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Physicochemical and pharmacokinetic characterization of water-soluble Coenzyme Q_{10} formulations

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ABSTRACT

Coenzyme Q_{10} (CoQ_{10}) has been used as a drug for chronic heart failure. Furthermore, various biological effects of CoQ_{10} have also been applied for food supplements and cosmetics. However, CoQ_{10} was found to be poorly soluble in water, so that its bioavailability was low and variable depending on food intake. In the present investigation, a novel liquid (nano-emulsion, NE) and water-soluble powder formulations, including cyclodextrin–Q10 complex (CoQ_{10}–CD) and dry-emulsion (DE), were prepared. The physicochemical properties of each formulation were characterized by dynamic light scattering (DLS), scanning electron microscopy (SEM), powder X-ray diffractometry (PXRD), and differential scanning calorimetry (DSC). In all powder formulations prepared, CoQ_{10} existed mainly as an amorphous form as determined by PXRD and DSC, and each powder formulation exhibited high solubility and dispersibility in water resulting in the formation of a nano-sized emulsion (NE; 60 nm) and micron sized particles (DEs and CoQ_{10}–CD; 0.77–2.4 μm). The pharmacokinetic study of each dosage form, in comparison to a CoQ_{10} crystal suspension, was also carried out in rats after a single oral dose. Although similar kinetic values were seen with T_{max} of 1.5 and 1.7 h, respectively, for NE and crystalline CoQ_{10}, NE exhibited ca 1.7-fold higher AUC and C_{max} than the crystalline CoQ_{10}.

1. Introduction

Coenzyme Q_{10} (CoQ_{10}), a lipophilic naturally-occurring chemical, acting as a vital intermediate of electron transport system in the mitochondria, has been approved for use in both foods and drugs. CoQ_{10} has been widely applied in food supplements and cosmetics in Japan, USA (GRAS certified), and many other countries. However, the bioavailability of CoQ_{10} is low and variable due to its poor solubility and high molecular weight (Bhagavan and Chopra, 2006). Pharmacokinetic profiles of CoQ_{10} have been reported from various studies on rats (Kimura et al., 1986), dogs (Kommuru et al., 1999), rabbits (Verma et al., 2007), and humans (Bhagavan and Chopra, 2006; Chopra et al., 1998; Joshi et al., 2003). A number of strategies to improve the absorption of CoQ_{10} have been proposed such as oily solution (Kommuru et al., 1999), self-emulsified drug delivery system (SEDDS) (Kommuru et al., 2001; Palamakula and Khan, 2004), esterification (Turunen et al., 1999), coadministration of pepper extract (Badmaev et al., 2000), binary solid dispersion (Bhandari et al., 2007; Nazzal et al., 2002), liposome (Verma et al., 2007; Xia et al., 2006, 2007), and cyclodextrin complex (Yang and Song, 2006). In addition, commercial products of food supplements have been studied to determine the bioavailability of CoQ_{10} (Ullmann et al., 2005).

Recently, novel liquid nano-emulsion (NE) and dry-emulsion (DE) formulations have been developed for the solubilization of lipophilic drugs. In practice, NE strategies were often applied to lipophilic drugs such as paclitaxel (Khandavilli and Panchagnula, 2007), primaquine (Singh and Vingkar, 2008), saquinavir (Vyas et al., 2008), and ramipril (Shafiq et al., 2007). DE formulations are characterized as microsphere systems, encapsulating lipophilic drug such as griseofulvin (Ahmed and Aboul-Einien, 2007), amlodipine, and vitamin E acetate (Takeuchi et al., 1991) into its matrix, and they formed emulsions when dispersed into water. It is well known that DE techniques also improve various physicochemical properties of solid and powder formulations, including solubility, photostability (Jang et al., 2006), and redispersibility, possibly leading to enhanced bioavailability (Dollo et al., 2003). Recently, highly lipophilic bioactive substances such as tocopherol, carotenoids, and fatty acids were emulsified and dispersed uniformly in beverage and liquid/gel foods using these solubilization

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Table 1
Composition of CoQ10–NE and –DE formulations

	Nano-emulsion (%)		Dry-emulsion (%)	
Components	CoQ_{10}	10.5	CoQ_{10}	21.0
	Surfactants	12.0	Gum arabic	36.0
	Soybean lecithin	3.0	Sugar alcohol	28.0
	Glycerol	55.0	MCT	15.0
	Deionized water	15.0		
	MCT	4.5		
Total		100		100

methods (Boon et al., 2008; McClements et al., 2007). Although these solubilizing techniques have been applied to food supplements and health foods, as well as pharmaceutical substances, pharmacokinetic and physicochemical profiles of CoQ_{10} dispersed with NE and DE methodologies have not been fully elucidated.

The aim of the present study is to identify physicochemical and pharmacokinetic properties of CoQ_{10} water-soluble formulations. We prepared liquid NE and solid DE formulations of CoQ_{10} with the use of solubilizing agents commonly used as food ingredients, and also prepared a cyclodextrin (CD) inclusion complex as a control dosage form. We characterized physicochemical properties and stability of these formulations by dynamic light scattering, zeta-potential measurement, scanning electron microscopy, powder X-ray diffraction, and differential scanning calorimetry. In addition, *in vivo* drug absorption tests in rats were carried out by oral administration of crystal dispersion and several emulsions of CoQ_{10}.

2. Materials and methods

2.1. Materials

CoQ_{10} was purchased from Asahi Kasei Pharma (Tokyo, Japan). CoQ_{10} cyclodextrin inclusion complex (CoQ_{10}–CD) was purchased from Cyclochem (Hyogo, Japan). Surfactants were purchased from Taiyo Kagaku (Mie, Japan). Soybean lecithin was purchased from Kyowa Hakko Kogyo (Tokyo, Japan). Medium chain triglyceride (MCT) was purchased from Kao (Tokyo, Japan). Gum arabic was purchased from Sanei Yakuhin Boueki (Osaka, Japan). Sugar alcohol was purchased from Towa Chemical Industry (Tokyo, Japan). Glycerol was purchased from Wako Pure Chemical Industries (Osaka, Japan). All chemicals used in HPLC analysis were from commercial sources and of reagent grade.

2.2. Sample preparation

2.2.1. CoQ_{10} nano-emulsion (CoQ_{10}–NE)

The composition of CoQ_{10}–NE is shown in Table 1. Briefly, 10% CoQ_{10} was dissolved in 5% of medium chain triglyceride (MCT) at 80 °C (lipid phase). Nonionic surfactants (12%), soybean lecithin (3%), glycerol (55%), and deionized water (15%; aqueous phase) were heated to 80 °C. The lipid phase was added into the aqueous phase and emulsified using a Homomixer (T.K. Robomix, Primix, Osaka, Japan) at 9000 rpm for 15 min. In addition, the emulsion was processed using a high pressure homogenizer (Microfluidizer, Mizuho Industry, Osaka, Japan) at 1000 kg/cm^2. The content of CoQ_{10} of the obtained NE was 10%.

2.2.2. CoQ_{10} dry emulsions (CoQ_{10}–DEs)

The compositions of CoQ_{10}–DEs are shown in Table 1. Briefly, 21% CoQ_{10} was dissolved in 15% MCT in 80 °C (lipid phase). Gum arabic (36%) as an emulsifier and sugar alcohol (28%) as solid carrier were dissolved in deionized water at 60 °C (aqueous phase). The lipid phase was added into aqueous phase and mixed using a Homomixer at 9000 rpm for 30 min and a portion of this emulsified slurry was dried using a spray-dryer (L-8i type spray-dryer, Ohkawara Kakohki, Kanagawa, Japan) to obtain the powder formulation, designated as primary dry emulsion (CoQ_{10}–PDE). The remainder of the emulsified slurry was processed by high pressure homogenizer at 500 kg/cm^2 and spray-dried, as was designated as homogenized dry emulsion (CoQ_{10}–HDE). A physical mixture (CoQ_{10}–DE–Pmix) was prepared by kneading the same composition of dry emulsion, heating to 80 °C, and cooling to room temperature. The content of CoQ_{10} of the obtained ND was 10%.

2.2.3. CoQ_{10} content of NE and DE formulations

Each formulation was dissolved in 50% EtOH and subjected to UPLC analysis for determination of CoQ_{10} content. All analyses were performed on Waters Acquity UPLC/MS system (Waters, Milford, MA), that include the binary solvent manager, sampler manager, column compartment, TUV detector with the detection wavelength of 275 nm and SQ detector, connected with Waters MassLynx software. An Acquity UPLC BEH C18 column (particle: size 1.7 μm, column size: Ø2.1 mm × 50 mm; Waters), also from Waters, was used. Column temperature was maintained at 60 °C. The standards and samples were separated using a gradient mobile phase consisting of ethanol (A) and acetonitrile (B). The gradient condition of mobile phase was 0–0.5 min, 40% A; 0.5–3.5 min, 40–80% A; and 3.5–4.0 min, 80% A, and the flow rate was set at 0.25 mL/min.

2.3. Characterization of formulations

2.3.1. Particle size analysis and zeta-potential in aqueous solution

Particle size and zeta-potential analysis of droplets in aqueous solution were performed with ELS-Z (Otsuka Electronics, Osaka, Japan) by a dynamic light scattering method. Prior to measurement, 0.5 g of each formulation was diluted with 50 mL distilled water and dispersed homogeneously. Mean diameter and size distribution was calculated using the photon correlation from light scattering. All measurements were performed at 25 °C at a measurement angle of 160°. The size distribution, which was calculated by histogram analysis of scattering intensity, was evaluated at cumulative values of 10%, 50%, and 90%. Zeta-potential was calculated using the Smolchowski equation from the electrophoresis mobility and electric field strength.

2.3.2. Scanning electron microscopy

The surface morphology of powder formulations was examined using a scanning electron microscope (SEM, TOPCON SM350, Topcon, Tokyo, Japan). Powder samples were manually dispersed on an aluminum stub with a thin self-adhered carbon film. The samples were made electrically conductive by coating in a vacuum (13 Pa) with gold (5 nm/min) using an ion coater (IB-3 ion coater, Eiko, Tokyo, Japan) for 120 s at 6 mA. The SEM picture was taken at an excitation voltage of 15 kV and a magnification of 500 times.

2.3.3. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was performed using a Rigaku Thermo Plus DSC8230 (Rigaku, Tokyo, Japan). About 3 mg of sample was placed in a sealed aluminum pan at a scanning rate of 5 °C/min from 0 to 85 °C. An empty aluminum pan was used as a reference.

2.3.4. Powder X-ray diffraction analysis

The powder X-ray diffraction (PXRD) pattern was collected with a Rigaku MiniFlex diffractometer (Rigaku, Tokyo, Japan) with Cu Kα radiation generated at 15 mA and 30 kV. Data were collected from 5° to 40° (2θ) at a step size of 0.02° and a scanning speed of 2°/min

2.4. In vivo absorption study

2.4.1. Animals

Male Sprague-Dawley rats, weighing 202–236 g, from SIPPR/BK Laboratory Animal Co. Ltd. (Shanghai, PR China) were acclimatized to the laboratory conditions for 1 week and observed for any sign of illness. Rats were housed in plastic cages (four rats/cage) on chip bedding. The animal room was maintained at 23–25 °C and 50–60% relative humidity with a 12 h light/dark cycle and room air was changed of about 12 times/h. All animals were supplied with a sterile commercial diet and tap water *ad libitum* throughout the acclimation and testing periods. All animal procedures were in strict accordance with the Guidelines approved by the Experimental Animal Ethical Committee of Dalian Medical University.

2.4.2. Experimental protocol

The animals were randomly assigned to five groups of 48 rats, and each group was randomly divided into eight subgroups of six rats each. The test substances were administered after rats were deprived of food for 16 h. Rats received CoQ_{10} at the dose of 60 mg/kg b.w. The volume administered to rats was 10 mL/kg b.w. Blood samples of six rats in each subgroup were collected at 0.5, 1, 2, 4, 8, 12, and 24 h after dosing. Blood samples of six rats in the untreated subgroup were used as a control to determine levels of endogenous CoQ_{10}.

2.4.3. Determination of CoQ_{10}

Rats were anaesthetized with ether. Blood samples were collected from the abdominal aorta with sodium citrate as an anticoagulant and blood samples were centrifuged to produce plasma. Each plasma sample (1 mL) was supplemented with 40 μL of vitamin K_1 (10 μg/mL) as an internal standard. The samples were then mixed with 2 mL of ethanol and vortexed for 10 s; 5 mL of hexane was added, followed by vortexing for 5 min and centrifugation (3000 rpm, 10 min). The organic layer was collected and evaporated to dryness under nitrogen. The sample residues were stored in a refrigerator (−20 °C). The residue was dissolved in 100 μL of ethanol, and 20 μL of each sample was injected into an HPLC. The HPLC comprised a Shimadzu Corporation (Kyoto, Japan) metering pump LC-10A, model SPD-10A UV detector, and C_8 analytical column (6.0 mm × 150 mm). A CLASS-VP LC workstation was used to record and measure peak areas. The column was maintained at 35 °C in column oven, and the mobile phase was methanol at a flow rate of 1.0 mL/min. Peaks were detected at 275 nm.

2.4.4. Data analysis

Pharmacokinetic parameters were estimated using a non-compartment model method. Individual C_{max} and T_{max} values were calculated from actual plasma CoQ_{10} concentrations. AUC was estimated using the linear trapezoidal rule. The k was estimated by the method of residuals, and $T_{1/2}$ was calculated using the equation ($T_{1/2} = 0.693/k$). Pharmacokinetic parameters were compared using one-way ANOVA and two-sided Student's t test. Differences were considered as significant at $P < 0.05$.

3. Result and discussion

3.1. 3-1.Particle size and zeta-potential of CoQ_{10} formulations in aqueous solution

NE formulation was found to be soluble in water without any sonication, stirring, or heating. Particle size, size distribution, and zeta-potential of prepared formulations were evaluated (Table 2) since these data would be indicative of the stability of colloidal dispersion system in solution. After the addition of CoQ_{10}–NE into water, CoQ_{10}–NE spontaneously formed a translucent emulsion system with a mean diameter and zeta-potential of 60 nm and −33 mV, respectively, resulting in uniform dispersion in water. The aqueous solution was stable without showing any creaming, aggregation, phase separation, or precipitation for at least 1 month (data not shown). Generally, an emulsion with a diameter of 50–100 nm, called a nano-emulsion, tends to show a translucent pale appearance, and the nano-emulsion should be stable in aqueous solution since the rate of Brownian motion is much faster than the rate of creaming or sedimentation (Mosqueira et al., 2000; Sarker, 2005). From these findings, higher physical stability of NE in aqueous solution can be attributed to its small particle size; therefore, NE methodology should be a suitable solubilizing strategy for CoQ_{10}.

Table 2
Particle size and zeta-potential of CoQ_{10} formulations

Formulation	Mean diameter (nm)	D10 (nm)	D50 (nm)	D90 (nm)	Zeta-potential (mV)
CoQ_{10}–NE	60	32	64	130	−33
CoQ_{10}–PDE	1700	770	1100	>7000	−39
CoQ_{10}–HDE	770	510	770	1300	−44
CoQ_{10}–CD	2400	900	2600	>7000	0

Each CoQ_{10} formulation was dissolved in distilled water. Data represent mean from four experiments.

CoQ_{10}–PDE, CoQ_{10}–HDE, and CoQ_{10}–CD could be dispersed into water by agitation and gave a cloudy appearance. On the contrary, CoQ_{10}–DE–Pmix exhibited extremely low dispersibility in water even though the sample was sonicated or stirred strongly, which prevented the measurement of particle size and zeta-potential. After dispersion, CoQ_{10}–DEs gradually developed creaming and precipitation. Although both CoQ_{10}–PDE and CoQ_{10}–HDE dispersion showed these morphological changes within 3 days and 1 week, respectively, they were easily redispersed by gently mixing. CoQ_{10}–HDE showed a narrower size range distribution and high stability in aqueous solution as compared to CoQ_{10}–PDE, and the mean diameter of CoQ_{10}–HDE (0.77 μm) was 2.2-fold smaller than that of CoQ_{10}–PDE (1.7 μm). Therefore, high pressure homogenization of emulsified slurry just prior to spray-drying might be effective for the preparation of a fine dry emulsion of CoQ_{10}. The zeta-potentials of CoQ_{10} powder formulations were calculated as −39 mV (CoQ_{10}–PDE), −44 mV (CoQ_{10}–HDE), and 0 mV (CoQ_{10}–CD). DEs reconstituted the micron-sized emulsion with a negative charge, so DEs should be stable in aqueous solution and be applicable to liquid foods. On the contrary, CoQ_{10}–CD, having no net charge, tended to precipitate immediately, so that CoQ_{10}–CD was likely to show poor water dispersibility, unlike other formulations tested.

3.2. Surface morphology and crystallinity of powder formulations

SEM images from CoQ_{10}, CoQ_{10}–CD, and CoQ_{10}–DE–Pmix are shown in Fig. 1. The pure drug consisted of a mixture of some large crystals (15–20 μm) with microparticles, which might be generated due to micronization or any other size reduction processes at the time of manufacturing. Spray dried formulations revealed significant changes in particle shape and surface topography due to the impact of spray drying process. Of all the powder formulations tested, CoQ_{10}–CD displayed the smallest particle size, and crystalline CoQ_{10} was also small and agglomerated to form a granule-like structure. CoQ_{10}–DEs were found to be spherical particles with corrugated surfaces; however, CoQ_{10}–DE–Pmix showed a massive appearance with lipid solid structure. Generally, spray-dried powder has a spherical shape as observed in DEs; however, the emulsified lipid phase is encapsulated into a matrix of microcapsules (Bunjes et al., 2001; Raffin Pohlmann et al., 2002). This

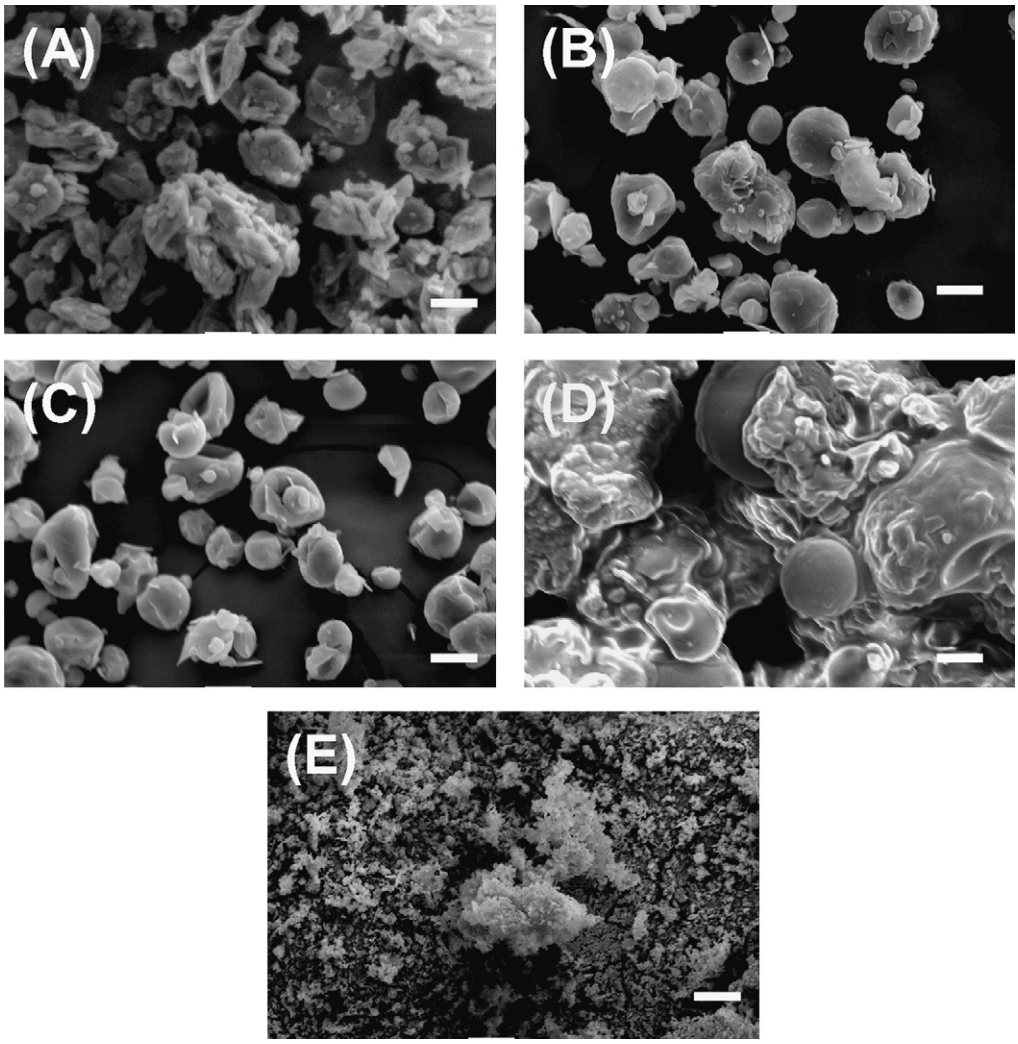

Fig. 1. Scanning electron micrographic images of CoQ_{10} powder formulations. (A) Crystalline powder, (B) primary dry-emulsion, (C) homogenized dry-emulsion, (D) physical mixture of dry-emulsion composite, and (E) cyclodextrin inclusion complex. Bar represents 20 μm.

could be a part of reasons why DEs and their physical mixtures exhibited a different morphology.

PXRD and thermal analyses on the powder formulations were carried out to evaluate the crystallinity of CoQ_{10}. According to the PXRD patterns of crystalline CoQ_{10} (Fig. 2), a sharp and intense peak observed at ca 18° (2θ) should be characteristic and helpful for identifying crystalline conditions. These data were consistent with previous observations (Siekmann and Westesen, 1995). Interestingly, a significant reduction of this peak was confirmed in all powder formulations, and especially PXRD patterns of CoQ_{10}–HDE and CoQ_{10}–CD suggest the lowest crystallinity. From these findings, the crystalline condition of CoQ_{10} can be variable depending on the type of formulation, and the order of crystallinity was evaluated as follows; crystal CoQ_{10} > CoQ_{10}–DE–Pmix > CoQ_{10}–PDE > CoQ_{10}–HDE ≒ CoQ_{10}–CD. In addition to the PXRD analysis, all formulations were subjected to DSC analysis for further elucidation of the crystal condition (Fig. 3). A DSC thermogram of crystalline CoQ_{10} showed an intense endothermal peak at ca 50 °C, corresponding to the melting point of CoQ_{10}; however, the intensity of the endothermal peak was quite different among the powder formulations of CoQ_{10}. As observed in PXRD experiments, the endothermal peak in CoQ_{10}–HDE was negligible, and the order of intensity of the endothermic peak was as follows; crystal CoQ_{10} > CoQ_{10}–DE–Pmix > CoQ_{10}–CD > CoQ_{10}–PDE > CoQ_{10}–HDE.

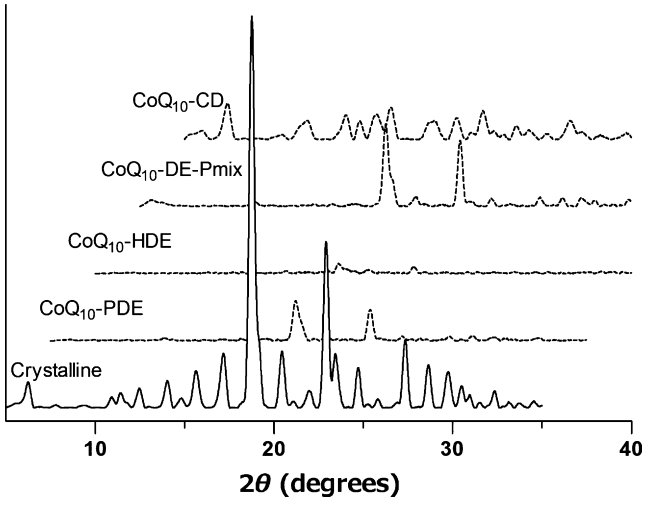

Fig. 2. Powder X-ray diffraction patterns of CoQ_{10} powder formulations. CoQ_{10}–PDE, primary dry-emulsion; CoQ_{10}–HDE, homogenized dry-emulsion; CoQ_{10}–DE–Pmix, physical mixture of dry-emulsion composition; and CoQ_{10}–CD, cyclodextrin inclusion complex.

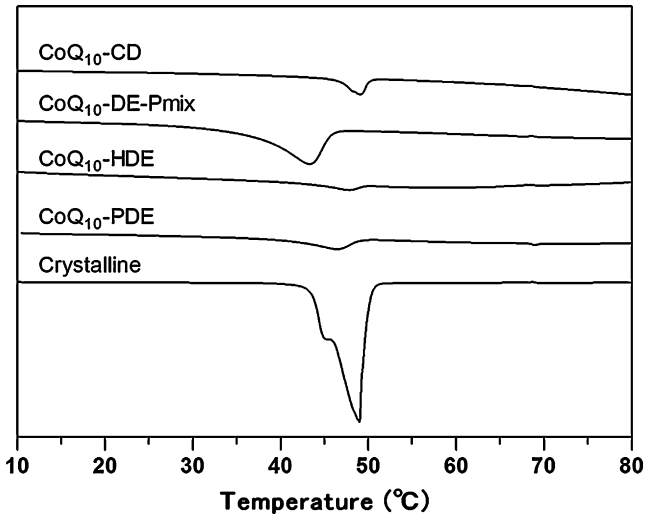

Fig. 3. Thermographs of CoQ_{10} powder formulations by differential scanning calorimetry. CoQ_{10}–PDE, primary dry-emulsion; CoQ_{10}–HDE, homogenized dry-emulsion; CoQ_{10}–DE–Pmix, physical mixture of dry-emulsion composition; and CoQ_{10}–CD, cyclodextrin inclusion complex.

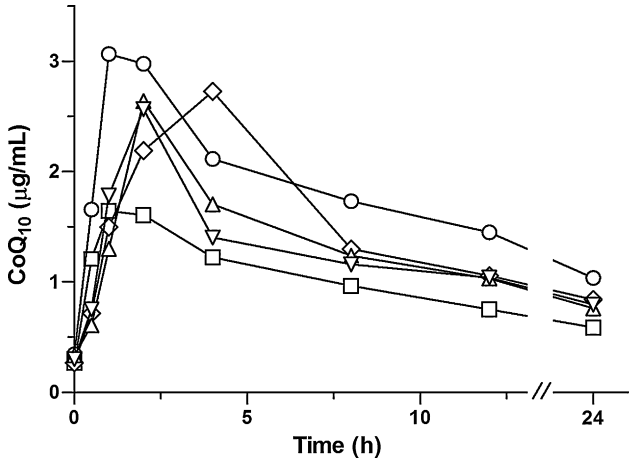

Fig. 4. Mean CoQ_{10} concentrations in bloods of rats after oral administration of CoQ_{10} formulations (60 mg CoQ_{10}/kg body weight of rat as a single dose). Each value represents mean from six experiments. (□) crystalline, (○) CoQ_{10}–NE (nano-emulsion), (△) CoQ_{10}–PDE (primary dry-emulsion), (▽) CoQ_{10}–HDE (homogenized dry-emulsion), and (◊) CoQ_{10}–CD (cyclodextrin inclusion complex).

These results were partly consistent with the result from PXRD data, suggesting that CoQ_{10} molecules in water-soluble powder formulations were basically present as an amorphous form in various proportions depending on the preparation procedure, conditions, and co-existent components of powder formulations. The present findings, taken together with the preparation scheme of powder formulations, suggested that high pressure homogenization of emulsified slurry before spray-drying could be effective to make a dry emulsion of CoQ_{10} with a higher amount of the amorphous form. The high internal energy and specific volume of the amorphous state relative to the crystalline state can lead to enhanced dissolution and bioavailability (Pouton, 2006; Singhal and Curatolo, 2004).

3.3. Improvement of bioavailability

To confirm the usefulness of water-soluble formulation in improving the bioavailability of CoQ_{10}, as well as solubility, an *in vivo* test was carried out with all the formulations dispersed in water. Fig. 4 shows the blood concentration–time profiles of CoQ_{10} in rats after oral administration of CoQ_{10}–NE, CoQ_{10}–DEs, CoQ_{10}–CD, or crystalline powder at the dose of ca 13 mg CoQ_{10}. CoQ_{10} levels in the blood were found to be very low when the crystalline powder was administered orally, and the C_{max} and AUC values were 1.9 μg/mL and 43.3 μg h/mL, respectively. According to the pharmacokinetic parameters in five dosage forms (Table 3),

Table 3
Pharmacokinetic parameters of CoQ_{10} formulations following oral administrations of 60 mg/kg of CoQ_{10}

	AUC (μg/mL h)	$T_{1/2}$ (h)	C_{max} (μg/mL)	T_{max} (h)
Crystalline CoQ_{10}	43.3 ± 20.2	23.0 ± 13.9	1.9 ± 0.5	1.7 ± 1.2
CoQ_{10} formulations				
CoQ_{10}–NE	71.3 ± 10.8*	21.4 ± 6.0	3.2 ± 0.6**	1.5 ± 0.5
CoQ_{10}–PDE	55.0 ± 16.1	23.3 ± 10.7	2.7 ± 0.6*	2.7 ± 1.0
CoQ_{10}–HDE	58.4 ± 12.5	26.4 ± 5.4	2.6 ± 0.4*	1.7 ± 0.5
CoQ_{10}–CD	50.9 ± 9.2	15.4 ± 4.6	2.9 ± 0.8*	2.8 ± 1.3

Values are expressed as means ± S.D. from six experiments. $T_{1/2}$: half-life; T_{max}: time to maximum concentration; C_{max}: maximum concentration; AUC: area under the curve of plasma concentration versus time from $t = 0$ to $t = \infty$ after oral administration. *$P < 0.05$, **$P < 0.01$ versus crystalline CoQ_{10}.

improvement of C_{max} and AUC was observed in four water-soluble formulations as compared to crystalline CoQ_{10}, whereas all the formulations, except for CoQ_{10}–CD, showed similar T_{max} and $T_{1/2}$. This could be primarily attributed to the improved solubility and the dissolution associated with the amorphization of CoQ_{10} by DE/NE strategies and CD complexation. Similar pharmacokinetic profiles were obtained for CoQ_{10}–DEs and CoQ_{10}–CD. Both AUC and C_{max} of CoQ_{10}–NE were found to be ca 1.7-fold higher than those of crystalline CoQ_{10}, indicating that oral absorption of CoQ_{10} is enhanced strongly by its administration as NE formulation. Previously, the use of γ-CD was proposed for formulation of CoQ_{10} in the pharmaceutical and nutrition fields since γ-CD improved solubility in water, dissolution rate and oral absorption of CoQ_{10} in dogs and humans (Terao et al., 2006). In our investigation, plasma levels of CoQ_{10} in rats tended to be higher after CoQ_{10}–CD administration in comparison with crystalline CoQ_{10}, showing ca 20% higher relative bioavailability compared with the crystalline CoQ_{10}. In addition, the absorption of CoQ_{10} from CoQ_{10}–NE showed a 40% increase in relative bioavailability compared with that of CoQ_{10}–CD. Thus, the order of AUC was as follows: CoQ_{10}–NE > CCoQ_{10}–HDE ≒ CoQ_{10}–PDE ≒ CoQ_{10}–CD > crystalline CoQ_{10}, being likely to correlate with the particle size after dissolution. Therefore, CoQ_{10}-loaded NE system might be a promising approach to the oral delivery of CoQ_{10}.

In addition to particle size, several factors could also be involved in the improvement of oral bioavailability by these strategies; e.g. capability of spreading to the aqueous phase in the gastrointestinal tract, permeability of intestinal membrane to drugs, stability in the stomach, and gastric empting rate (Ghosh and Murthy, 2006; Melander, 1978; Ratnam et al., 2006). In the present investigation, CoQ_{10}–NE was composed of nonionic surfactants and soybean lecithin as an emulsifier, MCT as an oil medium, and glycerol. Generally, the gastrointestinal absorption of poorly water-soluble drugs is enhanced when they are emulsified with an increment of surface area (Gursoy and Benita, 2004). Thus, the surfactants involved in the formulations could affect the permeability and solubility of drugs across the membrane of the gastrointestinal tract. From the results of physicochemical and pharmacokinetic studies, NE formulation seemed to be the most suitable strategy for the solubilization of CoQ_{10} in water. There appeared to be stability issues on CoQ_{10} during long-term storage, especially CoQ_{10} was found to be easily oxidized and sensitive to UV light, leading to

rapid photodegradation (Matsuda and Masahara, 1983). Interestingly, the liquid-state CoQ_{10} was found to be far more prone to photodegradation than the solid sample, as observed in other pharmaceutical substances including dihydropyridines and tamoxifen (Kojima et al., 2007; Onoue et al., 2008). Herein, DE strategies could also be beneficial for water-soluble formulation of CoQ_{10} with preventing photodegradation of CoQ_{10}, providing an alternative solid formulation to the commercial dosage forms of CoQ_{10}.

4. Conclusion

In the present investigation, novel CoQ_{10} formulations exhibited an improvement in the pharmacokinetic parameters as compared to crystalline CoQ_{10}. Based on the results from physicochemical characterization, CoQ_{10}-loaded NE systems exhibited negatively charged and highly stable dispersion with submicron diameter when they were dispersed in water. In DE systems, CoQ_{10} existed mainly as an amorphous form, and this could be attributed to the higher solubility and dispersibility as compared to the crystalline form. Considering significant increment of both C_{max} and AUC of CoQ_{10}, NE methodology could be the most effective among all formulations tested for the improvement of oral absorption of CoQ_{10}.

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