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Enhanced oral bioavailability of Coenzyme Q_{10} by self-emulsifying drug delivery systems

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ABSTRACT

To enhance the solubility and bioavailability of poorly water-soluble Coenzyme Q_{10} (CoQ_{10}), self-emulsifying drug delivery system (SEDDS) composed of oil, surfactant and cosurfactant for oral administration of CoQ_{10} was formulated. The solubility of CoQ_{10} was determined in various oils and surfactants. The formulations were prepared using two oils (Labrafil M 1944 and Labrafil M 2125), surfactant (Labrasol) and cosurfactant (Lauroglycol FCC and Capryol 90). In all the formulations, the level of CoQ_{10} was fixed at 6% (w/v) of the vehicle. These formulations were characterized by solubility of the drug in the vehicle, particle size of the dispersed emulsion, zeta potential and drug release profile. Ternary phase diagrams were used to evaluate the emulsification domain. The self-emulsification time following introduction into an aqueous medium under gentle agitation was evaluated. The optimized SEDDS formulation consist of 65% (v/v) Labrasol, 25% (v/v) Labrafil M 1944 CS and 10% (v/v) Capryol 90 of each excipient showed minimum mean droplet size (about 240 nm) and optimal drug release profile in water. The pharmacokinetic study in rats for the optimized formulation was performed and compared to powder formulation. SEDDS have significantly increased the C_{max} and area under the curve (AUC) of CoQ_{10} compared to powder ($P < 0.05$). Thus, this self-micro emulsifying drug delivery system should be an effective oral dosage form for improving oral bioavailability of lipophilic drug, CoQ_{10}.

1. Introduction

Coenzyme Q_{10} (CoQ_{10}), a yellow colored crystalline powder with a melting point of 48 °C is a vitamin like substance found in virtually all cells of the human body, including the heart, liver and skeletal muscles. Its deficiency is often implicated in several diseases. It functions as a coenzyme in the energy-producing metabolic pathways of every cell of the body, as an antioxidant, scavenges free radicals and inhibits lipid peroxidation (Aberg et al., 1992). Several studies have provided evidence of the potential of CoQ_{10} in prophylaxis and therapy of various disorders related to oxidative stress. CoQ_{10} has been found to be effective in cardiovascular disorders like cardiomyopathy, hypertension, angina pectoris and atherosclerosis (Joo, 2005). While there are numerous studies with human subjects on the therapeutic efficacy of CoQ_{10} supplementation for various indications, very little information is available regarding its bioavailability.

CoQ_{10} is practically insoluble even in the presence of 5% sodium lauryl sulphate in water and poorly absorbed from the gastrointestinal tract. The slow absorption of CoQ_{10} (T_{max} 2–10 h) from the gastrointestinal tract was attributed to its high molecular weight and poor water solubility (Chopra et al., 1998). Due to its high lipophilicity, the oral delivery of CoQ_{10} is challenging. Earlier reported formulation strategies included a solubilized system with soy lecithin (Takada et al., 1985), a micellar solution of CoQ_{10} with polyoxyethylene (60) hydrogenated castor oil (Kimura et al., 1986), lipid microspheres prepared as a soybean oil emulsified with yolk phospholipids (Ozawa et al., 1986), a redispersible dry emulsion (Takeuchi et al., 1992), the complexation of CoQ_{10} with cyclodextrins (Lutka and Pawlaczyk, 1995), a solubilized form of CoQ_{10} in a blend of polysorbate 80 and medium chain triglycerides (Chopra et al., 1998) and a solid dispersion formulation with P188 (Bhandari et al., 2007). However, bioavailability of CoQ_{10} in most of these formulations is very low because of the extremely poor water solubility of CoQ_{10} in these formulations or not reported. Specially, Nazzal et

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al. (2002) reported a eutectic based semisolid self-nanoemulsified drug delivery system for improved CoQ_{10} solubility. However, there has been lack of information on the enhanced bioavailability of CoQ_{10}. Furthermore, these approaches were tedious and time consuming. Thus, there is a great need for an efficient, easy, quick, and cost effective method to improve the solubility and bioavailability of CoQ_{10}.

In recent years much attention has been focused on lipid-microemulsion formulations with particular emphasis on self-emulsifying or self-micro emulsifying drug delivery systems (SEDDS and SMEDDS) to improve oral bioavailability of lipophilic drugs (Woo et al., 2007). The clinical usefulness of the SEDDS is evident from the commercially available formulations containing cyclosporin A, ritonavir and Saquinavir. SEDDS are comprised of mixture of drug, oil, surfactants and/or cosolvents which form fine oil in water and/or water in oil emulsions upon dilution with aqueous medium or *in vivo* administration. The digestive motility of the stomach and intestine provide the agitation necessary for self-emulsification *in vivo* (Shah et al., 1994). Factors controlling the *in vivo* performance of SEDDS include their ability to form small droplets of oil (<5 μm) and the polarity of the oil droplets to promote faster drug release into aqueous phase (Shah et al., 1994). The smaller oil droplets provide a large interfacial area for pancreatic lipase to hydrolyze triglycerides and thereby promote the rapid release of the drug and/or formation of mixed micelles of the bile salts containing the drug (New and Kirby, 1999). The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: (a) improved drug dissolution (Constanitinides et al., 1994), (b) increased intestinal epithelial permeability (Koga et al., 2006), (c) increased tight junction permeability (Koga et al., 2006) and (d) decreased GM efflux (Eaimtrakarn et al., 2002). Chi (1999) reported that the percentage release of biphenyl dimethyl dicarboxylate from SMEDDS was >12-fold higher than that from the tablet containing the drug. The percentage release of simvastatin from the SMEDDS was 1.5–2 times high than the conventional tablet (Kang et al., 2004). A few other studies have reported enhancement in the bioavailability of poorly soluble drugs when formulated as SEDDS (Kommuru et al., 2001; Woo et al., 2007).

In this study, we have developed an optimized formulation using a self-emulsifying drug delivery system in order to improve the solubility and bioavailability of CoQ_{10}. Composition of SEDDS was optimized using solubility, phase diagram, particle size, drug release and pharmacokinetics.

2. Materials and methods

2.1. Materials

CoQ_{10} was provided by Boryung Pharm. Co. (Seoul, Korea). Polyglycolyzed glycerides (Capryol 90, Labrafac CC, Labrasol, Labrafil M 1944 CS, Labrafil M 2125 CS, Plurol olique CC 49, Lauroglycol FCC, Lutrol E-400, Peceol and Transcutol P) were obtained from Gattefosse (Saint-Priest Cedex, France). All other chemicals and solvents were of reagent grade and used without further purification.

2.2. Solubility studies

Solubility studies were conducted by placing an excess amount of CoQ_{10} (approximately 250 mg) in a 2 mL micro tube (Axygen MCT-200) containing 1 mL of the vehicle, and the mixture was heated at 60 °C in a water bath to facilitate the solubilization using a vortex mixer. Mixtures were equilibrated at 25 °C for 48 h in a water bath. The equilibrated samples were centrifuged at 3000 × *g* for 15 min to remove the undissolved CoQ_{10}. The supernatant was taken and diluted with methanol for quantification of CoQ_{10} by high-performance liquid chromatography (HPLC) system (Shimadzu, Japan) consisting of Class VP computer software, LC 10AD VP pump, and SPD 10A VP UVVIS detector. Column was Inertsil ODS-3 C18 column (5 μm, 150 × 4.6 mm). Mobile phase, a mixture of methanol and 1-propanol (40:60, v/v) was filtered through 0.45-μm membrane filter and eluted at a flow rate of 1 mL/min. Effluents were monitored at 275 nm. The inter- and intra-day variance of this HPLC method was within the acceptable range.

Table 1
Vehicle compositions of various formulations of SEDDS.

Formulation I	*Formulation* II
Labrafil M 1944 CS	Labrafil M 1944 CS
Labrasol	Labrasol
Lauroglycol FCC	Capryol 90
Formulation III	*Formulation* IV
Labrafil M 2125 CS	Labrafil M 2125 CS
Labrasol	Labrasol
Lauroglycol FCC	Capryol 90

2.3. Preparation of SEDDS formulations

The formulations were prepared by dissolving the formulation amount of CoQ_{10} (6%, w/v) in the mixture of surfactant, oil and cosurfactant mixture at 60 °C in an isothermal water bath. The final mixture was mixed by vortexing until a clear solution was obtained. The formulation was equilibrated at ambient temperature for at least 48 h and examined for signs of turbidity or phase separation prior to self-emulsification and particle size studies. Since the commercial formulations in the market are available at 25 or 30 mg dosage for CoQ_{10}, size 0 capsule could be used to provide the dosage of CoQ_{10} (30 mg of 0.5 mL) with this SEDDS.

2.4. Construction of ternary phase diagram

The existence of self-emulsifying oil formulation fields that could self-emulsify under dilution and gentle agitation were identified from ternary phase diagrams of systems containing oil–surfactant–cosurfactant. The method reported by Craig et al. (1995) was modified and adopted in this study. A series of self-emulsifying systems were prepared in each of the four formulae (Table 1) with varying concentrations of oils; Labrafil M 1944 CS and Labrafil M 2125 CS (25–70%, v/v), surfactant; Labrasol (30–75%, v/v), and cosurfactants Lauroglycol FCC and Capryol 90 (0–25%, v/v).

The formulation (0.2 mL) was introduced into 300 mL of water in a glass beaker at 37 °C and the contents were mixed gently with a magnetic stir bar. The tendency to emulsify spontaneously and also the progress of emulsion droplets were observed. The tendency to form an emulsion was judged as 'good' when droplets spread easily in water and formed a fine milky emulsion, and it was judged 'bad' when there was poor or no emulsion formation with immediate coalescence of oil droplets, especially when stirring was stopped. Phase diagrams were constructed identifying the good self-emulsifying region. All studies were repeated thrice, with similar observations being made between repeats. Moreover, to investigate the effects of CoQ_{10} on the self-emulsifying performance of SEDDS, the formulation amount of CoQ_{10} (6%, w/v) was added to the boundary formulations of the self-emulsifying domain of the ternary phase diagrams. The self-emulsifying performance was visually assessed after infinite dilution using purified water.

2.5. Droplet size analysis and zeta potential

SEDDS (25 μL) was diluted with 25 mL of water in a volumetric flask. The flask was inverted and shaken gently to mix thoroughly.

Table 2
Composition of optimized SEDDS formulations.

Formulation (%)	I	II	III	IV
Labrafil M 1944 CS	25	25	–	–
Labrafil M 2125 CS	–	–	30	30
Labrasol	65	65	55	55
Lauoglycol FCC	10	–	15	–
Capryol 90	–	10	–	15

The particle size of so-formed microemulsion was determined by ELS-8000 Electrophoretic light scattering particle size analyzer. The values of mean emulsion droplet diameters (MEDD) were compared. The formulations were diluted with 0.1N HCl to obtain 25% (v/v) oil-in-water emulsions and the zeta potential of the resulting emulsions was measured using an ELS-8000 zeta potential analyzer.

2.6. Determination of emulsification time

The emulsification time of SEDDS was determined according to United State Pharmacopeia (USP) XXIII, dissolution apparatus II. In brief, 0.5 mL of each formulation (Table 2) was added drop wise to 500 mL of purified water at 37 °C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. The emulsification time was assessed visually as reported by Bachynsky et al. (1997).

2.7. Drug release studies

Drug release studies from SEDDS were performed using USP XXIII, dissolution apparatus II with 900 mL of water as medium at 37 ± 0.5 °C. The speed of the paddle was adjusted to 100 rpm. 0.5 mL of the formulation was (30 mg of drug) directly introduced into the medium and an aliquot (0.5 mL) of sample was collected at designated times and analyzed for the content of CoQ_{10} by HPLC as mentioned above. Control was studied with CoQ_{10} powder. An equivalent volume (0.5 mL) of fresh dissolution medium was added to compensate for the loss due to sampling.

2.8. In vivo study

The *in vivo* study of two formulations of CoQ_{10}, an optimized self-emulsifying formulation (formulation II) and control formulation (CoQ_{10} in 1% povidone solution) were compared in rats at 60 mg/kg dose. Male Sprague-Dawley rats were fasted for 10 h prior to the experiments but allowed free access to water. All animals care and procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted by the Society of Toxicology (USP) in 1999. The study was an open, randomized, multiple dose and cross over design. Since CoQ_{10} is poorly absorbed from the gastrointestinal tract, it was necessary to administer multiple doses or a few days to raise the plasma concentrations to quantifiable levels and also to facilitate the comparisons of the formulations. Two groups consist of six rats weighing approximately 320–380 g received the control formulation twice daily at 08.00 and 20.00 h for 4 days at a dose of 60 mg/kg. On day 5, following the 08.00 h dose of control or formulation (0.5 mL of SEDDS and 0.5 mL of water) at 60 mg/kg dose, 420 μL blood samples were collected at predetermined time intervals. The blood samples were collected from the subclavian vein or artery into heparinized tubes and 200 μL of plasma collected by centrifuging blood samples at 3000 g for 15 min. Plasma samples were stored with photo protection at −20 °C until further analysis.

Plasma concentrations of CoQ_{10} were determined under yellow light and all containers were wrapped with aluminum foil. Extractions were performed in 2 mL Axygen tube. To 200 μL of plasma, 20 μL of internal standard (CoQ_9, 25 μg/mL in hexane) was added and vortex mixed. The plasma was then mixed with 1 mL of 1-propanol, vortex mixed for 5 min and centrifuged at 3000 × *g* for 5 min to precipitate the proteins. The supernatant (1 mL) was evaporated in a rotary centrifugal vacuum evaporator. The residue was reconstituted with 100 μL of 1-propanol and 50 μL of the resulting solution was analyzed by HPLC as mentioned above. The calibration curve was constructed over a range of 0.1–10 μg/mL in plasma (R^2 = 0.999) and validated for inter- and intra-day differences, and the differences were within acceptable range.

The plasma concentration–time profile was corrected for endogenous levels of CoQ_{10} as follows. For each animal, the respective endogenous levels of CoQ_{10} at time 0 h were subtracted from the observed CoQ_{10} concentrations at each time point. The area under the curve (AUC) was calculated by linear trapezoidal rule from zero to the last plasma concentration. The maximum plasma concentration, C_{max}, and the time of its occurrence, T_{max}, were compiled from the concentration–time data. Student's *t*-tests were performed to evaluate the significant differences between the two formulations. Values are reported as mean ± S.D. and the data were considered statistically significant at $P < 0.05$.

3. Results

3.1. Solubility study

The self-emulsifying formulations consisted of oil, surfactants, cosurfactants, and drug should be a clear and monophasic liquid at ambient temperature when introduced to aqueous phase and should have good solvent properties to allow presentation of the drug in solution. The solubility of CoQ_{10} in various vehicles is presented in Fig. 1. Among the vehicles tested Transcutol P with 32.4 ± 5.2 mg/mL and Lutrol E with 0.36 ± 0.03 mg/mL showed lowest drug solubility. Labrasol with 113.70 ± 12.70 mg/mL and Lauroglycol FCC with 117.51 ± 12.27 mg/mL gave highest drug solubility. However, Labrafil M 1944 CS and Labrafil M 2125 CS (HLB 4) were chosen as oily phases for their more hydrophilic nature, good drug solubility and emulsion forming ability. Labrasol (HLB 14) was chosen as surfactant, Lauroglycol FCC (HLB 4) and Capryol 90 (HLB 6) were chosen as cosurfactants, for the optimal SEDDS

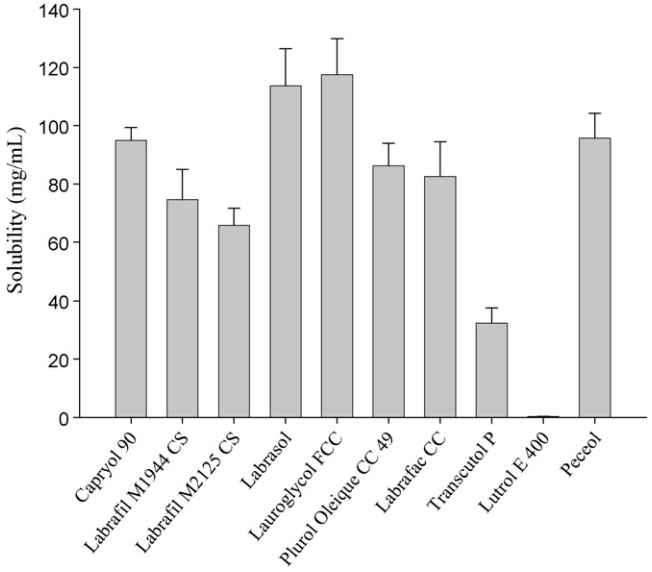

Fig. 1. Solubility studies of CoQ10 in various vehicles (n = 3). Each value represents the mean ± S.E. (n = 3).

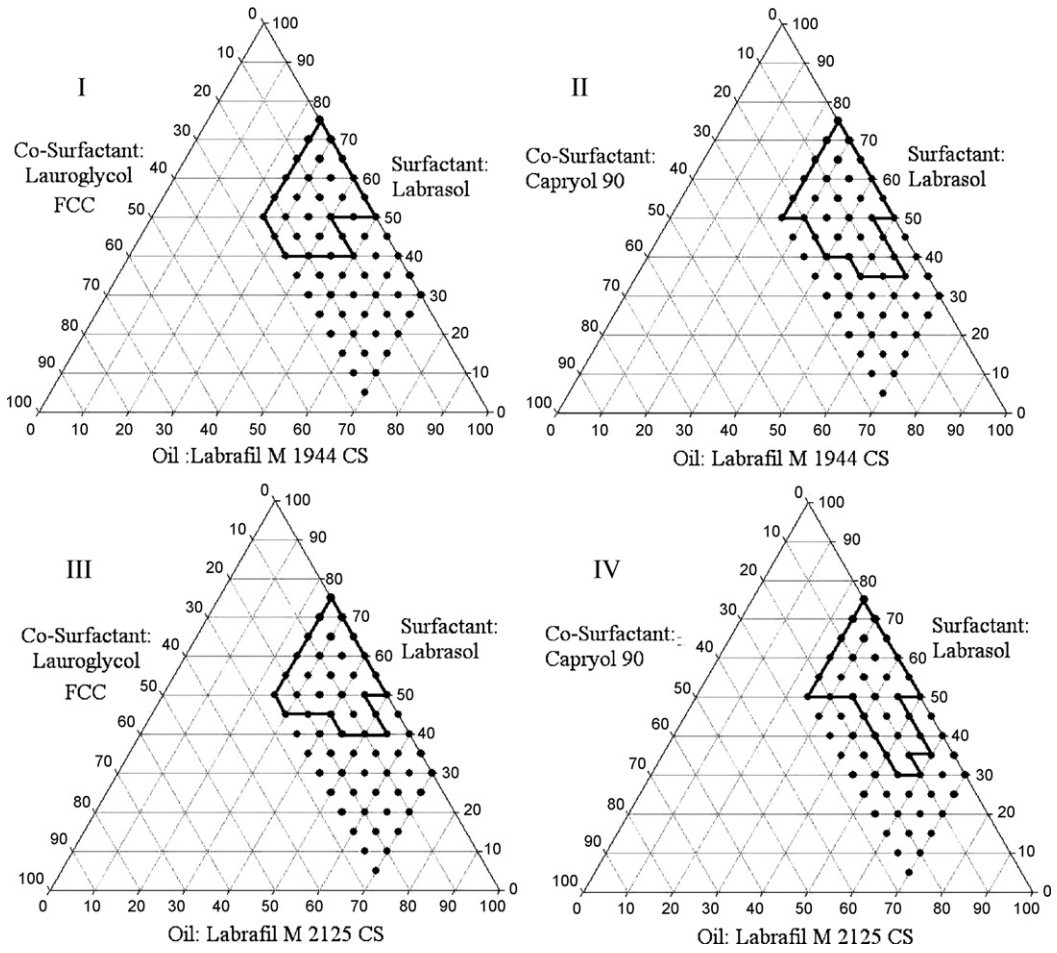

Fig. 2. Pseudo-ternary phase diagram of formulations I–IV mentioned in Table 1.

formulation resulting in improved drug loading and spontaneous emulsion forming capabilities.

3.2. Construction of pseudo-ternary phase diagrams

A series of SEDDS were prepared and their self-emulsifying properties were observed visually. Pseudo-ternary phase diagrams were constructed in the absence of CoQ_{10} to identify the self-emulsifying regions and to optimize the concentration of oil, surfactant and cosurfactant in the SEDDS formulations. The phase diagrams of the systems containing Labrasol as surfactant and different oils (Labrafil M 1944 CS and Labrafil M 2125 CS) and cosurfactants (Lauroglycol FCC and Capryol 90) are shown in Fig. 2. Both the PEG-6 ester oils showed significant difference with different cosurfactants. It was observed that increasing the concentration of the cosurfactants, Lauroglycol FCC and Capryol 90, within the self-emulsifying region increased the spontaneity of the self-emulsification process. The efficiency of emulsification was good when the S/CoS concentration was more than 60% of SEDDS formulation. It was observed that the emulsification was not efficient with less than 50% of surfactant ratio. In these two systems, the formulations surrounding the good self-emulsification region exhibited immediate coalescence of the droplets following the self-emulsification process.

It has been reported that the drug incorporated in the SEDDS may have some effect on the self-emulsifying performance (Pouton, 1985). In our study, no significant differences were found in self-emulsifying performance when compared with the corresponding formulations with CoQ_{10}.

3.3. Characterization of SEDDS

In SEDDS, the primary means of self-emulsification assessment is visual evaluation (Shah et al., 1994). The efficiency of self-emulsification could be estimated by determining the rate of emulsification, and droplet size distribution. The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption (Constanitinides et al., 1994). It was observed that increasing the surfactant concentration (from 30 to 70%, v/v) in SEDDS formulations I–IV (Table 1) decreased the mean droplet size of emulsion formed but above 65% with Labrafil M 1944 CS and 55% with Labrafil M 2125 CS the mean droplet size slightly increased (Fig. 3). The effect of the cosurfactants (Lauroglycol FCC and Capryol 90) concentration on the droplet size distribution in SEDDS was similar to that of the surfactant (Labrasol) at concentrations of Lauroglycol FCC and Capryol 90 from 0 to 15% (v/v). A decrease in droplet size was observed with an increase in the cosurfactant concentration of Lauroglycol and Capryol 90 from 0 to 15%, after which the droplet size was slightly increased (Fig. 4). We observed that the formulations composition ratio mentioned in Table 2 gave smaller particle size than other SEDDS formulations tested and chosen for further studies. Among the chosen formulations the smallest mean droplet size (243.3 nm) was observed with formulation containing Labrafil M 1944 CS 25%, Labrasol 65% and Capryol 90 10% (v/v) ratio. The charge of the oil droplets of SEDDS is another property that should be assessed for increased absorption (Gershanik et al., 1998). The charge of the oil droplets in SEDDS is negative due to the presence of free fatty acids, the zetapotential

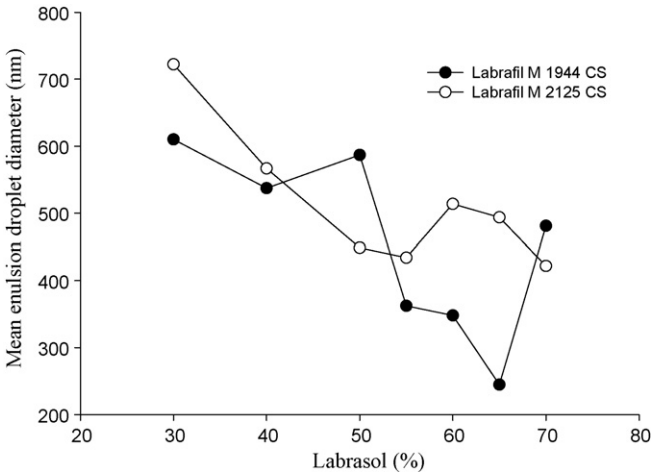

Fig. 3. Effect of the percentage volume ratio of surfactant to oil on the droplet size of microemulsion formed from oil/surfactant mixture.

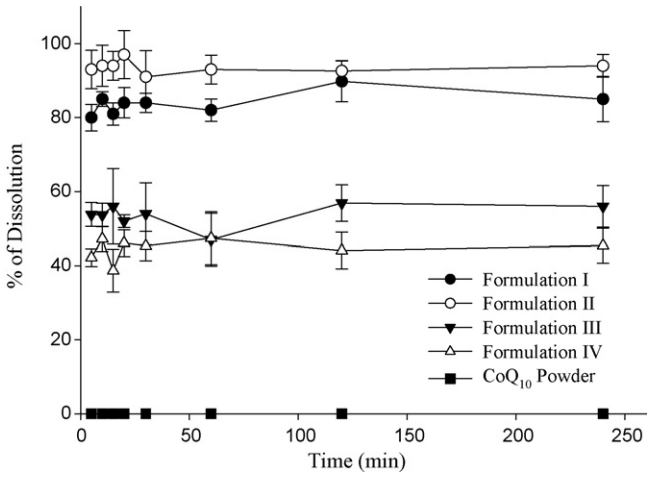

Fig. 5. Drug release profile of CoQ10 from SEDDS formulations I–IV and CoQ10 powder in water. Each value represents the mean ± S.E. ($n = 3$).

of the formulations I–IV was −26.80, −22.94, −33.18 and −55.13, respectively.

3.4. Emulsification time and drug release studies of SEDDS containing CoQ_{10}

The rate of emulsification is an important index for the assessment of the efficiency of emulsification (Pouton, 1997), that is the SEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. Emulsification time study showed that all the formulae employed could emulsify within 20 s (formulations I and II 10 ± 2, formulations III and IV 14 ± 2 and 16 ± 3 s, respectively). Among the tested formulations, formulations I and II showed shorter emulsification time than others.

In the self-emulsifying systems, the free energy required to form an emulsion was very low, thereby allowing spontaneous formation of an interface between the oil droplets and water. It is suggested that the oil/surfactant/cosurfactant and water phases effectively swell, decrease the oil droplet size and eventually increase the release rate. Dissolution studies were performed for the SEDDS formulations (Table 2) and the results of the release profile of formulations in water are presented in Fig. 5. As the emulsification time is below 20 s the maximum percentage of the drug released within 5 min; however, the dissolution studies conducted for 4 h to see the variance or occurrence of precipitation over a time. The percentage release of CoQ_{10} at 4 h were 85%, 91% 56% and 45.4% in water from SEDDS formulations I–IV, respectively. Formulations I and II showed better drug release profile than formulations III and IV.

3.5. In vivo study

The pharmacokinetic parameters of CoQ_{10} were determined after oral administration of powder suspension formulation contained 1% povidone as a suspending agent or the SEDDS formulation consists of Labrafil M 1944 CS, Labrasol and Capryol 90 (formulation II, Table 2). Fig. 6 shows the change of mean plasma concentration of CoQ_{10} after oral administration of preparations in rats. The total plasma concentrations of CoQ_{10} in SEDDS were higher compared with those in CoQ_{10} powder. In particular, the initial plasma concentrations of CoQ_{10} in SEDDS were significantly higher compared with those in CoQ_{10} powder ($P < 0.05$). The pharmacokinetic parameters are shown in Table 3. The SEDDS gave significantly higher AUC and C_{max} of CoQ_{10} than did CoQ_{10} powder ($P < 0.05$). In particular, the AUC of CoQ_{10} from SEDDS was about 2-fold higher than that

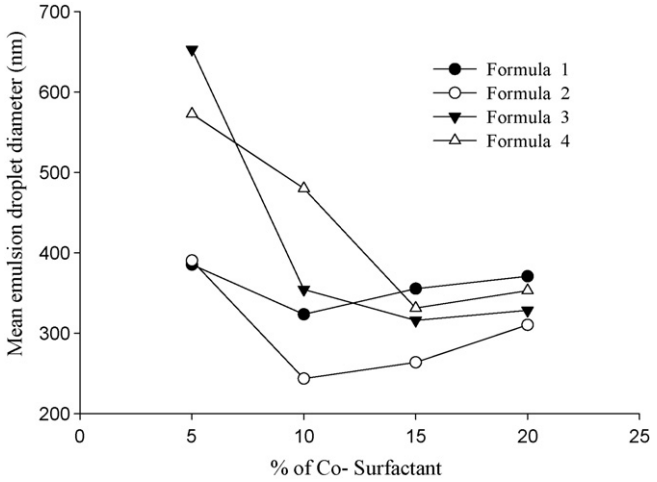

Fig. 4. Effect of cosurfactant percentage volume ratio on the mean emulsion droplet diameter of formulations contains constant surfactant volume. In formulation I and II Labrasol percentage volume kept constant at 65% and in formulation III and IV Labrasol percentage volume kept constant at 55%.

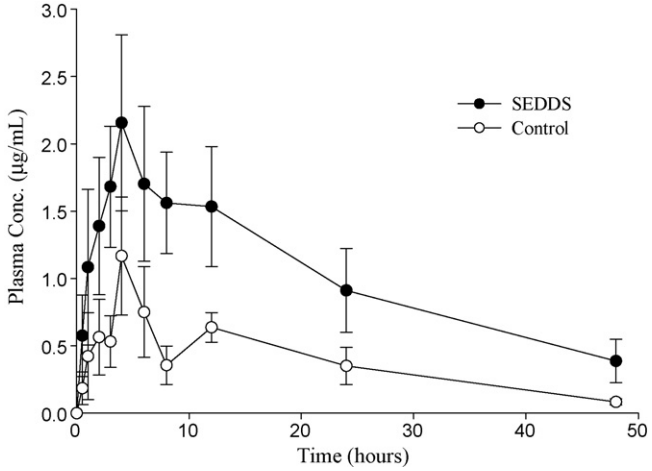

Fig. 6. Plasma profiles of CoQ10 from SEDDS and control formulations in rats. Each value represents the mean ± S.E. ($n = 6$).

Table 3
Pharmacokinetic parameters of SEDDS and control formulation.

Parameter	SEDDS formulation II	Control formulation
T_{max} (h)	4.0 ± 0	4.0 ± 0
C_{max} (μg/mL)	2.16 ± 0.65*	1.28 ± 0.39
$T_{1/2}$ (h)	35.25 ± 12.65	24.07 ± 7.06
K_e (h^{-1})	0.02 ± 0.011	0.03 ± 0.012
AUC (μg h/mL)	48.75 ± 12.72*	20.18 ± 3.26

Each value represents the mean ± S.E. ($n = 6$).
* $P < 0.05$ compared with control formulation.

from CoQ_{10} powder. However, the T_{max} value of CoQ_{10} from SEDDS was not different from those of CoQ_{10} powder.

4. Discussion

CoQ_{10} is reported to possess poor bioavailability and poor delivery properties owing to its solubility (Chopra et al., 1998). Self-emulsified systems are being extensively used to improve the solubility and bioavailability of poorly water-soluble drugs (Kang et al., 2004; Woo et al., 2007). Self-emulsifying formulations offer the potential for enhancing the absorption of poorly soluble and/or poorly permeable compounds. SEDDS form fine oil–water emulsions with only gentle agitation, upon its introduction into aqueous media. Since the free energy required to form an emulsion is very low, the formation is thermodynamically spontaneous (Craig et al., 1995). Surfactants form a layer around the emulsion droplets and reduce the interfacial energy as well as providing a mechanical barrier to coalescence. Instead of its profound advantages there are only few commercial formulations available in the market, because of its limitations in manufacturing methods and limited solubility of some drugs in lipid vehicles (Wilson and Mahony, 1997). In this study the solubility study on various vehicles showed that Labrafil M 1944 CS, Labrafil M 2125, Labrasol, Capryol 90 and Lauroglycol FCC had optimum solubility of CoQ_{10} to formulate a SEDDS formulation with desired drug loading.

Visual and particle size investigations confirmed that both oils studied formed emulsions on gentle agitation with water. The tendency of these oils to form such emulsions with a minimum of agitation and without the need for a complex manufacturing protocol is of interest, both for preparing self emulsions for subsequent use using a simple and inexpensive protocol and also for the possibility of the formation of emulsions on ingestion. The lipophilic surfactant nature of the oil phase (HLB 4 for Labrafil M 1944 CS and Labrafil M 2125) may reduce the w/o interfacial tensions; Labrafil oils contain mono- and di-glycerides of fatty acids and sometimes PEG esters, which act as lipophilic and hydrophilic surfactant molecules, respectively. Omotosho et al. (1986) noted a correlation between the water/oil interfacial tension and the size of the internal droplets, with lower interfacial tension systems correlated with smaller internal droplets. The rate of emulsion droplet formation was found to be dependent on the nature of the oil phase and the oil/surfactant ratio, higher surfactant concentrations resulted in more rapid maturation of the droplets. This may be due to excess penetration of water into the bulk oil causing massive interfacial disruption and ejection of droplets into the bulk aqueous phase (Pouton, 1997).

Irrespective of the mechanism of formation, a key feature associated with any applications for these systems is the stability of the formed formulations. When the product is stored at a lower temperature, there may be some precipitation of the active ingredient and/or the excipients. The precipitated materials should therefore be dissolved again when warmed to room temperature; otherwise the drug will not be presented in a solution or as a fine emulsion droplet (Kovacs et al., 1996). In this study crystallization of CoQ_{10} was not observed at room temperatures (25 °C), moreover formulations I and II were stable and did not show any precipitation at 10 °C for 12 weeks and the formulations III and IV were stable at 15 °C but below these temperatures precipitations appeared. In the present investigation drug release profile of SEDDS formulations in water showed that formulations I and II had higher drug release profile than other formulations and powder due to more hydrophilic nature of Labrafil M 1944 CS (Oleoyl macrogol glyceride) than Labrafil M 2125 CS (Linoleoyl macrogol glyceride). It ensures presenting the drug in a solution or as a fine emulsion droplet for better absorption. The lower negative zeta potential value of the formulation II explains higher drug release of this formulation (Gershanik et al., 1998).

The *in vivo* absorption study was undertaken to determine whether or not the enhanced solubility and *in vitro* dissolution of CoQ_{10} in SEDDS could increase the GI absorption of drug after oral administration in rats. The SEDDS formulation increased the AUC and C_{max}. However, T_{max} was consistently around 4 h which showed that CoQ_{10} was a rather large molecule water-insoluble and absorbed slowly in the intestine regardless of the formulations (Bhagavan and Chopra, 2007). The effects of oral administration of CoQ_{10} on the clinical response were reported in several studies. It was reported that the supplementation of CoQ_{10} is required for several weeks to months to see any significant pharmacological or therapeutic effect (Miles, 2007). Since the plasma threshold for the uptake of CoQ_{10} appeared to be different for different tissues. For instance, in one study with congestive heart failure (CHF) patients, it was reported that those with a plasma CoQ_{10} value of 2.4 μg/mL (2.780 μmol/L) showed the highest benefit (Belardinelli et al., 2006). In an earlier study with CHF patients, it was reported that a blood CoQ_{10} concentration of at least 3.5 μg/mL (4.054 μmol/L) appeared to be necessary before any therapeutic benefit from CoQ_{10} supplementation could be expected (Langsjoen and Langsjoen, 1998). The plasma threshold appeared to be much higher for neurodegenerative diseases such as Huntington's and Parkinson's disease (Bhagavan and Chopra, 2007). However, important questions involving the uptake and distribution of CoQ_{10} in the treatment of human diseases still remain unanswered. Early studies in rat and mouse, at doses ranging from 10 to 123 mg/kg/day indicated that CoQ_{10} tissue uptake was limited mainly to the liver and plasma (Miles, 2007). Recently, Bentinger et al. (2003) reported that the uptake of CoQ_{10} into various organs in rats showed wide differences; it was high in liver, spleen, adrenals, ovaries, and limited in thymus and heart, uptake in muscle, brain, and kidney was very low. Therefore, plasma CoQ_{10} concentrations need to be high (i.e. higher than "normal" values) in order to promote uptake by peripheral tissues and possibly also to cross the blood brain barrier (Miles, 2007). Hence, formulation which could enhance the bioavailability of poorly water-soluble CoQ_{10} would be favorable in clinical point of view.

For the oral delivery of poorly water-soluble drugs, there are two main barriers, i.e. the pre-epithelial, unstirred, aqueous layer and poor membrane permeability. Surfactants are known to increase the permeability of drugs by disturbing the cell membrane and modifying tight junctions between the cells (Jackson, 1987), which are the primary barrier for the absorption of majority drugs. Surfactants that are too hydrophobic are poor enhancers and surfactants that are very hydrophilic cannot partition into the hydrophobic environment of the lipid bi-layer (Swenson and Curatolo, 1992). A medium length alkyl chain surfactant may penetrate the lipid bi-layer easily, and because of its aqueous solubility has a greater monomer concentration and higher critical micellar concentration than a longer alkyl chain surfactant (Constanitinides et al., 1994; Lindmark et al., 1995). Labrasol is a surfactant that contains predominantly alkyl chain lengths of C_8 and C_{10}. Previous studies have indicated that Labrasol improve intestinal absorption of drugs

(Prasad et al., 2003). In the present investigations, the superior performance of self-emulsifying formulations may be attributed to the following factors: (a) larger surface area provided by the fine emulsion droplets, (b) improved diffusion of the fine emulsion droplets, (c) increased mucosal permeability due to surfactants and (d) improved lymphatic absorption due to the long-chain oil, Labrafil M 1944 CS. The earlier studies suggest that the molecules of long-chain fatty glycerides access the intestinal lymph in preference to the portal bloods (Caliph et al., 2000; Porter and Charman, 1997). The digestion products of long-chain triglycerides were preferentially resynthesized in the enterocyte, assembled into lipoproteins, and secreted into the mesenteric lymph, whereas medium chain triglycerides were primarily absorbed directly into the portal blood. And the digested lipids of medium chain triglycerides with bile salts formed lipophilic particles, and overcame the barrier of aqueous diffusion layer in the gastrointestinal (GI) tract (New and Kirby, 1999). The results of the bioavailability study indicate the existence of the possible absorption routes for the medium and long-chain fatty glyceride, which would contribute to the improved absorption of CoQ_{10} from the SEDDS formulation. The efficiency of the SEDDS or SMEDDS formulation is drug dependent in most instances (Chen et al., 2008), thus the successful composition of the SEDDS or SMEDDS should be carefully explored.

5. Conclusion

CoQ_{10} was formulated as a SEDDS in an attempt to increase its solubility and bioavailability. An optimized formulation of SEDDS containing CoQ_{10} was developed through the construction of pseudo-ternary phase diagram and particle size analysis. Following oral administration in rats, SEDDS provided significant increase in the bioavailability compared to a powder suspension formulation. Overall, the study has indicated that it is indeed possible to produce reasonably stable SEDDS via a simple one-step process for drugs that are poorly soluble and/or poorly permeable to achieve a significant improvement in the bioavailability.

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