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ScienceDirect
International Journal of Pharmaceutics 351 (2008) 15–22
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Development of a self-emulsifying formulation that reduces the food effect for torcetrapib

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Received 10 April 2007; received in revised form 10 September 2007; accepted 11 September 2007
Available online 19 September 2007

Abstract

Torcetrapib is a highly lipophilic (*C*log *P* = 7.45) and water insoluble cholesteryl ester transfer protein (CETP) inhibitor developed for the treatment of atherosclerosis. Self-emulsifying drug delivery system (SEDDS) formulations have been developed to reduce the food effect observed in early clinical trials using medium chain triglyceride (MCT) softgels and to increase the dose per capsule. MCT/Triacetin/Polysorbate 80/Capmul MCM (20/30/20/30) (MTPC) increased fasted exposure and thus reduced the food effect from 5- to 3-fold in dogs at a dose of 90 mg. Self-emulsifying formulations also accelerated absorption and generally decreased variability. Use of the lipophilic, GRAS cosolvent triacetin allowed a 2-fold increase in the dose per capsule. For the three formulations evaluated in dogs that showed significant differences in absorption, emulsion droplet size did not appear to play a significant role. Absorption did increase with Cremophor RH40 content, and at 50% Cremophor RH40 there was no food effect (at 30 mg). High polar surfactant content also resulted in poor dose proportionality, while there was good dose proportionality for MTPC. Studies of in vitro lipolysis are being conducted to aid in understanding the in vitro/in vivo relationships for torcetrapib SEDDS absorption.

Keywords: Self-emulsifying drug delivery system; Particle size; Medium chain triglycerides; Oral bioavailability; Food effect

1. Introduction

The poor oral bioavailability of water insoluble, highly lipophilic drugs can often result in a large food effect, i.e. much higher exposures in the fed than fasted state, which can lead to greater sensitivity of the pharmacokinetic profile to the fat content of meals and the timing of food administration. A widely utilized approach for overcoming poor fasted state bioavailability of lipophilic drugs is to utilize solutions in lipid vehicles containing surfactants that constitute a self-emulsifying drug delivery system (SEDDS), to effect spontaneous emulsification upon contact of the oil with fluids in the G.I. tract. (Shah et al., 1994; Constantinides, 1995; Pouton, 2000; Garrigue et al., 2006). If microemulsions are formed, these are often referred to as self-microemulsifying drug delivery systems (SMEDDS). An optimal surfactant hydrophilic lipophilic balance (HLB) for emulsification was found to be around 10 (Shah et al., 1994; Charman et al., 1992), which can be most readily achieved using a combination of polar and non-polar surfactants. Polar surfactants with high HLB's have been utilized to enable microemulsion formation, while inclusion of a non-polar surfactant (HLB < 8) such as medium chain mono/diglycerides can also improve the miscibility with triglycerides. Cosolvents are often employed to increase drug solubility or to improve miscibility. These pre-concentrates can be administered in softgels, which release the oil upon disintegration of the capsule in the stomach.

Compared to the crude emulsion (Sandimmune®) (Mueller et al., 1994; Ritschel, 1996), a self-microemulsifying formulation of Cyclosporin A (Neoral®) was shown to enhance fasted state bioavailability, decrease the food effect, increase dose linearity and reduce variability in exposures. Decreasing the emulsion droplet size for Sandimmune® emulsions by homogenization increased the rate of absorption (Tarr and Yalkowsky, 1989). This was proposed to be the result of the increased surface area that facilitated digestion of the glycerides by intestinal lipases

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doi:10.1016/j.ijpharm.2007.09.015

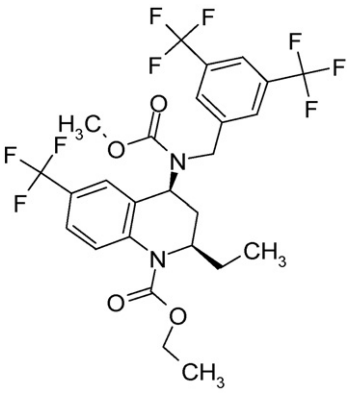

Fig. 1. Structure of Torcetrapib.

to form micelles, which elevated the solubility in the aqueous phase and thus promoted absorption. There is now considerable evidence that in vitro lipolysis to form solubilized species in the aqueous phase plays an important role in absorption from lipid formulations (MacGregor et al., 1997; Kossena et al., 2003; Porter et al., 2004; Grove et al., 2005).

Torcetrapib (structure shown in Fig. 1) is a highly lipophilic (*C*log *P* = 7.45), non-ionizable and very water insoluble molecule (solubility < 40 ng/mL), which is typical of the cholesteryl ester transfer protein (CETP) inhibitors due to the very lipophilic character of the natural substrates. Torcetrapib has been shown to elevate plasma HDL and thus may be beneficial for the treatment of atherosclerosis (Clark et al., 2004). Early clinical studies were conducted with Miglyol 812 (medium chain triglyceride, MCT) solutions in softgels that yielded a 20–30× food effect in man. The dose was also limited to 30 mg per 0.6 mL softgel due to the limited solubility in Miglyol 812 (65 mg/mL). The current study describes efforts to achieve a lower food effect and higher dose per unit through the use of self-emulsifying formulations.

2. Materials and methods

2.1. Materials

Miglyol 812 BP (medium chain (C8 and C10) triglycerides) was obtained from Condea Vista Inc. Olive oil and oleic acid were obtained from Croda Corp. Peceol (glyceryl monooleate), Maisine 35-1 (glycerol monolinoleate) and Labrafil M 1944 (polyglycolyzed glycerides of primarily oleic acid) were obtained from Gattefosse. Cremophor EL USP (polyoxyethylene castor oil) and Cremophor RH 40 USP (polyoxyethylene hydrogenated castor oil) were obtained from BASF. Polysorbate 80 NF (polyoxyethylene sorbitan monooleate) was obtained from Spectrum Laboratory Products. Capmul MCM (medium chain mono and diglycerides) was obtained from Abitec Corp. Propylene carbonate NF was obtained from Huntsman Corp. Triacetin USP (triacetyl glycerin) and Vitamin E TPGS NF (alpha tocopheryl polyethylene glycol 1000 succinate) were obtained from Eastman. Ethyl lactate was purchased from Purac. Air-filled lipophilic gelatin softgel shells were obtained from R.P. Scherer Corp. Hard gelatin capsules were obtained from Capsugel. Acetonitrile and 2-propanol were HPLC grade and phosphoric acid was reagent grade.

2.2. Equilibrium solubility measurements

Solubilities in excipients and in formulations were determined by adding an excess of compound to the medium in question. The mixture was agitated by rotation for at least 2 days at ambient temperature until the concentration in solution had reached an equilibrium as judged by similar measurements for consecutive time points.

The concentrations of drug in each vehicle were assayed at intervals by dilution of aliquots into acetonitrile and gradient HPLC analysis on a Waters Symmetry C-8 column (3.9 mm × 150 mm, 5 μ) at 30 °C at a flow rate of 1 mL/min. The mobile phase program was a 25 min gradient from 100% A to 50% A/50% B (A = 400/300/300/0.8 v/v/v/v, H_2O/acetonitrile/2-propanol/phosphoric acid and B = 2-propanol), followed by a 5 min hold at this condition and a 10 min gradient to the initial condition. The detection method was UV absorbance at 210 nm.

2.3. Emulsion droplet size analysis

Emulsions were prepared by mixing the pre-concentrate and water in a ratio of 1:100 by five times gentle inversion. Emulsions were examined by visual inspection and by using an optical microscope, using a polarizing filter to check for the appearance of crystals. Measurement of sub-micron droplet size was performed using a dynamic light scattering particle size analyzer (90 Plus, Brookhaven Instruments, Inc.). The formulation was filtered through a 0.2 μ Acrodisc PTFE syringe filter and then diluted 1:100 into filtered HPLC-grade water at a temperature of 37 °C. The resulting mixture was gently inverted five times to prepare the emulsion. Each emulsion sample was then analyzed at 37 °C. The droplet size populations were calculated as the average of the three measurements of 3 min duration by intensity weighting using the multi-modal distribution algorithm. The data are expressed as the mean of the distribution.

2.4. Preparation of formulations and softgels

The desired excipients were added to a glass vessel. Semi-solid excipients such as Capmul MCM were melted and mixed well prior to sampling and addition. After stirring to yield a homogeneous mixture, torcetrapib in the desired amount was then added, and the resulting mixture was stirred at ambient temperature, with scraping of vessel walls as needed, until a solution was obtained. The solution was filtered through a 70 μ glass fiber filter to remove gross particulates.

Softgels were manufactured on a rotary-die machine from selected fills by encapsulation using a shell prepared from gelatin, glycerin, and water with coconut oil/lecithin as lubricant.

2.5. Stability studies on encapsulated SEDDS

The fills prepared as described were transferred into hydrophobic softgel shells and heat sealed, or softgels were manufactured by machine. The capsules were placed on stability at 5 °C/75% RH, 30 °C/60% RH and 40 °C/75% RH in sealed HPDE bottles with CR caps. The fills were assayed at intervals by dilution into acetonitrile and gradient HPLC analysis conducted as described under Equilibrium Solubility Measurements. Disintegration times were measured according to USP < 701 > (15 min in 900 mL of water with disks at 37 °C).

2.6. Pharmacokinetic studies in dogs

Formulations were prepared as described above and then placed in #00 hard gelatin capsules. Male Beagle dogs ($n = 6$) between the ages of 2–5 and weighing 6–14 kg were dosed with capsules followed by 50 mL of water. In some cases there was emesis and therefore the number of animals was less than 6. Dogs were also dosed with 30 mg Miglyol 812 softgels. A crystalline drug suspension was prepared in a mortar and pestle using 0.1% Polysorbate 80/0.5% methyl cellulose (different set of dogs used for this formulation in the fasted state). The dogs were either fasted or fed just prior to dosing with a high fat meal of 14 g of dry dog food and 8 gm olive oil. The same dogs were used for all formulations, with the exception of 1 or 2 different animals in some instances. Blood samples were obtained from the jugular vein of each dog at 0, 0.5, 1, 2, 3, 4, 6, 8 and 12 h and analyzed by acidifying the plasma, solid phase extraction, and analysis by LC/MS/MS with a lower limit of quantitation of 25 ng/mL. Area under the curve (AUC), C_{max}, the maximum concentration of drug measured in the plasma, and T_{max}, the time in hours it took to reach C_{max}, were calculated from the plasma level results. All in vivo methods underwent veterinary review and approval by the Institutional Animal Use Committee.

AUC and C_{max} data were collected in a randomized block design, where the blocks were dogs and the treatments were formulations. Analysis of variance on the logarithmically transformed data was used to infer formulation effects, and post hoc pairwise tests using the Tukey's multiple comparison method were performed to group similar formulations. Significance was determined at the 5% level ($p < 0.05$). Summary results in tables are shown as the mean ± standard deviation (S.D.). Note that the reported standard deviations include subject-to-subject variability.

3. Results and discussion

3.1. Formulation development

The results in Table 1 show that the solubilities of torcetrapib in medium chain triglyceride Miglyol 812 and mono/diglyceride (ca. 80–90% monoglyceride) Capmul MCM are about 4× higher than in the long chain triglyceride olive oil and monoglyceride Maisine 35-1. The higher solubility of compounds in medium than long chain glycerides has been proposed to arise from the higher ester bond content per gram of the medium chain glycerides (Anderson and Marra, 1999; Cao et al., 2004). Therefore, medium chain glycerides were employed for further formulation development.

Table 1
Equilibrium solubility data for torcetrapib

Vehicle	HLB	Solubility (mg/mL)
Water		<0.00004
Oleic acid		8.5
Maisine 35-1	4	9
Peceol	3	10
Olive oil		17
Cremophor EL	13	20
Polysorbate 80	15	23
Labrafil M 1944	4	26
Capmul MCM	6	41
Miglyol 812		65
Propylene carbonate		227
Triacetin		235
Ethyl lactate		400

A cosolvent was also needed to improve solubility to permit the desired dose to be delivered in a softgel capsule. A lipophilic, non-volatile cosolvent is less likely to migrate to the shell than solvents such as ethanol and is also more likely to be retained by the oil phase upon dilution with aqueous media, thus avoiding precipitation (Constantinides, 1995; Pouton, 2000). Lipophilic cosolvents such as triacetin and propylene carbonate provide 4× higher solubility than in Miglyol 812 and solubility was even higher in ethyl lactate. Solubility was poor in polar solvents such as propylene glycol. Nearly all of the formulations contained Miglyol 812 as the triglyceride, a lipophilic cosolvent to enhance solubility and a combination of polar and non-polar surfactants to provide optimal emulsification and miscibility.

Microscopic examination of 1:100 oil:water emulsions was used as an initial screen. Only formulations that provided emulsions with droplet sizes <5 μ were selected for further study (Constantinides, 1995; Shah et al., 1994). Dynamic light scattering was utilized to characterize the sub-micron particle size distribution.

Properties of selected oil pre-concentrates and the corresponding 1:100 O/W emulsions are shown in Table 2. Emulsion droplet size distributions are given in Table 3. A solubility of ca. 140 mg/mL would readily allow a formulation concentration of 100 mg/mL and thus a dose of 60 mg in a 0.6 mL softgel. As the levels of cosolvent were increased, solubilities increased as well, but in general emulsion droplet size also increased since less surfactant could be employed. Solubilities for self-microemulsifying formulations often permitted only a 50 mg/mL fill (e.g. #1, 2, and 11). Use of propylene carbonate and triacetin as cosolvents allowed solubilities sufficient in some cases for a 100 mg/mL self-emulsifying fill (e.g. formulation #5, 6, 8 and 10). Use of propylene carbonate as a solvent (#5 and 6) allowed a 100 mg/mL self-microemulsifying fill, due to an apparent improvement in emulsification efficiency when propylene carbonate is used as a cosolvent instead of triacetin. Higher levels of surfactants were required to yield self-

Table 2
Properties of oil preconcentate and emulsions

Form.	Composition[a] (% v/v)				Fill properties		Mean emulsion droplet size (nm)
	Miglyol	Co-solvent	High HLB	Low HLB	Solubility (mg/mL)	Solidification at 5 °C[b]	
3	20	20 PC	20 TPGS	40 Labrafil	114	N	22
6	20	20 PC	20 TPGS	40 Capmul	145	N	79
10	10	40 Tri	20 TPGS	30 Labrafil	142	Y	441
1	20	15 Tri	50 poly 80	15 Capmul	64	N	20
5	20	20 PC	20 poly 80	40 Capmul	142	N	45
8	20	30 Tri	20 poly 80	30 Capmul	141	N	257
2	20	10 Tri	50 Cremophor	20 Capmul	67	Y[c]	22
11	17	13 Tri	39 Cremophor	31 Capmul	77	NT	27
4	0	28 Tri	30 Cremophor	42 Capmul	108	NT	32
7	20	30 Tri	35 Cremophor	15 Capmul	122	Y	245
9	11	50 EL	29 Cremophor	10 Capmul	203	NT	294

[a] PC: propylene carbonate; Tri: triacetin; EL: ethyl lactate; See Table 3 for other abbreviations.

[b] NT: not tested.

[c] Solidified at ambient temperature.

microemulsifying formulations (<100 nm droplet size) when triacetin was used as the cosolvent (#1, 2, 4, 11). Cosolvents often act as cosurfactants as well as solvents (Pouton, 1997). Propylene carbonate is far less viscous than triacetin and thus may be better able to promote emulsification via a process described by Pouton as "diffusion and stranding". The high solubility in ethyl lactate permits a 150 mg/mL fill to be prepared (e.g. #9), which would support a 90 mg dose per capsule.

Emulsions formed from formulation #2 are transparent and have a monomodal droplet distribution (Table 3). Solidification of the formulation during storage at 5 °C could occur when Cremophor RH40 was employed (Table 2); when 50% Cremophor RH40 was used (#2), solidification occurred upon standing at ambient temperature within a week, even in the absence of drug.

All of the emulsions prepared from these formulations exhibited good physical stability, i.e. there was no sign of crystallization or change in particle size based on microscopic examination after standing overnight at ambient temperature. Considering its very poor aqueous solubility, torcetrapib presumably remains almost entirely in the oil phase after emulsification.

3.2. Stability of capsules and softgels

Hand-filled softgel capsules containing pre-concentrates #3, 5, 6, and 8 were stored for 6 weeks at 5 °C/75% RH, 30 °C/60% RH and 40 °C/75% RH. There was no change in potency by HPLC and no impurity formed ≥ 0.1% peak area vs. parent for any formulation investigated. There was no sign of crystallization in the fill under any condition based on microscopic examination. There was also no indication of seal leakage. Disintegration times in water at 37 °C were less than 15 min after 6 weeks storage for #5, 6 and 8. Upon capsule disintegration the formulations rapidly emulsified in the USP disintegration apparatus based on visual observation and there was no indication of any gel formation that would hinder release. Softgels manufactured from formulation #8 were chemically and physically stable for 9 months under accelerated conditions.

Table 3
Dynamic light scattering analysis of torcetrapib 1:100 oil/water emulsions

Form.	Pre-concentrate composition[a] (% v/v)	Droplet size distribution (nm)[b]			
		Mean	Peak 1	Peak 2	Peak 3
1	Miglyol/Triacetin/Poly 80/Capmul (20/15/50/15)	20	13	64	(220)
2	Miglyol/Triacetin/Cremophor/Capmul (20/10/50/20)	22	22		
3	Miglyol/PC/TPGS/Labrafil (20/20/20/40)	22	17	38	(197)
4	Triacetin/Cremophor/Capmul (28/30/42)	32	26	(116)	
5	Miglyol/PC/Poly 80/Capmul (20/20/20/40)	45	33	217	
6	Miglyol/PC/TPGS/Capmul (20/20/20/40)	79	22	73	349
7	Miglyol/Triacetin/Cremophor/Capmul (20/30/35/15)	245	245		
8	Miglyol/Triacetin/Poly80/Capmul (20/30/20/30)	257	257		
9	Miglyol/Ethyl lactate/Cremophor/Capmul MCM (11/50/29/10)	294	324		
10	Miglyol/Triacetin/TPGS/Labrafil (10/40/20/30)	441	259	537	
11	Miglyol/Triacetin/Cremophor/Capmul (17/13/39/31)	27	27		

[a] Miglyol: Miglyol 812; Poly 80: Polysorbate 80; Cremophor: Cremophor RH40; PC: propylene carbonate; Et Lact: ethyl lactate; TPGS: Vitamin E TPGS; Labrafil: Labrafil M 1944; Capmul: Capmul MCM.

[b] Parentheses indicate trace levels (<5% of volume).

Table 4
Pharmacokinetic results for 90 mg torcetrapib formulations in crossover study in fasted dogs

#	Composition (v/v)[a]				Solubility (mg/mL)	Concentration (mg/mL)	Dog PK results (n = 5-6)			Mean Droplet Size (nm)
	Miglyol	Solvent	High HLB surfactant	Low HLB surfactant			AUC $_{0–12h}$ (μg h/mL)	C_{max} (μg/mL)	T_{max} (h)	
1	20	Triacetin 15	Poly 80 50	Capmul 15	64	50	2.7 ± 1.5	0.86 ± 0.31	1.3	20
2	20	Triacetin 10	Cremophor 50	Capmul 20	67	50	4.6 ± 1.4	1.35 ± 0.26	1.7	22
3	20	PC 20	TPGS 20	Labrafil 40	114	80	3.4 ± 1.3	1.2 ± 0.41	1.2	22
4	0	Triacetin 28	Cremophor 30	Capmul 42	108	75	1.9 ± 1.7	0.44 ± 0.26	1.3	32
5	20	PC 20	Poly 80 20	Capmul 40	142	100	2.3 ± 0.5	0.73 ± 0.16	1.8	45
6	20	PC 20	TPGS 20	Capmul 40	145	100	2.7 ± 0.9	0.67 ± 0.17	1.2	79
7	20	Triacetin 30	Cremophor 35	Capmul 15	122	100	2.8 ± 1.2	1.0 ± 0.4	1.0	245
8	20	Triacetin 30	Poly 80 20	Capmul 30	141	100	2.7 ± 0.7	0.97 ± 0.36	1.2	257
9	11	Et Lact 50	Cremophor 29	Capmul 10	203	150	1.5 ± 0.7	0.54 ± 0.17	0.9	294
10	10	Triacetin 40	TPGS 20	Labrafil 30	142	100	2.9 ± 0.8	1.1 ± 0.2	1.0	441

[a] See Table 3 for abbreviations.

3.3. In vivo evaluation

Formulations of interest due to solubility and emulsification properties were evaluated in a crossover study in fasted dogs. The formulations were administered in hard gelatin capsules with 50 mL of water. The results in Table 4 are listed in order of increasing emulsion droplet size, and show little correlation of AUC or C_{max} with emulsion droplet size. However, most of the formulations did not show significant differences in exposure. Formulation #4 exhibited low exposures despite its small droplet size. Formulation #2 exhibited exposures that were significantly higher ($p < 0.05$) than those of #4 despite similar droplet sizes, but it also performed better than #9, which had a much larger mean droplet size. The absence of any apparent relationship between exposure and emulsion droplet size, even for formulations with the same polar surfactant, is further illustrated in Fig. 2. It is possible that variation of the volumes of formulations administered, required in order to keep the dose constant at 90 mg, might also play some role. However, the 50% greater volume dosed for formulation #2 (1.8 mL) than for #4 (1.2 mL) is much less likely to have been a factor in the differences in absorption compared with the 300% greater volume dosed for #2 than for #9 (0.6 mL). There is more convincing evidence that AUC depends on the level of Cremophor RH40 in the formulation (see Figs. 3 and 4a). This relationship is not observed for formulations containing Polysorbate 80 (only one concentration of Vitamin E TPGS was employed). Cremophor RH40 has been reported to be a potent inhibitor of lipolysis (MacGregor et al., 1997). This may be particularly beneficial in the case of medium chain glyceride formulations, since extensive digestion or decreasing the lipid load was found to lead to precipitation of highly lipophilic halofantrine (Porter et al., 2004). As suggested by a recent study on Cremophor EL formulations (Sek et al., 2006), Cremophor RH40 or its long chain digestion products could also solubilize drug in mixed micelles.

Formulation #2 performed far better than any other formulation at a torcetrapib dose of 30 mg in terms of fasted exposure (e.g. ca. 4-fold better than MTPC), and there was no food effect for #2 at a dose of 30 mg (Table 5). Interestingly, the exposures were the same in the fasted state for 30 and 90 mg of formulation #2. Formulations #1 and especially #2 show less than dose proportional increases in exposure, while #8 shows better dose proportionality. The 3-fold difference in volume as the dose is increased (without any change in the formulation composition) appears to have had a substantial effect on absorption for the formulations with 50% polar surfactant. This may be due to poor digestion of large volumes of surfactant, which would reduce availability of solubilizing long chain glycerides or may, alter-

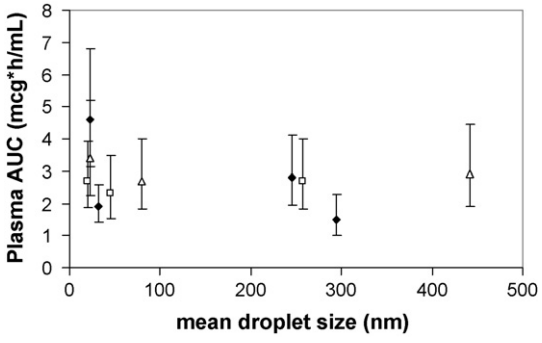

Fig. 2. Plasma AUC in dogs (90 mg dose) versus mean emulsion droplet size. Polar surfactant identity: (♦) Cremophor RH40; (□) Polysorbate 80, (△) Vitamin E TPGS. Error bars are 95% confidence intervals.

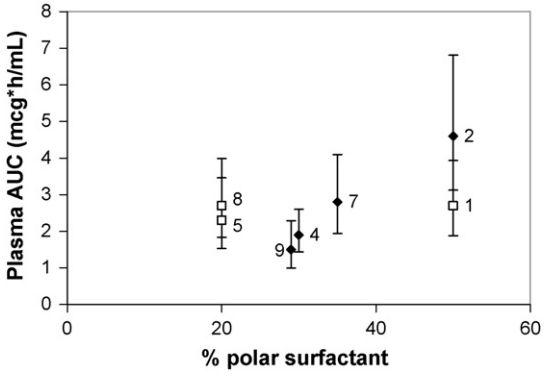

Fig. 3. Relationship between AUC in dogs (90 mg dose) and the percent of polar surfactant. Data points are labeled with formulation numbers (see Table 3 for the compositions). Polar surfactant identity: (♦) Cremophor RH40; (□) Polysorbate 80. Error bars are 95% confidence intervals.

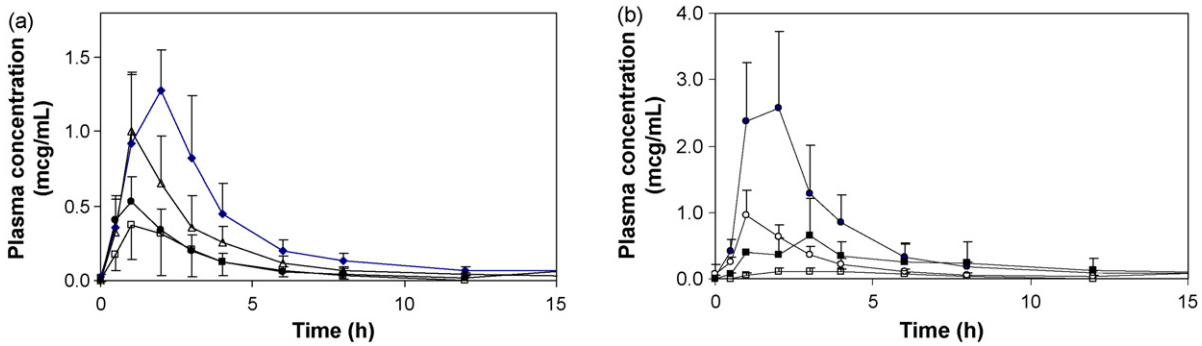

Fig. 4. Dog Plasma PK profiles for lipid formulations of 90 mg torcetrapib (a) ♦ 2; □ 4; △ 7; ● 9; (b) ● 8 fed; ◯ 8 fasted; ■ Miglyol fed; □ Miglyol fasted. Error bars are standard deviations.

natively, lead to sequestration in surfactant micelles (as opposed to mixed micelles). Micellar solubilization of Cyclosporin A by Cremophor EL has been found to sequester the drug in vitro (Chiu et al., 2003), and bile salt levels above the CMC have been found to hinder in vivo absorption of lipophilic drugs (Poelma et al., 1990). Formulation #7 that contains 35% Cremophor yielded a higher AUC when it was dosed at half the concentration, which could be due to better solubilization with a higher excess of excipient over drug.

Formulation #4 has poorer than expected (for a microemulsion) fasted and fed state exposures at a dose of 90 mg and exhibits a food effect of ca. 4. This formulation also lacks any Miglyol 812, while formulation #2 has 20% Miglyol 812. Formulation #9, the only formulation that could provide a 90 mg dose per softgel, has 11% medium chain triglyceride content and poor exposures (Table 4). High exposures were obtained for formulation #10, which has 10% Miglyol 812, but the AUC values are not significantly different from those of #9. Further study is needed with other formulations to assess the relative importance of the medium chain triglyceride level to bioavailability.

Miglyol 812 softgels were found to have significantly lower fasted exposures than any of the SEDDS formulations (Table 5 and Fig. 4b). Thus, a high food effect (5×) was observed for the Miglyol formulation in dogs, and torcetrapib is absorbed more slowly (longer Tmax) than for the self-emulsifying systems. The well absorbed SEDDS formulations generally exhibited consid-

Table 5
Food effects of torcetrapib formulations in dogs (n = 4–6)

Formulation	Fed state	Concentration (mg/mL)	Dose (mg)	PK results			Food effect
				AUC 0–12 h (μg h/mL)	C_{max} (μg/mL)	T_{max} (h)	
Miglyol 812 soft gels	Fasted	50	90	0.6 ± 0.3	0.2 ± 0.14	3.7	
	Fed	50	90	3.0 ± 2.0	0.77 ± 0.48	2.0	5
Aqueous suspension[a]	Fasted	–	90	0.16 ± 0.14	0.04 ± 0.11	1.3	
	Fed	–	90	2.9 ± 1.3	0.98 ± 0.53	2.7	18
1	Fasted	50	90	2.7 ± 1.5	0.86 ± 0.31	1.3	
	Fasted	50	30	1.7 ± 0.3	0.64 ± 0.21	1.0	
	Fed	50	30	3.8 ± 1.2	1.6 ± 0.6	1.0	2.2
2	Fasted	50	90	4.6 ± 1.4	1.35 ± 0.26	1.7	
	Fasted	50	30	4.6 ± 2.0	1.32 ± 0.60	2.0	
	Fed	50	30	4.7 ± 1.1	1.94 ± 0.74	1.0	1.0
3	Fasted	80	90	3.4 ± 1.3	1.2 ± 0.41	1.2	
	Fed	80	90	9.3 ± 3.5	4.31 ± 1.89	1.0	2.7
4	Fasted	75	90	1.9 ± 1.7	0.44 ± 0.26	1.3	
	Fed	75	90	7.3 ± 1.3	1.8 ± 0.5	1.5	3.8
6	Fasted	100	90	2.7 ± 0.9	0.67 ± 0.17	1.2	
	Fed	100	90	9.6 ± 3.4	2.49 ± 1.30	1.4	3.6
7	Fasted	100	90	2.8 ± 1.2	1.0 ± 0.4	1.0	
	Fasted	50	90	4.0 ± 1.3	1.1 ± 0.4	1.5	
8 (MTPC)	Fasted	100	90	2.7 ± 0.7	0.97 ± 0.36	1.2	
	Fed	100	90	8.5 ± 3.6	2.7 ± 1.0	1.5	3.1
	Fasted	100	30	1.1 ± 0.5	0.37 ± 0.22	1.0	

[a] Different set of dogs.

erably less variability in both AUC and C_{max} than the MCT (Miglyol 812) formulation. Crystalline torcetrapib in an aqueous suspension exhibited extremely poor fasted exposures. At the same dose of 90 mg of torcetrapib, self-emulsifying formulations such as #3, 4, 6, and 8 have higher exposures in fasted dogs than the MCT formulation and thus food effects of ca. 2.5–4-fold. The fed exposures were ca. 2.5–3× lower for Miglyol 812 softgels than for these self-emulsifying formations, and were again more variable. The crystalline drug was unexpectedly absorbed to about the same extent as the Miglyol formulation in the fed state, suggesting that the high content (8 mL) of long chain triglyceride administered in the high fat meal may have dominated absorption in these cases where fasted state absorption was very poor. The long chain triglyceride may have dissolved some or all of the crystalline drug based on the solubility data (Table 1). It has also been demonstrated that, relative to medium chain glycerides, long chain glycerides can more effectively facilitate lymphatic absorption for highly lipophilic compounds in dogs (Khoo et al., 2003) and enhance aqueous solubilization after digestion (Porter et al., 2004; Kossena et al., 2003). However, solubilization after digestion could be also enhanced by the high lipid load from the olive oil.

Formulations #5, 6, 7, 8, and 10 all would readily allow a dose of 60 mg per capsule (i.e. 100 mg/mL) and had similar exposures in dogs. As indicated in Table 2, Formulations 7 and 10 had the disadvantage of solidifying during storage at 5 °C, which could be an issue if temperature cannot be controlled during shipment or storage. Formulation #8 utilizes triacetin as the cosolvent, while #5 and 6 contain propylene carbonate. Triacetin has US pharmaceutical precedence, albeit at low doses as a plasticizer in film coats, but it also has GRAS status and a favorable toxicology profile (Bisesi, 1994; Opdyke, 1978). Propylene carbonate lacks US pharmaceutical precedence and GRAS status, although it was used in a softgel formulation in Europe (Enprostil®). Formulation #8 (MTPC) was therefore selected for further characterization. Softgels were manufactured from MTPC and were shown to be chemically and physically stable for 12 weeks under accelerated conditions.

4. Conclusions

A self-emulsifying formulation (MTPC) was developed that provided considerably higher fasted exposures of the highly lipophilic drug ($\log P = 7.45$) torcetrapib in dogs at a dose of 90 mg than the Miglyol 812 formulation that was initially used in the clinic. Absorption was rapid, the food effect was reduced, and there was also good dose proportionality and much lower variability between animals. The dose per capsule was increased through the use of triacetin as a lipophilic cosolvent that has a favorable pharmaceutical acceptability.

The data overall showed little apparent correlation between emulsion droplet size in the submicron range and oral absorption in dogs, but differences in exposures were generally not large enough to be statistically significant. Three formulations did show significant differences in exposures, and these results were not consistent with a strong dependence on emulsion droplet size. However, there was an increase in absorption with increased Cremophor RH40 content. Possible explanations for this dependence include inhibition of lipolysis and solubilization of drug by Cremophor RH40 after digestion of the lipid components. The formulation containing 50% Cremophor RH40 also performed far better than any other formulation at a torcetrapib dose of 30 mg and showed no food effect at this dose. However, exposure increases were considerably less than dose proportional for formulations containing 50% polar surfactant, perhaps due to sequestering of drug by undigested surfactant. This is in contrast with the very good dose proportionality for MTPC, which contains only 20% Polysorbate 80. Studies of lipolysis of torcetrapib lipid formulations, including measurement of aqueous concentrations after lipolysis, are being conducted to investigate its role in the formulation trends observed in dogs.

Acknowledgements

Greg Steeno is thanked for statistical analysis of the in vivo data. Hans von Steiger is thanked for assistance with softgel manufacture. Steve Sutton is thanked for helpful discussions and preliminary PK data. Valuable insight was provided by Professor Christopher Porter of Monasch University.

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