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Self-microemulsifying Formulation-based Oral Solution of Coenzyme Q10

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(Received March 31, 2009; Accepted September 11, 2009)

The goal of our investigation was to develop oral solution of coenzyme Q10 (CoQ10) by using self-emulsifying systems. CoQ10 is practically insoluble in water. Therefore, it is difficult to develop oral solution of CoQ10. To solubilize CoQ10 and to develop it as oral solution, self-emulsifying systems consisted of oil, surfactant and co-surfactant were studied and using the self-emulsifying system chosen, oral solution was developed. After the evaluation of solubilizing abilities of various oils and surfactants, the self-emulsifying system consisted of acetylated monoglyceride (AM) as oil, polyoxyethylene (20) sorbitan monolaurate (P2SM) as surfactant and propylene glycol laurate (PGL) as co-surfactant, was chosen because the emulsions prepared by that system showed spontaneous emulsification and transparent appearance. All of these components could be used for the development of functional foods. Finally, a CoQ10 solution with concentrations of 100 mg/70 ml and 100 mg/100 ml could successfully be developed by the addition of water to one milliliter of self-emulsifying system consisted of AM (10%), P2SM (70%) and PGL (20%) along with 100 mg of CoQ10. This oral solution formulation was stable for more than one month.

Key words——coenzyme Q10; self-emulsifying system; oral solution

INTRODUCTION

Coenzyme Q10 (CoQ10), also known as ubidecarenone (Fig. 1), is a vitamin-like and highly lipophilic compound. It is used as an antioxidant and also in the treatment of cardiovascular disorders such as angina pectoris, hypertension, and congestive heart failure.[1] It inhabits the inside of the inner mitochondrial membrane, where it functions as an integral part of electron transport of oxidative phosphorylation.[2] As it can be used as an antioxidant in everyday life, a proper preparation of CoQ10 is desirable for convenient consumption. Currently there are many dosage forms of CoQ10 available including tablets and capsules in the market. Recently a dose of 100 mg of CoQ10 is allowed in the functional food category. Despite a number of advantages of a solution dosage form such as rapid absorption and ease of swallowing, the formulation of a solution of CoQ10 having high content such as 100 mg per a certain drinkable volume of water is greatly limited due to its very low aqueous solubility.

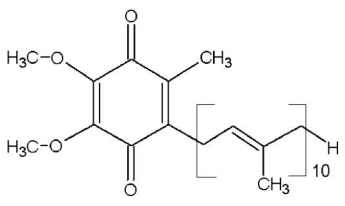

Fig. 1. Chemical Structure of Coenzyme Q10

CoQ10 is practically insoluble in water and, thereby poorly absorbed from the gastrointestinal tract. To increase the water solubility, various formulation strategies were employed in the literatures including the use of surfactants and oils, cyclodextrins, nanoparticles, solid dispersions and micronization.[3,4] Much attention has been focused on lipid-based formulations in recent years and among them, special emphasis has particularly been placed on self-emulsifying drug delivery systems (SEDDS) because of great potential of increasing solubility and bioavailability of poorly soluble compounds.[5–7]

An SEDDS is isotropic mixtures of oil, surfactant, co-surfactant and active substance. They form fine oil-in-water emulsions when introduced into aqueous media under mild agitation. The SEDDS formulation of CoQ10 was already introduced in other literature.[8] However, the fatal limitation of the previous endeavor is that the drug content was only about 6% (*i.e.*, 60 mg in 1 ml SEDDS) and some of the oils and surfactants used for SEDDS formulation were not approved for food or drug products.

Thus, in this study, to develop an oral solution of CoQ10 containing 100 mg of CoQ10, we investigated

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and characterized the self-emulsifying system of CoQ10 with CoQ10 solubility of 100 mg/ml (*i.e.*, 100 mg in 1 ml SEDDS) using oils and surfactants that can be used for functional food category. After that, an oral solution of CoQ10 was prepared by stably diluting the SEDDS with water to obtain CoQ10 content of 100 mg/70 or 100 ml of water.

MATERIALS AND METHODS

Materials CoQ10 was provided by RexgeneBio (Ochang, Korea). Acetylated monoglyceride (AM) was kindly supplied by Richwood Pharmaceuticals (Seoul, Korea). Polyoxyethylene (20) sorbitan monolaurate (P2SM) was purchased from Ilshinwells Company (Seoul, Korea). Propylene glycol monocaprylate (PGM), caprylocaproyl macrogolglycerides (CM), diethyleneglycol monoethyl ether (DME), caprylic/capric triglycerides (CT), propylene glycol monolaurate (PGM) and propylene glycol laurate (PGL) were purchased from Gattefosse (Westwood, NJ). Oleic acid was purchased from Duksan Pure Chemicals (Ansan, Korea). Polyoxyethylene (4) lauryl ether (P4LE) was purchased from Sigma-Aldrich Company (Steinheim, Germany). Olive oil was purchased from Shinyo Pure Chemicals (Osaka, Japan). Mineral oil was purchased from Acros Organics (NJ, USA). Cotton seed oil was purchased from Junsei Pure Chemicals (Tokyo, Japan). HPLC grade hexane, acetonitrile and isopropanol were purchased from Honeywell Burdick & Jackson Company (NJ, USA). Distilled and deionized water was used for the preparation of all solutions.

Solubility Measurement and Selection of Oils/Surfactants An excess amount of CoQ10 was added to various oils and surfactants as shown in Table 1, and then mixed by vigorous stirring for 10 min at ambient temperature. The mixture was then shaken at 30°C for two days until equilibrium. The equilibrated sample was centrifuged at 5000 rpm for 10 min to separate undissolved CoQ10. The supernatant was taken and diluted with hexane and the concentration of CoQ10 was quantified by HPLC. Criteria for the selection of oils and surfactants to be used for the formulation of self-emulsifying system based oral solutions of CoQ10 were set to be such as good solubility of CoQ10 and spontaneousness of emulsion formation.

HPLC Analysis CoQ10 was separated on an ODS column (150 mm×4.6 mm, 5 μm Capcell Pak, Shiseido, Tokyo, Japan) maintained at 30°C. The mobile phase was a 7 : 3 mixture of acetonitrile and isopropanol. The flow rate was set at 1.0 ml/min. The detection was performed at 275 nm and the injection volume was 30 μl.

Table 1. Solubilities of Coenzyme Q10 in Various Oils and Surfactants (mean±S.D., n=3)

Reagent	HLB	Solubility (mg/ml)
Oils		
Acetylated monoglyceride (AM)		110.37±4.14
Caprylic/capric triglycerides (CT)		110.62±5.04
Cotton seed oil		80.73±8.52
Mineral oil		54.47±13.04
Oleic acid		120.14±12.81
Olive oil		70.00±4.27
Propylene glycol monocaprylate (PGMC)		73.55±3.07
Surfactants		
Caprylocaproyl macrogolglycerides (CM)	14	7.47±0.72
Diethyleneglycol monoethyl ether (DME)	4.2	12.15±0.84
Polyoxyethylene (4) lauryl ether (P4LE)	9.7	52.71±2.91
Polyoxyethylene (20) sorbitan monolaurate (P2SM)	16.7	12.27±0.96
Propylene glycol laurate (PGL)	4	88.89±2.67
Propylene glycol monolaurate (PGML)	5	78.31±0.61

Construction of Phase Diagram and Preparation of SEDDS Based Oral Solution After selecting AM as oil, PGL as co-surfactant and P2SM as surfactant, for the preparation of self-emulsifying system of CoQ10, the ternary phase diagram was constructed to find out appropriate ratios of these three components (*i.e.*, AM/P2SM/PGL). One milliliter of various ratios of the self-emulsifying formulation containing 100 mg of CoQ10 was mixed with a fixed volume of water (100 ml) to identify whether emulsion or microemulsion can be formed. The representative self-emulsifying system with various ratios of oil, surfactant, co-surfactant and CoQ10 were presented in Table 2. The components of self-emulsifying system were accurately measured into screw-capped glass vials and heated up to 60°C and stirred at 300 rpm on hot plate/stirrer. One milliliter of self-emulsifying system containing 100 mg of CoQ10 was gently added to 100 ml of water.

Table 2. Emulsification Result of SEDDSs Consisting of Acetylated Monoglyceride (AM), Propylene Glycol Laurate (PGL), Polyoxyethylene (20) Sorbitan Monolaurate (P2SM) and CoQ10

Sample number	CoQ10[a]	AM (%)	PGL (%)	P2SM (%)	Water (ml)	Result
1		40	10	50	100	Emulsion
2		30	30	40	100	Emulsion
3		20	30	50	100	Emulsion
4		20	20	60	100	Microemulsion
5		20	10	70	100	Microemulsion
6		10	40	50	100	Emulsion
7		10	30	60	100	Microemulsion
8		10	20	70	100	Microemulsion
9		10	10	80	100	Microemulsion
10		10	20	70	70	Microemulsion

[a] One milliliter of SEDDS contains 100 mg of CoQ10.

Visual Observation and Emulsion Droplet Size Analysis A visual test to assess the ability of self-emulsifying system to form emulsion or microemulsion such as transparency and spontaneousness was performed in the present study. To examine emulsion droplet size reflecting transparency, the resultant solution was analyzed with Zetasizer Nano-ZS (Malvern Instruments, Worcestershire, UK) at 25°C. The values of mean emulsion droplet diameters were compared.

RESULT AND DISCUSSION

Solubilities of CoQ10 in various surfactants and oils are presented in Table 1. CT, oleic acid and AM showed higher solubility than 100 mg/ml. Even though CT and oleic acid showed better solubilities of CoQ10 than AM, the self-emulsifying systems containing AM as oil formed emulsions more spontaneously and readily. Therefore AM was finally chosen as oil for producing self-emulsifying systems in this study. CM, DME and P2SM demonstrated lower solubilities than 20 mg/ml. Despite exhibiting low solubility of CoQ10, P2SM was chosen as surfactant since the self-emulsifying systems containing P2SM as surfactant formed more transparent and clear emulsions compared to the systems containing the other surfactants. When using P2SM having the highest HLB value among the surfactants tested, relatively transparent self-emulsifying system based solution could be prepared. It is shown by the report that hydrophilic surfactants with HLB values exceeding 10 are much superior at providing fine and uniform emulsion droplets.[9]

When a co-surfactant is used together with a surfactant to a self-emulsifying system, it lowers the interfacial tension, fluidizes the hydrocarbon region of the interfacial film, and thereby decreases the bending stress of the interface.[10] For this reason PGL was employed as co-surfactant in this study. Although PGL and PGML have similar characteristics such as chemical structure and HLB value, PGL was used since it could solubilize more CoQ10 than PGML.

After oil, surfactant and co-surfactant were chosen, a ternary phase diagram was constructed. The reason why a ternary phase diagram was investigated was because a proper combination of oil, surfactant and co-surfactant, together with CoQ10 was required for the preparation of stable microemulsions. Thus, many various combinations of oil, surfactant and co-surfactant were prepared to build a ternary phase diagram. Figure 2 represents the ternary phase diagram consisting of AM, P2SM and PGL. In that figure the dotted line encloses the area, where microemulsions with a droplet size of less than 100 nm were formed upon addition of 100 ml water to 1 ml of self-emulsifying system. Clear and transparent emulsions could be prepared in this region. The area marked by solid line represents the area, where emulsions were formed upon addition of 100 ml of water to 1 ml of self-emulsifying system. The emulsions formed from the compositions outside the dotted area were less clear and transparent than the microemulsions formed with compositions within the dotted area. Microemulsions and emulsions could be prepared only in the specific areas marked in the phase diagram.

After constructing the ternary phase diagram, various self-emulsifying systems were chosen to prepare oral solutions. A 100 mg of CoQ10 could be solubilized in 1 ml of self-emulsifying systems listed in Table 2. The various self-emulsifying systems were then added to 70 or 100 ml of water and tendencies of emulsification were observed visually in terms of spontaneousness and transparency. The combinations of AM, P2SM and PGL shown in Table 2 demonstrated spontaneous emulsification without delay. With increasing P2SM content (samples 6, 7, 8, 9 in Table 2), the transparency of the emulsion also increased (Fig. 3) and at the same time, the mean droplet size decreased as a whole (Fig. 4). The decrease in the droplet size reflects the formation of a packed film of the surfactant at the oil-water inter-

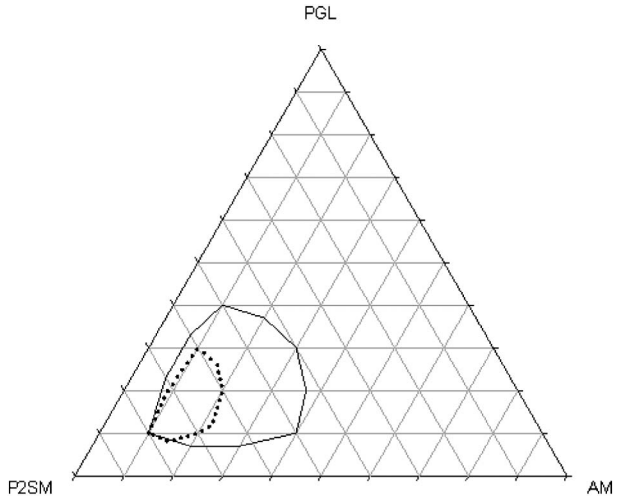

Fig. 2. The Ternary Phase Diagram Built with Acetylated Monoglyceride (AM), Propylene Glycol Laurate (PGL), Polyoxyethylene (20) Sorbitan Monolaurate (P2SM) and CoQ10

The dotted line area represents the area where microemulsions were formed upon addition of 100 ml water to 1 ml of self-emulsifying system. The solid line area represents the area where emulsions were formed upon addition of 100 ml water to 1 ml of self-emulsifying system.

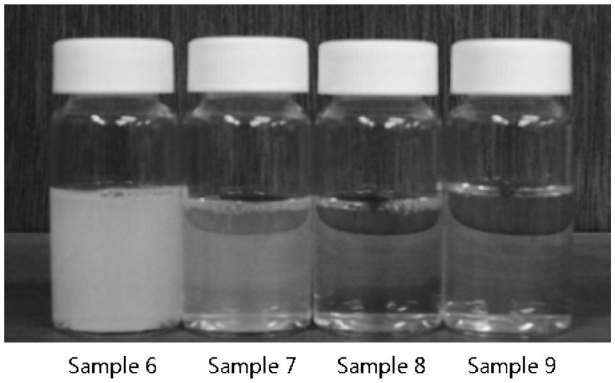

Fig. 3. The Visual Characteristics of the Self-emulsifying System-based Oral Solutions Having Different Ratios of Acetylated Monoglyceride (AM), Propylene Glycol Laurate (PGL) and Polyoxyethylene (20) Sorbitan Monolaurate (P2SM)

The compositions of each sample are listed in Table 2.

face, thereby it would stabilize the dispersion of the oil droplets.[11] In the microemulsion-based solution produced, precipitation or separation was not observed. Furthermore samples 8 and 10 appeared in Table 2 were the most transparent and stable over one month.

From the studies mentioned above, self-emulsifying system with a composition of 10% AM, 70% P2SM and 20% PGL (sample 8 in Table 2) was finally chosen for the preparation of self-emulsifying system based oral solution of CoQ10. With this system,

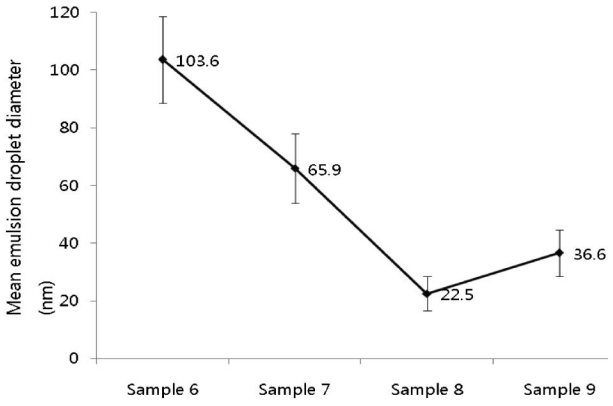

Fig. 4. The Mean Emulsion Droplet Diameter of the Self-emulsifying System Based CoQ10 Solutions Having Different Ratios of Acetylated Monoglyceride (AM), Propylene Glycol Laurate (PGL) and Polyoxyethylene (20) Sorbitan Monolaurate (P2SM)

The compositions of each sample are listed in Table 2 (mean±S.D., $n=3$).

the oral solution having a CoQ10 level of 100 mg/100 ml could be prepared by introducing the self-emulsifying system (1 ml) to water (100 ml). Even, the solution having the greater concentration of CoQ10, for instance, 100 mg/70 ml could be produced with clear appearance (sample 10 in Table 2).

CONCLUSION

Drinkable solution, or beverage form of CoQ10 has attracted an increasing attention for unique advantages such as rapid absorption and ease of swallowing. However, there have been difficulties in developing the oral solution of CoQ10 having high content due to its low aqueous solubility. In our study, orally drinkable and stable solution of CoQ10 with the concentration of 100 mg/100 ml or 100 mg/70 ml was produced from the self-emulsifying system consisting of AM, P2SM and PGL approved as functional food additives. The solutions possessed transparent appearance and the dispersion of the oil droplets containing CoQ10 was stable for more than one month.

Acknowledgement This Research was supported by the Chung-Ang University Research Grants in 2009.

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