Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q_{10}: formulation development and bioavailability assessment

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Abstract

The goals of our investigations are to develop and characterize self-emulsifying drug delivery systems (SEDDS) of coenzyme Q_{10} (CoQ_{10}), using polyglycolyzed glycerides (PGG) as emulsifiers and to evaluate their bioavailability in dogs. Solubility of CoQ_{10} was determined in various oils and surfactants. SEDDS consisted of oil, a surfactant and a cosurfactant. Four types of self-emulsifying formulations were prepared using two oils (Myvacet 9-45 and Captex-200), two emulsifiers (Labrafac CM-10 and Labrasol) and a cosurfactant (lauroglycol). In all the formulations, the level of CoQ_{10} was fixed at 5.66% w/w of the vehicle. The in vitro self-emulsification properties and droplet size analysis of these formulations upon their addition to water under mild agitation conditions were studied. Pseudo-ternary phase diagrams were constructed identifying the efficient self-emulsification region. From these studies, an optimized formulation was selected and its bioavailability was compared with a powder formulation in dogs. Medium chain oils and Myvacet 9-45 provided higher solubility than long chain oils. Efficient and better self-emulsification processes were observed for the systems containing Labrafac CM-10 than formulations containing Labrasol. Addition of a cosurfactant improved the spontaneity of self-emulsification. From these studies, an optimized formulation consisting of Myvacet 9-45 (40%), Labrasol (50%) and lauroglycol (10%) was selected for its bioavailability assessment. A two-fold increase in the bioavailability was observed for the self-emulsifying system compared to a powder formulation. SEDDS have improved the bioavailability of CoQ_{10} significantly. The data suggest the potential use of SEDDS to provide an efficient way of improving oral absorption of lipophilic drugs. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Approximately 40% of new drug candidates have poor water solubility and the oral delivery of

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such drugs is frequently associated with implications of low bioavailability, high intra- and inter subject variability, and lack of dose proportionality (Robinson, 1996). To overcome these problems, various formulation strategies are reported in the literature including the use of surfactants, cyclodextrins, nanoparticles, solid dispersions, micronization, lipids, and permeation enhancers (Aungst, 1993; Robinson, 1996). These approaches are successful in selected cases. In recent years much attention has been focused on lipid-based formulations (Humberstone and Charman, 1997) with particular emphasis on self-emulsifying drug delivery systems (SEDDS) to improve oral bioavailability of lipophilic drugs (Constantinides, 1985; Pouton, 1997). SEDDS are isotropic mixtures of an oil, surfactant, cosurfactant and drug. They form fine oil-in-water emulsions when introduced into aqueous media under mild agitation. 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 ($< 5\mu$) 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 (Tarr and Yalkowsky, 1989). The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: (a) improved drug dissolution (Constantinides, 1985); (b) increased intestinal epithelial permeability (Swenson and Curatolo, 1992); (c) increased tight junction permeability (Lindmark et al., 1995); and (d) decreased/inhibited p-glycoprotein drug efflux (Nerurkar et al., 1996, 1997; Lo et al., 1998; Yu et al., 1999). Recently Shah et al. (1994) have reported a three-fold increase in the bioavailability of a poorly soluble compound when formulated as SEDDS. A marketed formulation of cyclosporine (Sandimmune Neoral®), a microemulsion preconcentrate with self-emulsifying properties, is reported to improve oral bioavailability and reduce inter- and intra subject variability in cyclosporine pharmacokinetics (Friman and Backman, 1996). A few other studies have reported enhancement in the bioavailability of poorly soluble drugs when formulated as SEDDS (Lin et al., 1991; Charman et al., 1992; Klem et al., 1993; Matuszewska et al., 1996; Hauss et al., 1998).

Coenzyme Q_{10} (CoQ_{10}) also known as ubidecarenone (Fig. 1) is a lipid soluble compound that inhabits the inside of the inner mitochondrial membrane, where it functions as an integral part of electron transport of oxidative phosphorylation (Folkers et al., 1986). It is used as an antioxidant and also in the treatment of cardiovascular disorders such as angina pectoris, hypertension, and congestive heart failure (Greenberg and Fishman, 1990). CoQ_{10}, a yellow colored crystalline powder with a melting point of 48°C, is practically insoluble in water and poorly absorbed from the gastrointestinal tract. The slow absorption of CoQ_{10} (T_{max} 5–10 h) from the gastrointestinal tract was attributed to its high molecular weight and poor water solubility (Greenberg and Fishman, 1990). Oil based and powder filled capsule formulations are currently available on the market as nutritional supplements. However, oral bioavailability of these formulations differs widely (Kishi et al., 1984). Recently, we have reported that a simple oil-based formulation of CoQ_{10} did not significantly enhance bioavailability when compared to that of powder filled capsule formulation (Kommuru et al., 1999). SEDDS are sought to enhance the oral delivery of CoQ_{10}. For selecting a suitable self-emulsifying vehicle, it is important to assess: (a) the drug solubility in various components; (b) the area of self-emulsifying region in the phase diagram; and (c) droplet size distribution follow-
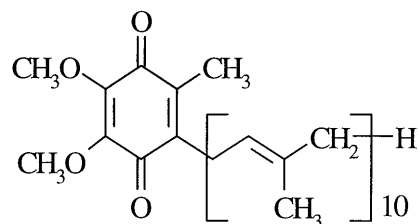

Fig. 1. Structure of coenzyme Q_{10}.

ing self-emulsification. The objectives of the present study were to develop and characterize SEDDS of CoQ_{10} using polyglycolyzed glycerides as surfactants and to assess their bioavailability in coonhounds.

2. Materials and methods

2.1. Materials

CoQ_{10} and triglyceride oils (peanut, soybean and corn) were purchased from Spectrum Chemicals (Gardena, CA). Polyglycolyzed glycerides (Labrafac CM-10 CM-10, Labrasol, Labrafill M-1944CS, Plurol olique and Lauroglycol) were obtained from Gattefosse (Westwood, NJ). Captex-200 was obtained from Abitec Corp. (Columbus, OH) and Neobee M-5 was obtained from Stepan Co (Maywood, NJ). The internal standard CoQ_9 was kindly supplied by Eisai Co. (Tokyo, Japan). Sep-Pak silica (100 mg) solid phase extraction cartridges were purchased from Waters (Milford, MA). All other chemicals and solvents were purchased from Fisher Scientific (Fair Lawn, NJ).

2.2. Solubility studies

The solubility of CoQ_{10} in various oils, surfactants and cosurfactants was determined. An excess of CoQ_{10} (approximately 500 mg) was placed in 2 ml of the vehicle in screw-capped glass vials and the mixture was heated at 60°C in a water-bath to facilitate the solubilization using a vortex mixer. Mixtures were equilibrated at 30°C for 48 h in a water bath and then centrifuged at 2000 *g* for 10 min to separate the undissolved drug. Aliquots of supernatant were diluted with methanol and quantified by HPLC.

2.3. Preparation of SEDDS

The CoQ_{10} levels in the marketed formulations such as tablets and capsules vary from 25 to 30 mg. A series of self-emulsifying systems were prepared in each of the four formulas

Table 1
Vehicle compositions of various formulations of SEDDSs

Formula 1	Formula 2
Captex-200[7]	Myvacet 9-45[7]
Labrafac CM10[7]	Labrafac CM10[7]
Lauroglycol	Lauroglycol
Formula 3	Formula 4
Captex-200[7]	Myvacet 9-45[7]
Labrasol	Labrasol
Lauroglycol	Lauroglycol

(Table 1) with varying concentrations of oil (30–70%), surfactant (5–30%), and cosurfactant (0–25%). In all the formulations, the level of CoQ_{10} was constant (i.e. 5.66% w/w of the vehicle). At this level, the fill volume of a size 0 capsule can represent 30 mg of CoQ_{10}. Components of SEDDS (oil, surfactant, cosurfactant and drug) were accurately weighed into screw-capped glass vials and heated at 60°C in a water bath to facilitate the solubilization and vortex mixed. The formulations were equilibrated to 30°C for 24 h and then stored at room temperature.

2.4. Visual observations

A visual test to assess the self-emulsification properties reported by Craig et al. (1995) was modified and adopted in the present study. 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 twice, with similar observations being made between repeats.

2.5. Emulsion droplet size analysis

Formulation (25 μl) of the was diluted with water to 25 ml in a volumetric flask and gently mixed by inverting the flask. The droplet size distributions of the resultant emulsions were determined using Malvern Particle Size Analyzer (Model No. 2600, 63 mm lens; Malvern, UK). The values of mean emulsion droplet diameters (MEDD) were compared.

2.6. Bioavailability studies

The bioavailability of two formulations of CoQ_{10}, an optimized self-emulsifying formulation (Formulation I) and a powder filled capsule formulation (Formulation II), were compared in dogs (coonhounds). Both the formulations contained 30 mg of CoQ_{10} per capsule. The compositions of these formulations are given in Table 2. The study was an open, randomized, multiple-dose, cross over design. Since CoQ_{10} is poorly absorbed from the gastrointestinal tract, it was necessary to administer multiple doses for a few days to raise the plasma concentrations to quantifiable levels and also to facilitate the comparisons of the formulations. Four dogs weighing approximately 20 kg each received the two formulations on separate occasions. In the first part of the study, blood samples (5 ml) were collected from each animal prior to dosing to determine the endogenous CoQ_{10} concentration. Two dogs were randomly assigned to each of the two groups. Each dog in the first group received Formulation I and the other group received Formulation II twice daily at 0800 and 2000 h for 4 days. On day 5, following the 0800 h dose, blood samples were collected at 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, and 72

h. The blood samples were collected from the cephalic vein into heparinized tubes. Blood samples were stored on ice in the dark until the plasma was separated by centrifugation. After centrifugation, plasma was separated into amber colored vials and stored at $-20°C$ until further analysis. Following a 7-day wash out period, the two groups were crossed-over to carry out phase II of the study. The dosing and sampling procedures were identical in both phases. 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. Analysis of variance (ANOVA) and t-tests were performed to evaluate the significant differences between the two formulations. Values are reported as mean $\pm$ SD and the data were considered statistically significant at $p < 0.05$.

2.7. Chromatography

The LC system consisted of Isco-2350 pump, Isco-V[4] variable wavelength ultraviolet absorbance detector. The chromatographic column was a 150×3.9 mm Nova-Pak C18 (4 μm) (Waters Corp., Milford, MA) and the guard column was a 7.5×4.6 mm Alpha Bond C18 (Alltech, San Jose, CA). A mobile phase of methanol:n-hexane (98:2 v/v) was pumped isocratically at a flow rate of 1.0 ml min^{-1}. A 100 μl volume was injected onto the column and the effluent was

Table 2
Composition of the formulations used in bioavailability studies

Formulation I	Amount (mg.cap)	Formulation II	Amount (mg.cap)
CoQ_{10}	30.0	CoQ_{10}	30.0
Myvacet 9-45	188.0	Sodium lauryl sulphate	0.3
Labrafac CM-10	235.0	Lactose	269.7
Lauroglycol	47.0		

monitored at 275 nm while the detector output was recorded using Isco-Chemresearch (Version 2.4) Software.

2.8. Plasma sample analysis

Plasma concentrations of CoQ_{10} were determined according to our method reported earlier (Kommuru et al., 1998). Since the solutions of CoQ_{10} are susceptible to photodegradation, studies were conducted under yellow light and all containers were wrapped with aluminum foil. Frozen plasma samples were thawed in the dark just prior to analysis at room temperature. Extractions were performed in 115×10 mm screw top borosilicate glass tubes. To 1 ml of plasma, 50 µl of internal standard (CoQ_9, 7.5 mg/ml in hexane) was added and vortex mixed. The plasma was then deproteinized with 1 ml of 10% trichloroacetic acid. To this sample, 2 ml of hexane were added, and the contents vortex-mixed for 5 min, and centrifuged at 2000 *g* for 5 min. The hexane phase was transferred to a 100 mg silica-solid phase extraction cartridge, previously activated with 5 ml of hexane and mounted on a vacuum manifold system. The extraction was repeated twice and the hexane supernates were collected on the extraction cartridge. A total of 6 ml of hexane was passed through the cartridge. The cartridge was then dried under vacuum for 2 min and eluted with 0.75 ml of methanol: hexane (85:15 v/v) mixture. A 100 µl volume of the eluted fraction was injected onto the HPLC column.

3. Results

3.1. Solubility studies

The self-emulsifying formulations consisted of one or more surfactants and drug dissolved in oil. The mixture should be a clear, monophasic liquid at ambient temperature, and should have good solvent properties to allow presentation of the drug in solution. The solubilities of CoQ_{10} in various surfactants and oils are presented in Table 3. These components are soluble in each other and form homogenous liquids. Medium chain

Table 3
Solubility of coenzyme Q_{10} in various vehicles

Vehicle	Composition	Solubility of CoQ_{10} (mg/ml) Mean $\pm$ SD
Oils		
Myvacet 9-45	Diacetylated monoglycerides of C-18 fatty acids	129.35 ± 85
Penut oil	Triglycerides of long chain fatty acids	80.92 ± 4.9
Soyabean oil	Triglycerides of long chain fatty acids	73.91 ± 2.9
Corn oil	Triglycerides of long chain fatty acids	85.37 ± 7.1
Captex-200	Diesters of caprylic/capric acids on propylene-glycol	169.31 ± 11.1
Neobee M-5	Caprylic/capric triglycerides	138.22 ± 13.4
Surfactants		
Labrasol	Saturated polyglycolyzed C8–C10 glycerides (HLB-14)	32.7 ± 2.6
Labrafac CM10	Saturated polyglycolyzed C8–C10 glycerides (HLB-10)	35.61 ± 3.6
Labrafill M-1944CS	Polyglycolyzed glycerides from apricot kernel oil (HLB 3-4)	69.16 ± 6.3
Lauroglycol	Propylene glycol laurate (HLB-4)	114.10 ± 14.8
Plurol olique	Polyglyceryl oleate (HLB-6)	31.73 ± 1.4

fatty acid glycerides and Myvacet 9-45 provided higher solubility than other oils. The oils, Captex-200 and Myvacet 9-45 are selected for formulation development because oils form a distinct core in the interior of the surfactant aggregate, resulting in enhanced solubilizing capacity of the oils with improved drug loading capabilities of the emulsion. It is well established that medium chain fatty acids influence the tight junctions of the epithelial cells (Lindmark et al., 1995) and long

chain fatty acids stimulate the lipoprotein synthesis and subsequent lymphatic absorption (Charman and Stella, 1991).

3.2. Excipients selection

Lipophilic surfactants with hydrophilic-lipophilic balance (HLB) < 10 are capable of promoting some emulsification of the oil, but the resulting emulsions are normally too crude (in terms of size) to be useful. Hydrophilic surfactants with HLB > 10 are much superior at this providing fine, uniform emulsion droplets which are more likely to empty rapidly from the stomach (Lacy and Embleton, 1997). Furthermore, the large surface area facilitates faster and more complete absorption. However, in most cases it is the right blend of low and high HLB surfactants that leads to the formation of a stable microemulsion upon exposure to water. Therefore, based on these considerations, two high value surfactants (Labrafac CM-10 and Labrasol) and one low HLB value surfactant (lauroglycol) were selected. Among the various low HLB value surfactants, lauroglycol provided a higher solubility of CoQ_{10} (Table 3). Accordingly, four formulations (Table 1) were developed for further characterization.

3.3. Visual observations

SEDDS form fine oil–water emulsions with only gentle agitation, upon their 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 hence reduce the interfacial energy, as well as providing a mechanical barrier to coalescence. However, the separation of the two phases is only delayed in these systems and the systems are still considered unstable from a thermodynamic standpoint (Craig et al., 1995).

The visual test is a measure of an apparent spontaneity of emulsion formation. A series of SEDDS were prepared and their self-emulsifying properties were observed visually. Pseudo-ternary phase diagrams were constructed to identify the self-emulsifying regions and also to establish the

optimum concentrations of oil, surfactant, and cosurfactant. It was reported that the mechanism of self-emulsification involved the erosion of a fine cloud of small droplets from the surface of large droplets, rather than a progressive reduction in droplet size (Pouton, 1997). The phase diagrams of the systems containing Labrafac CM-10 and different oils (Captex-200 and Myvacet 9-45) are shown in Fig. 2. Both medium and long chain oils provided almost identical self-emulsifying regions. Efficiency of emulsification was good when the surfactant concentration was more than 50%. It was observed that increasing the concentration of the cosurfactant, lauroglycol, within the self-emulsifying region increased the spontaneity of the self-emulsification process. When a cosurfactant is added to the system, it further lowers the interfacial tension between the oil and water interface and also influences the interfacial film curvature, which thereby readily deforms around oil droplets (Eccleston, 1992). The phase diagrams of the systems containing Labrasol, selected oils (Captex-200 and Myvacet 9-45), and lauroglycol are shown in Fig. 3. For both the systems, the self-emulsifying region was decreased and higher concentrations of Labrasol were required (in comparison to systems containing Labrafac CM-10) for good self-emulsification. In these two systems, the formulations surrounding the good self-emulsification region exhibited immediate coalescence of the droplets following the self-emulsification process. Therefore, much higher concentrations of Labrasol are required compared to Labrafac CM-10 to form a stable interfacial film in order to stabilize the oil droplets.

3.4. Droplet size analysis

The droplet size analysis showed the quality of emulsion formed.

3.4.1. Effect of surfactant concentration

The effect of the surfactant concentration, in various self-emulsifying systems, on the droplet size distribution is presented in Figs. 4 and 5. In cases of self-emulsifying systems containing Labrafac CM-10 and Captex-200 (Fig. 4), increasing the surfactant concentration (from 30 to 60%)

decreased the mean droplet size. A smaller/minimal droplet size was observed when the surfactant concentration was in the range of 60–80%. Similar observations were made when the medium chain oil (Captex-200) was replaced by the long chain oil (Myvacet 9-45). Such a decrease in droplet size may be the result of more surfactant being available to stabilize the oil–water interface. Furthermore, the decrease in the droplet size behavior reflects the formation of a better close packed film of the surfactant at the oil–water interface, thereby stabilizing the oil droplets (Levy and Benita, 1990).

The self-emulsifying systems containing Labrasol exhibited a very different pattern. In cases of the systems containing Captex-200 and Labrasol, significant decreases in droplet size were seen with increases in the surfactant concentration to 50%, after which the droplet size was increased (Fig. 5). A few studies have reported similar trends in droplet size with increases in surfactant concentration for various self-emulsifying systems (Wakerly et al., 1987; Craig et al., 1995). Visual observations indicated that at higher levels of surfactant, the spontaneity of the self-emulsification process was increased. 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). However, a higher level of surfactant decreases the solubility limit of the drug and may subsequently lead to precipitation. A larger mean droplet size was observed with the formulations containing long chain oil (Myvacet 9-45) compared to the formulations containing medium chain oil (Captex-200) (Fig. 5). This might be due to the differences in the penetration of long chain and short chain oils into the tail region of the surfactant and their subsequent influence on the curvature of the interfacial film, which is consistent with the reported findings (Malcolmson et al., 1998).

3.4.2. Effect of cosurfactant concentration

The effect of cosurfactant (lauroglycol) concentration on the droplet size distributions of various systems is presented in Table 4. When a cosurfactant is added (in addition to surfactant) to the system, it lowers the interfacial tension, fluidizes the hydrocarbon region of the interfacial film, and decreases the bending stress of the interface (Eccleston, 1992). In the case of self-emulsifying sys-
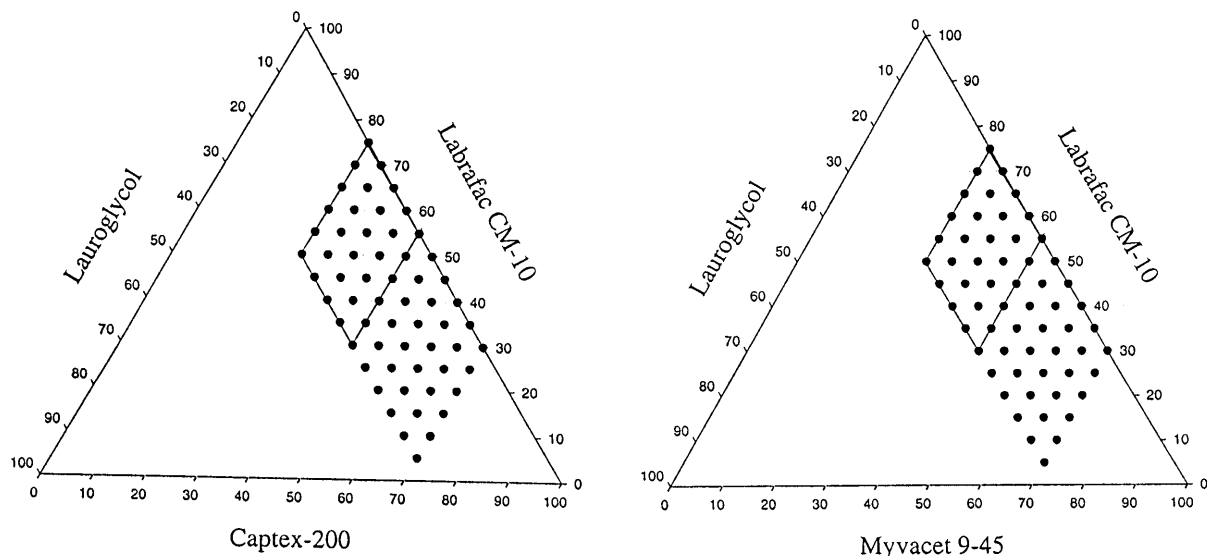

Fig. 2. Pseudo-ternary phase diagrams indicating the efficient self-emulsification region. (Key: The region of efficient self-emulsification is bound by the solid line; and the filled circles represent the compositions which were evaluated.)

Table 4
Effect of cosurfactant level on the emulsion droplet size distribution

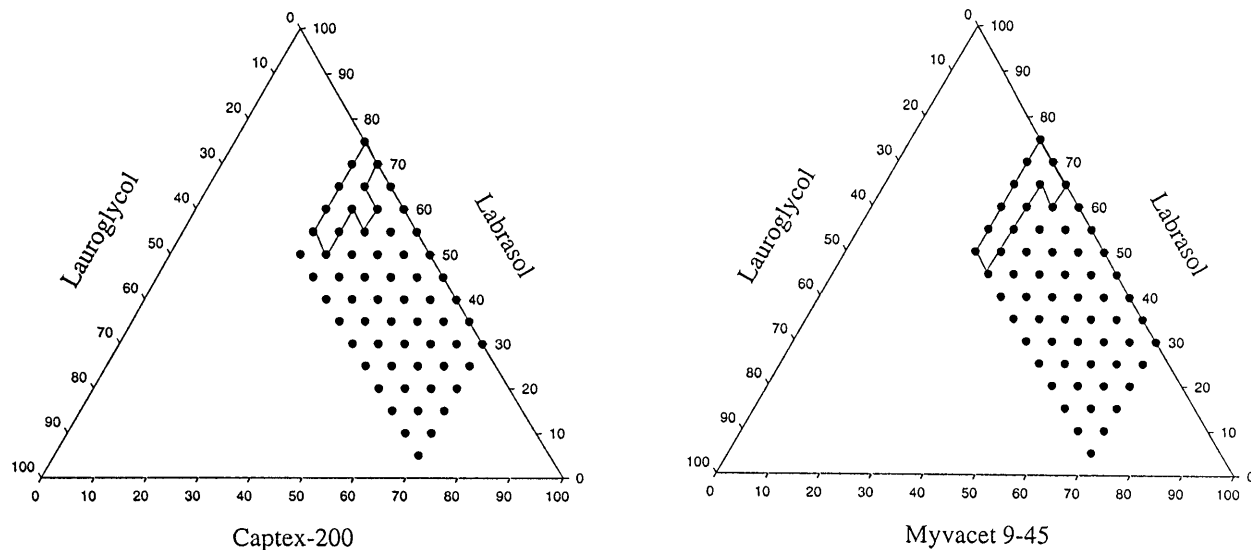| SEDDS composition (Myvacet 9-45/Labrafac/Lauroglycol) (%w/w)	Droplet size (m)			SEDDS composition (Captex-200/Labrafac/Lauroglycol) (%w/w)	Droplet size (m)		
	Mean	D(0.9)	D(0.1)		Mean	D(0.9)	D(0.1)
50:50:0	21.9	49.7	2.7	50:50:0	14.9	33.1	2.9
50:45:5	5.3	8.6	2.7	50:45:5	16.9	31.8	2.9
50:40:10	6.2	11.5	2.9	50:40:10	14.8	31.7	3.1
50:35:15	7.1	12.2	3.0	50:35:15	18.1	35.1	3.3
50:30:20	9.6	23.5	3.2	50:30:20	7.8	19.8	2.9
50:25:25	12.3	30.7	3.4	50:25:25	10.4	25.9	3.0

Fig. 3. Pseudo-ternary phase diagrams indicating the efficient self-emulsification region. (Key: The region of efficient self-emulsification is bound by the solid line; and the filled circles represent the compositions which were evaluated.)

tems consisting of Myvacet 9-45, Labrafac CM-10 and lauroglycol, a decrease in MEDD was observed with an increase in cosurfactant concentration from 0 to 10%, after which the MEDD was slightly increased. Similar observations were made when Myvacet 9-45 was replaced with Captex-200 (Table 4). Gao et al. (1998) have reported similar observations with the microemulsion systems containing Captex-355, Cremophor-EL, Trascutol and saline, where an increase in cosurfactant concentration increased the droplet size. However, larger MEDD was observed with the systems containing Labrasol (Table 5). Furthermore, the decrease in droplet size was not significant with the increase in cosurfactant concentration. In fact, the systems containing Captex-200, Labrasol and lauroglycol exhibited an increase in MEDD with an increase in cosurfactant concentration. These observations may indicate instability of the interfacial film provided by the systems containing Labrasol. The droplet size analysis indicated that the smaller MEDD could be obtained with the systems containing Myvacet 9-45, Labrafac CM-10 and lauroglycol (5–15%). Based on this information, an optimized formulation was developed (Table 2) and its bioavailability was compared with a powder formulation.

3.5. Bioavailability studies

The plasma profiles of CoQ_{10} in dogs following oral administration of powder filled capsules and self-emulsifying formulation were compared. The powder formulation contained 1% sodium lauryl sulfate as a wetting agent. Based on the in vitro self-emulsification properties, the formulation containing Myvacet 9-45, Labrasol and lauroglycol was selected for bioavailability studies. The
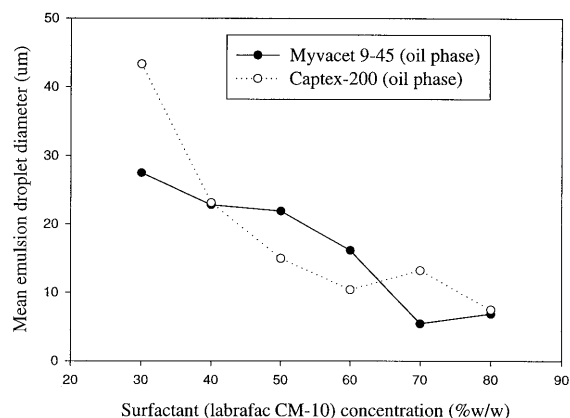

Fig. 4. Effect of surfactant (labrafac CM-10) concentration on mean emulsion droplet diameter.

Table 5
Effect of cosurfactant level on the emulsion droplet size distribution

SEDDS composition (Myvacet 9-45/Labrasol/Lauroglycol) (%w/w)	Droplet size (m)			SEDDS composition (Captex-200/Labrasol/Lauroglycol) (%w/w)	Droplet size (m)		
	Mean	D(0.9)	D(0.1)		Mean	D(0.9)	D(0.1)
50:50:0	29.4	64.4	4.8	50:50:0	13.4	28.7	2.5
50:45:5	28.5	72.5	3.8	50:45:5	23.8	44.8	4.0
50:40:10	20.4	43.2	3.3	50:40:10	23.0	39.3	5.1
50:35:15	26.5	62.6	4.0	50:35:15	27.5	49.8	6.0
50:30:20	26.9	64.7	3.1	50:30:20	23.8	42.2	5.0
50:25:25	29.5	69.3	4.5	50:25:25	17.8	31.3	4.1
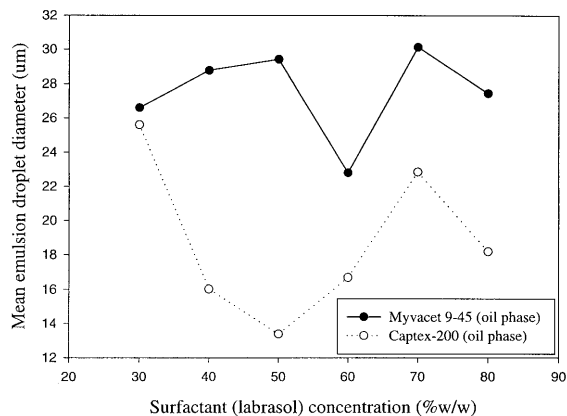
Fig. 5. Effect of surfactant (labrasol) concentration on mean emulsion droplet diameter.

Table 6
Pharmacokinetic parameters of SEDDS and powder formulation of CoQ_{10}

Parameter	SEDDS formulation I (Mean $\pm$ SD)	Powder formulation II (Mean $\pm$ SD)
AUC ($g.ml^{-1}$ h)	61.29 ± 14.1	27.41 ± 7.6
C_{max} (g/ml)	1.39 ± 0.4	0.61 ± 0.13
T_{max} (g/ml)	6.2 ± 1.8	5.8 ± 1.2

powder formulation. No significant difference was observed between T_{max} values ($p < 0.05$).

4. Discussion

Lipid based formulations including self-emulsifying formulations offer the potential for enhancing the absorption of poorly soluble and/or poorly permeable compounds. In addition to several patents (Hauer et al., 1994; Lacy and Embleton, 1997; Cho et al., 1998; Al-Razzak et al., 1999), there are a few commercial examples of

plasma concentration vs time profiles are presented in Fig. 6 and the pharmacokinetic parameters are given in Table 6. The absorption of CoQ_{10} from the self-emulsifying formulation resulted in a two-fold increase in bioavailability (as indicated by AUC and C_{max} values) compared with the
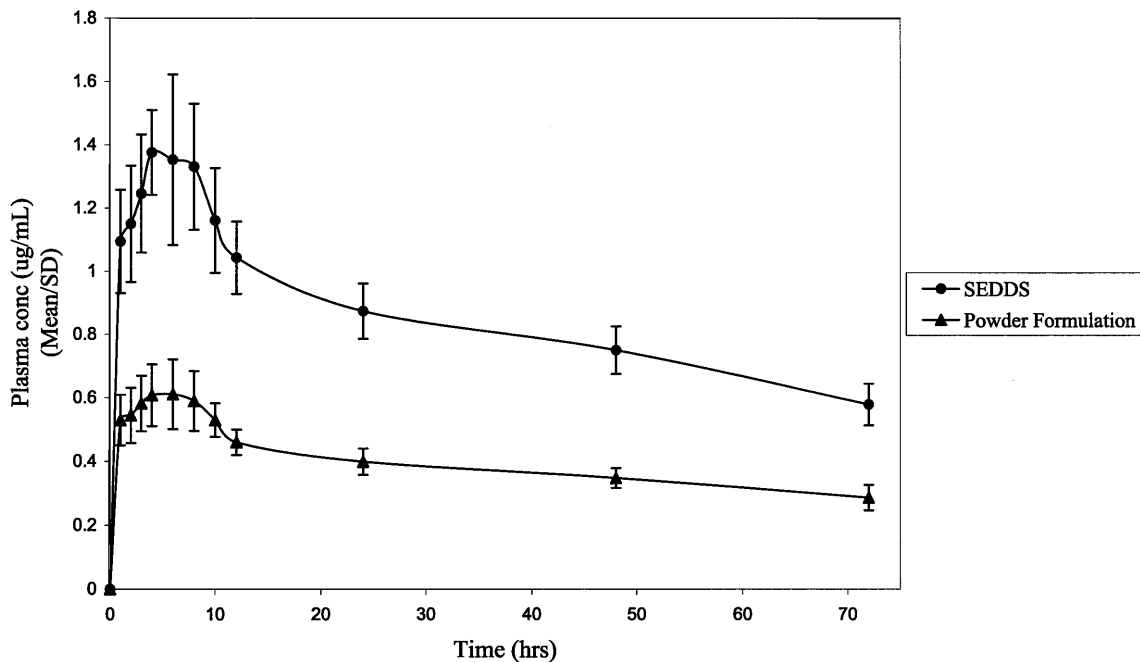

Fig. 6. Plasma profiles of SEDDS and powder formulation in dogs.

these formulations, which include cyclosporine, ritonavir saquinavir and amprenavir (Roman, 1999). However, there exist a few limitations associated with these formulations, including stability, manufacturing methods, interaction of the fill with the gelatin shell, and limited solubility of some drugs in lipid solvents (Wilson and Mahony, 1997). 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 our studies, crystallization of CoQ_{10} was observed at lower temperatures (5°C). With formulations containing higher levels of surfactant (> 70%), crystallization occurred even when stored at room temperature. Some studies have reported the use of solvents such as alcohol, isopropyl alcohol, propylene glycol, and PEG 400–600 to a limited extent in the formulation to increase the solubility limit of the active component (Hauer et al., 1994; Cho et al., 1998; Al-Razzak et al., 1999). In the present investigations, dissolution studies for these formulations could not be carried out, as CoQ_{10} is practically insoluble even in the presence of 5% sodium lauryl sulphate in water.

Surfactants are known to increase the permeability by disturbing the cell membrane (Swenson and Curatolo, 1992). The main rate-limiting barrier for the drug absorption/diffusion is the single layer of intestinal epithelial cells that covers the luminal surface of the intestinal wall. In addition, the pre-epithelial, unstirred, aqueous layer presents a barrier to hinder the poorly soluble drugs from reaching the absorption site (Jackson, 1987; Arthursson and Karlsson, 1991). For the majority of drugs, absorption occurs via passive transcellular transport and the paracellular transport is limited due to the tight junctions between the cells (Jackson, 1987). Lindmark et al. (1995) have used the medium chain fatty acids (e.g. sodium caprate) to enhance the absorption of hydrophilic drugs by modifying the tight junctions. It was reported that the intestinal mucosa is frequently subjected to dietary induced damage (i.e. by bile

salts, fatty acids and monoglycerides) and that mechanisms have evolved for rapid repair (Humberstone and Charman, 1997). Surfactant monomers are capable of partitioning into the cell membrane where they can form polar defects in the lipid bilayer. At high surfactant concentrations in the cell membrane, surfactant–surfactant contact occurs, and the membrane can be dissolved into surfactant–membrane mixed micelles (Swenson and Curatolo, 1992). In general, surfactants which are too hydrophobic to be water-soluble, are poor enhancers, whereas surfactants that are very hydrophilic cannot partition into the hydrophobic environment of the lipid bilayer (Swenson and Curatolo, 1992). In agreement with these observations, Crison and Amidon (1999) have reported a trend in the improvement of the bioavailability of nifedipine in dogs using a high HLB surfactant (Labrasol, HLB 14) over that of a surfactant with a low HLB value (lauroglycol, HLB 4), even though both formulations appeared to solubilize the drug to the same extent. In this study, a five-fold increase in bioavailability with Labrasol and a three-fold increase with lauroglycol were observed compared to a powder formulation. However, no general correlation exists between the extent of absorption enhancement and the HLB value of the surfactant (Miyamoto et al., 1983).

Incorporation of emulsifiers in the oil-based formulation was reported to improve the oral absorption of CoQ_{10} (Kommuru et al., 1999). In addition, several studies have reported that the self-emulsifying formulations containing polyglycolyzed glycerides have improved the bioavailability of lipophilic compounds (Sheen et al., 1991; Shah et al., 1994, 1996; Crison and Amidon, 1999). 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 and subsequent lipolysis and formation of mixed micelles; (b) improved diffusion of the fine emulsion droplets/mixed micelles across the unstirred aqueous layer; (c) increased mucosal permeability due to surfactants, and (d) improved lymphatic absorption due to the long chain oil, Myvacet 9-45. It was reported that the long chain

oils promote lipoprotein synthesis and subsequent lymphatic absorption (Charman and Stella, 1991). Further, CoQ_{10} is a highly lipophilic compound and has good solubility in tri/di-glyceride oils. These factors, therefore, may contribute towards absorption via the lymphatic route. Our earlier findings are in agreement with the reported studies where no significant differences in bioavailability were observed between the solid dosage form and simple oil-based formulations of CoQ_{10} (Kommuru et al., 1999).

In conclusion, the present investigation illustrated the potential use of SEDDS for improving the delivery of lipophilic compounds such as CoQ_{10} by the oral route. Following oral administration, SEDDS provided a two-fold increase in the bioavailability compared to a powder formulation. For drugs that are poorly soluble and/or poorly permeable, a significant improvement in reproducibility and bioavailability might be achieved with SEDDS.

Acknowledgements

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