Emulsification of Coenzyme Q\textsubscript{10} Using Gum Arabic Increases Bioavailability in Rats and Human and Improves Food-Processing Suitability

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Summary We evaluated the characteristics of a coenzyme Q\textsubscript{10} (CoQ\textsubscript{10}) formulation created with gum arabic. We defined the formulation’s “modulus of inclusion,” a reference index of the emulsified state, as the CoQ\textsubscript{10} not extracted by hexane as a percentage of the total CoQ\textsubscript{10} content of the formulation. The emulsified CoQ\textsubscript{10} formulation had a smaller particle size and larger modulus of inclusion value than the equivalent unemulsified formulation. In a kinetic study in rats, serum CoQ\textsubscript{10} levels were significantly greater with the emulsified CoQ\textsubscript{10} formulation than with the equivalent unemulsified formulation, which barely increased the levels. In a human study, oral intake of the emulsified formulation significantly increased plasma CoQ\textsubscript{10} levels, which peaked 6 h after intake, compared with the equivalent unemulsified formulation or CoQ\textsubscript{10} bulk powder. There was a significant positive correlation between baseline plasma CoQ\textsubscript{10} and total cholesterol levels, but no correlation was observed between absorption of CoQ\textsubscript{10} and baseline CoQ\textsubscript{10} levels. The emulsified CoQ\textsubscript{10} formulation was highly stable against heat and high humidity and in the presence of some materials (magnesium oxide, vitamin C, and vitamin E). In conclusion, emulsification of CoQ\textsubscript{10} using gum arabic increased bioavailability in both rats and humans and improved suitability for food processing.

Key Words CoQ\textsubscript{10}, emulsification, bioavailability, rat, human

Coenzyme Q\textsubscript{10} (CoQ\textsubscript{10}) is synthesized in the living body and is present in almost all cells, particularly in the organelles such as mitochondria, golgi bodies, and microsomes. It is involved in the electron-transport system for the synthesis of adenosine 5’-triphosphate (ATP), a source of biological energy (1–3). CoQ\textsubscript{10} that exists in a reduced form (as ubiquinol-10) outside the organelles such as mitochondria, golgi bodies, and microsomes. It is involved in the electron-transport system for the synthesis of adenosine 5’-triphosphate (ATP), a source of biological energy (1–3). CoQ\textsubscript{10} that exists in a reduced form (as ubiquinol-10) outside the mitochondria has an antioxidative effect (4, 5) and is considered to be involved in protection against the aging caused by oxidative stress.

After oral intake, CoQ\textsubscript{10} is absorbed from the small intestine and transferred into the blood circulation (6). There have been many reports of CoQ\textsubscript{10} deficiency in patients taking statins for the treatment of hyperlipidemia (7, 8). CoQ\textsubscript{10} supplementation has produced improvements in tachycardia heart failure (9), exercise performance, and vitality (10, 11). In addition, skin-care effects (12), improvements in periodontal disease (13), and fatigue alleviation (14) have been reported.

CoQ\textsubscript{10} has been widely used as a dietary and health supplement because of its important biological roles.

Because diverse CoQ\textsubscript{10} supplements are now needed everywhere, the production of CoQ\textsubscript{10} formulations suitable for a variety of types of intake would provide more choice for CoQ\textsubscript{10} use as a dietary and health supplement. Improved bioavailability would reduce the intake required. Because of its lipophilia, CoQ\textsubscript{10} is poorly absorbed in humans when taken orally, especially under fasting conditions (15, 16). Therefore, various methods of emulsification with modified food starch (17), lecithin (18), gum arabic (19), or polysorbate 80 (18, 20), or inclusion of γ-cyclodextrin (15), have been used to decrease the hydrophobicity of CoQ\textsubscript{10}. The strategy of emulsification of drugs to decrease hydrophobicity and boost bioavailability has already been used and reported (21, 22).

In addition, CoQ\textsubscript{10} is usually used in mixtures with various kinds of materials in food supplements. Therefore, it is important to develop CoQ\textsubscript{10} formulations that not only excel in bioavailability, but also excel in compatibility with various types of CoQ\textsubscript{10} processing. Here, we selected gum arabic, which is commonly and widely utilized as an emulsifier in food processing, and evaluated the characteristics of a CoQ\textsubscript{10} formulation emulsified with this substance.
MATERIALS AND METHODS

Materials. CoQ-10kyowa20 [20% CoQ₁₀ formulation: CoQ₁₀ content 20% (w/w) and CoQ-10kyowa (CoQ₁₀ bulk powder) were supplied by Kyowa Hakko Bio Co., Ltd. (Tokyo, Japan). CoQ-10kyowa20 is a product emulsified with gum arabic by high-pressure homogenization at 900 kg/cm². A mixture that was equivalent to CoQ-10kyowa20 but was unemulsified was prepared by mixing 72% gum arabic, 22% CoQ-10kyowa, and 6% methylcellulose under dry conditions. Other chemicals and solvents were of analytical grade.

“Modulus of inclusion” of CoQ₁₀ formulations. One hundred micrograms of CoQ₁₀ formulation was mixed with hexane to a total volume of 20 mL. After the mixture had been left for 30 min in the dark, the CoQ₁₀ content of the supernatant was quantified as extractable CoQ₁₀. The amount of CoQ₁₀ not extracted by the hexane was calculated as the difference between the CoQ₁₀ content before treatment and the extractable CoQ₁₀. The “modulus of inclusion” was defined as the amount of CoQ₁₀ not extracted by hexane as a percentage of the CoQ₁₀ content before treatment.

Kinetic study of oral administration in rats. Male rats (6 wk old, Sprague-Dawley) were maintained on 12 h dark/12 h light cycles (7:00–19:00), with free access to water and CE-2 diet (CLEA Japan, Inc., Tokyo, Japan). The rats were orally given CoQ-10kyowa20 (emulsified CoQ₁₀, group 1), CoQ-10kyowa (CoQ₁₀ bulk powder, group 2), or the unemulsified equivalent of CoQ-10kyowa20 (group 3) by feeding needle. Each CoQ₁₀ formulation was suspended in 0.5% methylcellulose 400 (Wako Pure Chemical Industries, Ltd., Osaka, Japan). After 16 h of fasting, rats were orally given the CoQ₁₀ suspension at 10 mL/kg body weight (dose: 30 mg/kg CoQ₁₀). Blood samples were collected in tubes from rats in groups 1 and 2 before administration and 1, 2, 4, 6, 8, and 12 h after. Rats were fed after the 8-h blood collection. Blood samples were collected from group 3 rats 2 h after administration of the suspension. Ethanol (99.5%, 0.3 mL) was added to 0.3 mL serum and vortexed. The serum was then extracted three times with n-hexane. HPLC analysis was performed in accordance with a procedure described previously (23).

All the animal tests complied with the Animal Experiment Guidelines of the Healthcare Products Development Center of Kyowa Hakko Bio Co., Ltd. and were approved by the Animal Care Committee of the Center.

Table 1. Characteristics of CoQ₁₀ formulations.

| Formulation                              | CoQ₁₀ content (%) | Modulus of inclusion (%) | Particle size (nm) | Cmax value in rat study (µg/mL) | AUC₀–₄h in rat study (µg·h·mL⁻¹) |
|------------------------------------------|-------------------|--------------------------|--------------------|--------------------------------|----------------------------------|
| CoQ₁₀ bulk powder                       | 100               | 0                        | —                  | 0.035                          | 0.123                            |
| 20% CoQ₁₀ formulation                    | 20                | 98                       | 536±62             | 0.310                          | 0.749                            |
| Unemulsified 20% CoQ₁₀ equivalent formulation | 20                | 44                       | >1.000             | 0.067                          | 0.197                            |

Cmax: maximum plasma concentration. AUC₀–₄h: 4-h area under the curve.

Kinetic study of oral administration in human subjects. This study was performed by the contract research organization TTC Co., Ltd. (Tokyo Japan) and had a double-blind, crossover design. The subjects were 12 healthy, nonsmoking male volunteers aged 20–29 y who had not taken any CoQ₁₀, vitamin supplements, or medication within the previous 4 wk. The volunteers received a single oral dose of 120 mg CoQ₁₀ in two different formulations, with a 2-wk interval between doses. CoQ-10kyowa20 (Emulsified CoQ₁₀) and CoQ-10kyowa (CoQ₁₀ bulk powder) were each encapsulated in four hard capsules. At each study, following at least 8 h of fasting, the subjects took the CoQ₁₀ capsules with a glass of water. Blood samples were collected in heparinized tubes before CoQ₁₀ intake and 2, 4, 6, 8, and 12 h after. Standardized meals were provided after the 4-h and 8-h blood collections. Plasma CoQ₁₀ levels (both reduced and oxidized forms) were measured by a method described previously (24). Plasma cholesterol levels in blood samples before CoQ₁₀ intake were also measured. LDL and HDL cholesterol levels were measured by a direct assay method using kits supplied by Sekisui Medical Co., Ltd. (Tokyo, Japan). Total cholesterol was measured by an enzymatic analysis method using kits supplied by Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

Written informed consent was obtained from all volunteers. The procedures used for human testing complied with the Helsinki Declaration, as revised in 1983, and were approved by the Ethical Board of Kyowa Hakko Bio Co., Ltd. and Shinjyuku Oiwa Clinic Ethics Committee (Tokyo, Japan).

Analysis of CoQ₁₀ formulation properties. The oxidized CoQ₁₀ in the formulations was quantified. The formulation was dissolved in water, mixed with ethanol (99.5%), and extracted with n-hexane. HPLC analysis was performed in accordance with a method previously described (23). The particle size of the CoQ₁₀-containing formulations was measured by Sub-Micron Particle Analyzer (N4, Beckman Coulter, CA, USA). The food-processing suitability of the formulation was assessed in terms of preservation stability, thermal stability, hygroscopicity, and stability with coexisting materials. In the preservation stability study, CoQ-10kyowa20 was preserved at 5, 20, or 40°C for 6 mo and then the CoQ₁₀ content was quantified. In the thermal stability study, CoQ-10kyowa20 was enclosed in an aluminum bag and heated at 120, 140, or 160°C for 30 min. In the...
bioavailability and stability of emulsified CoQ₁₀

hygroscopicity study, CoQ₁₀kyowa was placed in a sealed container at 11, 33, 52, or 75% relative humidity for 18 d. To test stability with coexisting materials, CoQ₁₀kyowa was enclosed in an aluminum bag at a ratio of CoQ₁₀ (2%) with each material (50% magnesium oxide, 50% vitamin C, or 0.1% vitamin E); the mixture was made up to 100% with powdered sugar. The bag was incubated for 6 d at 60˚C.

**RESULTS**

**Particle size and modulus of inclusion**

The relationship between particle size and the modulus of inclusion of CoQ₁₀—a reference index of the emulsified state—were evaluated (Table 1). The 20% CoQ₁₀ formulation had a smaller particle size and larger modulus of inclusion of CoQ₁₀ than its unemulsified equivalent.

**Kinetic study of oral administration in rats**

The serum concentration of total CoQ₁₀ in rats given the 20% CoQ₁₀ formulation reached a peak 2 h (Tₘₐₓ) after administration, with a maximum plasma concentration (Cₘₐₓ) value of 0.310/826 µg/mL, whereas there was no peak in rats given the CoQ₁₀ bulk powder (Fig. 1A and Table 1). The total CoQ₁₀ represented the sum of both oxidized and reduced forms of CoQ₁₀. The 20% CoQ₁₀ formulation gave significantly greater serum CoQ₁₀ levels than did the CoQ₁₀ bulk powder 1, 2, and 4 h after administration (*p<0.05 at 1 h, **p<0.01 at 2 and 4 h). The 20% CoQ₁₀ formulation gave an area under the curve for 4-h (AUC₀–₄h) six times that given by the CoQ₁₀ bulk powder (Table 1).

To assess the mechanism behind the increased absorbability of the 20% CoQ₁₀ formulation, serum concentrations of total CoQ₁₀ 2 h after administration were compared among the three formulations (Fig. 1B). The
20% CoQ10 formulation had a significantly higher serum concentration ($p < 0.05$) of total CoQ10 than either the bulk powder or the unemulsified 20% CoQ10 equivalent. Administration of the CoQ10 bulk powder or unemulsified 20% CoQ10 equivalent barely increased the serum CoQ10 concentration level, which did not differ significantly between these two dosage forms.

**Kinetic study of oral administration in human subjects**

When the volunteers took the 20% CoQ10 formulation, the Tmax for the plasma concentration of total CoQ10 was 6 h and the Cmax value of 1.21 g/mL, whereas the CoQ10 bulk powder gave no peak. The values of Cmax and AUC0–12h in patients given the 20% CoQ10 formulation were significantly higher than those in patients given the CoQ10 bulk powder ($p < 0.01$). The changes in plasma CoQ10 concentration from the initial value were plotted (Fig. 2). The 20% CoQ10 formulation gave significantly greater plasma CoQ10 levels 6, 8, and 12 h after intake than did the CoQ10 bulk powder ($p < 0.01$ for 12 h, $p < 0.001$ for 6 and 8 h). There was a significant correlation between baseline plasma CoQ10 and total cholesterol (test of correlation coefficient, $p < 0.05$, Fig. 3A). There was no correlation between absorption of CoQ10 and either baseline CoQ10 (data not shown) or plasma cholesterol level (Fig. 3B). Almost all the CoQ10 quantified in the plasma was in the reduced form, not the oxidized form (data not shown).

**Processing suitability of the 20% CoQ10 formulation**

To test the preservation stability of the 20% CoQ10 formulation, the formulation was preserved at 5, 20, or 40˚C for 6 mo and then its content of CoQ10 was quantified. The 6-mo incubation did not change the appearance, quality, or water dispersibility of the 20% CoQ10 formulation. The residual percentage of CoQ10 was over 90% at each temperature (Fig. 4A).

To test for thermal stability, the 20% CoQ10 formulation was enclosed in an aluminum bag and heated at 120, 140, or 160˚C for 30 min. The residual percentages of CoQ10 were over 90%, even at the highest temperature (Fig. 4B).

To test for hygroscopicity, the 20% CoQ10 formulation was placed in a sealed container at 11, 33, 52, or 75% relative humidity for 18 d. Although increases in moisture absorption were observed at 33 to 75%, changes in solid state property were observed only at 75% (Fig. 4C).

CoQ10 is unstable in the presence of some materials. More than 90% of the initial CoQ10 in the presence of magnesium oxide or vitamin E, and 85% in the presence of vitamin C, survived after a 6-d incubation at 60˚C (Fig. 4D).

**DISCUSSION**

Various factors affect the bioavailability of CoQ10. For example, when taken with meals, CoQ10 is better absorbed than under fasting conditions owing to the action of secreted bile acids. Addition of the oils commonly used in CoQ10 soft capsules, or of surfactants such as polysorbates, also increases the bioavailability of CoQ10 (25, 26). The CoQ10 formulation created with cycloextrin, for example, has increased bioavailability (15, 27). Emulsification is important for increasing the bioavailability of this lipophilic substance. Moreover, because, in supplements, CoQ10 is usually used in mixtures with a variety of food materials, it is important that we develop CoQ10 formulations that excel in bio-
availability and are compatible with the various types of processing.

In the kinetic study in rats, the 20% formulation of CoQ10 emulsified with gum arabic significantly boosted the serum concentration of total CoQ10 compared with CoQ10 bulk powder (Fig. 1A). To test how the emulsifying process affected CoQ10 absorbability, we then compared the 20% CoQ10 formulation with its unemulsified equivalent. The plasma CoQ10 levels yielded by the unemulsified 20% CoQ10 equivalent were as low as those yielded by the CoQ10 bulk powder (Fig. 1B), suggesting that the presence of all the materials alone was insufficient, and that the emulsification process was important to increase bioavailability. Because we assumed a positive correlation between emulsified state and bioavailability of CoQ10, we then evaluated the particle size and modulus of inclusion—a reference index of the emulsified state—for the 20% CoQ10 formulation and the unemulsified equivalent (Table 1). The 20% CoQ10 formulation had a small particle size and large modulus of inclusion, and these two variables were negatively correlated. The small particles of emulsified CoQ10 may be absorbed more easily from the digestive tract. Surrounding the CoQ10 particles with the gum arabic could prevent CoQ10 from interacting with, and adhering to, each other.

Hatanaka et al. reported that a CoQ10 formulation with gum arabic showed greater absorbability than crystalline CoQ10 (19). They used an emulsified formulation of CoQ10 with a mean particle size of 770 nm; it was prepared by homogenization at 500 kg/cm2. On the other hand, because the formulation we used was homogenized at a pressure of 900 kg/cm2 and had a mean particle size of 536 nm (Table 1), our formulation may have had greater bioavailability and stability than the formulation of Hatanaka et al. Homogenization pressure may be a critical factor in the stability of emulsified CoQ10.

The absorbability of CoQ10 formulations in human subjects was also tested. The 20% CoQ10 formulation, compared with the CoQ10 bulk powder, significantly increased plasma CoQ10 levels (Fig. 2). Emulsification enabled the CoQ10 to remain in aqueous solution after intake. In this state, a micellar structure including the CoQ10 could easily form with secreted bile acid and could therefore be promptly absorbed from the digestive tract. Because the 20% CoQ10 formulation, with its high absorbability and small particle size, also had a high modulus of inclusion, it may be possible to use this newly defined parameter to predict bioavailability.

Absorbed CoQ10 is taken up into lipoproteins and transferred to the blood (6). There have been many reports of increased blood concentrations of CoQ10 following its administration (28, 29). It has also been reported that CoQ10 is, for the most part, carried to the liver and then excreted through the bile duct, so that only part of the amount ingested is carried to other organs (30). In a study in which 14C-labeled CoQ10 was given intravenously to rats to investigate the distribution of exogenous CoQ10, radioactivity in the mitochon-
molecule is responsible for the molecule’s emulsifying ability (39). Because this CoQ₁₀ formulation emulsified with gum arabic excels in processing suitability, its use should expand the range of uses of CoQ₁₀ in foods. The strategy of emulsification with gum arabic to reduce hydrophobicity should be useful not only for CoQ₁₀, but also for various drugs and food materials.

Although the physicochemical properties and absorbability of CoQ₁₀ emulsified with gum arabic have been studied previously in rats (18), the new information obtained here on the compound’s absorbability in humans and stability under various conditions should be useful for the manufacture of products such as food supplements containing CoQ₁₀.

In conclusion, emulsification of CoQ₁₀ with gum arabic increased its absorbability in rats and humans and also improved its food processing suitability. The emulsified CoQ₁₀ formulation had a small particle size and large modulus of inclusion, a reference index of the molecule is responsible for the molecule’s emulsifying state. Furthermore, the emulsified CoQ₁₀ was highly stable under various conditions, including heat, high humidity, and the presence of other materials.

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