Improved Absorption of CoQ_{10} by Fine Particle Design

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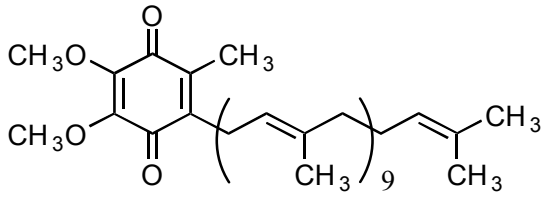
Introduction

Since the 1960s, Nisshin Flour Milling Inc. (Currently Nisshin Pharma Inc.) started industrial-scale production studies on Coenzyme Q_{10} (hereinafter referred to as CoQ_{10}) (Fig. 1) and established the industrial technologies, which permitted mass production of CoQ_{10} for the first time in the world. CoQ_{10} was approved as a food based on the revision of the Food and Drug Classification in 2001 while Ubidecarenone as the non-proprietary name was also permitted as a material for cosmetics in 2004. Accordingly, attention and expectation have been placed on both compounds as sources for functional foods or materials for cosmetics. [1–5)]



$C_{59}H_{90}O_4$: 863.34

Figure 1. Chemical structure of CoQ_{10}

CoQ_{10} possesses two major effects including a strong "anti-oxidization effect" in the body and a stimulating effect of intracellular "energy production," whereby CoQ_{10} can be designated as an essential compound in the living body. Because of such effects, one can expect expansion of the relevant market sizes for CoQ_{10} and upon merchandization, the product design is expected to be performed based on consideration of the physicochemical properties of CoQ_{10}[6)].

Absorption of CoQ_{10} and designing of fine particles

CoQ_{10} occurs as a yellow to orange crystalline powder with a melting point of about 48℃. This is a lipophilic product and barely soluble in water. It is gradually decomposed by exposure to light. Lipophilic CoQ_{10} is emulsified with bile acids in intestinal tracts and then transformed to micelle; subsequently, it is distributed to the liver via the lymphoduct and bound to lipoprotein therein, followed by transfer to cells. These features indicate that CoQ_{10} can be more easily absorbed after meals because its absorption is preceded by emulsification with bile acids, suggesting that it is barely absorbed under fasting conditions. Given all this, to be noted is the fact that easy micelle formation of lipophilic CoQ_{10} plays an important role in the improvement of absorption. With the objective of developing CoQ_{10} preparation which may feasibly be absorbed even if it is ingested at any time and at any place including during fasting conditions, we tried to provide CoQ_{10} with new utilities by the development of water-soluble CoQ_{10} through technical design to obtain fine particles of CoQ_{10}. The following is a description of the absorption mechanisms of lipophilic compounds and barely-absorbable compounds, as well as the technologies for improved absorption.

After our ingestion, long-chain fatty acid triglycerides (LCT) being composed of fats derived from animals or plants form the fat emulsion in the stomach, which is gradually moved to the duodenum. LCT in the small intestine is hydrolyzed by pancreatic lipase, followed by the formation of minute micelle with bile acids. The micelle is absorbed via villi into intestinal mucous cells. Subsequently, triglycerides are resynthesized to form chylomicron, which is transferred to the lymphatic system and

then enters into the blood flow, suggesting that all of these processes are hugely complicated in terms of digestion and absorption. Unlike LCT, middle-chain fatty acid triglycerides (MCT) follow extremely simple processes. MCT is more easily hydrolyzed with pancreatic lipase and then absorbed via villi into the intestinal mucous membrane. As is obvious from the above findings, it has been reported that digestion and absorption patterns are quite different depending on different fats[7]. Generally speaking, the absorption of drugs tends to be usually affected by meals ingested before and after the administration of the drugs, and in some cases, ingredients contained in the said drug preparations. Given the possibility that absorption of the drugs can be affected by physico-chemical compatibility between the ingested foods and the drugs, or the ingested foods provide influences on physiological conditions of the digestive tracts, it is necessary to pay due attention to these factors. When the drugs dissolved in oil are administered, the drugs are distributed from oil to aqueous solution and it is considered that the drugs are to be absorbed from the aqueous solution to the mucous membrane. As a natural consequence, absorption from the aqueous solution to the mucous membrane is retarded due to the difficulty of distribution from lipophilic oil to the aqueous solution. Therefore, we advanced the hypothesis that even in the case of lipophilic CoQ_{10}, appropriate modification by means of the latest technologies to design water-soluble fine particles will contribute to the improvement of absorbability in the living body[8]. For example, ethynylestradiol, a synthetic hormone was administered in the form of aqueous suspension but its absorption rate was found to be larger than that by administration of its solution in sesame oil.

According to the literatures on medicines, it was reported that following oral administration of solubilized ^{3}H-ubidecarenone with surfactants at a dose of 0.6mg/kg to rats (W, male), the radioactivity levels in blood reached about 60ng/ml as the maximum level calculated as the unchanged substance 1 hour after administration[9]. Absorption of ubidecarenone after oral administration is achieved mainly via the lymphatic system[10]. As regards possible influences of different preparations of CoQ_{10} on the plasma levels of CoQ_{10} in human blood, the orally ingested CoQ_{10} was emulsified with bile acid salts in digestive tracts, followed by absorption through small intestinal walls. Subsequently, they are incorporated into chylomicron and enter into the systemic circulation via the lymphatic systems[11].

It was reported that fine particle formation of the emulsified fat has a particle diameter of 0.1~0.2 μm which is the same level as that in fat emulsion for intravenous infusion stimulated absorption from the intestinal tracts, indicating favorable significance in both digestion and absorption[12]. Furthermore, to manufacture the preparations containing lipophilic drugs, it is necessary to improve the physicochemical properties and in particular, their solubilities. For the improvement of solubility of lipophilic drugs, various investigations have been performed such as crystalline polymorphism, utilization of solvation, non-crystallization, fine particle formation by mixed pulverization, improvement of wetting properties by cyclodextrine, and the formation of soluble salt. To improve the absorption of barely-soluble drugs, the particle sizes are generally decreased and the Noyes-Whitney's equation implies the apparent dissolution rate is proportional to the surface area. The smaller the particle diameter, the larger the surface area. Since the surface area is increased with decreasing particle sizes, the apparent dissolution rate is greatly changed by the particle sizes. It is documented that a 6-fold increase of the surface area is associated with a 2.5-fold elevation of its absorption. Achievement of fine particle formation of the drugs in intestinal tracts is required for the improvement of absorption in the elderly and patients who are characteristic of decreased excretion of bile juice and lipase together with weakened peristalsis of the stomach and intestines.

Recently, attention has been paid to the nanoparticle formation technique to improve the function of preparations through nanoparticle formation pulverizing lipophilic drugs to nanosized particles in their diameters. It is reported that nanosized particles could invade deeper into areas of digestive mucous membranes compared with micrometer-sized particles. Nanoparticle formation of barely-water-soluble drugs not only improves solubility of the drug particles themselves, but also makes possible deep invasion into the mucous membrane of intestinal tracts by encapsulation of them into fine particle carriers consisting of surfactant or high molecular weight films. Subsequently, these carriers release the encapsulated drugs therein. Accordingly, thanks to these specific modalities, the absorption of less absorbable drugs can be expected[13].

Water-solubilization techniques for CoQ_{10}

We performed water-solubilization study on CoQ_{10} including selection of the additives and manufacturing conditions based on the data consisting of biological features and physicochemical characteristics. In particular, improvement of wetting of the pulverized particles and maintenance of fine particles after dispersion in water were raised as the major issues. To overcome these technical problems, we conducted various studies on formulation and manufacturing procedures, leading to the development of 3 kinds of "CoQ_{10} material for water-solubilization." The newly developed CoQ_{10} material for water-solubilization possesses many advantages, thereby qualifying for application to food industries. Because of its properties, this new model can be added to beverages, tablets, granules and various foods.

As the first example, "Aqua Q_{10} L10" occurs as a water-soluble solution containing 10% CoQ_{10} and can be mainly formulated into beverages. Upon dispersion in water, this provides a mean particle diameter of about 50 nm, which meets the requirements for designing nanoparticles. As the results of monitoring the time-course changes in plasma concentration of CoQ_{10} following single oral administration of CoQ_{10} 60 mg to male adults, favorable absorption was attained even under fasting conditions. Figure 2 shows the particle distribution upon dispersion in water while Fig. 3 illustrates the results obtained on absorption in humans.

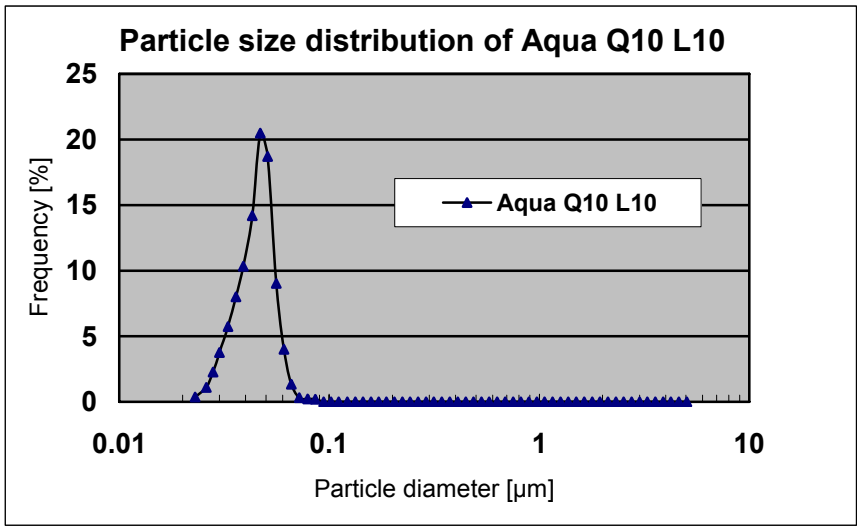


Figure 2. Particle size distribution of "Aqua Q_{10} L10" upon dispersion in water

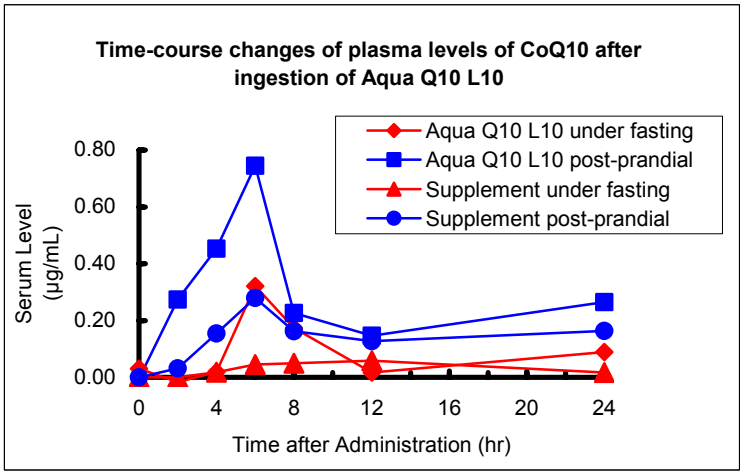


Figure 3. Male adults (Time-course changes of plasma levels after single oral administration of CoQ_{10} 60mg)

As the second example, "Aqua Q_{10} P5" is a water-soluble powder containing 5% CoQ_{10}. This can be added as it is to various supplements and this is obtained by nanoparticle design to make the mean particle diameter about 0.8 μm upon dispersion in water. The manufacturing procedures have been registered in Patent No. 3549197, while the relevant patent has been established in the US. This powder has characteristics such as good stability, dispersion in water and good absorption. Figure 4 shows particle size distribution of the powder upon dispersion in water. Figure 5 illustrates electron micrographs of this powder while Figure 6 shows the results on the confirmed absorption in human volunteers. In male adults, we confirmed the time-course changes of plasma concentrations of CoQ_{10} following single oral administration of CoQ_{10} at a dose of 60mg, together with verification of absorption of CoQ_{10}. The results obtained demonstrated excellent absorption of CoQ_{10} even under fasting conditions.

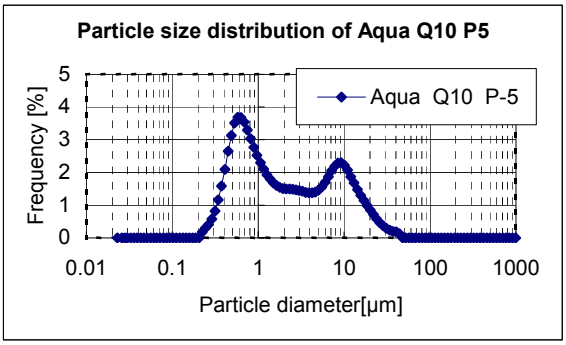


Figure 4. Particle size distribution of "Aqua Q_{10} P5" upon dispersion in water

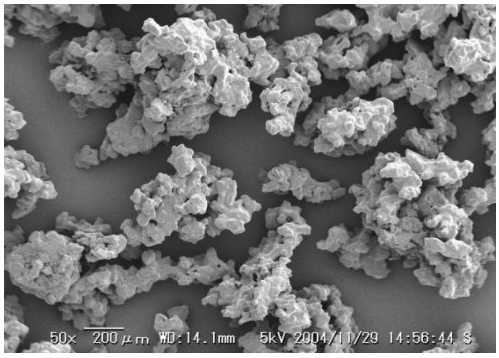


Figure 5. Electron micrographs of "Aqua Q_{10} P5"

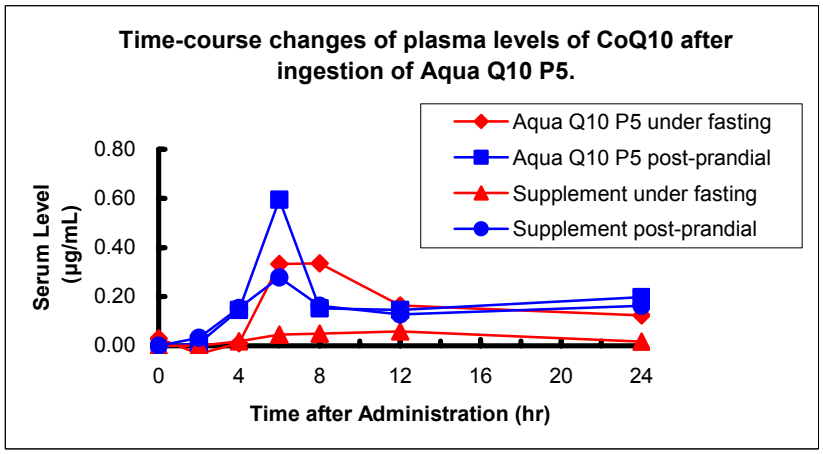


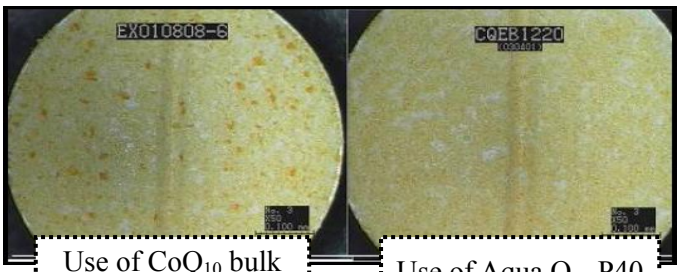
Figure 6. Male adults (Time-course changes of plasma concentrations of CoQ_{10} after single oral administration of CoQ_{10} at a dose of 60mg)

This water-soluble powder contains gum arabic as the base; however, this is a natural water-soluble gum with a molecular weight of 200~500 thousand. Gum Arabic has a chemical structure consisting of polypeptide combined with arabinogalactane as the polysaccharide moiety. The polysaccharide moiety comprises complicated polysaccharides containing salts and basic amino acids[14]. As a natural consequence, the addition of organic acids was found to contribute to higher stabilization of CoQ_{10}.

As the final example, "Aqua Q_{10} P40" is a water-soluble powder containing higher concentrations of CoQ_{10} amounting to 40%, and can be directly added to various supplements. The mean particle diameter when dispersed in water was about 0.19 μm, indicating that this can be designated a powder obtained by nanoparticle designing. This water-soluble powder is a value-added powder obtained by alteration of the physicochemical properties of CoQ_{10}; more specifically, the main objective was nanoparticle formation (particle design), improvement of the surface features (improvement of wetting characteristics) and improved absorption due to non-crystallization. This water-soluble powder was prepared to stimulate invasion of CoQ_{10} into the mucous membrane in intestinal tracts and dispersion within digestive tracts and to improve micelle formation. The results obtained by powder X ray refraction determination suggested that the crystal form became the non-crystalline type thereby improving absorption. The characteristics of powder included reduction of both the incidence of problems in tabletting such as the so-called sticking, and the frequency of stains derived from the bulk chemical; accordingly, we could obtain powder with good fluidization for tabletting, which improved the hard-capsule filling properties. Figure 7 shows a photograph of the surface of tablets while Fig. 8 illustrates the results obtained by a powder X ray refraction determination.

Figure 7.

Photographs of tablets manufactured on trial

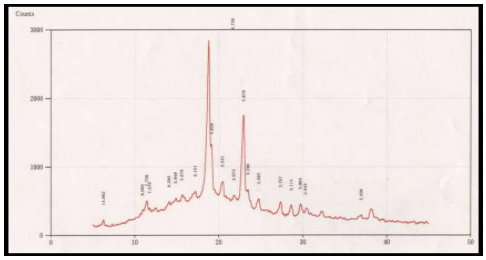


Use of CoQ_{10} bulk material

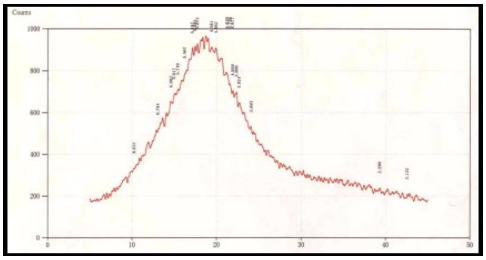
Use of Aqua Q_{10} P40

Figure 8.

Results of powder X ray refraction determination



Powder X ray refraction (Bulk chemical)



Powder X ray refraction (Aqua Q_{10} P40)

Employment of this water-soluble powder containing higher concentrations of CoQ_{10} enabled designing of small-sized tablets containing higher concentrations of CoQ_{10}, and furthermore, made it possible for its application to many general foods. This powder possesses characteristics including good stability and dispersion in water, as well as favorable absorbability. Particularly when tablets are manufactured, this powder provides powder characteristics conducive to easy processing and it was suggested that this could be favorably absorbed even under fasting conditions. Figure 9 shows particle size distribution when this powder is dispersed in water. Table 1 shows the powder features while Fig. 10 illustrates electron micrographs of the powder. The time-course changes of plasma concentrations after single oral administration of CoQ_{10} at a dose of 60mg in male adults were confirmed and the results of verification of CoQ_{10} absorption demonstrated that good absorption was observed even under fasting conditions. Figures 11 and 12 show the results obtained on the absorbability of CoQ_{10} in humans using conventional "lipophilic CoQ_{10} (Soft capsules)."

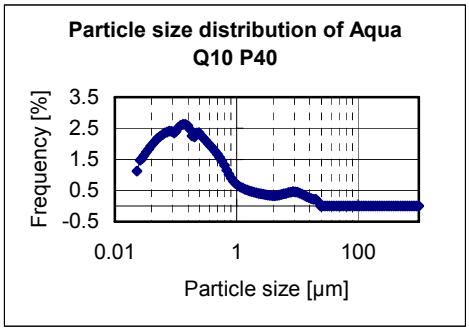


Figure 9. Particle size distribution of "Aqua Q_{10} P40" when dispersed in water

Table 1. Data on powder characteristics of "Aqua Q_{10} P40" (Observed values)

Mean particle diameter [μm]		Apparent specific gravity	Apparent specific gravity	Compression degree	Repose angle
Water dispersion	Powder	(Loosen) [g/mL]	(Tighten) [g/mL]	[%]	[degree]
0.19	59	0.32	0.50	36.3	50.1

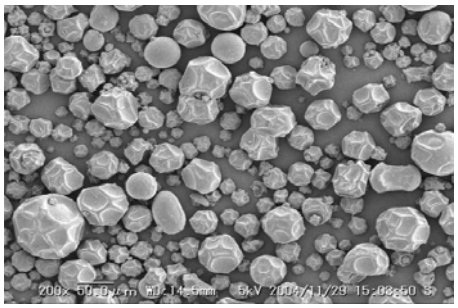


Figure 10. Electron micrograph of "Aqua Q_{10} P40"

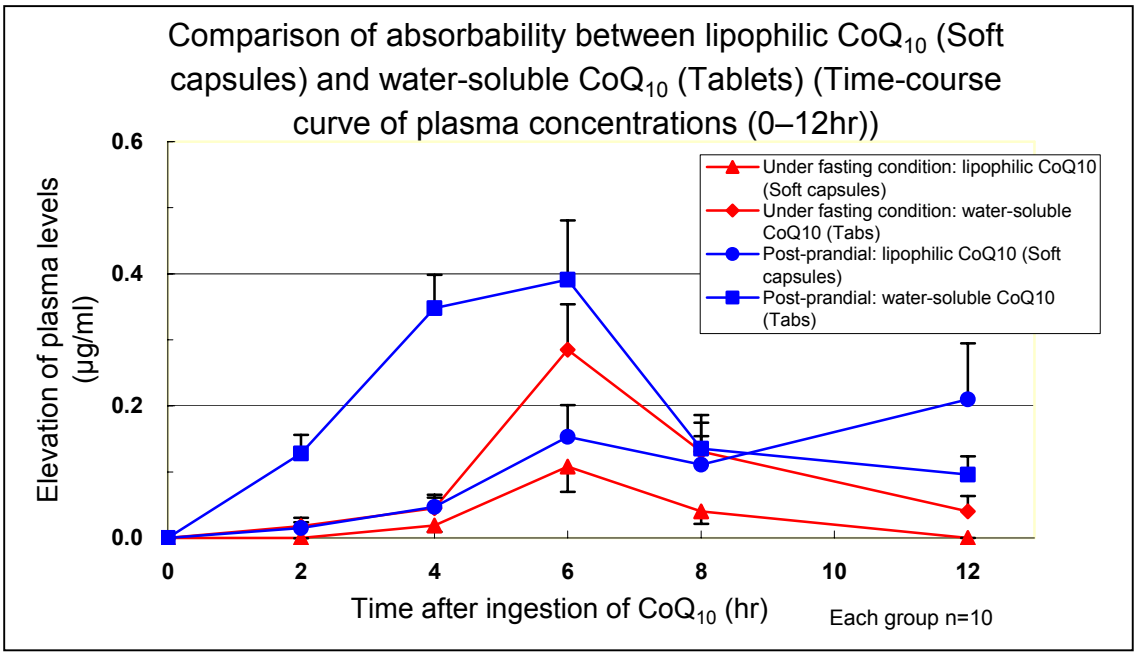


Figure 11. Male adults (Time-course changes of plasma concentrations of CoQ_{10} after single oral administration of CoQ_{10} at a dose of 60 mg)

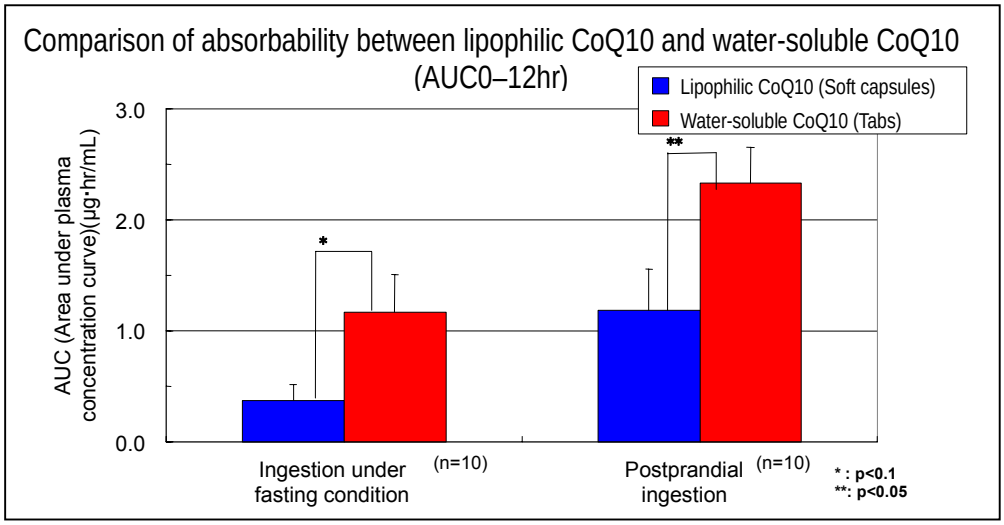


Figure 12. Male adults (Time-course changes of plasma concentration $AUC_{0–12}$hr after single oral administration of CoQ_{10} at a dose of 60mg)

Many patent applications have been submitted to cover the water-solubilization technologies for CoQ_{10} and manufacturing technologies on the materials as well as merchandizing technologies. For example, Patent No. 3549197 describes the manufacturing method for water-soluble powder in its patent specification while Patent No. 3618336 concerning stabilization technologies of CoQ_{10} has already been granted. In addition, other patent applications have been conducted for processing technologies such as tablet manufacturing procedures.

Characteristics of water-soluble CoQ_{10}

Because of its lipophilic property, CoQ_{10} cannot be absorbed unless ingested together with meals. On the other hand, the water-soluble CoQ_{10} is well dispersed to produce fine particles immediately after being dispersed in water and then becomes emulsified and micelle-formed; subsequently, they are absorbed via the lymph ducts. Fine particle designing enabled the absorption of CoQ_{10} even under fasting conditions although CoQ_{10} itself is barely-absorbable. As regards absorbability in the body, "Aqua Q_{10} L10" shows that the particle diameters in the emulsified solution following solubilization

reached nano-orders whereby they can be absorbed into the mucous membrane of digestive tracts. Therefore, it is postulated that they can be promptly absorbed because micelle formation occurs by means of bile acids. "Aqua Q_{10} P5" and "Aqua Q_{10} P40" use the powder with higher solubility and dispensability in water as the base; as a natural consequence, they show good dispersion and dissolution in water. Thanks to easy transformation into micelle by means of bile acids, they can invade deeper into the mucous membrane layers in digestive tracts, leading to easy absorption. They are well absorbed without ingestion together with high fat foods. Accordingly, they are appropriated to be given to persons taking a limited volume of food, persons taking low-fat foods, persons under calorie control, persons controlling food before physical exercises, persons engaged in busy lifestyles, as well as the elderly taking limited foods.

Conclusion

Because of adequate exertion of two major effects such as "Stimulation of energy production" and "Strong anti-oxidation effects," the development of new functional foods containing water-soluble CoQ_{10} can be expected. In particular, the water-soluble CoQ_{10} which is produced by nano-particle designing is proud of its good absorbability in the body; therefore, irrespective of ingesting occasions, this can provide new foods from which CoQ_{10} can be assuredly absorbed. Fundamental researches as the biofactor have been energetically performed and future new development can be expected[15-16].

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