

# A Study on the Bioavailability of a Novel Sustained-Release Coenzyme Q10- $\beta$ -Cyclodextrin Complex

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## Abstract

**Objectives:** The objective of this study was to compare the relative bioavailability of a coenzyme Q<sub>10</sub> (co-Q<sub>10</sub>)- $\beta$ -cyclodextrin inclusion complex (MicroActive Co-Q<sub>10</sub> complex by BioActives in Worcester, Massachusetts) with 2 commercially available formulations: a hard gelatin capsule of crystalline co-Q<sub>10</sub> and an oil-solubilized co-Q<sub>10</sub> softgel containing a proprietary absorption enhancer.

**Materials and Methods:** The first study compared the MicroActive Co-Q<sub>10</sub> complex to both a crystalline product and a solubilized product. Five subjects were included in a 24-hour crossover design with a single dose of 180 mg of co-Q<sub>10</sub>. The second study compared the MicroActive Co-Q<sub>10</sub> complex with the solubilized form, using 60 mg of co-Q<sub>10</sub> 1 $\times$ /day. The study had an acute phase (0-24 h, single dose) and a 21-day accumulation phase, with 11 subjects per group.

**Results:** The results of the first study indicated that the MicroActive Co-Q<sub>10</sub> complex showed a sustained release and that

its bioavailability was significantly better than the crystalline form by a factor of 3.7 ( $P < .0001$ ). The intersubject variance in the bioavailability of the solubilized form was significantly greater than in the other 2 forms ( $P < .05$ ).

In the second study, the 0- to 24-hour absorption confirmed the sustained-release property of the MicroActive Co-Q<sub>10</sub> complex as well as the significantly higher and uniform bioavailability ( $P < .006$ ). All the subjects in the accumulation phase of the study showed a minimum of doubling in the plasma co-Q<sub>10</sub> levels after 21 days of MicroActive Co-Q<sub>10</sub> supplementation, which represents a 100% response rate. The solubilized form showed a response rate of only 44%, again confirming the greater and more uniform bioavailability of the MicroActive product.

**Conclusions:** Sustained release MicroActive Co-Q<sub>10</sub> is more universally bioavailable, thereby improving its ability to deliver both maintenance and therapeutic doses of co-Q<sub>10</sub>.

**Disclosure:** Doddabele Madhavi, PhD, a biochemist, is a managing partner of BioActives LLC where she is head of research and development. She is the author or coauthor of more than 20 peer-reviewed papers and book chapters. Daniel Kagan, PhD, a business strategist, is a managing partner of BioActives LLC and head of strategic business development. He holds a PhD in entrepreneurial studies.

Coenzyme Q<sub>10</sub> (co-Q<sub>10</sub>), a lipid-soluble nutrient widely used as a dietary supplement, is a crystalline powder formulated into various dosage forms such as granules, tablets, hard capsules, wafers, and softgels. Co-Q<sub>10</sub> plays a key role in mitochondrial electron transport and additionally functions as a powerful antioxidant. Besides dietary intake, co-Q<sub>10</sub> is endogenously synthesized via the mevalonate pathway. Cellular co-Q<sub>10</sub> content is reduced as part of the aging process<sup>1</sup> in a number of disease states<sup>2-4</sup> and during therapy with statins.<sup>5</sup> Hence, supplementation of co-Q<sub>10</sub> has therapeutic benefits for aging and several diseases, such as heart disease,<sup>6</sup> periodontal disease,<sup>7</sup> and Parkinson disease.<sup>8</sup>

Due to its lipophilic nature and large molecular weight, crystalline co-Q<sub>10</sub> has poor bioavailability in humans. A number of formulations have been developed to improve the bioavailability of crystalline co-Q<sub>10</sub>, such as oil dispersions and solubilized forms suitable for softgels. Many of these formulations rely on some form of micronization or micellization, often coupled with absorbance enhancers. Because they require softgel encapsulation, these products are relatively expensive and have limitations common to all softgel products, such as the amount of the active

compound that can be encapsulated as a solution, larger capsule size for higher dosages, and a specific selection of formulation ingredients that are compatible with the shell.

Cyclodextrins (CDs) have been widely used in the pharmaceutical industry to improve the bioavailability of lipophilic compounds. Cyclodextrins are cyclic ( $\alpha$ -1,4)-linked oligosaccharides with hydrophobic inner cavities and hydrophilic outer surfaces that provide a microenvironment for various lipophilic molecules by forming inclusion complexes. The  $\alpha$ -,  $\beta$ -, and  $\gamma$ -CDs are the most common natural CDs consisting of 6, 7, and 8 D-glucopyranose residues, respectively, linked by  $\alpha$ -1,4 glycosidic bonds into a macro cycle.<sup>9,10</sup> The complexation with CDs improves the dissolution rate and bioavailability of poorly water-soluble molecules.<sup>11</sup> Furthermore, complexes with hydrophobic cyclodextrins have exhibited a sustained-release mechanism that might improve the overall bioavailability of lipophilic compounds.<sup>12</sup>

Complexation of co-Q<sub>10</sub> with cyclodextrins has been tried by a few investigators to improve the dissolution properties and stability of the compound.<sup>13</sup> However, very little information is available on the oral bioavailability of the co-Q<sub>10</sub> complexed with natural cyclodextrins such as  $\gamma$ - or  $\beta$ -cyclodextrin. Cuomo and Rabovsky have reported a modest improvement in the uptake of co-Q<sub>10</sub> complexed with  $\gamma$ -cyclodextrin in a single-dose study.<sup>14</sup> In another study, Terao et al reported an improvement in the bioavailability of co-Q<sub>10</sub> complexed with  $\gamma$ -cyclodextrin.<sup>15</sup> This study, however, relied on an acute 0- to 48-hour increase in the plasma co-Q<sub>10</sub>, leaving open the question of uptake and accumulation during a prolonged period more similar to day-to-day use.

BioActives LLC (Worcester, Massachusetts) has developed a co-Q<sub>10</sub>- $\beta$ -cyclodextrin inclusion complex marketed as MicroActive Co-Q<sub>10</sub>. The patented complex is a free-flowing, stable powder suitable for use in solid dosage and in powder formulations.<sup>16</sup> This study compared the bioavailability of the MicroActive Co-Q<sub>10</sub> complex to 2 commercially available formulations: an oil-solubilized co-Q<sub>10</sub> softgel containing a proprietary absorption enhancer and a hard gelatin capsule of crystalline co-Q<sub>10</sub>.

Two studies were designed to explore the bioavailability of the MicroActive Co-Q<sub>10</sub> complex. The first compared MicroActive Co-Q<sub>10</sub> with both a crystalline co-Q<sub>10</sub> formulation and an advanced solubilized form in an acute 0- to 24-hour study. The second study compared MicroActive Co-Q<sub>10</sub> with only the advanced solubilized form over 3 weeks of dosing.

## Materials and Methods

### Subjects

The study was reviewed by the Ethical Review Committee Inc, Independence, Missouri. Written informed consent was obtained from all subjects. Healthy, nonsmoking male and female volunteers between the ages of 25 and 65 years were selected for the study. The subjects were judged to be in good general health on the basis of medical interview, physical examination, and lipid panel (total cholesterol, low- and high-density lipoprotein, triglycerides). The subjects were not taking any medications at the time of the study. As part of the screening process, baseline plasma co-Q<sub>10</sub> was determined for all subjects.

Subjects were excluded based on the following conditions:

- 1) baseline plasma co-Q<sub>10</sub> >1.0  $\mu$ g/mL,
- 2) body mass index (BMI) <18 kg/m<sup>2</sup> or >30 kg/m<sup>2</sup>,
- 3) total cholesterol <110 mg/dL or  $\geq$ 240 mg/dL,
- 4) intake of co-Q<sub>10</sub> supplements within 4 weeks prior to the start of the trial,
- 5) engaging in high-intensity/power exercise during the study (ie, aerobic activity at 90%-100% maximum heart rate or a rating of perceived exertion at 16+ on a 10-20 scale or resistance training at 85%-100% with a 1-repetition maximum),
- 6) 1-sided nutrition (ie, vegan), (infection, acute or chronic hepatitis B or C, or any condition the principal investigator believed may put the subject at undue risk,
- 8) chronic medication intake,
- 9) history or current abuse of drugs, medication, or alcohol, or intake >2 alcoholic beverages per day,
- 10) known hypersensitivity to study product or any ingredient in the study preparation,
- 11) pregnancy or lactation, and
- 12) participation in another clinical trial within the previous 4 weeks or concurrent participation in another clinical trial.

### Study Design

#### Study 1

Three formulations were tested:

- 1) MicroActive Co-Q<sub>10</sub> hard gelatin capsules,
- 2) commercially available crystalline co-Q<sub>10</sub> hard gelatin

capsules, and

- 3) commercially available oil-solubilized co-Q<sub>10</sub> softgels containing a proprietary absorption enhancer.

As previously mentioned, MicroActive Co-Q<sub>10</sub> contained a co-Q<sub>10</sub>- $\beta$ -cyclodextrin inclusion complex. The crystalline co-Q<sub>10</sub> formulation contained rice flour as the excipient. The oil-solubilized co-Q<sub>10</sub> contained rice bran oil, soybean oil, vitamin E, and lecithin as excipients. For all formulations, a single dose equivalent to 180 mg/day co-Q<sub>10</sub> was used in the study.

The study was conducted with 5 subjects (2 women, 3 men); mean age, 37 years (minimum 24 and maximum 50 years); and a mean baseline plasma co-Q<sub>10</sub> of 0.769  $\mu$ g/mL. A single-dose, multicrossover design was used with a 2-week wash-out period between test preparations. On the first morning of the study, an overnight fasting blood sample was taken to ascertain baseline co-Q<sub>10</sub> concentration. The capsules (equivalent to 180 mg co-Q<sub>10</sub>) were taken with a suggested breakfast each morning (~500 kcal, 15% protein, 30% fat, and 55% carbohydrate). Blood samples were collected at postdose hours 3, 6, 9, and 24. After a 2-week washout period, the study was repeated with the next test preparation at the same dose of co-Q<sub>10</sub> until all 3 preparations had been tried.

#### Study 2

This study had an acute phase and an accumulation phase using 60 mg co-Q<sub>10</sub>, 1 $\times$ /day. A lower dosage was used, as it is representative of the maintenance dose used by consumers. Twenty-two subjects between 25 and 57 years of age were randomly divided into 2 groups for the study: Group A, MicroActive Co-Q<sub>10</sub> hard gelatin capsules; and Group B, commercially available oil-solubilized co-Q<sub>10</sub> softgels containing a proprietary absorption enhancer. There were no statistically significant differences with respect to age, BMI, total cholesterol, and baseline plasma co-Q<sub>10</sub> levels between the 2 groups.

At the beginning of the trial, an overnight fasting blood sample was taken to determine baseline co-Q<sub>10</sub> concentration, and dosing was started afterward. The capsules (equivalent to 60 mg co-Q<sub>10</sub>) were taken with a suggested breakfast each morning (~500 kcal, 15% protein, 30% fat, and 55% carbohydrate). The subjects were instructed to always take the test preparation in the morning with the suggested breakfast. On day 1 of dosing, blood samples were collected at postdose hours 3, 6, 9, 12, and 24 for the acute phase of the study. Dosing continued for the next 21 days. For the accumulation phase, the blood samples were collected on days 8, 15, and 22. On days 7, 14, and 21, the study preparation was consumed 24 hours before blood samples were taken on the following day. Blood draw times were fixed with the subjects.

#### Sample Collection and Processing

Venous blood samples were collected in tubes containing ethylenediaminetetraacetic acid and immediately refrigerated. The tubes were centrifuged within 1 hour of collection at 3000 rpm for 10 min at 5°C. Plasma was separated and stored at -80°C until analysis.

### Plasma Co-Q<sub>10</sub> Analysis

Plasma total co-Q<sub>10</sub> was analyzed by high-performance liquid chromatography with electrochemical detection using the validated method of Tang et al.<sup>17</sup> The solvent 1-propanol was used for the extraction of co-Q<sub>10</sub> from the plasma as described by Tang et al.<sup>17</sup> Precolumn oxidation was used to convert all the co-Q<sub>10</sub> to the oxidized form for analysis.

### Statistical Analysis

The statistical analysis was conducted using Prism 4 for Macintosh published by GraphPad Software 2005 edition (GraphPad Software Inc, La Jolla, CA). Area under the plasma co-Q<sub>10</sub> concentration versus time curve (AUC) was calculated using the trapezoidal rule.

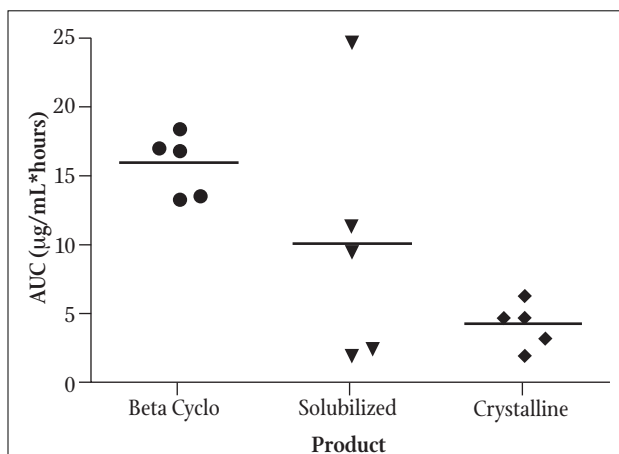
## Results

### Study 1

The results of the acute study 1 are presented in Table 1. The mean AUC<sub>0-24h</sub> for the MicroActive product was 3.7 times greater than the crystalline ( $P < .0001$ ).

Values	Subject Group		
	MicroActive	Solubilized	Crystalline
Mean	15.98	10.13	4.318
SD	2.269	9.213	1.654
SE	1.015	4.120	0.7399

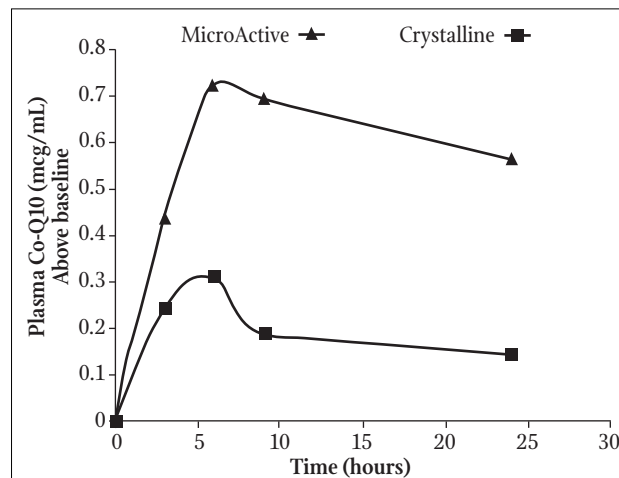
A large variance was observed in the uptake of co-Q<sub>10</sub> with the solubilized product. Bartlett's test revealed a significant difference comparing the variances across the 3 treatments ( $P < .05$ ). Given the large variance in the solubilized group, it was dropped from further analysis. The scatter plot (Figure 1) offers some insight into the distribution of uptake of the 3 products by individual subjects.



**Figure 1. A comparison of uptake of co-Q<sub>10</sub> by individual subjects after a single oral dose of 180 mg co-Q<sub>10</sub>.**

Abbreviations: AUC=area under the curve

Finally, a timed-plotted comparison in uptake between the MicroActive product and crystalline co-Q<sub>10</sub> (Figure 2) indicated that the MicroActive product has a sustained-release feature unlike the crystalline co-Q<sub>10</sub>. At 24 hours postdose, the average plasma co-Q<sub>10</sub> level for the MicroActive product was more than 3 times that of the crystalline co-Q<sub>10</sub> product.



**Figure 2. A comparison of the mean plasma co-Q<sub>10</sub> concentrations\* after a single oral dose of 180 mg MicroActive or crystalline co-Q<sub>10</sub>.**

\*Plasma co-Q<sub>10</sub> as µg/mL

### Study 2: Acute Phase

Table 2 presents a summary of the demographic data and baseline plasma co-Q<sub>10</sub> values for the 2 arms of the study. Two subjects from the solubilized group were not included because 1 dropped out after the acute phase and the other was disqualified for nonadherence.

	Subject Group	
Demographics	MicroActive	Solubilized
Sex		
Female	6	3
Male	5	6
Age (years)		
Mean	40	33
SD	12.5	8.5
Body mass index (kg/m <sup>2</sup> )		
Mean	23.5	25.6
SD	3.05	2.56
Total cholesterol (mg/dL)		
Mean	156.8	163.6
SD	30.68	28.09
Baseline plasma Co-Q <sub>10</sub> (µg/mL)		
Mean	0.580	0.531
SD	0.100	0.180

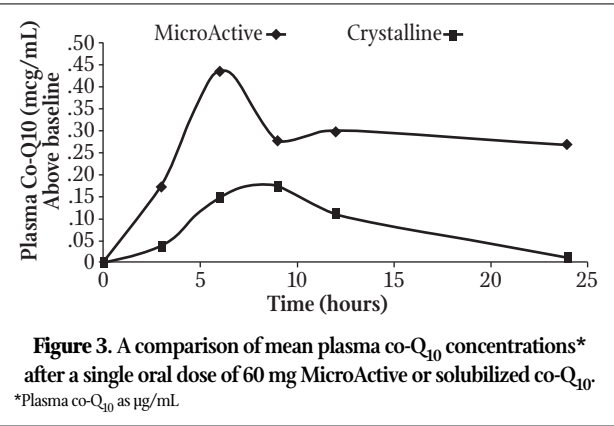
The results of the acute phase of Study 2 are presented in Table 3. Because the primary purpose of these studies was to understand the properties of MicroActive Co-Q<sub>10</sub> complex, it was not necessary to further compare the solubilized product

with the crystalline co-Q<sub>10</sub> product. To reduce the standard error, more subjects were recruited for each group.

Table 3. A Comparison of Uptake of Co-Q <sub>10</sub> from a 60-mg Dose [AUC <sub>0-24hr</sub> (µg/mL*h)]		
Value	Study Group	
	MicroActive	Solubilized
Mean	6.490	2.425
SD	2.231	3.045
SE	0.6725	1.015

Because the distribution of the group taking the solubilized product did not support a normal distribution, the Mann Whitney test replaced the Student *t* test. The results showed greater absorption for the MicroActive group (*P* < .006).

A timed plot of the comparison in uptake between the MicroActive product and the solubilized product again indicated that the MicroActive product has a definite sustained-release feature, unlike the solubilized product (Figure 3).



Study 2: Accumulation Phase

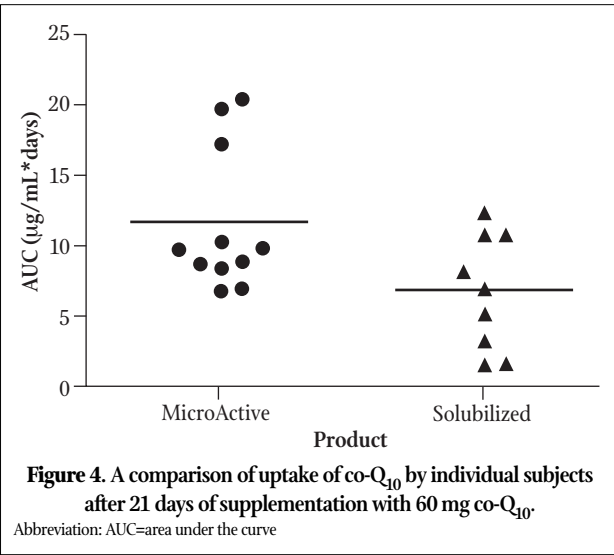
Table 4 presents the results of the 3-week study. The group taking the MicroActive product showed higher uptake of co-Q<sub>10</sub> over the 3-week period compared with the group taking the solubilized product. The mean AUC of the group taking the MicroActive product was significantly higher by the second week of supplementation.

A reasonable measure of improved and uniform bioavailability was defined as a doubling of co-Q<sub>10</sub> levels over the 3-week

treatment period. By this definition, it was observed that the subjects in the group taking the MicroActive product had a 100% response rate, whereas the group taking the solubilized product had a 44.4% response rate (Table 5). The difference in the number of subjects doubling co-Q<sub>10</sub> plasma level was significant (*P* < .008; Fisher’s Exact Test).

Table 5. Subjects Showing a Doubling of Plasma Co-Q <sub>10</sub> Level (µg/mL) after 21 Days Supplementation		
	Number of Subjects Doubling	Number of Subjects Not Doubling
MicroActive	11	0
Solubilized	4	5

It was also observed that some subjects in the group taking the solubilized product showed very low absorption of co-Q<sub>10</sub> over the 3-week period. Note, for example, the scatter plot for co-Q<sub>10</sub> blood levels at week 3 showing the uptake by individual subjects (Figure 4). Relative to the size of the mean, the variance for the group taking the MicroActive product was small compared with the group taking the solubilized product (Table 4).



Discussion

The objective of this study was to compare the relative bioavailability of a proprietary co-Q<sub>10</sub>-β-cyclodextrin inclusion

Table 4. Mean Plasma Co-Q <sub>10</sub> Area Under the Curve [AUC (µg/mL*days)] During 21 Days of Supplementation						
	Week 1 AUC		Week 2 AUC		Week 3 AUC	
	MicroActive	Solubilized	MicroActive	Solubilized	MicroActive	Solubilized
Mean	2.00	0.98	6.36	3.40	11.66	6.86
SD	1.24	0.84	3.36	2.44	5.03	4.08
SE	0.38	0.28	1.01	0.81	1.52	1.36
Significance	ns*		P<.002		P <.03	
*Not significant						

complex with commercially available solubilized softgel and crystalline co-Q<sub>10</sub> formulations. The solubilized formulation used in the study included absorbance enhancers.

The baseline plasma co-Q<sub>10</sub> levels were found to be within the range of 0.320 to 0.815 µg/mL, with a mean of approximately 0.556 µg/mL. The data are similar to the literature, indicating a healthy group of subjects.<sup>1</sup>

In the 5-subject, 180 mg/day single-dose study, the MicroActive Co-Q<sub>10</sub> complex showed a higher uptake compared with crystalline co-Q<sub>10</sub>. In comparison with the advanced solubilized form, the absorption of MicroActive Co-Q<sub>10</sub> did not reach statistical significance because of high variance in the absorption of the solubilized form. Some of the subjects showed a high absorption, whereas others did not absorb any co-Q<sub>10</sub> from the solubilized form. Such individual variation in the absorption of co-Q<sub>10</sub> has been reported in the literature.<sup>18</sup> However, the MicroActive Co-Q<sub>10</sub> showed a trend toward better and more uniform bioavailability compared with the solubilized form. All subjects showed absorption from the MicroActive Co-Q<sub>10</sub>.

To reduce the standard error, the number of subjects was increased for the second study comparing the MicroActive Co-Q<sub>10</sub> with the solubilized co-Q<sub>10</sub>. The dosage was reduced to 60 mg/day co-Q<sub>10</sub>, similar to the day-to-day maintenance dosage. The MicroActive Co-Q<sub>10</sub> was clearly superior to the solubilized form in both the acute and accumulation phases of the study.

The results of the study indicate that MicroActive Co-Q<sub>10</sub> reduced the variance in the absorption of co-Q<sub>10</sub> in the study population. The complexation with β-cyclodextrin also results in a sustained-release formulation of co-Q<sub>10</sub>, as shown in Figures 2 and 3. The sustained release was observed irrespective of the sex and age of the subjects. The reduction in variance can be attributable to the sustained-release properties of the complex. Also, all of the subjects in the accumulation phase showed a minimum of doubling in the plasma co-Q<sub>10</sub> levels after 21 days of MicroActive Co-Q<sub>10</sub> supplementation, which reflects a 100% response rate. The solubilized product showed only a 44% response rate. Because response rates define an actual threshold as opposed to a mean, a stronger claim might be made for the unique properties of the MicroActive Co-Q<sub>10</sub> as useful in ensuring uptake in the elderly and in patients with chronic diseases. Higher doses of co-Q<sub>10</sub> are used by a wide spectrum of individuals, young and old, and for therapeutic purposes in chronic conditions. It has been reported that the efficiency of absorption of co-Q<sub>10</sub> is reduced as the dosage is increased; split dosing is reported to be superior to a single large dose.<sup>19</sup>

The sustained-release MicroActive Co-Q<sub>10</sub> complex, with a universal absorption profile, can be used as a once-a-day supplement both for maintenance and therapeutic purposes. However, the study used a healthy group of subjects. Further studies are warranted with a broader population of subjects and with subjects who are not healthy and may benefit from co-Q<sub>10</sub> supplementation.

## Conclusions

MicroActive Co-Q<sub>10</sub> complex showed significantly higher uniform bioavailability compared with crystalline co-Q<sub>10</sub> and an advanced solubilized form of co-Q<sub>10</sub>. The complex exhibited

sustained-release property at both the 180-mg and 60-mg doses, irrespective of the sex and age of the subjects. All the subjects in the accumulation phase showed a minimum doubling of the plasma co-Q<sub>10</sub> levels after 21 days of MicroActive Co-Q<sub>10</sub> complex supplementation, which reflects a 100% response rate. The solubilized product showed only a 44% response rate, again confirming the greater and more uniform bioavailability of the MicroActive product. Sustained-release MicroActive Co-Q<sub>10</sub> is more universally bioavailable, thereby improving its ability to deliver both maintenance and therapeutic doses of co-Q<sub>10</sub>.

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