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Short Communication

Increase of Bioavailability of Coenzyme Q_{10} and Vitamin E

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ABSTRACT Commercial coenzyme Q_{10} (CoQ_{10}) and α-tocopherol (vitamin E) formulations often show poor intestinal absorption. Delivery of CoQ_{10} and vitamin E was enhanced when used with a new formulation, NanoSolve (Lipoid GmbH, Ludwigshafen, Germany), as shown by an open, comparative monocenter, crossover study of 24 volunteers. Plasma CoQ_{10} and vitamin E were determined from predose until +14 hours. To compare bioavailability, corrected maximum concentration, time to reach maximum concentration, and area under the curve from 0 to 14 hours were assessed. The NanoSolve test formulation contained 100 mg of CoQ_{10} and 120 mg of vitamin E. The pure substances in hard gelatin capsules served as the reference. Although identical amounts of CoQ_{10} and vitamin E were administered, absolutely higher serum concentrations of the active ingredients were achieved by the NanoSolve formulation than by the pure materials in gelatin capsules. The bioavailability of CoQ_{10} increased fivefold after administration of the NanoSolve formulation, and the bioavailability of vitamin E was enhanced 10-fold both compared to the pure substances.

KEY WORDS: • ***bioavailability*** • ***coenzyme Q_{10}*** • ***drug delivery*** • ***human study*** • ***NanoSolve*** • ***phospholipids*** • ***vitamin E***

INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}), also known as ubiquinone, is a lipophilic, redox-active molecule, present in plant as well as in animal cell membranes. The main sources in human diet are fish, meat, oil, nuts, and wheat. Daily intake from food typically ranges between 3 and 5 mg/day, which cannot significantly raise blood and tissue levels.[1] Owing to its important role in biological functions, CoQ_{10} is able to be synthesized on its own by the human body. With increasing age, the activity of CoQ_{10} syntheses is reduced, and therefore lower plasma levels are found in elderly people.[2] Another indication for higher need is in high-performance sports, given the athletes' high energy requirements. The literature shows that different diseases are associated with a shortage of CoQ_{10} and the occurrence of increased lipid peroxidation. These include cardiovascular or neurodegenerative diseases like Parkinson's disease.[3]

Vitamin E is a generic term for a group of lipid-soluble derivatives of tocol and tocotrienol that show qualitatively biologic activity of α-tocopherol. In nature, vitamin E is synthesized by plants. Rich sources of this nutrient are nuts, plant sprouts, and the oils and fats produced from them, including sunflower seed or olive oil. In the body vitamin E is located in membranes, and, because of its antioxidative property, this vitamin prevents lipid peroxidation.

The primary purpose of this study was to determine the bioavailability of CoQ_{10} and vitamin E formulated in NanoSolve (Lipoid GmbH, Ludwigshafen, Germany) preparations in humans in direct comparison with capsules containing pure material. In previous papers we introduced the NanoSolve technique as a new way to solubilize lipids or lipophilic actives for oral application.[4,5] Purified phospholipids are one of the key components of NanoSolve. This natural emulsifier, derived by extraction from soybeans, has successfully been used in the dietetic, cosmetic, and pharmaceutical industries for decades. NanoSolve results in transparent emulsions with particle sizes between 30 and 60 nm obtained by using sophisticated techniques and special formulations. Particle size is a primary determinant of bioavailability; phospholipids are considered as a sorption promoter. Additionally, NanoSolve is mixable with water in any ratio. Commercial preparations of CoQ_{10} are often of poor bioavailability. Especially in humans with impaired fat absorption the bioavailability of vitamin E is significantly improved when a water-soluble formulation of vitamin E is administered.[6] NanoSolve is therefore a promising carrier system for both active agents.

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The trial was performed as an open, comparative monocenter, crossover design. Twenty-four volunteers (12 women and 12 men) were enrolled in the trial. The study was approved by the ethics committee of the Landesärztekammer Baden-Württemberg, Stuttgart, Germany. It was conducted at the laboratories of the BioTeSys GmbH (Esslingen, Germany) with financial support of PM-International AG (Luxembourg) and reviewed by Lipoid GmbH. The study was performed with informed consent. In the screening phase an anamnestic questionnaire was given, and a blood picture, lipid screening, and determination of safety parameters including liver enzymes and creatinine were carried out to check the health status and to look for any abnormal features. A physical examination, including determination of pulse and blood pressure, was also administered. Written informed consent was obtained before any data were collected. Volunteers were randomly assigned to one of the two treatment periods with either (1) NanoSolve with CoQ_{10} and vitamin E or (2) reference products CoQ_{10} and vitamin E in capsules, each as an oral dose of 100 mg of CoQ_{10} and 120 mg of tocopherol equivalents. At the beginning of the trial, following an overnight fast, baseline blood samples for levels of CoQ_{10} and vitamin E were taken. The pharmacokinetics in plasma were observed over a 14-hour period. Standardized meals were given 1, 5, and 10 hours post-dosing. Further snacks were served 3, 8, and 12 hours post-dosing. Water itself was not restricted. Other beverages and food were forbidden during kinetic days. Identical food was served on kinetic days I and II. After a 2-week washout phase, treatment phase II was started. Lipid status was determined on kinetic day I, and all routine parameters were controlled at kinetic day II.

During the screening phase and on kinetic day II, blood samples were taken after an overnight fast to determine routine blood parameters. For consecutive blood sampling at the kinetic days a permanent venous catheter was placed in the cubital area. At each sampling time 2.7 mL of venous blood was collected through the catheter in EDTA-Monovetten® (Sarstedt, Nümbrecht, Germany). The blood samples were centrifuged at 3,000 *g* for 10 minutes at 4°C. Plasma was collected and aliquoted for CoQ_{10} and vitamin E determination (500 μL per tube). The samples were stored at −80°C until analysis.

For CoQ_{10} and vitamin E determination, plasma samples were defrosted at room temperature. An aliquot was taken, and CoQ_{10} was determined by a modification of the high-performance liquid chromatography method described elsewhere.[7] Vitamin E was determined with a fluorescence detector (2475 Multi Wavelength Fluorescence Detector, Waters, Eschborn, Germany) with 293 nm for excitation and 325 nm for emission. Peak areas were analyzed, and the quantification was performed by calibration with external standards.

Data were analyzed using Graph Pad (San Diego, CA) Prism and Microsoft (Redmond, WA) Excel software. Probability values of .05 or less were considered statistically significant.

Twenty-four volunteers were enrolled and randomly assigned. Women and men were nonsmokers and on average of the same age. Overall mean age was 26.71 ± 6.8 years. The test persons showed an overall mean body mass index of 22.15 ± 2.43 kg/m^2. One vegetarian woman was included in the trial. No other diet restrictions were reported.

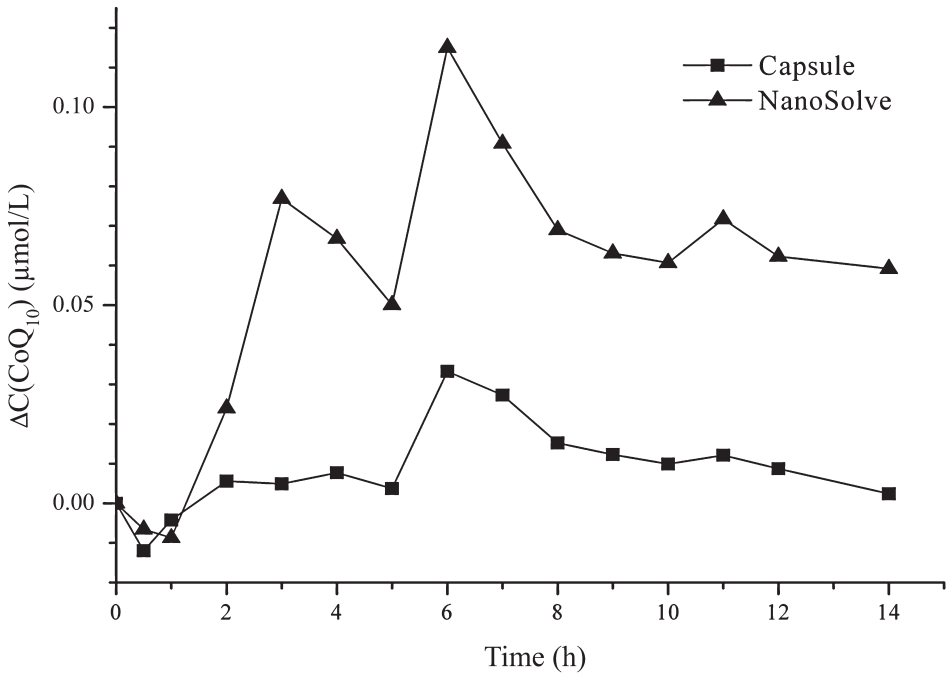

FIG. 1. Mean changes in CoQ_{10} plasma concentrations following administration of 100 mg of CoQ_{10}. The displayed changes in CoQ_{10} plasma concentrations (in μmol/L) over time are the means of the hematocrit-corrected data of 23 volunteers. The significance difference for the two formulations over time was checked with one-way analysis of variance repeated measures. The difference is statistically significant ($P_{\text{Capsule}} = .006$ and $P_{\text{NanoSolve}} < .001$).

TABLE 1. OVERVIEW OF THE PHARMACOKINETIC PARAMETERS

Active	*Dosage*	*Number of subjects*	C_{max} *(μmol/L)*	T_{max} *(hours)*	$AUC_{0\rightarrow 14\ hours}$ *(μmol hours/L)*	$AUC_{0\rightarrow 14\ hours}$ *relative to reference (%)*
CoQ_{10}	Capsule	23	0.03	6	0.14	100
	NanoSolve	23	0.12	6	0.72	500
Vitamin E	Capsule	23	0.59	9	1.69	100
	NanoSolve	23	2.35	6	16.89	1,000

The measured pharmacokinetic parameters are shown for both formulations and both active agents (capsule form). The values for C_{max}, T_{max}, and $AUC_{0\rightarrow 14}$ hours show the median (minimum − maximum). C_{max} (in μmol/L), T_{max} (in hours), and $AUC_{0\rightarrow 14\ hours}$ (in μmol hours/L) are derived from hematocrit-corrected data. One volunteer was excluded as a nonresponder.

The study preparations were well tolerated. Pre- and post-study safety visits took place, including standard laboratory tests. No evidence of clinically relevant disorders or changes was found in the laboratory data. For status assessment, baseline plasma levels of CoQ_{10} and vitamin E were determined on both kinetic days in repeat determination. The average baseline level of CoQ_{10} was 0.62 ± 0.14 μmol/L on kinetic day I and 0.62 ± 0.13 μmol/L on kinetic day II. CoQ_{10} and vitamin E in plasma were performed in repeat determination. Within samples the average relative deviation was 2.64 ± 2.21% for CoQ_{10} and 1.84 ± 1.94% for vitamin E.

Derived from hematocrit-corrected concentration–time curves, the pharmacokinetic parameters maximum concentration (C_{max}), time to reach C_{max} (T_{max}), and area under the curve from 0 to 14 hours ($AUC_{0\rightarrow 14\ hours}$) were determined. Pharmacokinetic parameters were derived from the medians. The Wilcoxon matched pairs test was applied to test for statistically significant differences of both formulations. One volunteer was a nonresponder, which means that the derived concentration–time curves differed significantly from those of the other volunteers, and thus this volunteer was not included in the analysis.

In total, CoQ_{10} concentration peaked 6 hours after application of 100 mg as pure material in capsules and returned nearly to baseline within 14 hours. In contrast, after intake of the NanoSolve formulation, a two-peak pattern of CoQ_{10} could be seen. The first peak occurred after 3 hours, and the second after 6 hours. A third peak, less developed, can be discerned at 11 hours. It seemed that peaks followed meals with standardized fat content. Even after 14 hours CoQ_{10} levels were still raised above the baseline (Fig. 1). Statistically higher C_{max} levels were detected after intake of NanoSolve compared to pure material in capsules ($P = .0131$). Fourfold higher C_{max} values were achieved when supplemented with NanoSolve. The comparison of $AUC_{0\rightarrow 14\ hours}$ indicated that NanoSolve enhanced the absorption of CoQ_{10}. The bioavailability was fivefold higher ($P = .0006$). The results are summarized in Table 1.

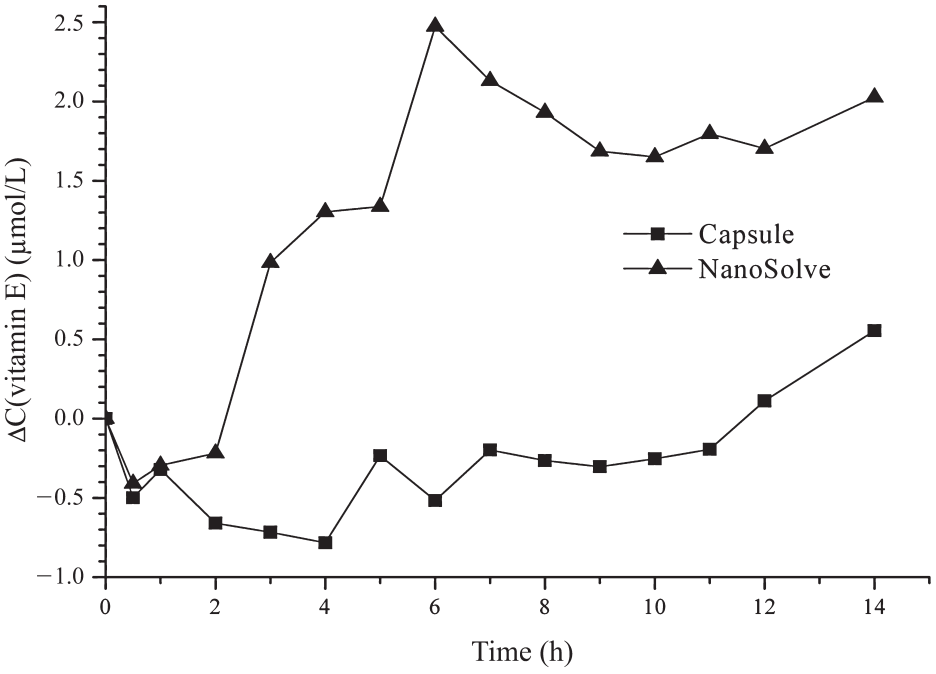

FIG. 2. Mean changes in vitamin E plasma concentrations following administration of 120 mg of vitamin E. The changes in vitamin E plasma concentrations (in μmol/L) seen over time are the means of the hematocrit-corrected data of 23 volunteers. The difference for the two formulations over the time was checked with one-way analysis of variance repeated measures. The difference is statistically significant ($P_{Capsule} = .003$ and $P_{NanoSolve} < .0001$).

After intake of 120 mg of vitamin E in capsules, total concentration–time curves showed negative profiles, indicating very poor absorption rate. The mean changes in the curve rose until the 14th hour, indicating that T_{max} levels were still not met in all volunteers. In contrast, after supplementation with NanoSolve, peak maximum was achieved at 6 hours, with rising levels from 2 hours on. Within 14 hours vitamin E concentration did not return to the baseline value (Fig. 2). Statistically significant higher C_{max} levels were detected after intake of NanoSolve compared to pure vitamin E in capsules ($P = .0013$). Fourfold higher C_{max} values could be achieved when supplemented with NanoSolve. Vitamin E administered as net substance in capsules took longer to reach C_{max} ($T_{max, Capsule} = 9$ hours; $T_{max, NanoSolve} = 6$ hours). Differences were statistically significant ($P = .0122$). The comparison of the $AUC_{0\rightarrow 14\ hours}$ indicated that NanoSolve enhanced the absorption of vitamin E: the bioavailability was 10-fold higher ($P = .0009$). The results are summarized in Table 1.

This trial under standardized conditions showed that supplementation with a single dose in NanoSolve resulted in a statistically significant increase ("improvement") in the bioavailability of CoQ_{10} as well as vitamin E compared to the pure substances in capsules. The improvement in vitamin E levels was greater than the improvement observed for CoQ_{10} levels. The NanoSolve preparation was well tolerated by all volunteers. The fast response and significant increase of plasma concentrations after one single dose in NanoSolve makes this new preparation an interesting alternative to common commercial formulations for oral application of actives of poor bioavailability.

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