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Relative Bioavailability of Two Forms of a Novel Water-Soluble Coenzyme Q10

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Key Words

Coenzyme Q10 · Ubiquinone · CoQ10 · Bioavailability · Pharmacokinetics · Q10Vital® · Antioxidants

Abstract

Background: Coenzyme Q10 (CoQ10) is a naturally occurring compound that plays a fundamental role in cellular bioenergetics and is an effective antioxidant. Numerous health benefits of CoQ10 supplementation have been reported, resulting in growing demands for its use in fortifying food. Due to its insolubility in water, the enrichment of most food products is not easily achievable and its in vivo bioavailability is known to be poor. Water solubility was increased significantly with the use of an inclusion complex with β -cyclodextrin. This complex is widely used as Q10Vital® in the food industry, while its in vivo absorption in humans has not previously been studied. **Methods:** A randomized three-period crossover clinical trial was therefore performed in which a single dose of CoQ10 was administered orally to healthy human subjects. The pharmacokinetic parameters of two forms of the novel CoQ10 material were determined and compared to soft-gel capsules with CoQ10 in soybean oil that acted as a reference. **Results:** The mean increase of CoQ10 plasma concentrations after dosing with Q10Vital® forms was determined to be over the reference formulation and the area under the curve values, extrapolated to infinity (AUC_{inf}), were also higher with the tested forms; statistically significant

120 and 79% increases over the reference were calculated for the Q10Vital® liquid and powder, respectively. **Conclusions:** The study revealed that the absorption and bioavailability of CoQ10 in the novel formulations are significantly increased, probably due to the enhanced water solubility.

Introduction

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a crucial component of the oxidative phosphorylation process in mitochondria, which converts the energy from carbohydrates and fatty acids into ATP to drive cellular machinery and synthesis [1]. It is essentially connected with the electron transfer and proton translocation in cooperation with mitochondrial dehydrogenases and cytochromes [2]. Further, CoQ10 has been known as a very effective antioxidant for over three decades [3], protecting against lipid peroxidation, DNA and protein oxidation and capable of functioning synergistically with other antioxidants [4–7]. In humans it is chiefly present in the most active organs like the heart, kidney and liver. Only 5–10% of total CoQ10 is located in cytosol, while there is about 50% in mitochondria, making it very accessible to free radicals that mainly form during the oxidative phosphorylation process [8].

The important role of CoQ10 in various clinical aspects has been established [9–12]. Several studies show a beneficial effect in cardiovascular [13–15], neurological and mitochondrial conditions [16–18], diabetes [19], along with male infertility [20]. A helpful effect in the treatment of cancer patients was observed either due to its antioxidant or bioenergetic activity [21–23], while an improvement in the tolerability of cancer treatment with CoQ10 supplements has yet to be confirmed [24, 25]. Its reduction of the formation of oxidative stress in human skin, mainly connected with increasing age, has also been reported [26]. Further, the endogenous synthesis of CoQ10 has been discovered to be inhibited by statins, drugs regularly used to treat many hypercholesterolemia patients, and therefore supplementation is suggested in these cases [27, 28].

CoQ10 is a lipid-soluble compound found in all organisms [11], but tissue levels decrease progressively after the age of 21 [9]. It is also supplied to the organism by exogenous sources, e.g. meat, migratory fish, dairy products and some vegetables (e.g. broccoli and spinach) as major sources in the human diet [29, 30], but these sources contribute just 3–5 mg CoQ10/day in the diet of populations of Western countries [31]. For this reason, the use of CoQ10 in the concept of functional food is very promising especially since its properties are in accordance with the basic criteria for food fortifiers, which should have the ability to beneficially influence the body functions to help promote the state of well-being and health and reduce the risk of diseases [32]. Nevertheless, due to the compound's lipophilicity, the enrichment of most food-stuffs, particularly aqueous-based low-fat products, is not easily achievable.

The future of functional foods depends on continuing advances in food science and the development of innovative technologies [33], and this also includes the use of CoQ10. Fortification was successfully achieved with increased water solubility achieved by the formation of an inclusion complex with β -cyclodextrin [34], a commonly used compound in the food industry and as a drug carrier system [35]. This novel patented form of CoQ10, available as Q10Vital® in liquid or powder form, was determined to be stable, well soluble in diverse aqueous media without taste or odor, and therefore very attractive to the food industry which immediately used it as a CoQ10 fortifier in various food products across Europe, such as dairy products (e.g. milk, yoghurt, kefir, etc.), fruit nectars, syrups and other beverages, honey, tea, etc. In addition, this novel form is also convenient as a food supplement in formulations such as hard-gel capsules, efferves-

cent tablets and syrups. It is also very appropriate for veterinary applications [36]. Interest in applications of Q10Vital® is justified not only by its technological convenience but also by the *in vitro* results and promising superior *in vivo* bioavailability and efficacy, which have been confirmed in a clinical study involving children with mitochondrial diseases and a bioavailability study in dogs, with both exhibiting encouraging results [unpubl. data].

For the further evaluation of Q10Vital® in humans, a study was performed in which the rate and extent of the absorption of the CoQ10 from the liquid and powder forms of this novel water-soluble CoQ10 material was studied in comparison with soft-gel capsules.

Several studies have been performed to examine the plasma CoQ10 response to perorally ingested CoQ10 formulations as an indicator of the compound bioavailability in these products [37, 38]. Due to its insolubility in water (<0.1 $\mu\text{g/l}$) and relatively high molecular weight ($M_r = 863$), CoQ10 is very poorly absorbed *in vivo*. The importance of the product formulation for bioavailability has been suggested by the continuous search for formulations with increased absorption [37, 39, 40]. Oil dispersions (soft-gel capsules) are found to be bioequivalent to CoQ10 powder in some cases [31, 39], while some other studies show increased bioavailability [41, 42]. Since the increased absorption of CoQ10 has been reported for some solubilized formulations [37, 43, 44], this was also expected in the case of Q10Vital®. Further, γ -cyclodextrin complex has already been shown to have increased bioavailability [45] but, unfortunately, the study was based on CoQ10 powder as a reference product, with extremely poor absorption capacity.

Here we report the results of a bioequivalence study in which relative bioavailability was investigated for two forms, namely liquid and powder, of the novel CoQ10 material with increased water solubility in comparison to soft-gel capsules with CoQ10 in soybean oil, currently the most widely used CoQ10 supplement on the European market.

Preparations, Subjects and Methods

CoQ10 Formulations

Q10Vital® liquid (T1; 7.5% water suspension of CoQ10 in the form of a complex with β -cyclodextrin) and Q10Vital® powder (T2; 5% CoQ10 in the form of a complex with β -cyclodextrin in a maltodextrin base) as test products were obtained from Valens Int., Ljubljana, Slovenia. Soft-gel capsules with 30 mg of CoQ10 in soybean oil were used as a reference product (R; Bio-Quinon®

Q10 from Pharma Nord, Vejle, Denmark). The CoQ10 content was analytically confirmed in all three preparations.

Study Population

Fourteen healthy non-smoking male volunteers aged 30–52 years with a body mass index between 20 and 25 were recruited in the Kutno area of Poland. Exclusion criteria included the intake of any drugs or food supplements within 2 weeks of the beginning of the study, hypotension, any clinically significant history of digestive tract, liver, kidney, cardiovascular or hematological disease, ECG abnormalities, gastrointestinal disorders or other acute or chronic diseases. The subjects did not participate in an investigational study or blood donation within 3 months prior to our study. A physiological and ECG examination and laboratory tests were carried out before the study. A summary of the demographic data of the study population is presented in table 1.

Relative Bioavailability Study Design

The study was approved by the Bioethics Committee at the Regional Physicians Chamber in Plock, Poland, and conducted at the Bioklinika clinic, Kutno, Poland, in accordance with current Good Clinical Practice guidelines, the Declaration of Helsinki and its amendments. Informed consent was obtained from each participant prior to their enrolment in the trial. The study was performed as a single-center, randomized, open-label, three-period crossover, single-dose trial in healthy subjects under fasting conditions. Because of the nature of the test substances (liquid, powder and soft-gel capsules) the study was performed as an open-labeled type in the clinical part. The study was divided into three 12-hour treatment periods, separated by a 1-week washout period. The subjects abstained from alcohol, caffeine, grapefruit products and citrus fruits from 24 h prior to the product administration until the end of the sample collection in each part of the study. Following an overnight fast, a blood sample to determine the baseline CoQ10 was taken the next morning (day 1) and a single dose of the product containing the equivalent of 60 mg of CoQ10 was administered perorally together with approximately 150 ml of water, according to the randomization scheme. Blood samples for the CoQ10 analyses were taken at 20 min, 40 min, 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after the administration. Two hours after the administration, a standardized breakfast was served; in addition two standardized meals were served, based on a 1,500-kcal daily diet, during the next 10 h. The treatment continued in accordance with the randomization scheme on days 8 and 15 when the protocol was repeated.

Analytical Procedures

The concentrations of the CoQ10 in the plasma were determined by extraction to hexane, followed by high-pressure liquid chromatography (HPLC) on the RP column and equipped with a mass spectrometer in accordance with the standard procedures of the QASKI quality assurance system of the National Institute of Chemistry and reasonably transferred current guidelines of the European regulatory authorities. LC grade chemicals and reagents were used; the CoQ10 standard was purchased from Sigma Aldrich.

Standard Solutions

A stock solution of 500 mg/l was prepared by dissolving 10 mg of CoQ10 in 20 ml of 2-propanol. The stock solution was stable for

Table 1. Population demographic data (n = 14, male subjects)

Parameter	Age years	Height cm	Weight kg	BMI
Range	30–52	169–192	62–92	20.2–24.9
Mean ± SD	39.6 ± 6.4	180 ± 6.7	76.3 ± 8.6	23.5 ± 1.5

1 month when stored in the dark at 4°C. From the stock solution, eight different calibration standard solutions were prepared from 0.1 to 20 mg/l. These solutions were used for quantification.

Sample Preparation

Blood samples were drawn into blood collection tubes containing EDTA and centrifuged at 4,500 rpm for 15 min at 5°C. The plasma was separated and kept frozen at $-80 \pm 10^\circ\text{C}$ until the analysis. For determining the CoQ10, exactly 400 µl of plasma was denaturated with 200 µl of 10% perchloric acid in ethanol. The samples were extracted 3 times with 2 ml of *n*-hexane. The combined organic extracts were concentrated with a rotary evaporator (Rotavapor R-144 equipped with a water bath B-480; Büchi, Flawil, Switzerland). The residue was redissolved in 200 µl of 2-propanol and analyzed with the HPLC/MS method that was developed in our laboratory.

HPLC/MS

The separation and quantitative determinations of CoQ10 were performed with the Surveyor LC system (Thermo Finnigan, Riviera Beach, Calif., USA) equipped with a LCQ mass detector (Finnigan MAT, San Jose, Calif., USA).

The gradient separation with two mobile phases was used for the quantitative determination of CoQ10. Phase A was a mixture of 1.4-dioxan, methanol, ethanol and acetic acid (5:30:65:0.1, v/v/v/v), while phase B was pure 100% acetonitrile. The starting condition with 30% A and 70% B was applied for 1 min, then the amount of the mobile phase A was linearly increased to 100% within a period of 11 min and stood at 100% for the next 3 min. At the end of a run the concentration was reverted to the initial conditions and kept for 2 min. A Gemini C18 column, 100 × 4.6, 3 µm (Phenomenex, Torrance, Calif., USA) was used, the flow rate was 1.0 ml/min, the injection volume was 10 µl, and the temperature of the column was 45°C. MS identification and quantification were undertaken in a positive APCI ionization mode. The ionization discharge current was 5.0 µA and the source temperature was 450°C. The capillary voltage was 23.0 V, the tube lens offset was 10.0 V, the capillary temperature was 250°C, the sheath gas pressure was 2.7 bar, while the auxiliary gas flow was 3 l/min. The data were processed using Xcalibur 1.3 software (Thermo Finnigan Corp., USA). The chromatograms were obtained in the SIM mode with a molecular mass of CoQ10 (M+H)⁺ m/z 863.4 ± 0.5, while the retention time was 10.6 ± 0.1 min.

Statistical Analyses

The data were analyzed using the GraphPadPrism v.3.02 (GraphPad Software), Equiv Test 2.00 (Statistical Solution) and Excel 2000 (Microsoft) software. The mean, standard deviation of the mean (SD), coefficient of variation [CV (%)] and range (min

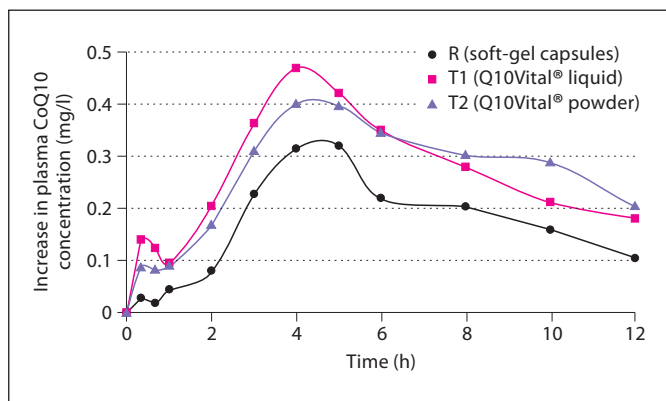


Fig. 1. Increase of plasma concentration of CoQ10 versus the time profiles for oral administration of 60 mg CoQ10 in different formulations in fasting conditions ($n = 14$).

Table 2. Summary of the pharmacokinetic parameters ($n = 12$)

Parameter	Δc_{\max} mg/l	AUC_t mg·h/l	AUC_{inf} mg·h/l	t_{\max} h
<i>Mean (\pm SD)</i>				
T1 (Q10Vital® liquid)	0.58 ± 0.32	7.0 ± 2.5	22.9 ± 15.6	4.1 ± 1.3
T2 (Q10Vital® powder)	0.55 ± 0.19	7.2 ± 2.8	19.0 ± 10.3	4.1 ± 2.3
R (soft-gel capsules)	0.44 ± 0.16	5.5 ± 1.2	11.4 ± 4.5	4.0 ± 1.2
<i>Ratio for mean, %</i>				
T1/R	132	125	220	–
T2/R	125	129	179	–

and max) were calculated. The maximum plasma concentration (c_{\max}), maximum increase in plasma concentration (Δc_{\max}), time to reach the peak plasma concentration (t_{\max}) and areas under the curve ($AUC_{0-12\text{ h}}$, AUC_{inf}) were calculated for each subject. AUC values were calculated according to the trapezoidal method, while individual pre-dose plasma CoQ10 concentrations were used as the baseline concentration. Two volunteers, one with the highest and one with the lowest relative bioavailability for T1, were excluded from the statistical evaluation. A normal distribution analysis for pharmacokinetic parameters (untransformed and ln-transformed data) was performed using the Kolmogorov test (significance level $\alpha = 0.05$) while an F test was used for a variance homogeneity analysis applying the same significance level. Confidence intervals for the relations of the chosen parameters of the relative bioavailability were constructed at an interval of 80–125% for c_{\max} , Δc_{\max} , AUC_t and AUC_{inf} (ln-transformed data); a 90% (1–2 α) confidence level was used (according to the EMEA and FDA guidelines). Bioequivalence was tested by null hypotheses; two Schuirmann one-sided tests were performed by the construction of two series of one-sided hypotheses for untransformed and ln-transformed values.

Results

All 14 subjects completed all three 60-mg CoQ10 single-dose treatment periods. The mean endogenous plasma CoQ10 concentration (\pm SD) in the group was determined to be 0.26 ± 0.10 mg/l. The increase in the mean plasma CoQ10 concentration versus the time profile for all three CoQ10 formulations is presented in figure 1. The curves for the formulations are quite similar regarding the time the peak plasma concentration was reached, while an additional smaller peak was observed about half an hour after the administration of the tested products (T1, T2); in both cases, a higher mean plasma CoQ10 concentration was observed along the whole 12-hour time scale.

Twelve individuals were included in the pharmacokinetics analyses while two outliers, the one with the highest and the one with the lowest relative bioavailability for tested product T1, were excluded. The results are summarized in table 2. t_{\max} was determined to be at about 4 h after the administration; almost no difference was observed between the formulations.

The maximum plasma concentration parameters (c_{\max} , Δc_{\max}) show a normal gaussian distribution; the mean Δc_{\max} (\pm SD) was determined to be higher for the Q10Vital® liquid (T1: 0.58 ± 0.32 mg/l) than for the Q10Vital® powder (T2: 0.55 ± 0.19 mg/l), while almost the same c_{\max} was observed (T1: 0.85 ± 0.37 mg/l, T2: 0.85 ± 0.25 mg/l). In comparison with the reference soft-gel formulation, both forms show a higher Δc_{\max} by 32 and 25% respectively (R: 0.44 ± 0.16 mg/l); a similar observation was made for c_{\max} (R: 0.71 ± 0.14 mg/l), while the variance difference between the tested and reference formulations was not significant (F test), which is probably due to the limited number of subjects.

The areas under the curves were also calculated to evaluate the relative bioavailability; the mean AUC_t (\pm SD) 7.0 ± 2.5 mg·h/l was determined for the Q10Vital® liquid (T1) and 7.2 ± 2.8 mg·h/l for the powder (T2), in contrast with the lower value for the reference product (R: 5.5 ± 1.2 mg·h/l). The area extrapolated to infinity (AUC_{inf}) is also substantially higher for both tested products with enhanced water solubility; a 120% increase was observed for the Q10Vital® liquid (T1: 22.9 ± 15.6 mg·h/l), while 19.0 ± 10.3 mg·h/l for the powder (T2) represents a 79% increase over the reference capsules (R: 11.4 ± 4.5 mg·h/l). The difference was confirmed to be statistically significant and a normal gaussian distribution was observed.

Substantial variations were detected in the ability to absorb CoQ10 between the individual subjects. This resulted in high standard deviations of the calculated pharmacokinetic parameters. The evaluation of the area under the curve shows a statistically important difference in the bioavailability of the studied products. Both tested formulations (Q10Vital[®] liquid and powder) failed the bioequivalent limits (EMA, FDA) because they had a greater extent of absorption compared to the soft-gel capsules (R) and can be claimed to express a supra-bioavailability. High interindividual variations in the CoQ10 absorption were observed. This variation is most easily shown in an example of an individual subject for whom the relative bioavailability of CoQ10 in the Q10Vital[®] liquid (T1/R) was determined to be 9.2 times greater than in the soft-gel capsules. This subject (age 34, BMI 21.7 kg/m²) also had the lowest detected endogenous CoQ10 level (0.12 ± 0.03 mg/l) and was excluded from the statistical evaluation.

Discussion

While CoQ10 has very limited use in the food industry due to its insolubility in water, its inclusion complex with β -cyclodextrin has become widely used for achieving the functional food concept. For example, 8.5 g of CoQ10 in this form, known as Q10Vital[®], can be dissolved in 1 kg of milk, increasing the CoQ10 content in low-fat milk to over 5,000 times its natural concentration. While a better *in vivo* absorption was determined for some other CoQ10 formulations with increased water solubility, the aim of the study was to examine the relative bioavailability of the novel CoQ10 material with enhanced water solubility (Q10Vital[®]) in both powder and liquid forms with the reference soft-gel capsules. No safety issues were detected during the study; this was expected as many large-scale clinical trials have shown that even chronic oral doses of 800 mg CoQ10/day are considered to be safe [9]. Some minor adverse effects have been reported at doses higher than those used in our case, and they are mainly connected with mild gastrointestinal disturbances, especially after an overnight fast [43].

The trial was conducted under fasting conditions, while a standardized breakfast was consumed 2 h after the dosage, based on a 1,500-kcal daily low-fat diet. This was performed to minimize any potential confounding effect of food containing CoQ10 and its analogues when given upon administration. Further, a very low intake of CoQ10 is reported with a normal diet [31] and it would therefore be unlikely to affect the bioequivalence esti-

mates of the study. We should note that the consumption of any food supplements was prohibited 14 days prior to the end of the study since a substantial effect on the CoQ10 plasma level could have been created.

Baseline plasma CoQ10 concentrations were found to be around 0.3 mg/l, slightly lower than previously reported in apparently healthy humans from the Czech Republic, a neighboring country (0.22–0.89 mg/l) [46]. We determined that the baseline plasma concentration of CoQ10 was not related to the application of the formulation in the previous study period, meaning that an appropriate washout period between the treatments was used. A 12-hour observation period was used after each treatment, like in many previous studies [40, 41, 44, 47]. Nevertheless, the plasma CoQ10 level did not reach the baseline completely after the observed time. The areas under the curves were therefore also extrapolated to infinity (AUC_{inf}) for a more realistic comparison. A longer observation period should be used in future studies.

Only minor differences in the time to reach the peak plasma concentration (t_{max}) were observed with a mean at 4 h after the administration for all three formulations. Longer t_{max} values (6 h) had previously been observed for soft-gel capsules when dosing with food [42]. A higher mean increase in plasma CoQ10 concentration ($\Delta c_{max} \pm SD$) was determined for the novel formulations in comparison to the reference product: 0.58 ± 0.32, 0.55 ± 0.19 mg/l for Q10Vital[®] liquid (T1) and powder (T2) and 0.44 ± 0.16 mg/l for soft-gel capsules (R), respectively; 32% over the reference formulation for T1 and 25% for T2. The better absorption of water-soluble formulations was also confirmed with AUC values; a statistically significant difference in the bioavailability of CoQ10 between the tested products and the reference formulation was detected and FDA bioequivalence limits (90–125%) were exceeded for both Q10Vital[®] products: 120 and 79% increases in AUC_{inf} over the reference soft-gel capsules was observed for Q10Vital[®] liquid (T1: 22.9 ± 15.6 mg·h/l) and powder (T2: 19.0 ± 10.3 mg·h/l), respectively. The efficacy of absorption was calculated for all three products as a percentage of the initial dose present in the plasma at t_{max} , assuming a 2.5-liter total plasma volume: 1.8% efficacy was determined for the reference product (R) and 2.4 and 2.3% for the tested T1 and T2, respectively.

Quite high standard deviations were observed that were mainly due to differences in the ability to absorb CoQ10 in individual subjects, a phenomenon already reported in the literature [40]. Higher standard deviations of pharmacokinetic parameters were observed for both novel unformulated forms compared to the reference (in

the form of formulated oily soft-gel capsules). This phenomenon can be explained by the sensitivity of the tested CoQ10 form to individual pH differences, particularly in the gastric part of the gastrointestinal tract as the acidic pH may affect interactions between the guest (CoQ10) and host (β -cyclodextrin) molecules. The use of Q10Vital® in an appropriate formulation, e.g. in a food matrix, could therefore reduce the variability in absorption and further improve its superior bioavailability. Therefore, further studies of the CoQ10 bioavailability of the novel tested form should be performed and focus primarily on the effects of different food matrixes, especially since the form is very appropriate for, and is already widely used in, the food industry for fortification and as a food supplement.

In conclusion, this single-dose bioequivalence study revealed that the oral absorption and bioavailability of CoQ10 can be significantly affected by increasing the water solubility with the formation of a CoQ10/ β -cyclodex-

trin complex, which demonstrates the novel tested form's superior bioavailability over the soft-gel capsules. This result is in line with previous estimations related to the improved bioavailability of CoQ10 forms with enhanced water solubility. In addition, the higher standard deviations for the tested forms of the novel CoQ10 material as compared to the reference product indicate that its bioavailability could be further improved by using it as a food additive or food supplement. That is because the appropriate matrixes reduce its pH sensitivity, stabilize its solutions in the gastrointestinal tract and thereby improve its in vivo absorption.

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