Biomolecules & Therapeutics, **18(1)**, 99-105 (2010)
www.biomolther.org

ISSN: 1976-9148(print)/2005-4483(online)
DOI: 10.4062/biomolther.2010.18.1.099

Relative Bioavailability of Coenzyme Q10 in Emulsion and Liposome Formulations

Chee Ho Choi[1], Si-Hun Kim[1], Srinivasan Shanmugam[2], Rengarajan Baskaran[2], Jeong-Sook Park[1], Chul Soon Yong[2], Han-Gon Choi[2], Bong Kyu Yoo[2,*], and Kun Han[1,*]

[1]College of Pharmacy, Chungbuk National University, Cheongju 361-763,
[2]College of Pharmacy, Yeungnam University, Gyengsan 712-749, Republic of Korea

(Received December 24, 2009; Revised January 21, 2010; Accepted January 21, 2010)

Abstract − The purpose of this study was to evaluate relative bioavailability of the coenzyme Q10 (CoQ10) in emulsion and three liposome formulations after a single oral administration (60 mg/kg) into rats. Emulsion formulation of CoQ10 was prepared by conventional method using Phospholipon 85G as an emulsifier, and three liposome formulations (neutral, anionic, and cationic) of CoQ10 were prepared by traditional lipid film hydration technique using Phospholipon 85G, cholesterol, and charge carrier lipids (1,2-dioleoyl-3-trimethyl-ammonium-propane chloride salt for cationic liposome and 1,2-dimyristoyl-*sn*-glycero-3-phosphate mono-sodium salt for anionic liposome). Mean particle size of all CoQ10-loaded liposome was less than a micron, and size distribution of the liposome population was homogeneous. Bioavailability of CoQ10 in emulsion was 1.5 to 2.6-fold greater than liposome formulations in terms of $AUC_{0\text{-}24\ h}$. T_{max} was 3 h when administered as emulsion while it was greater than 6 h in liposome formulations. Notably, it was approximately 8 h in cationic liposome. C_{max} was highest in emulsion and was significantly decreased when administered as liposome. Charged liposome showed even lower C_{max} than neutral liposome, especially in cationic liposome. In conclusion, therefore, it is suggested that clinicians and patients consider bioavailability issue a primary concern when choosing a CoQ10 product, especially when very high plasma level is required such as in the treatment of heart failure and Parkinson's disease.

Keywords: Coenzyme Q10, Liposome, Bioavailability, Pharmacokinetic parameters, Photostability

INTRODUCTION

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a fat-soluble quinone compound with chemical structure of 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone in all-trans configuration (Fig. 1)(Greenberg and Frishman, 1990; Tran *et al*., 2001). CoQ10 is found anywhere in the body, and is found in high concentration in tissues with high energy turnover such as heart, brain, liver, and kidney (Leonhauser *et al*., 1962; Sun *et al*., 1992; Bonakdar and Guarneri, 2005). CoQ10 is an essential component to electron transport chain in the mitochondria as a cofactor of the oxidative phosphorylation process for the production of ATP. Furthermore, CoQ10 in its reduced form (ubiquinol) is a potent lipophilic antioxidant and is capable of recycling and regenerating other antioxidants such as tocopherol and ascorbate (Hyun *et al*., 2006). Other important function of CoQ10 includes expression of genes involved in the cell signaling (Crane, 2001).

CoQ10 is available as over-the-counter dietary supple-

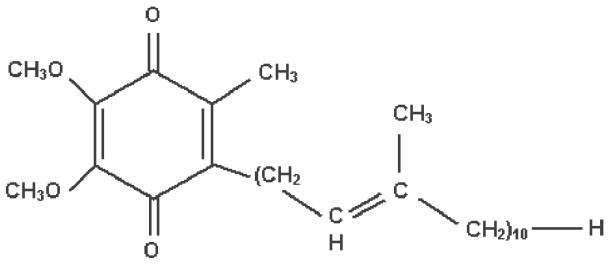

Fig. 1. Chemical structure of coenzyme Q10.

*Corresponding authors
Tel: +82-53-810-2822 (BK Yoo), +82-43-261-2820 (K Han)
Fax: +82-53-810-4654 (BK Yoo), +82-43-273-3350 (K Han)
E-mail: byoo@ynu.ac.kr (BK Yoo), khan@chungbuk.ac.kr (K Han)

ment and is one of the most commonly used supplements in developed countries. Potential benefits of CoQ10 supplementation have been recognized in the management of patients with cardiovascular and neurodegenerative diseases such as heart failure and Parkinson's diseases (Shults *et al*., 2004; Littarru and Tiano, 2005; Shults and Haas, 2005; Bonuccelli and Del Dotto, 2006; Janson, 2006; Buettner *et al*., 2007; Singh *et al*., 2007). CoQ10 supplementation has also been reported to restore plasma CoQ10 levels in patients receiving statin therapy for the treatment of dyslipidemia (Laaksonen *et al*., 1994; Sassi *et al*., 1994; Young *et al*., 2007). Recently, CoQ10 is gaining popularity as a supplement that may help in the treatment of various other diseases such as oncologic and endocrinologic disorders (Hodgson *et al*., 2002; Roffe *et al*., 2004; Conklin, 2005; Ratnam *et al*., 2006).

CoQ_{10} has poor stability against light and very poor solubility in water. Poor solubility of this compound is caused by very long isoprenoid chain in its chemical structure and relatively high molecular weight (MW: 864 g/mole) (Fig. 1) (Bhagavan and Chopra, 2006). Due to its poor water solubility, bioavailability of CoQ10 is very limited when administered by oral route. A number of strategies have been investigated to improve solubility and bioavailability using formulations with oil solution, emulsion, solid dispersion, and inclusion complex with cyclodextrin. Liposome-incorporated CoQ10 (Makabi-Panzu *et al*., 1998) and nanoparticle system engineered from oil-in-water microemulsion precursors (Hsu *et al*., 2003) are other type of water-soluble formulations.

In the present study, we prepared emulsion and liposome formulations of CoQ10 and evaluated their relative bioavailability. Specifically, we prepared emulsion and liposomal formulations of CoQ10 using phospholipid which is widely used in the emulsion and liposome technologies and also is a food additive in various fatty meal. We chose phospholipid for the preparation of the emulsion and liposome formulations of CoQ10 because co-administration of CoQ10 with dietary lipids enhances absorption of the drug in the gastrointestinal tract (Bhagavan and Chopra, 2006). We also studied the effect of charge in the CoQ10-containing liposome on the bioavailability of the drug by adding charge carrier lipids: 1,2-Dioleoyl-3-trimethylammonium- propane chloride salt (DOTAP) and 1,2-dimyristoyl-*sn*-glycero-3-phosphate monosodium salt (DMPA) for cationic and anionic charge, respectively.

MATERIALS AND METHODS

Materials

CoQ10 was kindly donated by Yuhan Corporation (Seoul, Korea), and was handled as of light-protected during all experimental procedures. CoQ9 was purchased from Fluka. Phospholipon 85G (PL 85G, lecithin fraction enriched with phosphatidylcholine) was generously provided by the Phospholipid GmbH. Cholesterol (CH) was purchased from Wako Pure Chemical Industries (Osaka, Japan). 1,2-Dioleoyl-3-trimethylammonium-propane chloride salt (DOTAP) and 1,2-dimyristoyl-*sn*-glycero-3-phosphate monosodium salt (DMPA) were obtained from Avanti Polar Lipids (Alabama, USA). All other chemicals were analytical grade and were used without further purification.

Preparation of emulsion and liposome formulations of CoQ10

Emulsion formulation of CoQ10 was prepared by conventional method. PL 85G (160 mg) was dissolved in 4 ml of warm distilled water as an emulsifier. After the phospholipid is completed dissolved, CoQ10 in cotton seed oil (20 mg in 1 ml) was added and mixed using homomixer at 9,500 rpm for 10 sec.

Liposomal formulations were prepared by traditional lipid film hydration technique. Compositions for neutral and charged liposomes are listed in Table I. For each of the formulation, a lipid film was prepared in a round-bottom flask by dissolving appropriate quantities of phospholipid and CH in a mixture of chloroform and methanol (2:1, v/v) fol-

Table I. Composition of emulsion and liposome formulations containing CoQ10

Formulation code		Phospholipid (mg)	CH (mg)	Charge carrier lipid		CoQ10 (mg)	Vehicle
				DOTAP	DMPA		
Emulsion	E-85G	160 (as of PL 85G)	–	–	–	20	CSO 1 ml and DW 4 ml
Liposome	Neutral L-85G	160 (as of PL 85G)	40	–	–	20	DW 5 ml
	Anionic L-85G	160 (as of PL 85G)	40	–	20	20	DW 5 ml
	Cationic L-85G	160 (as of PL 80H)	40	20	–	20	DW 5 ml

CH: cholesterol, CoQ10: coenzyme Q10, CSO: cotton seed oil, DMPA: 1,2-dimyristoyl-sn-glycero-3-phosphate monosodium salt, DOTAP: 1,2-dioleoyl-3-trimethylammoniumpropane chloride salt, DW: distilled water, E-85G: emulsion formulation of CoQ10 using Phospholipon 85G, L-85G: liposome formulation of CoQ10 using Phospholipon 85G, PL 85G: Phospholipon 85G.

lowed by removal of the organic solvent by rotary evaporator at 40°C (Eyela Rotary Vacuum Evaporator N-1000 series) under vacuum. The lipid film formed on the wall of the flask was suctioned under high vacuum for 2 h to remove the residual organic solvent and subsequently hydrated for 2 h in water bath at 58°C with distilled water containing CoQ10. The liposome thus obtained was allowed to anneal overnight at 4°C and sonicated for 10 min in bath sonicator (42 KHz) for size reduction. The resultant liposome suspension was transferred to nitrogen purged vials and stored in 4°C until further studies. Charged liposome was prepared in the same way with addition of DOTAP or DMPA as charge carrier lipid for cationic or anionic charge of the liposome, respectively.

Animal study

Nine-week-old male Sprague Dawley rats weighing approximately 300 g were supplied by OrientBio (Seoul, Korea) and housed in groups not exceeding six per cage and maintained under standard conditions. Food and tap water were available ad libitum. The acclimation period was one week before the experimental procedure with a dark/light cycle of 12:12 at a temperature of 23 ± 2°C and 55 ± 5% relative humidity. Study protocol was approved by the Animal Care and Use Committee, College of Pharmacy, Yeungnam University. Animal experiments were carried out according to the guidelines for animal use in toxicology and current Korean laws when the experiment was carried out.

Rats were randomly separated into four test groups. Rats in each test group were orally administered with a single dose of CoQ10 (60 mg/kg) as emulsion or liposome formulations. Blood samples of 0.5 ml were serially withdrawn under anesthesia via subclavian vein into small heparinized Eppendorf tubes at 0, 1, 2, 3, 4, 6, 8, 12, and 24 h after CoQ10 administration. The blood samples were immediately centrifuged at 3,000 g for 10 min, and the plasma was taken out and stored at −70°C until HPLC assay of CoQ10 concentration.

HPLC assay of CoQ10

Concentration of CoQ10 in plasma sample was assayed by HPLC. The frozen plasma samples were thawed at room temperature and aliquots of 200 μl were spiked with 10 μl of internal standard solution (CoQ9, 50 μg/ml in 1-propanol). After a few seconds of vortex-mixing, 1 ml of cold 1-propanol was added for extraction and deproteination of the plasma sample. Precipitation of the protein was facilitated by centrifugation using Eppendorf microcentrifuge for 1 min at 12,000 g and the resultant clear supernatant (1 ml) was transferred to Eppendorf tube and dried in vacuum using centrifugal evaporator. The dried residue was reconstituted by 120 μl of 1-propanol and injected to HPLC system (Shimadzu, Japan) by using autoinjector (AS-2050, Jasco, Japan). Column used was Kromasil C18 (5 μm, 4.6×250 mm), and mobile phase consisted of mixture of 1-propanol:methanol:hexane (58:40:2). The plasma level of CoQ10 was assayed by UV detector at 275 nm. Flow rate was 1.0 ml/min and the injection volume of the sample was 70 μl. Before measuring the plasma level of CoQ10 by HPLC, validation of the assay was performed in the range of 50-1,500 ng/ml. HPLC assay of CoQ10 for physicochemical properties was performed in the same way after appropriate dilution of the sample with 1-propanol and filtration using 0.45 μm syringe filter (but without extraction and deproteination procedures). The pharmacokinetic parameters were calculated using the software WinNonlin Standard Edition Version 1.1 by noncompartmental method.

Physicochemical properties of liposome

Particle size and zeta potential of the liposome formulations of CoQ10 were measured by electrophoretic light scattering spectrophotometer (ELS-8000, Otsuka Electronics, Japan) at room temperature. Liposome formulations were diluted with distilled water before the measurement to adjust the intensity. The system was used in the automeasuring mode at 80 mV. Polydispersity index (PI) was also determined as a measurement of particle size homogeneity of the prepared liposome. A small value of PI (<0.3) indicates homogeneous vesicle population.

Entrapment efficiency (EE) was determined by ultracentrifugation method (16,000 g for 1 h) at 4°C. Total amount of CoQ10 in the liposome formulation was measured before centrifugation, and the amount of CoQ10 in the supernatant after centrifugation was measured by HPLC. EE was calculated as follows: $EE\ (\%)=100\times(CoQ10_{bc}-CoQ10_{ac})/CoQ10_{bc}$, where $CoQ10_{bc}$ and $CoQ10_{ac}$ are total amount of CoQ10 before centrifugation and amount of $CoQ10_{ac}$ in the supernatant after centrifugation, respectively. Photostability of CoQ10 in the lipid-based formulations was also measured in the stability tester under 20,000 Lux at 25°C for 24 h by HPLC.

Data analysis

All the data obtained were analyzed using SPSS 12.0 for Windows program and significance level of $p<0.05$ was used to indicate the statistically significant difference between data sets.

RESULTS

Validation of HPLC assay was performed by repeating five times a day on the first day and for five consecutive days. Limit of quantification (LOQ) was 50 ng/ml and precisions of intra-day and inter-day at the LOQ were less than 15%. Accuracies of intra-day and inter-day were within about ± 15%, showing an acceptable variation for the quantification of CoQ10 in rat plasma. Linearity of calibration curve for determination of CoQ10 in rat plasma was r^2=0.9998, and the equation of the curve was $Y=3.62\times10^{-4}X+0.01431$ in the range of 50-1,500 ng/ml, where X and Y are concentration of CoQ10 in rat plasma and the ratio of peak areas of CoQ10 versus internal standard (CoQ9). The retention times for CoQ10 and the internal standard were 10.6 and 8.7 min, respectively (Fig. 2).

Mean particle size of all CoQ10-loaded liposome was less than a micron, showing 310.6, 225.7, and 225.8 nm for neutral, anionic, and cationic liposome, respectively (Table II). Mean particle size of the charged liposome was significantly smaller than that of neutral liposome ($p<0.05$). PI of the all CoQ10-loaded liposomes was less than 0.3, indicating homogeneous vesicle population. Zeta potentials for the CoQ10-loaded anionic and cationic liposome were −32.6 and +40.4 mV, respectively. EE of CoQ10 in the neutral liposome was 28.91 ± 0.16%, and it was increased to 46.78 ± 0.12% in the anionic liposome ($p<0.05$). EE of CoQ10 in the cationic liposome was similar to that in the neutral liposome.

Fig. 3 shows the plasma concentration of CoQ10 after a single oral administration (60 mg/kg) into six rats. Maximum plasma concentration of CoQ10 (C_{max}) was highest in emulsion with PL 85G. C_{max} was significantly decreased when the drug was administered as neutral liposome. Charged liposomes showed even lower C_{max} than neutral liposome, especially in cationic liposome. Time to reach maximum plasma concentration (T_{max}) was 3 h in emulsion with PL 85G while it was greater than 6 h in the three liposome formulations. Notably, it was approximately 8 h in cationic liposome of CoQ10. Area under the curve ($AUC_{0\text{-}24\,h}$) was 8,982 ± 725 ng×min/ml when CoQ10 was administered as emulsion formulation with PL 85G, while it was

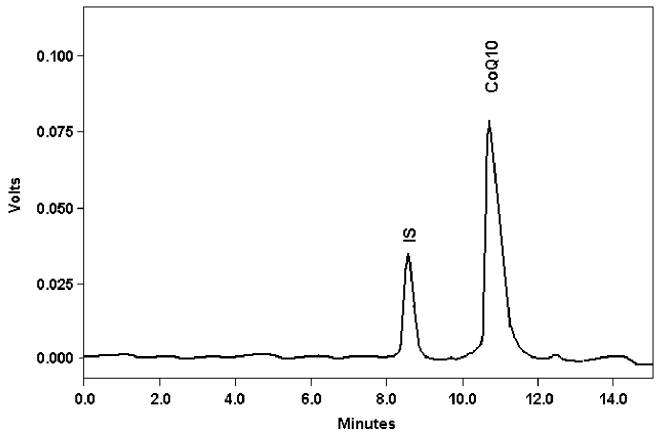

Fig. 2. Typical HPLC chromatogram of CoQ10 in rat plasma sample (HPLC system: Shimadzu Class VP computer software equipped with LC 10 AD VP pump and SPD 10A UV-VIS detector, detector: UV at 275 nm, column: Kromasil C18 (5 μm, 4.6x250mm), mobile phase: mixture of 1-propanol:methanol, hexane (58:40:2), flow rate: 1.0 ml/min, injection volume: 70 μl). CoQ10: coenzyme Q10, IS: internal standard (coenzyme Q9).

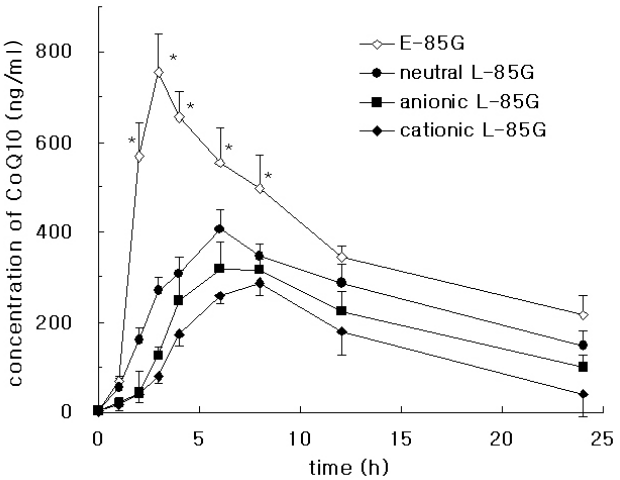

Fig. 3. Plasma concentration of CoQ10 after a single oral administration (60 mg/kg) into rats (n=6). CoQ10: coenzyme Q10, E-85G: emulsion formulation of CoQ10 using Phospholipon 85G, L-85G: liposome formulation of CoQ10 using Phospholipon 85G. *$p<0.05$ in comparison to all three L-85G.

Table II. Physicochemical properties of liposome formulations of CoQ10 (n=6)

	Size (nm)	PI	Zeta potential (mV)	EE (%)
Neutral L-85G	311 ± 8	0.25 ± 0.03	−2.24 ± 0.35	28.9 ± 0.2
Anionic L-85G	226 ± 1[a]	0.21 ± 0.02	−32.6 ± 1.91	46.8 ± 0.12[a]
Cationic L-85G	226 ± 1[a]	0.18 ± 0.05	+40.4 ± 0.8	28.6 ± 0.06

Data represent mean ± standard deviation. CoQ10: coenzyme Q10, EE: entrapment efficiency, L-85G: liposome formulation of CoQ10 using Phospholipon 85G, PI: polydispersity index. [a]$p<0.05$ in comparison to neutral L-85G.

Table III. Pharmacokinetic parameters of CoQ10 in rat following a single oral administration of 60 mg/kg (n=6)

Parameters	E-85G	Neutral L-85G	Anionic L-85G	Cationic L-85G
T_{max} (h)	3	6[b]	6[b]	8[b]
C_{max} (ng/ml)	756 ± 54	405 ± 24[b]	318 ± 36[b]	287 ± 26[b]
$AUC_{0\text{-}24\ h}$ (ng×min/ml)	8,980 ± 725	5,960 ± 405[a]	4,530 ± 315[b]	3,440 ± 296[b]
$t_{1/2}$ (h)	14.1 ± 2.01	13.0 ± 2.24	9.81 ± 1.14[a]	5.61 ± 1.02[b]

AUC: area under the curve, C_{max}: maximum plasma concentration, CoQ10: coenzyme Q10; T_{max}: time to reach maximum plasma concentration, [a]$p < 0.05$ in comparison to E-85G, [b]$p < 0.01$ in comparison to E-85G.

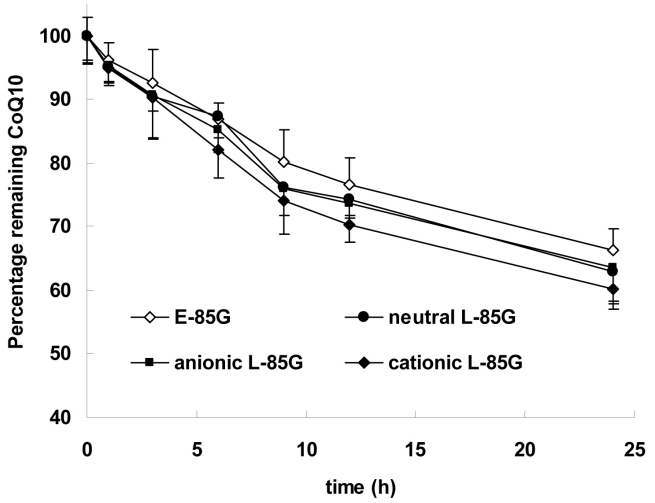

Fig. 4. Stability of CoQ10 in the lipid-based formulations against light exposure (20,000 Lux). CoQ10: coenzyme Q10, E-85G: emulsion formulation of CoQ10 using Phospholipon 85G, L-85G: liposome formulation of CoQ10 using Phospholipon 85G.

5,961 ± 405, 4,526 ± 315, and 3,436 ± 296 ng×min/ml when the drug was administered as neutral, anionic, and cationic liposome, respectively. This result represents that $AUC_{0\text{-}24\ h}$ of CoQ10 as neutral, anionic, and cationic liposome was approximately two-third, one-half, and one-third of the drug as emulsion in the corresponding order. Table III summarized the pharmacokinetic parameters of CoQ10 in rats after a single oral dose of 60 mg/kg.

Stability of CoQ10 against light exposure (20,000 Lux) was also studied and the result is shown in Fig. 4. Although statistically not significant, the emulsion formulation resulted in slightly better stability profile against light exposure than the liposomal formulations, showing 66.2% and 60.1-62.9% remaining after 24 h of the light exposure in the corresponding order. We also performed stability study of CoQ10 against different pH (2.6 and 8.0) and temperature (4°C and 50°C). However, there was no significant difference between the emulsion and liposome formulations.

DISCUSSION

Since CoQ10 is practically insoluble in aqueous solution and has very poor bioavailability, there have been a number of efforts to improve solubility and bioavailability of the drug. Schulz *et al*. compared relative bioavailability of different CoQ10 formulations and reported that CoQ10 solubilized with the aid of medium-chain triglycerides and polysorbate 80 was superior to oil dispersion of the drug in soybean oil (Schulz *et al*., 2006). Another research performed by Zmitek *et al*. reported that bioavailability was significantly enhanced in the soluble form of CoQ10 (inclusion complex with β-cyclodextrin, either aqueous suspension or dry powder) compared to soybean oil suspension of the drug in soft-gel capsule (Zmitek *et al*., 2008). Recently, Liu and Artman investigated relative bioavailability of colloidal CoQ10 (compositions not detailed) in healthy volunteers in comparison to other two solubilized formulation and an oil-based formulation of CoQ10 (Liu and Artman, 2009). They reported that AUC of the colloidal CoQ10 was about 3-5 times greater than other solubilized forms of CoQ10 after a single oral administration of 120 mg.

While there have been several reports on the relative bioavailability among different CoQ10 preparations, the relative bioavailability of CoQ10 between emulsion formulation and liposome formulation of CoQ10 has not been investigated. In the present research, therefore, the aim of the study was to evaluate relative bioavailability of emulsion and liposome formulations of CoQ10.

Relative bioavailability can be compared by pharmacokinetic study, specifically in terms of rate and extent of absorption. As a pharmacokinetic parameter for rate of absorption comparison, we calculated T_{max} of CoQ10 in emulsion and three liposome formulations. T_{max} of all formulations studied were 3-8 h which is consistent with previously reported findings (Tomono *et al*., 1986; Kurowska *et al*., 2003; Schulz *et al*., 2006). CoQ10 in emulsion with PL 85G was absorbed significantly faster than liposome formulations: T_{max} was 3 h and 6-8 h in emulsion and liposome, respectively. Like other lipophilic substances such as oil-soluble vitamins, parts of CoQ10 are absorbed by

lymphatic route with the aid of transportation by triglyceride-rich lipoproteins (chylomicron), which takes longer than capillary blood vessel route (Liu and Artman, 2009). Chylomicrons are the lipoprotein fraction mainly responsible for transportation of lipophilic substances out of enterocytes into the lymphatic route. Therefore, it is speculated that CoQ10 in emulsion is more prone to direct absorption to blood circulation in the microvilli of the small intestine while the drug in liposome is more prone to absorption to lymphatic circulation in the microvilli. It is also speculated that CoQ10 in liposome may be engulfed or endocytosed by enterocytes especially the drug in cationic liposome due to electrostatic interaction between positive charge of the liposome and negative charge of enterocytes cell membrane. Delayed T_{max} of CoQ10 in the cationic liposome may be an evidence to support this speculation.

As a pharmacokinetic parameter for extent of absorption comparison, we calculated C_{max} and $AUC_{0\text{-}24\ h}$ in emulsion and three liposome formulations. C_{max} of CoQ10 in emulsion was approximately 2-fold greater than that in the neutral liposome formulation, and it was 2.6-fold greater than that in the cationic liposome formulation. $AUC_{0\text{-}24\ h}$ of CoQ10 in the emulsion represented about 1.5-fold greater than that in the neutral liposome formulation, and it was approximately 2.6-fold greater than that in the cationic liposome formulation. Based on our pharmacokinetic study for rate and extent of absorption, bioavailability of CoQ10 in emulsion appears superior to the drug in liposome formulations. Charged liposome showed even lower bioavailability probably due to electrostatic interaction between the liposome and enterocyte cell membrane. However, since this study was performed under fasting, bioavailability of CoQ10 might be different if the drug was administered with standard diet and appropriate amount of dietary lipid. Further research is warranted in this regard.

After the last two decades of clinical research with CoQ10, it became clear that only patients with very high plasma CoQ10 level (>2.5 μg/ml) showed clinical benefit in the treatment of heart failure. Plasma CoQ10 level of >3.5 μg/ml is now required for the treatment of patients with heart failure (Liu and Artmann, 2009). Likewise, very high doses of coenzyme Q10 are tried for the treatment of various other diseases such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The dosage under clinical trials is currently up to 3,000 mg/day for human use (Ferrante *et al*., 2005; Levy *et al*., 2006). For animal study, the dosage was up to 20,000 mg/kg/day as reported by previous researchers (Yang *et al*., 2005; Smith *et al*., 2006).

Taking into consideration that CoQ10 is very poorly absorbed from gastrointestinal tract and needs to reach very high plasma level for clinical benefit, bioavailability of CoQ10 formulation is of great importance. Clinicians should be aware of the huge variation in the bioavailability between various CoQ10 products among the over-the-counter dietary supplements marketed in USA and other countries. Dietitians and nutritionists should also be aware of it and try to educate general public about the bioavailability issue of the CoQ10 products.

CONCLUSION

We studied relative bioavailability of CoQ10 when the drug was orally administered into rats as emulsion and liposome formulations. Rate of absorption was significantly improved when CoQ10 was administered as emulsion. In terms of extent of absorption comparison, $AUC_{0\text{-}24\ h}$ of CoQ10 in emulsion with PL 85G showed 1.5 to 2.6-fold greater bioavailability compared to liposome formulations. Since relative bioavailability significantly varies depending upon formulations used, it is suggested that clinicians and patients consider bioavailability issue a primary concern when choosing a CoQ10 product, especially when very high plasma level is required such as in the treatment of heart failure and Parkinson's disease.

ACKNOWLEDGMENTS

This research was supported by the Yeungnam University research grants in 2009.

REFERENCES

Bhagavan, H. N. and Chopra, R. K. (2006). Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radical Research* **40**, 445-453.

Bonakdar, R. A. and Guarneri, E. (2005). Coenzyme Q10. *Am. Fam. Physician* **72**, 1065-1070.

Bonuccelli, U. and Del Dotto, P. (2006). New pharmacologic horizons in the treatment of Parkinson disease. *Neurology* **67**, S30-38.

Buettner, C., Phillips, R., Davis, R., Gardiner, P. and Mittleman, M. (2007). Use of dietary supplements among United States adults with coronary artery disease and atherosclerotic risks. *Am. J. Cardiol*. **99**, 661-666.

Conklin, K. (2005). Coenzyme q10 for prevention of anthracycline-induced cardiotoxicity. *Integr. Cancer Ther*. **4**, 110-130.

Crane, F. (2001). Biochemical functions of coenzyme Q10. *J. Am. Coll. Nutr*. **20**, 591-598.

Ferrante, K., Shefner, J., Zhang, H., Betensky, R., O'Brien, M., Yu, H., Fantasia, M., Taft, J., Beal, M., Traynor, B., Newhall, K., Donofrio, P., Caress, J., Ashburn, C., Freiberg, B., O'Neill, C., Paladenech, C., Walker, T., Pestronk, A.,

Abrams, B., Florence, J., Renna, R., Schierbecker, J., Malkus, B. and Cudkowicz, M. (2005). Tolerance of high-dose (3,000 mg/day) coenzyme Q10 in ALS. *Neurology* **65**, 1834-1836.

Greenberg, S. and Frishman, W. H. (1990). Co-enzyme Q10: a new drug for cardiovascular disease. *J. Clin. Pharmacol*. **30**, 596-608.

Hodgson, J., Watts, G., Playford, D., Burke, V. and Croft, K. (2002). Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. *Eur. J. Clin. Nutr*. **56**, 1137-1142.

Hsu, C. H., Cui, Z., Mumper, R. J. and Jay, M. (2003). Preparation and characterization of novel coenzyme Q10 nanoparticles engineered from microemulsion precursors. *AAPS Pharm. Sci. Tech*. **4**, E32.

Hyun, D., Emerson, S., Jo, D., Mattson, M. and De Cabo, R. (2006). Calorie restriction up-regulates the plasma membrane redox system in brain cells and suppresses oxidative stress during aging. *Proc. Natl. Acad. Sci. USA* **103**, 19908-19912.

Janson, M. (2006). Orthomolecular medicine: the therapeutic use of dietary supplements for anti-aging. *Clin. Interv. Aging* **1**. 261-265.

Littarru, G. and Tiano, L. (2005). Clinical aspects of coenzyme Q10: an update. *Curr. Opin. Clin. Nutr. Metab. Care* **8**, 641-646.

Kurowska, E. M., Dresser, G., Deutsch, L., Bassoo, E. and Freeman, D. J. (2003). Relative bioavailability and antioxidant potential of two coenzyme q10 preparations. *Ann. Nutr. Metab*. **47**, 16-21.

Laaksonen, R., Ojala, J., Tikkanen, M. and Himberg, J. (1994). Serum ubiquinone concentrations after short- and long-term treatment with HMG-CoA reductase inhibitors. *Eur. J. Clin. Pharmacol*. **46**, 313-317.

Leonhauser, S., Lebold, K., Krisch, K., Standinger, H., Gale, F., Page, A. Jr. and Folkers, K. (1962). On the presence and significance of coenzyme Q in microsomes. *Arch. Biochem. Biophys*. **96**, 580-586.

Levy, G., Kaufmann, P., Buchsbaum, R., Montes, J., Barsdorf, A., Arbing, R., Battista, V., Zhou, X., Mitsumoto, H., Levin, B. and Thompson, J. (2006). A two-stage design for a phase II clinical trial of coenzyme Q10 in ALS. *Neurology* **66**, 660-663.

Liu, Z. X. and Artmann, C. (2009). Relative bioavailability comparison of different coenzyme Q10 formulations with a novel delivery system. *Altern. Ther. Health Med*. **15**, 42-46.

Makabi-Panzu, B., Sprott, G. D. and Patel, G. B. (1998). Coenzyme Q10 in vesicles composed of archaeal ether lipids or conventional lipids enhances the immuno-adjuvanticity to encapsulated protein. *Vaccine* **16**, 1504-1510.

Ratnam, D., Ankola, D., Bhardwaj, V., Sahana, D. and Kumar, M. (2006). Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective. *J. Control. Rel.* **113**, 189- 207.

Roffe, L., Schmidt, K. and Ernst, E. (2004). Efficacy of coenzyme Q10 for improved tolerability of cancer treatments: a systematic review. *J. Clin. Oncol*. **22**, 4418-4424.

Sassi, S., Genova, M. and Lenaz, G. (1994). Exogenous CoQ10 preserves plasma ubiquinone levels in patients treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Int. J. Clin. Lab. Res*. **24**, 171-176.

Schulz, C., Obermüller-Jevic, U. C., Hasselwander, O., Bernhardt, J. and Biesalski, H. K. (2006). Comparison of the relative bioavailability of different coenzyme Q10 formulations with a novel solubilizate (Solu Q10). *Int. J. Food Sci. Nutr*. **57**, 546-555.

Shults, C., Flint Beal, M., Song, D. and Fontaine, D. (2004). Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. *Exp. Neurol*. **188**, 491-494.

Shults, C. and Haas, R. (2005). Clinical trials of coenzyme Q10 in neurological disorders. *Biofactors* **25**, 117-126.

Singh, U., Devaraj, S. and Jialal, I. (2007). Coenzyme Q10 supplementation and heart failure. *Nutr. Rev*. **65**, 286-293.

Smith, K., Matson, S., Matson, W., Cormier, K., Del Signore, S., Hagerty, S., Stack, E., Ryu, H. and Ferrante, R. (2006). Dose ranging and efficacy study of high-dose coenzyme Q10 formulations in Huntington's disease mice. *Biochim. Biophys. Acta* **1762**, 616-626.

Sun, I., Sun, E., Crane, F., Morro, D., Lindgren, A. and Low, H. (1992). Requirement for coenzyme Q in plasma membrane electron transport. *Proc. Natl. Acad. Sci. USA* **89**, 11126-11130.

Tomono, Y., Hasegawa, J., Seki, T., Motegi, K. and Morishita, N. (1986). Pharmacokinetic study of deuterium-labelled coenzyme Q10 in man. *Int. J. Clin. Pharmacol. Ther. Toxicol*. **24**, 536-541.

Tran, M. T., Mitchell, T. M., Kennedy, D. T. and Giles, J. T. (2001). Role of coenzyme Q10 in chronic heart failure, angina, and hypertension. *Pharmacotherapy* **21**, 797-806.

Yang, H., Lin, S., Huang, S. and Chou, H. (2005). Acute administration of red yeast rice (Monascus purpureus) depletes tissue coenzyme Q(10) levels in ICR mice. *Br. J. Nutr*. **93**, 131-135.

Young, J., Florkowski, C., Molyneux, S., McEwan, R., Frampton, C., George, P. and Scott, R. (2007). Effect of coenzyme Q(10) supplementation on simvastatin-induced myalgia. *Am. J. Cardiol*. **100**, 1400-1403.

Zmitek, J., Smidovnik, A., Fir, M., Prosek, M., Zmitek, K., Walczak, J. and Pravst, I. (2008). Relative bioavailability of two forms of a novel water-soluble coenzyme Q10. *Ann. Nutr. Metab*. **52**, 281-287.