to KGK Synergizes' Standard Operating Procedures. Accordingly, data were entered into a database and verified by an independent researcher. All data remained blinded to all personnel involved through analysis. Raw data and standard operating procedures used in this trial were maintained and archived to satisfy regulatory requirements.

2.7. *Statistical analysis*

All statistical analyses were by repeated measure analysis of variance to evaluate changes in plasma levels of Coenzyme Q10 vs. time zero to analyze differences in pharmacokinetic parameters (AUC, $t_{1/2}$, T_{max} and C_{max}) between the supplements. In order to calculate individual subject AUC_{0-t}, data were corrected to their respective baselines. Data were log transformed prior to statistical analysis using repeated measures one way analysis of variance (RM ANOVA) followed by Holm–Sidak analysis to determine statistically significant differences between groups. Probability values less than 0.05 were considered statistically significant.

3. Results

3.1. *Baseline characteristics and compliance*

The demographics, blood characteristics and concomitant medications for all subjects are presented in Tables 1–3. There were no withdrawals and all subjects completed the study, and 100% compliance was achieved in this study.

3.2. *Results of pharmacokinetics*

The plasma concentration–time curves of Coenzyme Q10 as oxidized CoQ10, reduced CoQ10 and total CoQ10 for both formulations are depicted in Fig. 1. A biphasic pattern for the plasma profiles was demonstrated by both formulations. Statistically significantly higher ($P < 0.001$) plasma concentrations were evident for the CoQH-CF formulation at 5, 6, 8, 12, 24, 48 and 72 h post-dose compared to the CoQ10 formulation.

The average AUC in healthy subjects after supplementation with the two Coenzyme Q10 formulations is presented in Table 4. The AUC of reduced and total Coenzyme Q10 was statistically significantly higher in subjects administered CoQH-CF compared to those receiving Coenzyme Q10, resulting in 4.3-fold higher plasma $AUC_{0-72\,h}$ (430% increase) in subjects receiving CoQH-CF compared to those receiving Coenzyme Q10. Oxidized Coenzyme Q10 in plasma $AUC_{0-24\,h}$, $AUC_{0-48\,h}$ and $AUC_{0-72\,h}$ was statistically significantly higher in subjects receiving CoQH-CF compared to those on Coenzyme Q10 resulting in a 3.3-fold higher plasma $AUC_{0-72\,h}$ (329% increase) (Fig. 2).

The time at which maximum concentration (T_{max}) of Coenzyme Q10 occurred in the plasma after supplementation with the two test products is depicted in Fig. 3. T_{max} was calculated for each individual receiving the two test supplements. It was observed that total CoQ10 reached maximum plasma concentration 15.5 ± 19.6 h after supplementation with CoQH-CF and 26.5 ± 25.8 h after supplementation with Coenzyme Q10, suggesting a faster rate of absorption for

Table 3 – Concomitant treatments during study for all subjects ($N = 10$)

Randomization number	Medication name	Dose	Indication	Used for AE	Date started
1207Q1001	Ramipril	10 mg/QD	High blood pressure	No	01/01/2003
1207Q1001	Simvastatin	20 mg/QD	High cholesterol	No	01/01/2003
1207Q1001	Aspirin EC	81 mg/QD	General health	No	01/01/2003
1207Q1001	Calcium	QD	General health	No	01/01/2006
1207Q1001	Multivitamin	QD	General health	No	01/01/1997
1207QCF02	Aspirin	325 mg/QD	General health	No	01/01/2004
1207QCF02	Multivitamin	QD	General health	No	01/01/2004
1207QCF02	Vitalux lutene	400 mg/QD	Eye sight	No	01/01/2004
1207QCF02	Tylenol arthritis	650 mg QD	Arthritis pain	No	01/01/2004
1207QCF03	Levothyroxine	0.1 mg/QD	Hypothyroidism	No	01/01/1997
1207QCF03	Norvasc	5 mg/QD	High blood pressure	No	01/01/2004
1207QCF03	Atacand	16 mg/QD	High blood pressure	No	01/01/2004
1207QCF03	Didrocal	QD	Prophylaxsis for osteoporosis	No	01/01/2005
1207Q1004	Lipitor	20 mg/QD	High Cholesterol	No	01/01/1996
1207Q1004	Actonel	35 mg/QD	Osteopenia	No	01/06/2006
1207Q1004	Vitamin D	1000IU/QD	General health	No	01/11/2007
1207Q1004	Calcium + Magnesium + Zinc	BID	General health	No	01/01/2002
1207Q1004	Synthroid	0.25 mg/QD	Hypothyroidism	No	01/07/2007
1207QCF05	Tylenol extra strength	500 mg/PRN	Back pain	No	01/11/2007
1207Q1006	Vitamin D	PRN	General health	No	01/01/2008
1207Q1008	Calcium	QD	General health	No	01/10/2007
1207Q1008	Multivitamin	QD	General health	No	01/10/2007
1207QCF10	Vitamin E	QD	General health	No	01/01/2006
1207QCF10	Vitamin D	QD	General health	No	01/01/2006
1207QCF10	Vitamin B	QD	General health	No	01/01/2006
1207QCF10	Eltroxin	0.05 mg/QD	Hypothyroid	No	30/11/2007
1207QCF10	Calcium + Magnesium + Vitamin D	TIB	General health	No	01/01/2006

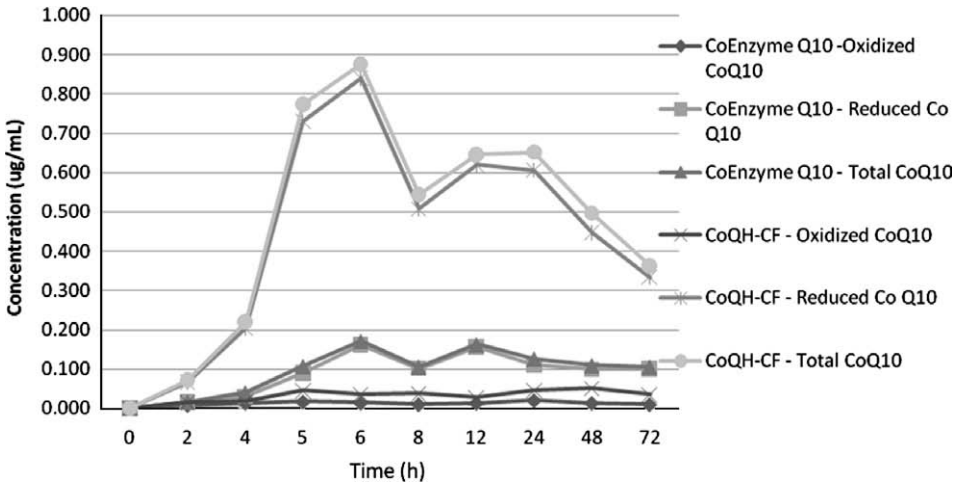

Fig. 1 – Plasma response after supplementation with different Coenzyme Q10 formulations.

Table 4 – Area under plasma concentration–time curve after oral supplementation with two Coenzyme Q10 formulations (*N* = 10)

Treatment	Oxidized CoQ10 Mean ± SD	Reduced CoQ10 Mean ± SD	Total CoQ10 Mean ± SD
$AUC_{0-12\ h}$ (*μg h/mL*)			
Coenzyme Q10	0.862 ± 0.953	8.293 ± 7.681	8.756 ± 7.436
CoQH-CF	2.214 ± 1.617	39.632 ± 25.165	41.743 ± 25.899
P value	$P < 0.001$	$P < 0.001$	$P < 0.001$
$AUC_{0-24\ h}$ (*μg h/mL*)			
Coenzyme Q10	0.862 ± 0.953	8.293 ± 7.681	8.756 ± 7.436
CoQH-CF	2.214 ± 1.617	39.632 ± 25.165	41.743 ± 25.899
P value	$P < 0.001$	$P < 0.001$	$P < 0.001$
$AUC_{0-48\ h}$ (*μg h/mL*)			
Coenzyme Q10	0.862 ± 0.953	8.293 ± 7.681	8.756 ± 7.436
CoQH-CF	2.214 ± 1.617	39.632 ± 25.165	41.743 ± 25.899
P value	$P < 0.001$	$P < 0.001$	$P < 0.001$
$AUC_{0-72\ h}$ (*μg h/mL*)			
Coenzyme Q10	0.862 ± 0.953	8.293 ± 7.681	8.756 ± 7.436
CoQH-CF	2.214 ± 1.617	39.632 ± 25.165	41.743 ± 25.899
P value	$P < 0.001$	$P < 0.001$	$P < 0.001$

the reduced form of Coenzyme Q10. There was little difference in the rate of absorption of the oxidized form of Coenzyme Q10.

The maximum concentration (C_{max}) of Coenzyme Q10 occurring in the plasma after supplementation of test product is depicted in Fig. 4. Maximum plasma CoQ10 concentrations were statistically significantly higher for oxidized CoQ10 (0.074 ± 0.046 vs. 0.034 ± 0.029), reduced CoQ10 (0.969 ± 0.626 vs. 0.274 ± 0.155) and total CoQ10 (1.022 ± 0.638 vs. 0.290 ± 0.158) in subjects receiving CoQH-CF compared to those receiving Coenzyme Q10 ($P < 0.015$, $P < 0.001$ and $P < 0.001$, respectively).

These results suggest that delivery of a reduced form of CoQ10 in the formulation studied in this trial was superior to Coenzyme Q10 (DIN# 02245852), a typical commercial formulation.

3.3. *Adverse events evaluation*

The individual adverse events and the severity analysis of adverse events are presented in Tables 5 and 6. The analysis of adverse events in relation to treatment and categorized by MedDRA organ system is presented in Tables 7 and 8, respectively. Overall there were seven adverse events, experienced by six subjects. The adverse events experienced in this study included any adverse events noted by the subject at any point following the first test dose. Five adverse events were noted by five subjects on or following the Coenzyme Q10 test date. Two adverse events were noted by two subjects on or following the CoQH-CF test date. Of all combined adverse events, six were mild and one was categorized as moderate. There were no serious adverse events. One adverse event, headache (in subject 1207Q1004), was suspected as being possibly related

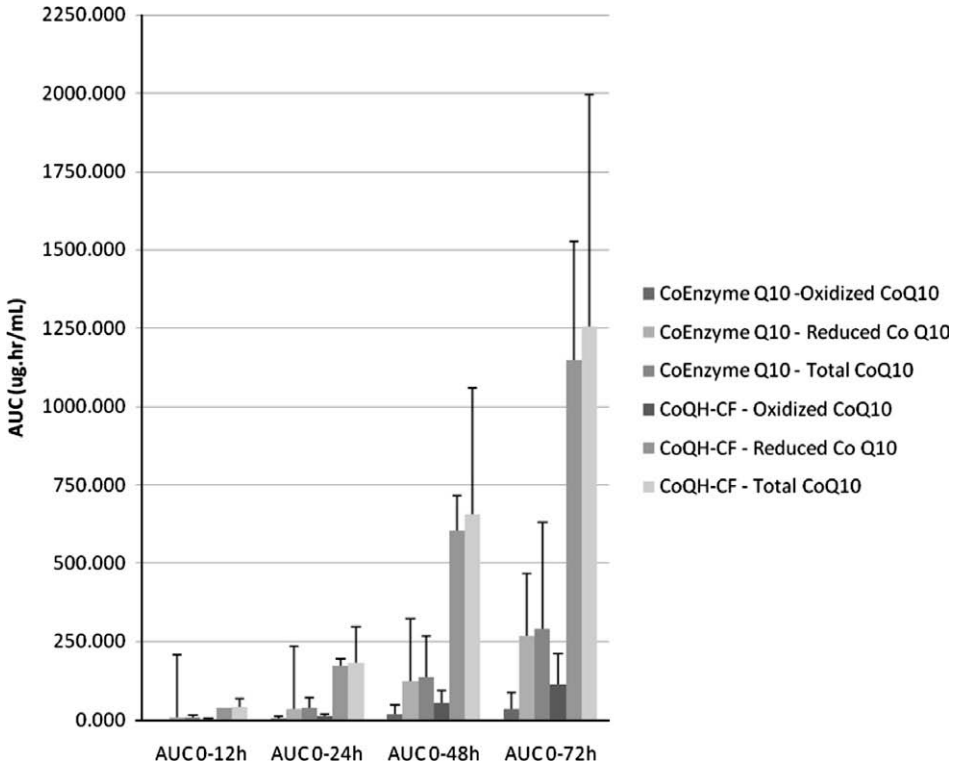

Fig. 2 – Average $AUC_{(0-t)}$ in healthy subjects after supplementation with two different Coenzyme Q10 products.

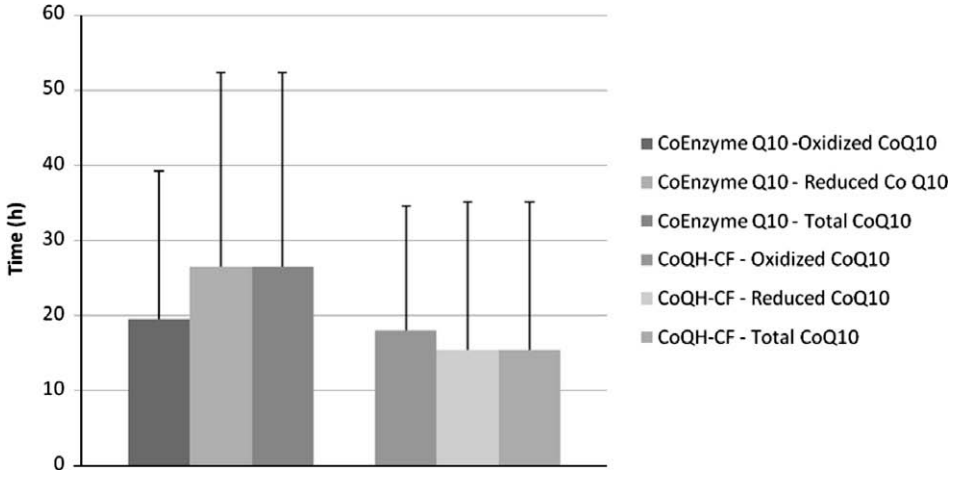

Fig. 3 – Time at which the maximum concentration of Coenzyme Q10 was measured in plasma of subjects after supplementation with two different Coenzyme Q10 products.

to the test product (Coenzyme Q10), whereas the other six were considered to be unlikely or not related to the test product. The treatment was not discontinued by any subject due to adverse events. There were no statistically significant differences between treatments for adverse events, by severity, causality, or organ system.

There were no statistically significant differences between the number of adverse events between the two supplements ($P = 0.350$). No patients or patient groups were considered to be at increased risk in using either of the Coenzyme Q10 supplements. Based on the adverse event data, both Coenzyme Q10 formulations should be considered safe.

4. Discussion

Comparison of baseline CoQ10 concentrations prior to each dose of the two formulations showed that plasma concentrations were within the normal endogenous range for this population of subjects (Grossi et al., 1992). There was no evidence of carryover effects from one treatment period to the next as concentrations returned to baseline levels before each dosing.

The average range of CoQ10 levels of healthy subjects is reported to be in the range of 0.8 ± 0.20 mg/L, and is age dependant with decreasing plasma levels reported with increasing age (Grossi et al., 1992). Others have reported total concentra-

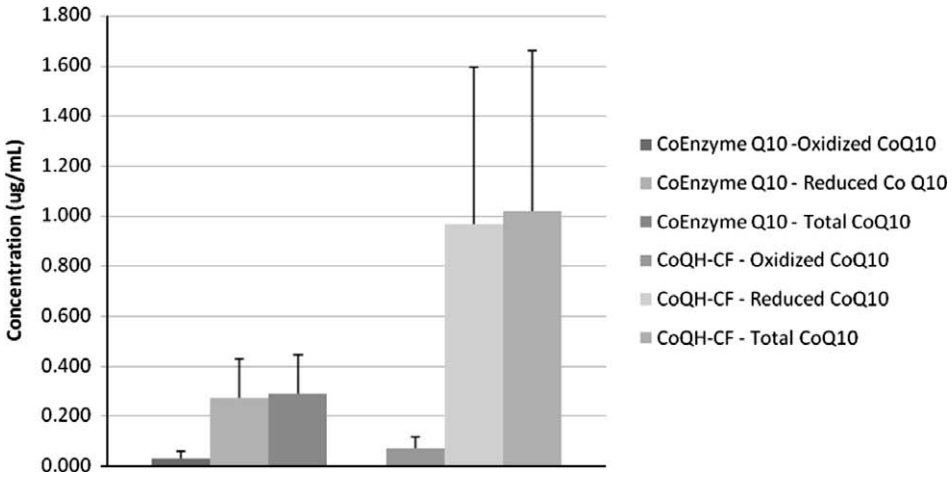

Fig. 4 – Maximum concentration of Coenzyme Q10 was measured in plasma of subjects after supplementation with two different Coenzyme Q10 products.

Table 5 – Individual adverse events

Randomization number	Treatment	Visit	Description	Severity	Relationship to product	Start stop	Action	Resolved	OrgSyst
1207Q1001	CoQ10	2	Dry mouth	Mild	Unlikely	28/01/0809/02/09	None	Yes	Gastrointestinal
1207Q1001	CoQH-CF	3	Nosebleeds	Mild	Unlikely	12/02/0813/02/08	None	Yes	Haemorrhaging/ bleeding
1207QCF03	CoQ10	3	Constipation	Mild	Unlikely	12/02/0814/02/08	None	Yes	Gastrointestinal
1207Q1004	CoQ10	2	Headaches	Moderate	Possible	28/01/0830/01/08	None	Yes	Pain
1207QCF05	CoQCF	2	Nausea/ cramping	Mild	Unlikely	30/01/0830/01/08	None	Yes	Gastrointestinal
1207Q1009	CoQ10	2	Fatigue	Mild	Not related	30/01/0815/02/08	None	Yes	Constitutional symptoms
1207QCF10	CoQ10	3	Sinus congestion	Mild	Not related	22/02/08	None	Ongoing at time of last visit	Infection

Table 6 – Severity analysis of adverse events (day of or period following use of Coenzyme Q10 product)

Treatment	Mild	Moderate	Severe
CoQ10	4	1	0
CoQH-CF	2	0	0
Total	6	1	0

Table 7 – Analysis of adverse events and relatedness to treatment, all subjects ($N = 10$)

Relation to test product	Treatment	
	CoQ10	CoQH-CF
Not related	2	0
Unlikely	2	2
Possible	1	0
Probable	0	0
Most probable	0	0

Table 8 – All adverse events categorized by MedDRA organ system

MedDRA organ system	Number of events		Number of subjects	
	CoQ10	CoQH-CF	CoQ10	CoQH-CF
Gastrointestinal disorders	2	1	2	1
Constitutional symptoms	1	0	1	0
Infection	1	0	1	0
Haemorrhage/ bleeding	0	1	0	1
Pain	1	0	1	0
All events	5	2	5	2

tions of reduced and oxidized forms for normal, healthy individuals to be in the range of 0.4–2.0 μg/mL (Jiménez et al., 2007). The plasma levels reported in this study are consistent with the population studied.

Monitoring of plasma levels of CoQ10 and CoQ10H2 is reported to be important in assessing bioavailability of orally administered CoQ10 (Jiménez et al., 2007). Plasma response curves showed two peaks for total and reduced CoQ10 for both formulations. The levels were statistically significantly

different ($P < 0.001$) with higher plasma concentrations evident for the CoQH-CF formulation at 5, 6, 8, 12, 24, 48 and 72 h post-dose. The characteristic biphasic peak for plasma Coenzyme Q10 has previously been reported by others (Constantinescu et al., 2007; Weis et al., 1994). The biphasic profile is thought to be associated with the redistribution and the enterohepatic recycling of CoQ10. The first phase of the biphasic peak occurred approximately 6 h after baseline followed by a second peak between 12 and 24 h from baseline, consistent with the times previously reported in the literature (Constantinescu et al., 2007). Though the pattern of the plasma response curves was similar, the results demonstrated that the plasma total CoQ10 response was 4.3-fold higher after supplementation with CoQH-CF as compared to the CoQ10 commercial formulation. A 3.5-fold higher total CoQ10 C_{max} was achieved when subjects were supplemented with CoQH-CF formulation. A T_{max} of 6 h has been confirmed by others, and the pharmacokinetic profiles for ubiquinone and ubiquinol are reported to be identical (Langsjoen et al., 1994). This is attributed to the fact that over 90% of the circulating CoQ10 is in the form of ubiquinol (Tomono et al., 1986) as well as the conversion of ubiquinone to ubiquinol occurring in the enterocytes prior to the lymphatic transport into circulation (Langsjoen et al., 1994).

Statistically significantly higher ($P < 0.001$) AUC, mean C_{max} and mean T_{max}, were demonstrated for the reduced and total Coenzyme Q10 when subjects were administered the CoQH-CF formulation compared to the Coenzyme Q10 formulation at all time points measured. The mean AUC was greater for the CoQH-CF formulation than the Coenzyme Q10 preparation representing a 430% increase over the commercial grade formulation. The fast and significant increase of plasma Total CoQ10 (T_{max}, 15.5 h) for CoQH-CF when compared to Coenzyme Q10 (T_{max}, 26.5 h) of a single dose is significant and suggests that the CoQH-CF formulation was readily bioavailable.

It is noteworthy that supplementation with a single dose of CoQH-CF resulted in a statistically significant increase in the bioavailability of CoQH-CF compared to the Coenzyme Q10 preparation. Coenzyme Q10 is vital to a number of activities related to energy metabolism (Ochiai et al., 2007). It is endogenously synthesized in the human body and is a cofactor in all living cells. CoQ10 is also found in many dietary sources, for example, fish, meats, oils, nuts and wheat (Wajda et al., 2007). Daily intake from food is reported to typically range between 3 and 5 mg/day, and is not considered to be sufficient in order to significantly raise blood and tissue levels (Wajda et al., 2007). Increasing age and various disease conditions are associated with reduced endogenous synthesis of CoQ10 leaving the body susceptible to increased lipid peroxidation (Wajda et al., 2007). Further, higher needs are associated with high energy requirements of individuals participating in high performance sports (Wajda et al., 2007). Over 90% of CoQ10 in human serum and biological tissue exist as reduced ubiquinol-10 ($CoQ10H_2$), which is a powerful lipid soluble antioxidant (Jiménez et al., 2007).

Previous research has demonstrated that reduced CoQ10 protects low density lipoproteins (LDLs) from lipid peroxidation by scavenging peroxyl radicals and reducing α-tocopherol radicals (Thomas et al., 1997). It has also been reported that despite its lower concentration, ubiquinol-10 is the first reacting antioxidant in plasma (Niklowitz et al., 2007). Oxidative stress plays a significant role in the aging process in different pathological conditions such as cardiovascular diseases, diabetes and cancer (Miles et al., 2005). Increasing interest in diagnosis, therapy and prevention of oxidative damage has centred on the levels of reduced CoQ10 and the ratio of CoQ10H2/CoQ10 (Jiménez et al., 2007). Reduced ratios have been reported in diseases associated with oxidative stress. In its reduced form as the hydroquinone (ubiqinol) CoQ10 is a potent lipophilic antioxidant and functions to protect the intra- and extra-cellular components from free radical damage.

The health benefits of CoQ10 have been studied and its efficacy in cardiovascular diseases when used as an adjunct to standard medication has been reported (Greenberg & Frishman, 1990; Langsjoen et al., 1994). The beneficial effects of CoQ10 have been attributed to its most fundamental role in mitochondrial energy production (Langsjoen et al., 1994).

In recent years, CoQ10 has become popular as a dietary supplement and is available as an over-the-counter supplement in various product forms. In its most pure form it is a crystalline powder insoluble in water, but with limited solubility in lipids, leading to poor absorption rates (Langsjoen et al., 1994). Previous studies have indicated the importance of product formulation (Bhagavan & Chopra, 2007). The presence of fat in product formulations has been indicated as promoting better absorption of CoQ10. While there seems to be a choice in dosage forms available, a major issue with the use of CoQ10 as a dietary supplement, or for therapeutic use is its potential efficacy. Absorption and/or the bioavailability of CoQ10 are a major determinant of efficacy.

Previous clinical trials have reported that higher than normal CoQ10 concentrations are necessary to promote uptake by peripheral tissues and to cross the blood–brain-barrier (Bhagavan & Chopra, 2006; Langsjoen et al., 1994). Blood CoQ10 levels of 2.4 μg/ml were demonstrated as having the highest benefit in congestive heart failure, while levels of at least 3.4 μg/ml were needed before therapeutic effects were seen from dietary supplementation in patients with congestive heart failure (Linnane et al., 2002). However, in neurodegenerative disease conditions the required plasma threshold levels appear to be much higher to produce a clinical response. It has been speculated that this may be a factor contributing to the lack of beneficial effects of CoQ10 and hence attributed to both the dosage and bioavailability.

In this bioavailability study, it was found that the increase per 100 mg value of the reduced formulation CoQH-CF was remarkably high when offered with oil. Several studies have reported on the pharmacokinetic parameters of orally ingested CoQ10 in the form of ubiquinone. The redox status of CoQ10 in plasma is thought to be a sensitive biomarker for oxidative stress (Niklowitz et al., 2007). Orally ingested CoQ10 regardless of whether it is in the form of ubiquinol or ubiquinone and regardless of dose is reported to appear in the plasma with little or no change in its redox status, suggesting that an efficient mechanism is in place to convert orally administered CoQ10 as ubiquinone to ubiquinol *in vivo*. Craft et al. (2005) demonstrated that this conversion took

place in the intestine following absorption and before entry into the lymphatic system.

In the current study, both formulations studied were presented as capsules; however, CoQH-CF was formulated using reduced CoQ10 with stabilizing ingredients in a soft gel capsule compared to the typical commercial formulations. It can be inferred that the product maintained integrity leading to an increased rate of absorption, resulting in greater bioavailability. In conclusion, the reduced CoQH-CF preparation was found to be far superior to the commercial formulation for bioavailability and warrants consideration not only as a dietary supplement, but also for clinical application.

Acknowledgement

This study was sponsored by Soft-Gel Technologies, Los Angeles, CA, USA.

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