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Enhancement of oral bioavailability of coenzyme Q_{10} by complexation with γ-cyclodextrin in healthy adults

Keiji Terao[a], Daisuke Nakata[a], Hiroshi Fukumi[a], Gerhard Schmid[b], Hidetoshi Arima[c], Fumitoshi Hirayama[c], Kaneto Uekama[c,*]

[a]*CycloChem Co., Ltd., KIBC, Kobe, 650-0047, Japan*
[b]*Wacker-Chemie GmbH, 81737 Muenchen, Germany*
[c]*Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto 862-0973, Japan*

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Abstract

The objective of this study was to determine the effect of molecular encapsulation of coenzyme Q_{10} (CoQ_{10}) by complexation with γ-cyclodextrin (γ-CD) (CoQ_{10}-γ-CD) compared with a mixture of CoQ_{10} with microcrystalline cellulose (CoQ_{10}-MCC) on absorption and bioavailability of CoQ_{10} in supplement form in healthy adults. Twenty-two volunteers received a single dose of a 150-mg capsule containing 30 mg CoQ_{10} under fasting conditions in an open-label, crossover design with a 2-week washout period. Blood was collected before dosing and after dosing periodically over 48 hours. Plasma levels of CoQ_{10} were determined by high-performance liquid chromatography using an electrochemical detector and an online reduction system. After 6 and 8 hours of dosing there was a significant increase in mean CoQ_{10} plasma levels of subjects after a single oral administration of the CoQ_{10}-γ-CD capsule compared with those with the CoQ_{10}-MCC capsule. In addition, the mean plasma levels at 24 and 48 hours tended to be higher after CoQ_{10}-γ-CD administration in comparison with CoQ_{10}-MCC administration. The area under the plasma CoQ_{10} concentration curve and the maximum plasma concentration (C_{max}) values as well as their corresponding log-transformed values, log area under the plasma CoQ_{10} concentration curve, and log C_{max} for the CoQ_{10}-γ-CD formulation were significantly higher than those for the CoQ_{10}-MCC formulation. These results indicate that the oral absorption and bioavailability of CoQ_{10} in healthy adult volunteers could be significantly enhanced by complexation with γ-CD, suggesting the potential use of γ-CD as formulation aid for orally administered CoQ_{10}.

Keywords: Coenzyme Q_{10}; γ-Cyclodextrin; Complex; Microcrystalline cellulose; Human; Bioavailability

1. Introduction

There is growing interest in the usage of coenzyme Q_{10} (CoQ_{10}) as a nutrition supplement. Coenzyme Q_{10} is a fat-soluble, vitamin-like benzoquinone compound that functions primarily as an antioxidant, a membrane stabilizer, and a cofactor in the oxidative phosphorylation production of adenosine triphosphate (ATP) [1,2]. It has also been shown to help preserve myocardial sodium-potassium adenosine triphosphatase activity and stabilize myocardial calcium-dependent ion channels. Because of the lipophilic property of CoQ_{10}, it is not well absorbed when taken orally by humans. Therefore, formulations that could improve CoQ_{10} solubility in water and enhance its bioavailability are necessary.

The solubilization of poorly water-soluble drugs is essential for the pharmacologic evaluation and drug development. There are various methods for improvement of aqueous solubility of lipophilic compounds in the food and pharmaceutical fields: amorphous form [3], grinding [4], solid dispersion [5], micelle [6], and inclusion complex [7]. Among them, the use of cyclodextrins (CDs) has been known

* Corresponding author. Tel.: +81 96 371 4160; fax: +81 96 371 4420.
E-mail address: uekama@gpo.kumamoto-u.ac.jp (K. Uekama).

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in the pharmaceutical and nutrition fields because CD inclusion complexes are stable against heat, oxidation, and UV, and better suited for these formulations. The α-, β-, or γ-CDs are widely used natural CDs, consisting of 6, 7, and 8 D-glucopyranose residues, respectively, linked by α-1,4 glycosidic bonds into a macrocycle [8,9]. Cyclodextrins can generally form inclusion complexes with a number of lipophilic substances and thus have been used for improving their water solubility, stability, and bioavailability [10,11]. Lukta et al [12-15] found that γ-CD and methyl-β-CD increased CoQ_{10} solubility in an aqueous solution and stabilized CoQ_{10} in a solid state through an inclusion complexation. Our laboratory also reported that dimethyl-β-CD as well as γ-CD improves solubility in water, and the dissolution rate and oral absorption of CoQ_{10} in dogs [16,17]. However, the clinical evaluation of oral bioavailability of the CoQ_{10} complex with γ-CD still remains unknown. Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose that is prepared by treating α-cellulose, in the form of a pulp manufactured from fibrous plant material, with mineral acids to produce a degree of polymerization of about 200 to 300. Microcrystalline cellulose is used as an excipient in pharmaceutical formulations [18,19]. Furthermore, it is known that the exudation of bile acids during a meal helps the bioavailability of lipophilic substances. Because some nutritional supplements and pharmaceuticals are not taken with a meal, the enhancing method for oral bioavailability of lipophilic substances such as CoQ_{10} without the aid of bile acids is very important for developing nutritional supplements.

The objective of this study was to compare the pharmacokinetic properties such as the area under the plasma CoQ_{10} concentration curve from time 0 to 48 hours (AUC), maximum plasma concentration (C_{max}), and the time to maximum plasma concentration (T_{max}) of CoQ_{10} after an oral administration of 2 CoQ_{10} hard capsule formulations in healthy adult male and female subjects. The capsules contained the CoQ_{10} complexed with γ-CD (CoQ_{10}-γ-CD) or the mixture of CoQ_{10} with MCC (CoQ_{10}-MCC).

2. Methods and materials

2.1. Materials

The MCC product named VIVAPUR 101 was purchased from Riverson Corporation Japan manufactured by JRS Pharma (Rosenberg, Germany). Methanol and isopropyl alcohol (IPA) were purchased from Nakalai Tesque (Kyoto, Japan). Sodium perchlorate was obtained from Sigma-Aldrich (Tokyo, Japan). Water was purified using a Millipore Ultrapure Water Purification System (Tokyo, Japan). Other chemicals and solvents were of analytical reagent grade.

2.2. Subjects

The study was performed following the requirements of (1) the National Guidelines for Biomedical/Behavioral Research of the National Ethics Committee of the Philippines, (2) the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, (3) the World Medical Association Declaration of Helsinki regarding protection of the rights and welfare of human subjects participating in this study, (4) applicable government regulations, and (5) the Ina Research Philippines, Inc, Institutional Research Policies and Procedures. Human subject use and the protocol were approved by the institutional ethics review committee. The protocol was carefully explained to the volunteers and their written informed consent was obtained. Subjects were eligible if they fulfilled the following inclusion criteria: (1) apparently healthy based on the results of the medical interview and physical examination, and blood chemistry examination (glutamyl oxaloacetic transaminase [GOT], glutamyl pyruvic transaminase [GPT], lactate dehydrogenase [LDH], albumin, total bilirubin, blood urea nitrogen [BUN], creatinine, glucose, and total cholesterol conducted during prescreening, (2) age range of 20 to 50 years, (3) not under any medication at the time of the trial, (4) female nonpregnant volunteers whose menstruation did not fall on the study days (except during the interval period), and (5) signed a written informed consent.

Subjects were excluded based on the following conditions: (1) failure to meet any of the above inclusion criteria, (2) failure to receive food supplements known to affect or with the potential to affect the activity of CoQ_{10}, (3) having a history of allergic reactions attributed to compounds of similar composition to the CoQ_{10} used in the study, and (4) inability to comprehend and comply with the informed consent procedure. No medication or food supplements were allowed during the study period of the trial. As a result, as shown in Tables 1 and 2, 12 male and 10 female healthy subjects were selected from 18 males and 10 females who were screened based on the results of the following procedures: (1) medical interview, (2) physical examination (vital signs [heart rate, respiratory rate, blood pressure, body

Table 1
Vital signs of the subjects during the pretrial period

Subject		Vital signs				
		Body temperature (°C)	Heart rate (bpm)	Respiratory rate (min^{-1})	Systolic/diastolic blood pressure (mm Hg)	
Males (n = 12)	Mean	36.4	63	18	116	80
	SD	0.5	7	2	11	5
Females (n = 10)	Mean	36.5	68	20	116	78
	SD	0.4	7	3	11	8

Table 2
Blood chemistry results of male and female subjects during the pre- and posttrial periods

Parameter	Male (n = 12)		Female (n = 10)	
	Pretrial mean ± SD	Posttrial mean ± SD	Pretrial mean ± SD	Posttrial mean ± SD
GOT (IU/L)	25 ± 6	22 ± 5	17 ± 4	19 ± 4
GPT (IU/L)	19 ± 5	19 ± 7	14 ± 3	14 ± 4
GLU (mg/dL)	92 ± 6	93 ± 4	85 ± 6	95 ± 6
LDH (IU/L)	312 ± 44	321 ± 46	274 ± 64	292 ± 31
ALB (g/dL)	4.6 ± 0.4	4.7 ± 0.3	4.3 ± 0.3	4.4 ± 0.2
BL (mg/dL)	0.79 ± 0.24	0.74 ± 0.23	0.58 ± 0.19	0.55 ± 0.10
BUN (mg/dL)	8.7 ± 2.2	10.2 ± 2.3	8.3 ± 2.8	8.2 ± 1.9
CREA (mg/dL)	0.93 ± 0.08	0.94 ± 0.09	0.57 ± 0.11	0.65 ± 0.10
CHOL (mg/dL)	162 ± 19	167 ± 17	164 ± 24	174 ± 27

GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; GLU, glucose; LDH, lactate dehydrogenase; ALB, albumin; BL, total bilirubin; BUN, blood urea nitrogen; CREA, creatinine; CHOL, cholesterol.

temperature], body weight, and height measurements), (3) blood chemistry examination for GOT, GPT, LDH, albumin, total bilirubin, BUN, creatinine, glucose, and total cholesterol using an autoanalyzer, and (4) blood glucose measurement using a glucose meter.

2.3. Preparation of CoQ_{10}-γ-CD and CoQ_{10}-MCC

The CoQ_{10} was purchased from Mitsubishi Gas Chemical Company (Tokyo, Japan). CoQ_{10}-γ-CD and CoQ_{10}-MCC were used as the test materials. Coenzyme Q_{10}–γ-CD containing 20% (wt/wt) CoQ_{10} was purchased from Wacker Chemical Corporation (Adrian, Mich) as product named CAVAMAX W8/CoQ_{10} Complex. The complex was prepared by a conventional spray-dry method. Coenzyme Q_{10}–MCC was prepared by mixing both 20% (wt/wt) CoQ_{10} and 80% (wt/wt) MCC in a mortar, followed by passing through a sieve (42 mesh). The distribution of particle size for the suspension of CoQ_{10}-γ-CD in water showed 2 peaks around 1 to 10 μm and 20 to 40 μm, giving an apparent average size of 11 μm. Both formulations were prepared as 150-mg capsules containing 30 mg as CoQ_{10} and were kept refrigerated and protected from light. The CoQ_{10} content in a capsule for CoQ_{10}-MCC was determined to be 30 ± 1 mg by a high-performance liquid chromatography (HPLC) analysis.

2.4. Study design

This open-label, single-dose crossover comparative bioavailability trial was conducted over a 4-week period. The trial consisted of 2 studies (study 1 and study 2). The day corresponding to CoQ_{10} formulations administration was designated day 1, whereas the day immediately before day 1 was designated as day 0. The subjects were followed up until day 3 of study 2. Subjects were fasted from 9:00 PM of day 1 of each study and only water intake was allowed. On the day of dosing (day 1), the subjects were given one capsule of the appropriate CoQ_{10} formulation, which was taken orally with water. Study 1 was conducted within a week after subject selection. On the day of dosing (day 1), group A was treated with CoQ_{10}-MCC, whereas group B received CoQ_{10}-γ-CD. Study 2 was conducted after a 2-week washout period. On the day of dosing (day 1), group A was treated with CoQ_{10}-γ-CD, whereas group B received CoQ_{10}-MCC. However, the control experiments (oral administration of γ-CD alone or MCC alone–containing capsule) were not carried out because of a simple comparison of oral bioavailability between CoQ_{10}-γ-CD and CoQ_{10}-MCC formulations.

2.5. Trial procedures and evaluation parameters

A clinical examiner interviewed all the subjects before and after dosing on day 1 and after blood collection on days 2 and 3 of studies 1 and 2. All subjects were examined before dosing on day 1 of each study (1 and 2). The capillary blood was collected and examined using a glucose meter (Accu-chek Advantage Blood Glucose Monitoring System, Roche Diagnostics, Indianapolis, Ind). Observance of proper fasting conditions was confirmed in subjects with glucose values of ≤110 mg/dL or ≤6.1 mmol/L. Approximately 3 mL of whole blood was extracted from each subject during both studies (1 and 2) via a heparinized needle or direct venipuncture according to the following collection points: before dosing, 1, 2, 3, 4, 6, 8, 24 hours (day 2), and 48 hours (day 3) after dosing. On day 1 of each study, the subjects remained fasting during the first 4 extraction points postdosing, and meals were provided only after the 4-hour blood collection. Plasma was separated by centrifugation at 3000 rpm (ca 1600 × *g*) at room temperature for 10 minutes. The samples were kept frozen at −85°C to −88°C before analysis of plasma. For blood chemistry examination, approximately 3 mL of blood was collected from all subjects on day 3 of study 2 after the 48-hour blood collection. The collected blood was allowed to clot for about 30 minutes after collection, and serum was separated by centrifugation at 3000 rpm (ca 1600 *g*) at room temperature for 15 minutes. The following parameters as shown in Table 2 were examined using the BM Hitachi 911 Autoanalyzer (Tokyo, Japan): GOT, GPT, LDH, albumin, total bilirubin, BUN, creatinine, glucose and total cholesterol.

2.6. Determination of plasma CoQ_{10} level

The concentrations of plasma CoQ_{10} were calculated by changing all of the contents of CoQ_{10} into reduced form (ubiquinol), which was determined using an HPLC with an

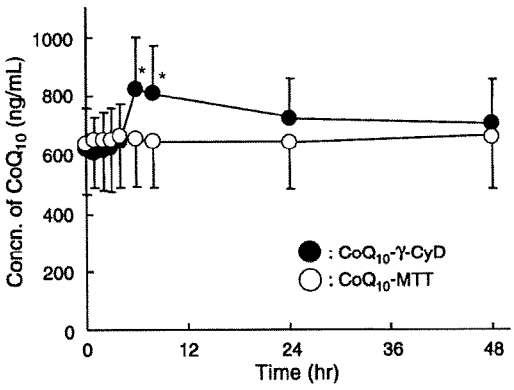

Fig. 1. Time course of plasma level of CoQ_{10} after an oral administration of CoQ_{10}-γ-CD–containing capsule and CoQ_{10}-MCC–containing capsule for 22 healthy adult subjects. Data points represent mean ± SD. Asterisk indicates $P < .05$ compared with CoQ_{10}-MCC.

electrochemical detector and online reduction system according to the method reported by Yamashita and Yamamoto [20], but with slight modification. The HPLC–electrochemical detector system consisted of a model Nanospace SI-2 CoQ_{10} (Shiseido, Tokyo, Japan) composed of an injector, a pump, a guard column, an analytical column, a reduction column, an electrochemical detector (650 mV, Ag/AgCl), and an integrator [21]. Approximately 3 mL of whole blood was extracted from each subject, and then plasma was separated by centrifugation at 3000 rpm (ca 1600 *g*) at room temperature for 10 minutes. Before the analysis, each 20 μL of plasma was mixed with 100 μL of IPA, and then an additional 100 μL of IPA was added to the mixture. The resulting mixture was centrifuged at 1200 rpm at 4°C for 5 minutes and then the supernatant was collected to give the plasma IPA solution for quantitative analysis. Next, the resulting solution (20 μL) was injected to the C18 cartridge column (Capcell Pak C18AQ S5; internal diameter [id], 2.0 × 35 mm, 5 μm, Shiseido) to concentrate CoQ_{10}, and then CoQ_{10} was eluted by flowing the eluent (methanol/IPA, 19:1 vol/vol) containing 6.122 g/L sodium perchlorate at a flow rate of 200 μL/min for 2 minutes. The concentrated CoQ_{10} mixture was injected into the reduction column (Shiseido; id, 2.0 × 35.0 mm) to hydrogenate CoQ_{10}, and sequentially the hydrogenated CoQ_{10} (ubiquinol) was separated using the C18 cartridge column (Capcell Pak C18AQ S5; id, 2.0 × 150 mm, 3 μm, Shiseido) using a mixed solution consisting of methanol/IPA (19:1 vol/vol) containing 6.122 g/L sodium perchlorate at a flow rate of 400 μL/min for 11 minutes followed by the determination of the plasma CoQ_{10} levels. The retention time of ubiquinol was 12.5 minutes under these conditions.

2.7. Statistical analysis

Data were analyzed using the SAS statistical software package (SAS/STAT version 9.1; SAS institute, Inc, Cary, NC) [22]. The estimates of the pharmacokinetic parameters (AUC, C_{max}, and T_{max}) for CoQ_{10}-γ-CD and CoQ_{10}-MCC were expressed as means ± SDs. The measured and logarithmic transformed pharmacokinetic parameters, AUC and C_{max}, and measured T_{max} were analyzed for the differences between the effects of the 2 formulations using analysis of variance. The independent *t* test was used to compare the plasma concentration values for both 2 formulations at specific time points. *P* values for significance were set at .05.

3. Results

Table 1 summarizes vital signs of the subjects during the pretrial period. Body temperature, heart rate, respiratory rate, and blood pressure values of all of the subjects were in the reference ranges. Table 2 presents the blood chemistry data of the subjects before and after the trials. No remarkable changes in blood chemistry values were observed the subjects. The blood glucose values were 80 ± 5 and 83 ± 5 mg/dL for the male and female subjects, respectively, before dosing on day 1 of study 1, and 83 ± 7 and 87 ± 3 mg/dL for the male and female subjects, respectively, before dosing on day 1 of study 2. These data indicate the observance of proper fasting conditions and no adverse events in the subjects after oral administration of the 2 formulations during the course of the study.

Fig. 1 shows the plasma concentrations of CoQ_{10} after oral administration of 2 CoQ_{10} preparations in healthy volunteers. Baseline plasma CoQ_{10} levels ranged from 358 to 1010 ng/mL. The mean plasma CoQ_{10} level tended to be higher before dosing with CoQ_{10}-MCC than the baseline level before CoQ_{10}-γ-CD administration, but the difference was not statistically significant (Fig. 1). The mean plasma levels of CoQ_{10} at 6 and 8 hours after single oral administration of CoQ_{10}-γ-CD were significantly higher compared with their corresponding plasma levels after CoQ_{10}-MCC administration (Fig. 1). The mean plasma levels

Table 3
Comparison of pharmacokinetic parameters after an oral dose of the test (CoQ_{10}-γ-CD) and comparative (CoQ_{10}-MCC) materials for 22 subjects

Formulation	N	Actual values				Log-transformed values		
		Baseline value (C_0) (ng/mL)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}48\ h}$ (ng/mL × h)	Baseline value (C_0) (ng/mL)	Log C_{max} (ng/mL)	Log $AUC_{0\text{-}48\ h}$ (ng/mL × h)
CoQ_{10}-γ-CD	22	608.09 (119.19)	15.45 (16.61)	875.50**	34811.84* (5129.24)	6.39 (0.20)	6.76** (0.19)	10.45* (0.15)
CoQ_{10}-MCC	22	644.091 (71.29)	12.50 (17.83)	723.00 (169.13)	31221.80 (7820.24)	6.43 (0.27)	6.56 (0.25)	10.32 (0.26)

Each value represents the mean (SD) of 22 subjects.
* $P < .05$ compared with CoQ_{10}-MCC.
** $P < .01$ compared with CoQ_{10}-MCC.

at 24 and 48 hours tended to be higher after CoQ_{10}-γ-CD administration in comparison with CoQ_{10}-MCC administration (Fig. 1). Table 3 summarizes the baseline plasma CoQ_{10} levels, AUC, T_{max}, C_{max}, log AUC, and log C_{max} values for the 2 CoQ_{10} formulations. The AUC and log AUC values for CoQ_{10}-γ-CD were significantly higher compared with those for CoQ_{10}-MCC, respectively. Significantly higher C_{max} and log C_{max} values were recorded for CoQ_{10}-γ-CD compared with CoQ_{10}-MCC. Furthermore, the T_{max} values were not different between the 2 CoQ_{10} formulations (Table 3). These results indicate that the oral absorption and bioavailability of CoQ_{10} could be significantly enhanced by the complexation with γ-CD compared with the mixture with MCC.

4. Discussion

Several clinical trials and case studies have been conducted to support the use of CoQ_{10} in the prevention and treatment of various conditions and disorders related to oxidative stress [23]. However, the large molecular weight (863.63) and lipophilic property (aqueous solubility <0.1 μg/mL) of CoQ_{10} affects its oral absorption and consequent beneficial effects in humans [24]. In fact, the oral bioavailability of currently available CoQ_{10} formulations including a nanoparticle and a solid dispersion is very low, although reports have differed widely [25,26]. Thus, there is a need to develop improved formulations for the oral delivery of CoQ_{10}. Several commercial CoQ_{10} formulations in the market have been developed with MCC as the standard excipient. In this study, the bioavailability of CoQ_{10} was compared after the single oral administration of a CoQ_{10}-γ-CD and a CoQ_{10}-MCC formulation to healthy adult volunteers.

The baseline CoQ_{10} plasma levels in this study were within the range of 358 to 1010 ng/mL. This is similar to the baseline ranges (0.26-1.03 mg/mL with a mean concentration of 0.47 mg/mL) in healthy individuals reported by Kaplan et al [27] and those (0.5-1.0 mg/mL) by Tomono et al [28]. Lu et al [29] also reported a relatively higher morning baseline CoQ_{10} level of 0.88 ± 0.48 mg/L in Asian men. Kaikkonen et al [30] demonstrated that a single dose of 30 mg of CoQ_{10} equivalent to the suggested maximum daily dose had only a marginal elevating effect on plasma CoQ_{10} levels in non-CoQ_{10}–deficient subjects. In the present study, a 47.60% average increase from the baseline plasma CoQ_{10} level was associated with CoQ_{10}-γ-CD compared with only a 13.83% rise with CoQ_{10}-MCC. Noticeably, maximum increases of more than 120% were seen in 2 subjects after CoQ_{10}-γ-CD administration. In addition, the single-dose administration of CoQ_{10}-γ-CD was associated with 3 distinct absorptive profiles among the subjects: (1) a typical sharp rise to peak plasma CoQ_{10} levels after 4 hours that was noted in most of the subjects, (2) a slow gradual sustained increase in plasma levels until 24 hours, and (3) the lack of any remarkable rise in plasma CoQ_{10} levels suggestive of poor absorption, which was also consistent with the absorptive pattern seen with CoQ_{10}-MCC administration. The significantly higher C_{max} and AUC values in the CoQ_{10}-γ-CD system provided sound evidence that the oral absorption and bioavailability of CoQ_{10} could be enhanced by its complexation with γ-CD. As described above, Lukta et al reported that γ-CD increased CoQ_{10} solubility in an aqueous solution and stabilized CoQ_{10} in a solid state through an inclusion complexation compared with α-CD and β-CD [12-15]. We recently reported that γ-CD improved solubility in water, and the dissolution rate and oral absorption of CoQ_{10} in dogs, probably due to the soluble complex formation and nanometer-sized particle formation [17]. Taken together, these enhancing effects of the complexation of CoQ_{10} with γ-CD on oral bioavailability of CoQ_{10} in healthy volunteers could be attributed to the solubilizing effect and the fast dissolution rate.

The bioavailability of CoQ_{10} is highly affected by diet [31]. Because the absorptive profile for the various formulations of CoQ_{10} could be different when given together with food, CoQ_{10} was administered to fasting subjects in the present study followed by a meal 4 hours postdosing. This was performed to minimize any potential confounding effect of food containing CoQ_{10} and its various analogues when given at the time of dosing. Nevertheless, some subjects in this trial had minor variations in baseline CoQ_{10} levels between studies for the 2 different CoQ_{10} formulations, although the mean difference was not statistically significant.

In conclusion, the single-dose administration of CoQ_{10}-γ-CD to healthy adult male and female subjects resulted in significantly increased plasma CoQ_{10} levels, and higher C_{max} and AUC values in comparison to that of CoQ_{10}-MCC. The results indicate that the oral absorption and bioavailability of CoQ_{10} could be significantly enhanced by the complexation with γ-CD, suggesting the potential use of γ-CD for an oral capsule formulation containing CoQ_{10} powder.

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