GATTEFOSSÉ

Maisine® CC

A pharmaceutical oil for solubility and oral bioavailability enhancement

People make our name

ABBREVIATIONS

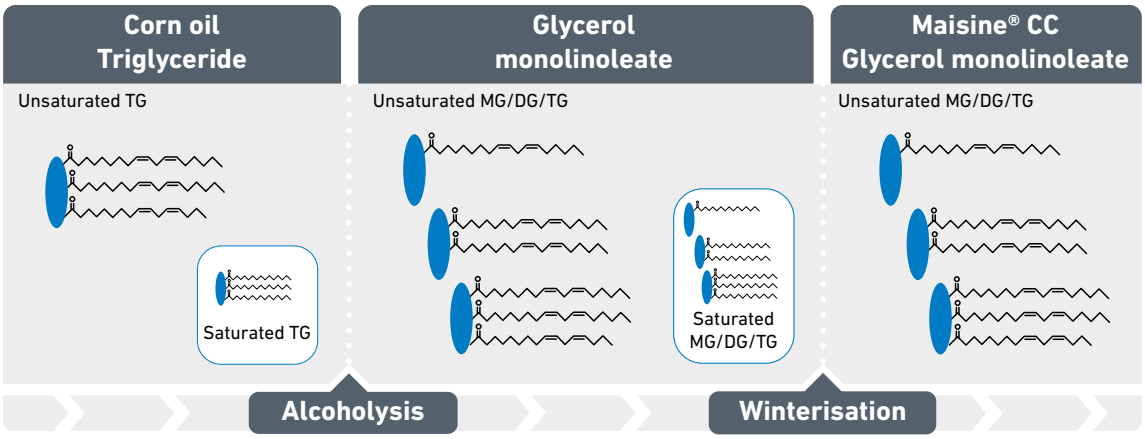
API: Active Pharmaceutical Ingredient; **AUC:** Area under the curve; **BCS:** Biopharmaceutics Classification System; **DMF:** Drug Master File; **FA:** Fatty acids; **FDA:** US Food & Drug Administration; **HLB:** Hydrophilic Lipophilic Balance; **INCI:** International Nomenclature of Cosmetic Ingredients; **LBF:** Lipid-Based Formulation; **LC:** Long chain; **LCT:** Long Chain Triglycerides; **MC:** Medium chain; **MCT:** Medium Chain Triglycerides; **MG:** Monoglycerides; **SCT:** Short Chain Triglycerides; **SEDDS:** Self Emulsifying Drug Delivery System; **SMEDDS:** Self Micro Emulsifying Drug Delivery System; **TG:** Triglycerides; **UNII:** Unique Ingredient Identifier

Contents

Product description

Maisine® CC is an oily vehicle used to enhance the solubility and oral bioavailability of lipophilic drugs.

It is a mixture of mono-, di- and triglycerides of oleic and linoleic acid ($C_{18:1}$/$C_{18:2}$) from vegetable origin. It is obtained by an alcoholysis reaction between glycerol and refined corn oil, followed by a winterization process to eliminate certain saturated mono-, di- and triglycerides.



The glyceride specifications for Maisine® CC conform to the glycerol (glyceryl) monolinoleate monograph:

- 32-52% of monoglycerides
- 40-55% of diglycerides
- 5-20% of triglycerides

Maisine® CC is an optimized grade of product due to the winterization process which ensures it is a limpid liquid at ambient temperature. Maisine® CC is a 'crystal clear' liquid.

Monograph specifications	Value
Aspect at ambient temperature	liquid
Color (Gardner scale)	≤ 8.0
Acid value	≤ 2.0 mg KOH / g
Peroxide value	≤ 12 meq O_2 / Kg
Iodine value	100 to 140 g I_2 / 100g
Water content	≤ 0.5%
Properties	**Value**
Surface tension	32.2 ± 0.1 mN / m
Viscosity at 20°C	120 mPa.s
HLB	1

Product functionality

Maisine® CC is a unique pharmaceutical oil recommended for use in oral lipid-based formulations (LBF) due to:

- Its high monoglyceride content which improves the solubilization of lipophilic drugs (log P>2)
- Its ability to maintain/increase drug solubility in post-digestive phases through mixed micelles
- Its long chain fatty acid ($C_{18:1}$/$C_{18:2}$) composition which favors the uptake of highly lipophilic drug (log P>5) into the lymphatic transport system

These features explain the performance benefits of Maisine® CC in LBF for oral bioavailability enhancement.

Reliable solubilizer of lipophilic APIs

Maisine® CC is derived from corn oil with a unique and highly reproducible composition in mono- , di- and triglycerides. The major advantage of Maisine® CC compared to triglyceride vegetable oils (i.e. soybean oil) is its higher capacity to solubilize drugs due to the presence of mono- and diglycerides.

The current literature shows that Maisine® is an oily vehicle routinely used in solubility screening when developing a LBF. Numerous solubility data of APIs in Maisine® are available.

Maisine® is an excellent solubilizer of lipophilic drugs with logP from 2 to 8 (Table 1).

Table 1: Comparative data of API solubility in Maisine® and soybean oil at 37°C (from Alskär *et al.*, 2015)

API	Log P	Solubility* in Maisine® (mg/g)	Solubility* in soybean oil (mg/g)
Halofantrine	8.2	71.2	52.8
Clofazimine	6.9	11.7	9.5
Clotrimazole	5.2	75.4	15.1
Danazol	4.9	14.7	3.9
Ethinylestradiol	4.9	22.1	13.4
Disulfiram	4.6	49.0	21.4
Indomethacin	4.2	13.0	2.0
Perphenazine	4.2	92.5	16.7
Tolfenamic acid	4.1	14.1	3.8
Saquinavir	3.9	>123	2.3
Felodipine	3.6	37.7	9.6
Progesterone	3.6	66.2	30.4
Diflunisal	3.1	31.6	7.9
Naproxen	2.8	19.5	5.5
Carbamazepine	2.7	30.0	1.4

** Experimentally determined equilibrium solubility*

Furthermore, when Maisine® is administered orally it is digested due to its lipidic nature. This digestion process plays an important role in maintaining drug solubility *in vivo* (Figure 1).

Maisine® droplets in the stomach are digested by lipase/colipase enzymes into smaller vesicles down to mixed micelles; then absorbed in the enterocyte.

Lipophilic drugs exhibiting good solubility in Maisine® are solubilized in the mixed micelles enabling enterocytic absorption.

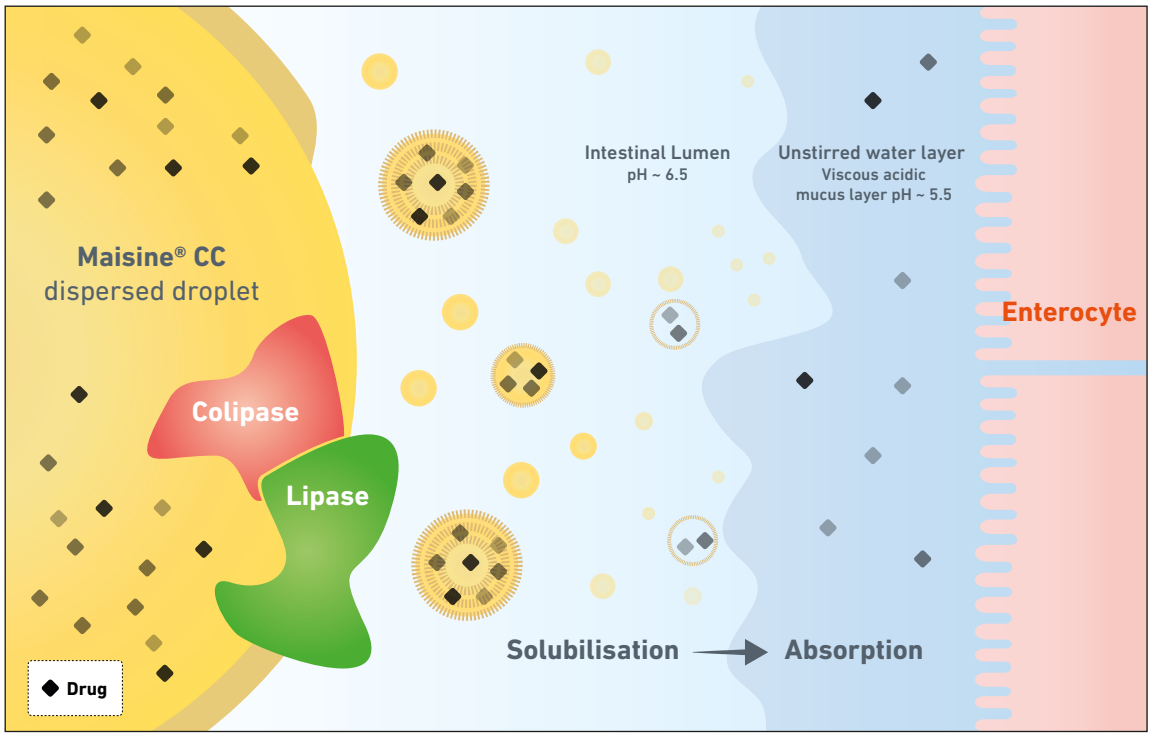


Figure 1: Maisine® digestion (adapted from Feeney *et al., 2016*)

Promotor of lymphatic absorption

The main fatty acid in Maisine® is linoleic acid ($C_{18:2}$). It is known that glycerides with unsaturated long chain fatty acid are absorbed via the lymphatic system.

Figure 2 shows that after digestion, triglycerides are transformed into monoglycerides and fatty acids, which are then absorbed into the enterocyte. Medium chain lipids, with fatty acid chain length below 12, diffuse across the enterocyte directly into the blood circulation. Long chain lipids, with fatty acid chain length equal to or above 12, are reassembled into triglycerides in the endoplasmic reticulum. Here they are combined with proteins to form chylomicrons. These vesicles are too large to access the blood capillary. As the interstitial lymph capillary allows larger molecules to penetrate, they are transferred to the lymph via a passive diffusion.

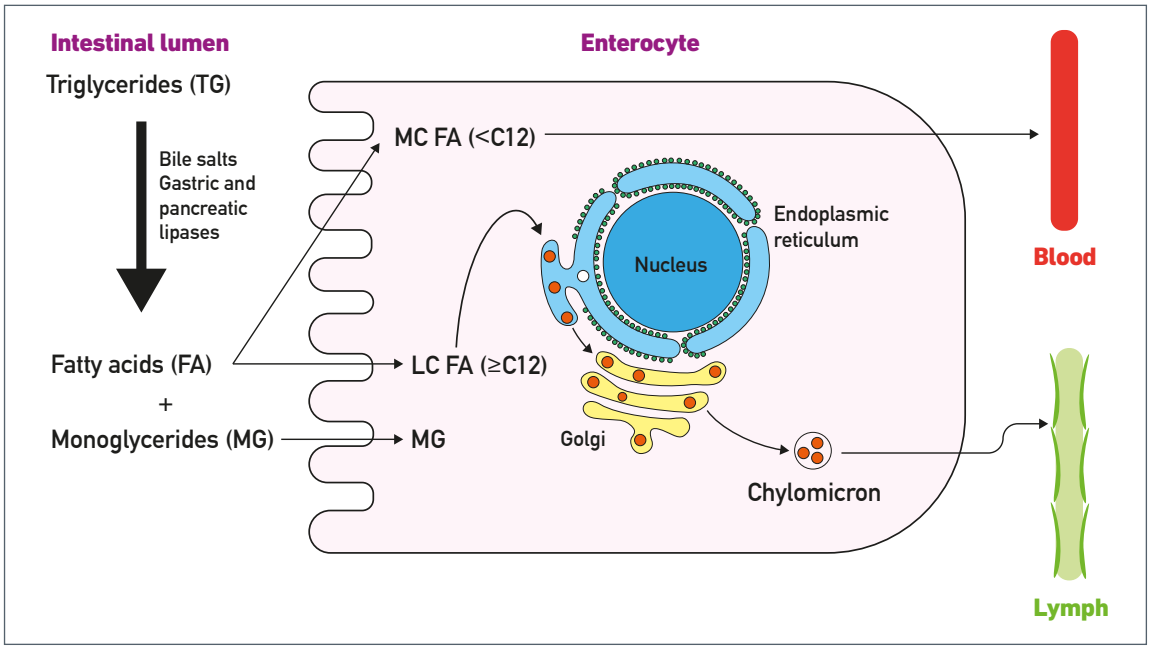


Figure 2: Lipid absorption into the enterocyte

The lymph pathway avoids the first-pass metabolism in the liver as it drains directly into the systemic circulation. The feasibility of specifically targeting the lymphatic transport system by using LCT-LBF is now being explored (El-Laithy *et al.*, 2015; Garg *et al.*, 2016; Trevaskis *et al.*, 2009, 2010, 2015) to treat cancer, metabolic, inflammatory and immune diseases.

This drug delivery route is restricted to highly **lipophilic drugs with a solubility in unsaturated long chain glycerides ($C_{18:1}$/$C_{18:2}$) above 50 mg/g.**

The ability of Maisine® to promote the lymphatic transport of lipophilic drugs has been demonstrated in several published *in vivo* studies with halofantrine and danazol. (See the Case studies section).

Oral bioavailability enhancer

Bioavailability enhancement is achieved when the excipients used in the LBF are able to provide effective solubilization of the drug in the dosage form and maintain the drug in a solubilized state *in vivo* during digestion and absorption.

In some cases bioavailability may also be impacted by lymphatic drug absorption which bypasses first pass metabolism in the liver. As explained before, Maisine® as a long chain glyceride promotes lymphatic uptake.

Some drug formulations are associated with variable bioavailability when administered with food (i.e. food effect). This is due to the physiological digestion of lipids in food and their ability to alter drug solubility. This can be a problem in drug development. It is known that Maisine®, due to its composition can mitigate food effect (See the Case studies section).

Most LBFs are multi-component systems which are carefully designed to provide and maintain drug solubility. There are numerous studies describing the use of Maisine® in LBFs which are associated with improved oral bioavailability (Table 2).

Table 2: *In vivo* studies using LBF containing Maisine® with improved oral bioavailability

Drug	Optimized LBF composition		Species	Reference
Atazanavir	Maisine® Transcutol®	46% 54%	Rat	Singh and Pai, 2014
Danazol	Maisine® Soybean oil Cremophor® EL Ethanol	30% 30% 30% 10%	Dog	Porter *et al.*, 2004
Ezetimibe	Maisine® Labrasol®	36% 64%	Rat	Bandhyopadhyay *et al.*, 2012
Halofantrine	Maisine® Soybean oil Cremophor® EL Ethanol	30% 30% 30% 10%	Dog	Khoo *et al.*, 2003
Indirubin	Maisine® Cremophor® EL Transcutol®	15% 40% 45%	Rat	Chen *et al.*, 2012
Lopinavir	Maisine® Tween 80 Transcutol®	30% 43% 27%	Rat	Garg *et al.*, 2016
Nelfinavir mesylate	Maisine® Tween 80 Transcutol®	20% 50% 30%	Rabbit	Kamboj and Rana, 2016
Simvastatin	Maisine® Plurol® oleique Labrasol® Transcutol®	12% 11% 75% 1%	Rat	Singla *et al.*, 2009
Vinpocetine	Maisine® Cremophor® EL Transcutol®	10% 50% 40%	Rabbit	Abuhrama *et al.*, 2010

Use of Maisine® CC in oral lipid-based formulations

Maisine® CC is an oily vehicle that can be formulated in LBF Type I, II and III (see Table 3).

Key benefits of Maisine® CC in LBF:

- **+ Unique composition in mono- and diglycerides of linoleic acid ($C_{18:2}$)**
- **+ Transparent liquid at room temperature**
- **+ Excellent solubilizing capacity for lipophilic drugs**
- **+ Digested *in vivo* forming mixed micelles**
- **+ Long chain unsaturated fatty acids absorbed via the lymphatic path**
- **+ Safety**
- **+ Precedence of use**
- **+ Compatibility with gelatin capsule**

More information can be found in our Formulation guideline:
Developing lipid-based formulations
for oral bioavailability enhancement.

Table 3: LBF classification and Maisine® CC recommendations (Pouton, 2006)

		Type I	Type II	Type IIIA	Type IIIB	Type IV
Composition	Oily vehicle: **Maisine® CC**	100%	40 - 80	40 – 80	<20	
	Water insoluble surfactants		20 - 60			0 - 20
	Water soluble surfactants			20 - 40	20 - 50	30 - 80
	Hydrophilic co-solvents			0 - 40	20 - 50	0 - 50
Particle size of the dispersion (nm)		Coarse	100 - 250	100 - 250	50 - 100	<50
Characteristics *in vitro*		Non-dispersing; requires digestion	SEDDS Turbid o/w dispersion	SEDDS/SMEDDS Almost clear dispersion	SMEDDS Clear dispersion	SNEDDS Oil free micellar solution
Possible advantages		GRAS status; simple; mitigate food-effect; induce lymphatic transport	Unlikely to lose solvent capacity on dispersion; digestion can help; mitigate food-effect; induce lymphatic transport	Digestion can help; mitigate food-effect; induce lymphatic transport	Drug absorption without digestion	Good solvent capacity for many poorly-soluble drugs
Possible disadvantages		Only for highly lipophilic drug	For highly lipophilic drugs	Possible loss of solvent capacity on dispersion *in vivo*	Likely loss of solvent capacity *in vivo*; less easily digested	Loss of solvent capacity *in vivo*; may not be digestible; no glycerides

Case studies

Cyclosporine A: the first historical success

Cyclosporine A is a hydrophobic peptide used to prevent graft rejection in organ and tissue transplantation. It is classified as BCS type IV – low soluble, low permeable (Czogalla, 2009).

The first registered dosage form (*Sandimmune*®) was designed as an oil-in-water emulsion preconcentrate. The original formulation contained corn oil as the oily phase with Labrafil® M 2125 CS (Table 4). This formulation showed a bile-dependent absorption profile and exhibited significant intra- and inter-individual variability. Thus, a new formulation (*Neoral*®) was launched 10 years later. **Neoral® is a microemulsion preconcentrate providing improved and more consistent bioavailability (Strickley, 2004)**. The major difference between Sandimmune® and Neoral® was the use of a surfactant and replacement of the triglyceride corn oil with the more powerful solubilizer corn oil mono-, di- and triglycerides (i.e. glyceryl monolinoleate).

Table 4: Cyclosporine A formulations (From Strickley, 2004)

Sandimmune® soft gelatin capsule	Neoral ® soft gelatin capsule
Cyclosporine A	Cyclosporine A
Ethanol	Ethanol
Corn oil	**Corn oil mono- di- triglycerides**
Glycerol	Propylene glycol
Labrafil® M 2125 CS	Polyoxyl 40 hydrogenated castor oil

Cinnarizine: Maisine® CC increases drug solubility during digestion

Cinnarizine is an antihistaminic drug, with a LogP of 5.8, poor water solubility, BCS Class II. The cinnarizine dose was 25 mg / 1 g capsule.

Solubility screening of drug with lipid-based excipients (Table 5) led to the development of an initial LBF containing Labrasol® ALF as water dispersible surfactant and Capryol™ 90 as water insoluble surfactant. This initial formulation was able to solubilize the entire dose when dispersed into 250 ml of water at 37°C (formulation F1). However, using the lipolysis assay for LBF, the formulation was shown to be unable to maintain drug in a solubilized state during digestion (Figure 3).

The formulation was optimized by the addition of Maisine® CC to enhance drug solubility through micellization (F2). The addition of 15% of Maisine® CC improved drug solubilization before (≈ 50% of the dose) and after *in vitro* digestion (up to 85% of the dose). The rationale is that cinnarizine is solubilized in mixed micelles formed by the digestion of glycerides in Maisine® and by the complexation of cinnarizine and fatty acids.

Table 5: Cinnarizine solubility in selected excipients of LBF

Formula	Excipient	Quantity % W/W	Drug solubility in excipient mg/mL
F1	Labrasol® ALF	90	28
	Capryol™ 90	10	38
F2	Labrasol® ALF	75	28
	Capryol™ 90	10	38
	Maisine® CC	15	19

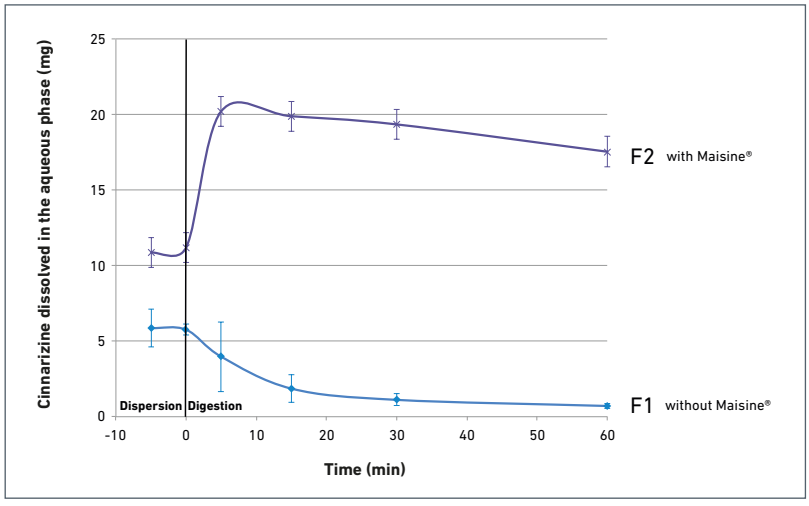


Figure 3: LBF containing Maisine® (F2) increases cinnarizine solubility *in vitro*

This case study highlights the potential of Maisine® CC to increase drug solubility on dispersion and during the digestive phase *in vitro*.

Danazol: Performance of LCT to increase oral bioavailability and mitigate the food effect

Danazol is a synthetic heterocycle steroid derivative of ethisterone used in the treatment of endometriosis. It has a high LogP (4.6) and poor water solubility, BCS Class II.

Porter *et al.* (2004) studied the impact of the chain length (MC vs LC) on oral bioavailability of danazol in beagle dogs:

- LC-SMEDDS contained 30% of soybean oil ($C_{18:1}$ triglycerides) and 30% of Maisine® ($C_{18:2}$ mono/diglycerides) as the oily phase.
- MC-SMEDDS contained 36% of MCT (C_8/C_{10} triglycerides) and 18% of Capmul® MCM (C_8/C_{10} mono/diglycerides) as the oily phase.

Both formulations contain Cremophor® EL (now Kolliphor® EL) as surfactant and ethanol as solvent. The pharmacokinetic parameters are reported in Table 6.

Table 6: LCT increase oral bioavailability and reduce food effect in dogs (adapted from Porter, 2004)

	Fasted state			Fed state
	Micronized powder	LC-SMEDDS	MC-SMEDDS	Micronized powder
C_{max} (ng/mL)	16.0 ± 3.6	96.2 ± 4.0	26.3 ± 10.9	117.5 ± 11.1
T_{max} (h)	2.6 ± 0.7	1.0 ± 0.1	1.9 ± 0.9	1.2 ± 0.1
AUC $^{0-10}$ (ng.h/ml)	35.3 ± 5.2	270.5 ± 38.5	47.7 ± 25.9	265.1 ± 33.5
Relative bioavailability (%)	100	766 ± 109	135 ± 76	751 ± 95

MC-SMEDDS gave a 5-fold lower relative bioavailability of danazol when compared to LC-SMEDDS in fasted conditions. The LC-SMEDDS delivered equivalent danazol release compared to the postprandial administration of the micronized powder in fed state (where lipid intake in a meal is close to 30 g).

The study concluded that LC glycerides (for example Maisine®) provide better oral bioavailability enhancement of danazol than MC glycerides.

In 1993, Charman *et al.* published data on the food effect observed on danazol oral bioavailability in humans using a glycerol monooleate emulsion and a non-lipidic formulation.

It showed that LC monoglycerides mitigate the food effect (Figure 4). The authors concluded that LC-monoglycerides enable better intrinsic emulsification without the necessity of lipid hydrolysis compared with LC-triglycerides.

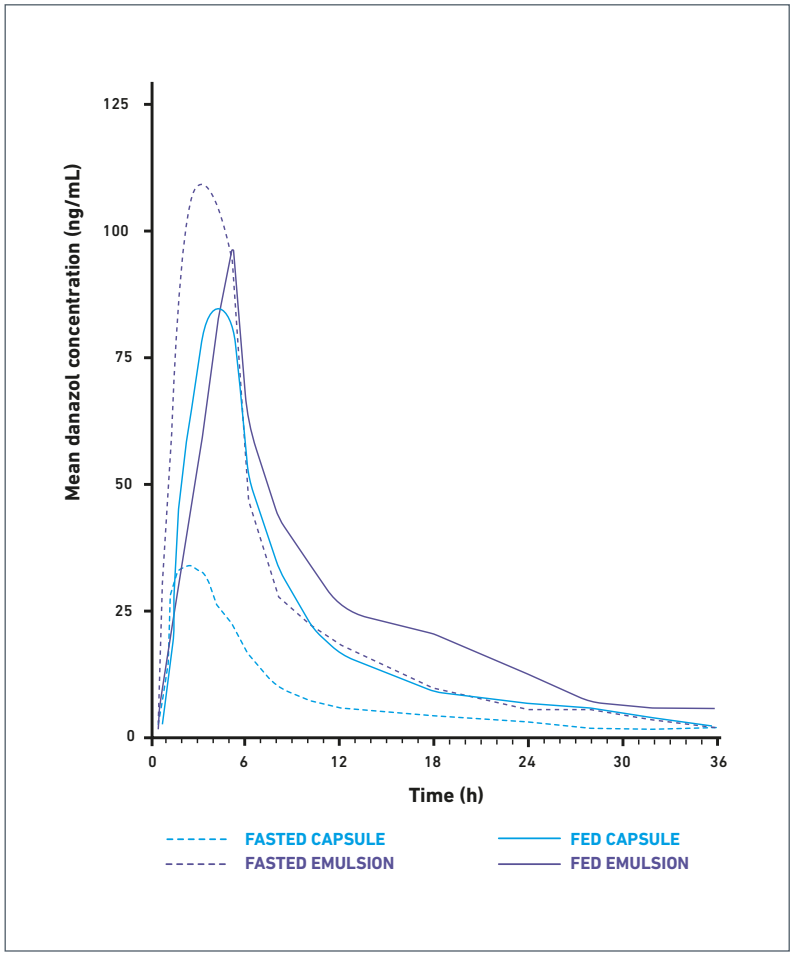


Figure 4: LCT mitigate the food effect (adapted from Charman, 1993).

Both studies show that the use of LC glycerides in LBF significantly increases the oral bioavailability of danazol and mitigates the food effect.

Halofantrine: LC fatty acids promote drug absorption via lymphatic pathway

Halofantrine is an anti-malarial drug, highly lipophilic (logP = 8.5), poorly water soluble and soluble in triglycerides (>50 mg/g), BCS Class II.

Caliph *et al.* compared the lymphatic transport in rats of three lipidic solutions of halofantrine:

- LCT (peanut oil $C_{18:1}$)
- MCT (C_8/C_{10})
- SCT (C_4).

Figure 5 shows that the lymphatic transport of halofantrine was increased 3- and 9 fold with LCT, compared to MCT and SCT respectively. The results indicated that drug was transported within chylomicrons constituted of resynthesized LCT and then absorbed in the lymph. The lymphatic transport of MCT and SCT remains negligible (<5%).

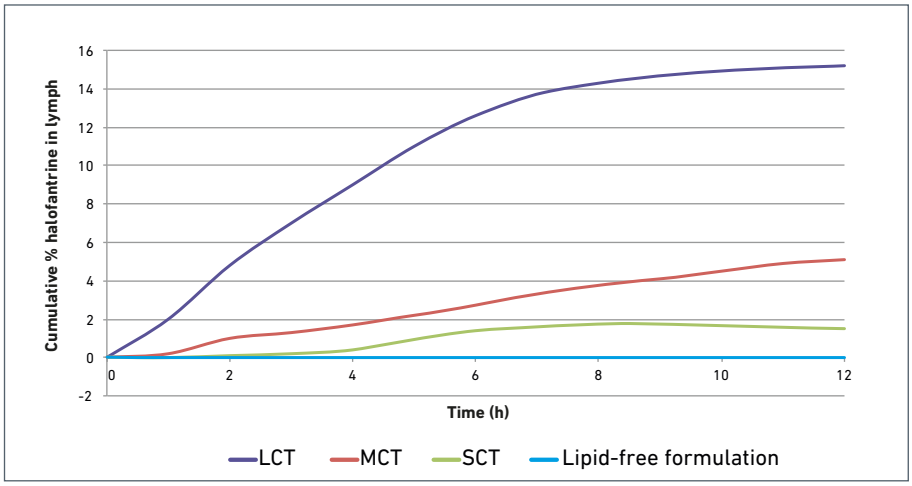


Figure 5: Halofantrine recovery in lymph in rats (adapted from Caliph *et al.*, 2000)

Khoo *et al.* studied the impact of fatty acid chain length (MC vs LC) on oral bioavailability of halofantrine in beagle dogs:

- LC-SMEDDS containing 29% of soybean oil ($C_{18:1}$ triglycerides) and 29% of Maisine® ($C_{18:2}$ mono-, diglycerides) as the oily phase
- MC-SMEDDS containing 29% of triglycerides (C_8/C_{10}) and 29% of Capmul® MCM (C_8/C_{10} mono-, diglycerides) as the oily phase.

Both formulations contain Cremophor® EL (now Kolliphor® EL) as surfactant and ethanol as solvent. Both plasma and lymph concentrations of halofantrine were measured.

The LC glycerides (contained in LC-SMEDDS) significantly increased the oral bioavailability of halofantrine, as shown with the plasma pharmacokinetics parameters (Table 7). The study showed that the cumulative concentration of halofantrine within the lymph was much higher with LC-SMEDDS compared to MC-SMEDDS (Figure 6).

Table 7: LCT increase halofantrine oral bioavailability in fasted dogs (adapted from Khoo *et al.*, 2003)

	LC-SMEDDS	MC-SMEDDS
C_{max} (ng/mL)	102 ± 5.1	59.1 ± 21.0
T_{max} (h)	3.0 ± 0.6	2.7 ± 0.6
AUC $^{0-10}$ (ng.h/ml)	550 ± 147	372 ± 116

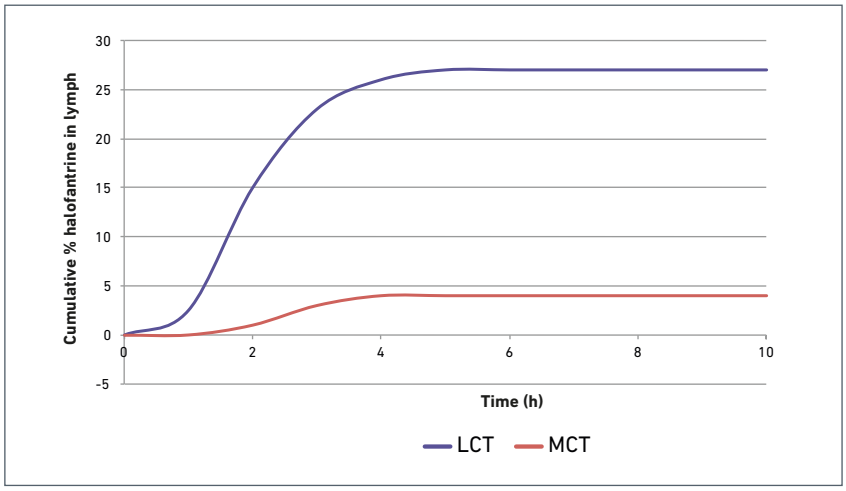


Figure 6: Halofantrine recovery in lymph in dogs (adapted from Khoo *et al.*, 2003)

Both studies show that the lymphatic absorption of halofantrine is greatly increased in formulations containing long-chain glycerides. The amount of lipid excipient used in one capsule was sufficient to promote lymphatic uptake for lipophilic drugs.

Regulatory status

Maisine® CC meets the current specifications for the European monograph for glycerol monolinoleate and the US pharmacopoeia for glyceryl monolinoleate.

A type IV drug master file is registered with the FDA in the US (DMF N° 5797).

Maisine® has a GRAS status (21CFR § 184.1505 mono- and diglycerides).

Chemical synonyms of Maisine® include:

- glyceryl linoleate (INCI name)
- corn glycerides (UNII: 1DAF35W3S2)
- mixture of mono-, di- and triglycerides derived from corn oil

Corn glycerides (UNII: 1DAF35W3S2) are used in authorized oral medicinal products (capsule, soft gelatin capsule, oral solution and tablet).

The regulatory, toxicology and safety overview dossier is available from Gattefossé.

Technical support

Gattefossé can provide technical support to help you with the selection of excipients for solubility enhancement, screening methods and solubility measurements, ternary phase diagram development and *in vitro* characterization assays for lipid-based formulation.

Please contact your local Gattefossé representative
or email us at: infopharma@gattefosse.com

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