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Coenzyme Q10
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Absorption
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Capsules
Tablets
Dosage forms

Relative Bioavailability of Coenzyme Q10 Formulations in Human Subjects

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Summary: *The relative bioavailability of typical commercially available forms of coenzyme Q10 (CoQ10) was compared with that of Q-Gel, a new solubilized form of CoQ10, in human subjects in two separate trials. In the first, standard softgel capsules containing CoQ10 suspension in oil, powder-filled hardshell capsules and powder-based tablets were tested along with Q-Gel using a daily dosage of 120 mg for three weeks. The baseline plasma CoQ10 values were all very tight (0.50–0.52 µg/mL) and after three weeks the values were 1.37, 1.63 and 1.60 µg/mL for the first three products and 3.31 µg/mL for Q-Gel. The relative bioavailability calculated using the areas under the plasma CoQ10 curve (AUC) were (µg/mL × time in days) 7.16 (100%), 8.97 (125%), 9.19 (128%) and for Q-Gel 22.86 (319%). The second trial, carried out to replicate the findings in the first, employed only two groups, namely the standard softgel capsules containing the suspension and Q-Gel, and the duration was extended to four weeks. Plasma CoQ10 values were: baseline 0.40 and 0.38 and after four weeks 1.26 and 2.80; the corresponding AUCs were: 8.33 (100%) and 22.75 (273%). Thus, the data from both the trials show that Q-Gel, the new solubilized form of CoQ10, is vastly superior to typical commercially available preparations of CoQ10. This means much low-*

er doses of Q-Gel will be required to rapidly reach and maintain adequate blood CoQ10 values than with any of the other currently available products.

Introduction

Coenzyme Q10 (CoQ10), also known as ubiquinone-50, is a naturally-occurring compound which plays a key role in energy metabolism as an integral part of the electron transport system. As such, its importance in the function of the muscle tissue, especially the heart, has been well recognized. CoQ10 supplementation has been an accepted preventative and therapeutic modality in many western countries and also in Japan not only for heart disease but for other ailments as well [1–3].

Commercially available CoQ10 supplements are usually oil-based suspensions in softgel capsules and powder-filled hardshell capsules, the former being more common. While there have been many clinical studies using these products, there are very few reports in the literature on the absorption or bioavailability of CoQ10 in these preparations either in animal models or human subjects [4–6]. Also, there is very little informa-

tion on the plasma kinetic profile of CoQ10 upon its oral administration in human subjects.

When we tested the commercially available products in the laboratory for their performance characteristics, we discovered to our great surprise that not only did these products fail the current dissolution test (U.S. Pharmacopeia 23) but also showed a total lack of dissolution (0% instead of the required > 75%). This was clearly suggestive of their poor absorption *in vivo*. We therefore undertook the present study to examine the relative bioavailability of CoQ10 in commonly available CoQ10 products on the market and also to compare them with a new softgel formula containing a fully-solubilized form of CoQ10 (Q-Gel Softsules) in human subjects. A preliminary report of our findings was presented at the Experimental Biology '97 meeting [7].

Materials and Methods

The study was carried out at the New York Medical College – Our Lady of Mercy Medical Center in Bronx, NY, and the protocols were approved by their institutional review board. Prior to running the human trials, the dosage forms were assayed in the laboratory for their actual CoQ10 content (label claim: 15 mg CoQ10 per tablet/capsule) and also tested for their dissolution properties using the USP 23 methodology [8]. Briefly, this involves determining the amount of CoQ10 dissolved in 60 min using USP Apparatus 2 (with paddle) at 75 RPM in a medium of 0.1 N HCl (500 mL) at 37°C. Coded unit doses of the products (120 mg CoQ10/dose) were then prepared by the hospital pharmacy for use in the human trials.

The study was carried out in two parts. In the first experiment, an oil-based capsule, a powder-filled capsule and a tablet formula were compared with a new solubilized form of CoQ10 in softgel capsules (Q-Gel Softsules, Tishcon Corp., Westbury, NY) based on a process developed by Biosytes (USA). This is a proprietary formula (patent pending) containing CoQ10 in a blend of sorbitan monooleate, polysorbate 80,

medium chain triglycerides, propylene glycol, d-alpha tocopherol and PVP (Plasdone). In the second experiment, the standard oil-based softgel capsules containing CoQ10 suspension were compared with Q-Gel. These were randomized double-blind trials, and the general design of the experiments was as follows.

Normal healthy subjects (20–56 years old) were selected for the study after obtaining their informed consent. Those who smoke, consume alcohol or take any type of non-prescription or prescription medication were excluded. In addition, only those with a fasting plasma CoQ10 value between 0.2–0.6 µg/mL on two consecutive tests (days –7 and 0) were selected for the study. We purposely selected subjects with tight plasma CoQ10 values in the low normal range so as to allow for adequate increases and also to minimize individual variability. Their dietary intake of CoQ10 was roughly estimated to be in the range of 3–5 mg a day. After the second baseline blood sample was drawn on day 0, the subjects were given coded CoQ10 preparations (total daily dose 120 mg) to swallow in the presence of the principal investigator followed by a standard breakfast. Thereafter, they visited the clinic everyday to ingest their daily dose of CoQ10. Fasting blood samples (EDTA) were collected on a weekly basis and plasma stored at –85°C until analysis (within four weeks). Total coenzyme Q10 in plasma was determined by reverse-phase HPLC using hexane extraction on a C-18 column (15 cm, 5 micron) with methanol:hexane (95:5) as the mobile phase and UV detection [9].

Experiment 1: Groups (four): 1. Oil suspension in softgel capsules 2. Tablets 3. Solubilized CoQ10 in softgel capsules (Q-Gel Softsules) 4. Powder-filled hardshell capsules.

Number of subjects per group: Six. Duration: Three weeks. Blood collection: Two baselines and then at weekly intervals.

Experiment 2: Groups (two): 1. Oil suspension in softgel capsules. 2. Solubilized CoQ10 in softgel capsules (Q-Gel Softsules). Number of subjects per group: 12. Duration: Four weeks. Blood collection: Two baselines and then at weekly intervals.

Data Analysis: Analysis of variance (ANOVA) and t-tests were employed to evaluate differences between groups with respect to (a) plasma CoQ10 values at baseline and at weekly intervals and (b) area under the curve (AUC) for plasma CoQ10 [10]. The relative bioavailability was calculated using the plas-

Table I: Mean Plasma CoQ10 Values at Baseline and After 21 Days (Experiment 1)

CoQ10 Formulations	Mean Plasma CoQ10 (µg/mL) ± S.D. ¹		p Value ²
	Baseline	21 Days	
Softgels (suspension)	0.50 ± 0.11	1.37 ± 0.25	0.0004
Tablets	0.52 ± 0.11	1.60 ± 0.22	0.0004
Q-Gel softgels	0.50 ± 0.11	3.31 ± 1.35	–
Hardshells (powder-filled)	0.50 ± 0.12	1.63 ± 0.21	0.0004

¹ Standard deviation of the mean

² 21-Day values compared with Q-Gel

Table II: Mean Plasma CoQ10 Area Under the Curve (AUC) (Experiment 1)

CoQ10 Formulations	Mean AUC ± S.D. ¹ µg/mL × time (days)	Percent of Reference	p Value ²
Softgels (suspension)	7.16 ± 1.58*	100	0.0003
Tablets	9.19 ± 1.02	128	0.0003
Q-Gel softgels	22.86 ± 10.77	319	–
Hardshells (powder-filled)	8.97 ± 1.64	125	0.0003

¹ Standard deviation of the mean

² Compared with Q-Gel

ma CoQ10 AUC data. The mean AUC following supplementation with CoQ10 was calculated as:

$$\frac{n}{\sum_{i=1}^n (t_i - t_{i-1})} \left(\frac{[v_i + v_{i-1}]}{2} - v_0 \right)$$

where t refers to the day following initiation of supplementation, i refers to the specific sampling period, v equals the plasma CoQ10 value at t , and n refers to the number of data points during supplementation. The variable v at period one is the arithmetic mean of two baseline measurements.

Results

The dissolution test showed a total lack of dissolution (0%) with the softgel capsules containing the CoQ10 suspension, tablets containing the powder and powder-filled hardshell capsules, whereas Q-Gel, containing the new solubilized form of CoQ10, showed complete dissolution (100%). These results were suggestive of what one might expect from the human bioavailability studies.

Experiment 1: Plasma CoQ10 values at baseline were practically identical in the four groups, ranging from 0.5–0.52 $\mu\text{g/mL}$. There was a significant increase in plasma values following three weeks of supplementation in all the four groups, with the Q-Gel group showing the highest increase. These data are shown in Tables I and II, and in Figure 1. The Q-Gel group (Group 3) showed a 6.6-fold increase over baseline values whereas the other three groups were much lower and ranged from 2.7 to 3.3. The relative bioavailability calculated using the AUC data (Table II) shows that Group 3, i.e. the Q-Gel group is vastly superior to the other three products. Using the softgels containing the oil suspension as the reference product (since this is the more commonly available dosage form), Q-Gel shows a markedly higher response (about 3.2-fold in three weeks), with continued increase in plasma CoQ10 values projected beyond the three-week period as shown in Figure 1.

Experiment 2: The second experiment was carried out in order to confirm the results of the first trial showing the superiority of Q-Gel capsules. Here, only two groups were employed, viz. Q-Gel and the reference capsules, containing

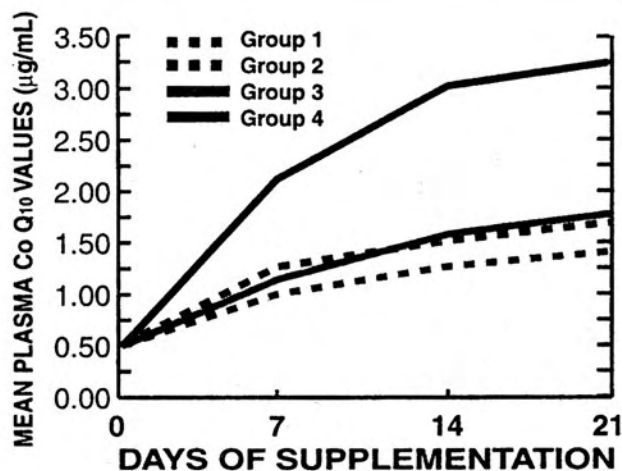


Figure 1: Mean plasma CoQ10 values during three weeks of supplementation with CoQ10 formulations. Group 1 Softgel capsules containing CoQ10 suspension in oil, Group 2 Powder-based tablets, Group 3 Q-Gel Softsules (softgel capsules) and Group 4 Powder-filled hardshell capsules. Q-Gel significantly different from the other three products at 21 days, $p = 0.0004$.

CoQ10 suspension in oil and the duration of the study was extended to four weeks. The results are shown in Tables III and IV and in Figure 2. Overall, they are remarkably similar to those of the first experiment. The increase in plasma CoQ10 values over baseline was 7.37-fold for Q-Gel and 3.15-fold for the oil suspension. The AUC values likewise reflected the superiority of Q-Gel, and all these differences were highly significant. Again in this experiment the plasma CoQ10 values in the Q-Gel group rose steadily, showing a far greater increase at the end of the four week period.

Discussion

The objective of the study was to compare the relative bioavailabilities of typical commercially available CoQ10 products along with Q-Gel, a new solubilized form of CoQ10 as softgel capsules. We undertook the development of the water-miscible form of CoQ10 after we discovered that none of the currently marketed products would pass the USP dissolution test (all showing a total lack of dissolution, i.e. 0% as opposed to the required >75% dissolution) and this was certainly indicative of their poor bioavailability. When the new product Q-Gel was first tested in the laboratory for its dissolution profile, it

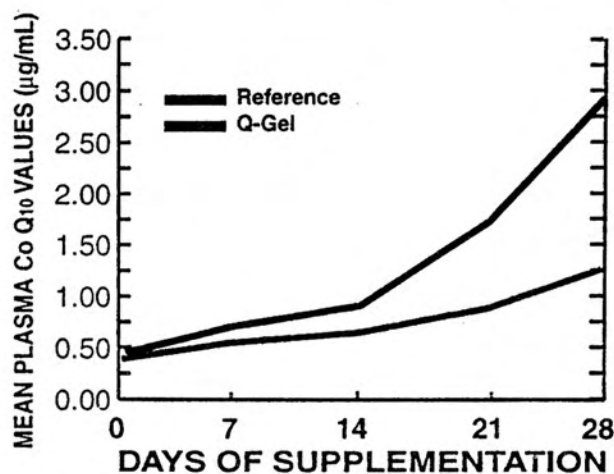


Figure 2: Mean plasma CoQ10 values during four weeks of supplementation with CoQ10 suspension in oil (softgel capsules) as the reference and Q-Gel Softsules (softgel capsules). Q-Gel significantly different from CoQ10 suspension in oil at 28 days, $p = 0.0000$.

showed complete dissolution (100%). This finding was suggestive of its superior absorption and bioavailability and this has now been confirmed in two separate human trials in the present study.

One other interesting observation made in this study is that most of the subjects in the Q-Gel group in both the experiments reported having a «higher» energy level about a week after Q-Gel ingestion and continued thereafter. While this was anecdotal in nature and not quantifiable, a thorough investigation of this phenomenon will be very useful. There are a few similar qualitative observations of this nature in the literature [11].

There are very few reports on the relative bioavailability of CoQ10 and no systematic study on the efficacy of the different products on the market has been carried out thus far. Although the data on bioavailability is sparse, there have been numerous reports on the therapeutic efficacy of CoQ10 in human subjects [1–3]. They have generally involved rather large doses (hundreds of mg) and in instances where blood plasma or serum CoQ10 was determined, the values rarely reached 2.5 µg/mL, a value considered desirable for observing a potential clinical benefit [12, 13]. To cite a few reports where blood CoQ10 was determined, in one study by Laaksonen *et al* [14] 120 mg of CoQ10 in powder-filled capsules was administered for six weeks and serum CoQ10 values increased from about

0.79 to 1.70 µg/mL. Porter *et al* [11] gave 150 mg in a tablet formula for two months and found an increase in whole blood CoQ10 values from about 0.71 to 1.07 µg/mL. In the study by Lonrot *et al* [15] the effect of a combined dose of CoQ10 (going upto 300 mg in powder-filled capsules) and ascorbic acid (upto 1000 mg) was examined and the plasma CoQ10 reached a value of 2.13 µg/mL after four weeks. These examples demonstrate the difficulty in achieving adequate blood levels with the available CoQ10 preparations despite using rather high doses.

Of the few studies on the bioavailability of CoQ10 cited earlier, the one by Weis *et al* [4] involved four formulations in a single-dose study. These were a powder-filled capsule, and three softgel formulas containing CoQ10 suspension in soybean oil, two with emulsifiers and one without, and the dose was 100 mg. The data showed that the soybean oil suspension without the emulsifiers was better than the others. In another study, Folkers *et al* [5] examined the effect of longterm supplementation with CoQ10 (suspension in soybean oil, dose 90 mg a day) and according to their data blood levels plateau at about three months (reaching a value of 2.03 µg/mL from a baseline value of 0.98) and no further change was seen at nine months (1.9 µg/mL). In a very recent report, Kaikkonen *et al* [6] compared an oil-based (suspension) and granule preparations both as capsules (90 mg for two months) and they concluded that there was no difference in bioavailability between the two formulations.

While the above findings are inconclusive as to which type of product is better, one thing is clear, i.e. none of them is able to rise plasma CoQ10 values to an adequate range to confer any potential benefit. In the present study we compared in the same trial the relative bioavailability of CoQ10 in all three types of commer-

Table III: Mean Plasma CoQ10 Values at Baseline and 28 Days (Experiment 2)

CoQ10 Formulations	Plasma CoQ10 (µg/mL) ± S.D. ¹		p Value ²
	Baseline	28 Days	
Softgels (suspension)	0.40 ± 0.11	1.26 ± 0.50	0.0000
Q-Gel softgels	0.38 ± 0.11	2.80 ± 0.80	–

¹ Standard deviation of the mean

² 28-Day values

Table IV: Mean Plasma CoQ10 Area Under the Curve (AUC) (Experiment 2)

CoQ10 Formulations	Mean AUC $\pm$ S.D. ¹ $\mu\text{g/mL} \times \text{time (days)}$	Percent of Reference	p Value
Softgels (suspension)	8.33 ± 3.20	100	0.0001
Q-Gel softgels	22.75 ± 8.69	273	—

¹ Standard deviation of the mean

cially available products, viz. oil suspension in softgel capsules, powder-filled hardshell capsules and tablets (powder), along with Q-Gel, the new solubilized CoQ10 formula in softgel capsules (using the new Biosolv process). Our data thus clearly demonstrate that the enteral absorption and bioavailability of CoQ10 can be greatly enhanced by using appropriate solubilization techniques. With Q-Gel, plasma CoQ10 values showed a sharp increase reaching the "therapeutic" range (above $2.5 \mu\text{g/mL}$) within 3–4 weeks and further increases with time as evidenced by the slopes in both the experiments. Since the study was not extended beyond 4 weeks, we do not know how long it would have taken for plasma CoQ10 values to reach a plateau under these conditions. Nevertheless, it is clear from the present data that because of the vastly superior relative bioavailability of Q-Gel, much lower doses of Q-Gel will be required to rapidly reach and maintain adequate blood levels than with any of the currently available CoQ10 products on the market.

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