



Lipid Excipients for Cannabinoid Drug Products



People make our name



ABOUT GATTEFOSSÉ

Gattefossé provides innovative excipients and drug delivery solutions to health industries worldwide. Simplifying formulation decisions and shortening the drug development path are at the heart of the Gattefossé product offer.

Our product list includes solubilizers; penetration, permeation, and bioavailability enhancers; modified and sustained-release matrix formers; and inert vehicles for oral, topical, injectable, and mucosal routes of administration.

Each excipient is fully characterized by physicochemical properties and safety profile. In addition we provide guidance documents for formulation design in preclinical as well as late development stages.

Gattefossé ensures timely technical support to its customers with highly trained technical staff and a well-established network of affiliates and distributors in 70 countries.



Contents



This brochure provides an overview of the formulation opportunities with Gattefossé excipients in developing medicinal cannabinoids for oral, topical, transdermal, and alternative routes of administration.

4 Medicinal Cannabinoids

5 Properties of Cannabinoids

The Benefits of Lipid Based Excipients in:

7 Oral Drug Delivery

11 Dermal Drug Delivery

13 Alternative Drug Delivery Routes

16 Technical Support

Medicinal Cannabinoids

The introduction of the cannabis plant into Western medicine dates to the 19th century when the plant was first used as an additive to patented medicines. The development of cannabis based therapies in the modern sense however came to a halt in the 1970's after the passing of laws that have since categorized cannabis as a scheduled (narcotic) substance.

Amidst the regulatory constraints, over one hundred active molecules (phytocannabinoids) of the plant have been identified. Synthetic forms of cannabinoids such as dronabinol, nabilone, and cannabidiol have been developed and marketed for treatment of nausea associated with chemotherapy and for myoclonic seizures in patients two years of age and older.

However, it was not until 2018 that the US FDA approved Epidiolex®, the first purified phytocannabinoid isolated from the cannabis plant. Epidiolex® is indicated for severe forms of epilepsy, namely Lennox-Gastaut and Dravet syndromes (Table 1).

Table 1. Marketed cannabinoid drugs as of 2018

Marketed Drug	Indication	Dosage Form	API Molecule	Drug Strength
Epidiolex®	Myoclonic seizure	Oral Solution	Cannabidiol	100 mg/mL
Marinol®	Nausea and emesis associated with chemotherapy	Soft Gel Capsules	Dronabinol	10 mg
Syndros®	Nausea and vomiting associated with cancer	Oral Solution	Dronabinol	5 mg/mL
Cesamet™	Nausea and vomiting associated with cancer	Oral Capsule	Nabilone	1 mg
Sativex®	Neuropathic pain from Multiple Sclerosis (MS) and for intractable cancer pain	Buccal Spray	Cannabidiol; Dronabinol	25 and 27 mg/mL

With an enhanced understanding of the medicinal benefits and looming ease of regulations around the globe, there is an expressed need for science based, adequately dosed, and age appropriate cannabinoid medicines.

The benefits of medicinal cannabinoids include:

- ✓ **Controlled and measured dosing**
- ✓ **Age appropriate, patient-centric dosage forms**
- ✓ **Alternatives to unhealthy modes of intake such as vaping or smoking**

Properties of Cannabinoids

Among the hundreds of phytocannabinoids and terpenes isolated from cannabis, two very lipophilic molecules stand out: tetrahydrocannabinol (THC) and cannabidiol (CBD). Amounting between 30% and 50% of a single plant's weight, they are known to affect physiological processes such as mood, memory, appetite, and pain sensation. They function by activating the endocannabinoid receptors of the nervous system which are found throughout the body, including in the brain.

THC and CBD have been extensively studied and are found to have unique qualities of their own.

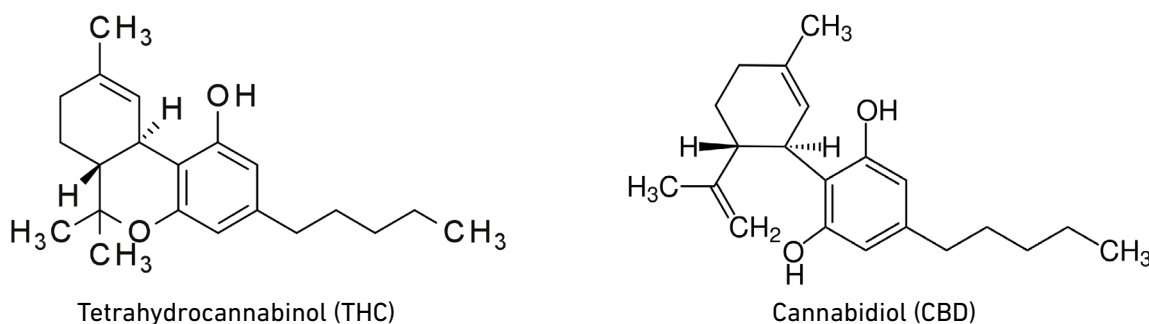


Figure 1. Primary constituents of cannabis extract

THC is responsible for the euphoric and psychoactive effects of cannabis and has applications as medicine for treatment of chronic pain and nausea associated with chemotherapy. Another indication for THC is the treatment of amyotrophic lateral sclerosis (ALS), i.e. potential delay in the progression of the disease and alleviation of the ALS symptoms. CBD on the other hand is a non-psychoactive, anti-inflammatory medicine. It is preferred over THC by patients in need of treatment for arthritis, mood disorders, and nausea.

Studies have shown that THC and CBD have oral bioavailability of approximately 3% to 8% and this varies by formulation and type of vehicles used. This poor bioavailability is in part attributed to the poor gastrointestinal (GI) solubility of these compounds resulting in erratic and variable absorption from the GI tract. Additionally, a significant first pass metabolism may ensue in the liver following GI absorption. These properties render cannabinoids as excellent candidates for Lipid-Based Drug Delivery (LBDD).



The Benefits of Lipid Excipients in Oral Drug Delivery

Lipid formulations are shown to improve the bioavailability of cannabinoids by improving solubility, intestinal permeability, and enhancement of the lymphatic route of absorption. Among the key mechanisms associated with oral lipid formulations in enhancing bioavailability is the **improved drug wettability and dispersion in the GI fluids, through natural digestion mechanisms that help maintain drug solubilization *in vivo***. The effect lasts long enough for the drug to approach the enterocytes for absorption. Recent studies have found that the bioavailability of THC and CBD from a sesame oil formulation was 2.5-fold and 2.9-fold higher compared to a lipid-free formulation (Zgair, 2016, 2017).

However, not all lipids are equal in the nature of their impact on permeability and absorption. Lipid systems may vary by fatty acid chain length and the type/degree of esterification. The choice of excipient is guided by the overall objectives of the dose and the type of dosage form e.g. tablet, capsule, or powder. The formulation may be fine-tuned to improve lymphatic absorption and/or rate of drug release.

Due to their unique properties and versatility, lipid formulations may be designed to tackle several of the below listed bioavailability objectives in a single lipid formulation:

- ✓ Solubilization of the API in the dose
- ✓ Drug dispersion and dissolution in the GI tract
- ✓ Enhanced permeability across enterocytes and wider absorption window
- ✓ Enhanced lymphatic transport of lipophilic drugs

Excipients for Oral Delivery

Gattefossé offers a range of excipients for achieving one or more of the objectives listed above. They may be categorized by physical state (liquid vs. solid), melting point, HLB value, as well as biopharmaceutical aspects.

As summarized in Table 2, products like **Maisine® CC**, **Peceol®**, **Labrafil® M 1944 CS**, **Labrafil® M 2125 CS** and the **Highly Purified Oils** are suitable for oily formulations which may be filled into capsules. They may also be used as oil phase in self-emulsifying formulations. Long chain fatty acids (LCFA) constitute the bulk of the fatty acids found in the products listed, exceptions being **Labrafac®** series, **Lauroglycol™** series, **Capryol™** series, and **Labrasol®** which are composed of medium chain fatty acids (MCFA) with carbon chain lengths of C8 and C10.

Table 2. Excipients by function, category, and suitability for oral dosage forms

		Applications and Dosage Forms					
		Tincture Oils	SEDDS/ SMEDDS	Soft Shell Capsules	Hard Shell Capsules	Sachets	Tablets
Excipient Functionality	Highly purified oils		Soybean Oil, Olive Oil, Sesame Oil				
	Oily vehicles		Labrafac® Lipophile WL 1349				
			Geloil™ SC, Geleol™, Maisine® CC, Peceol®				
	Solubilizers/co-surfactants		Lauroglycol™ 90, Lauroglycol™ FCC, Capryol™ 90, Capryol™ PGMC, Plurol® Oleique CC497				
	Liquid and semi-solid surfactants		Labrafil® M 1944 CS, Labrafil® M 2125 CS, Labrafil® M 2130 CS, Gelucire® 44/14, Labrasol® ALF				
	Solid surfactants		Gelucire® 48/16, Gelucire® 50/13				
	Taste masking, sustained release agents				Compritol® 888 ATO, Precirol® ATO 5		

Lymphatic vs. Hepatic Absorption

The fatty acid chain length plays a key role in the emulsification, permeation, and route of absorption. The medium chain esters are known for rapid, hepatic absorption, whereas products consisting of unsaturated LCFA tend to stimulate chylomicron secretion and increase lymphatic uptake. The process can enhance the bioavailability of highly lipophilic drugs through preferential absorption within the lymphatic transport system, consequently decreasing first-pass metabolism of the drug in the liver (Haus, 1998; Charman, 1991; O’Driscoll, 2002).

Since absorption by the lymph means bypassing the liver, formulation with unsaturated LCFA can be a promising strategy for cannabinoids, which are metabolized extensively in the liver. Moreover, lipid excipients may be selected for their surfactive and often self-emulsification properties. Self-emulsification refers to the unique property of certain lipids that disperse spontaneously in aqueous media, forming micellar and lamellar self-assemblies, which are key in maintaining solubility and improving permeability of poorly soluble drugs such as cannabinoids.

SEDDS/SMEDDS

With careful selection of the excipients having the right fatty acid chain length, melting point, and emulsification properties, it is possible to design sophisticated dosage forms. As an example, **self (micro) emulsifying drug delivery systems known as SEDDS and SMEDDS are a suitable solution to improving oral drug delivery of poorly soluble and low permeability drugs.**

Labrasol®, **Gelucire® 44/14**, **Gelucire® 48/16**, **Gelucire® 50/13** and the **Labrafil®** series (Table 2) consist of self-emulsifying excipients that may be in SEDDS / SMEDDS. Several of these products listed are liquid or semi-solid, hence suitable for soft or hard shell capsules.

Other products, such as **Gelucire® 48/16** and **Gelucire® 50/13** are solids (higher melting points) and so are suitable also for preparation of granules and powders which can subsequently be filled into hard shell capsules or sachets. Alternatively, the powders may be compressed into tablets.

Generally, self-emulsifying formulations provide a rapid (immediate release) profile (Figure 2). **Compritol® 888 ATO** and **Precirol® ATO 5** on the other hand are applicable to taste masking and the preparation of sustained release delivery systems in the form of granules or tablets.

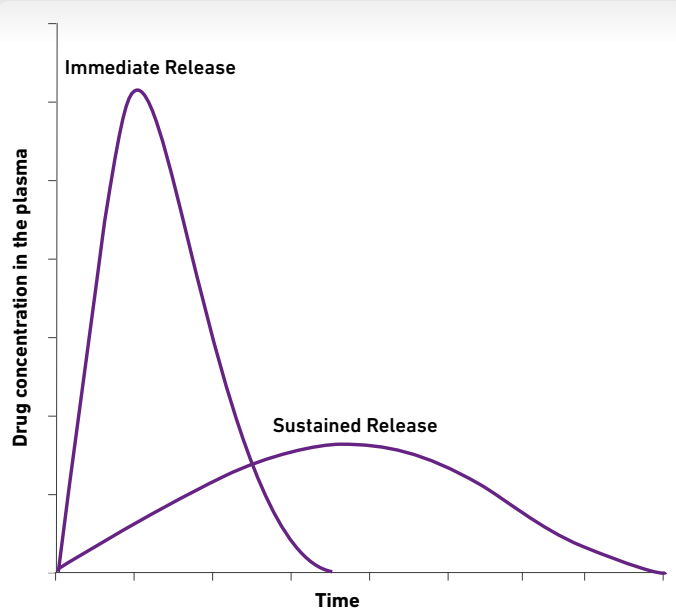


Figure 2. Idealized plasma concentration using time to compare immediate and sustained release dosage forms

Formulation Guidelines

Further practical information regarding formulation considerations for lipid formulations can be found in our Formulation Guidelines: ***Developing Lipid Based Formulations for Oral Bioavailability Enhancement.***

Additionally, it is possible to develop unique combinations of excipients to simultaneously achieve enhanced bioavailability and sustained delivery. Additional information on sustained release development is available in our ***Sustained Release Formulation Guidelines.***

The Benefits of Lipid Excipients in Dermal Drug Delivery

Skin as Route of Administration

With an average thickness of 1.2 mm and an acidic pH ranging from 4.2 to 6.1, the skin makes up roughly 15% of the total weight of an adult. Certain therapies may target the skin, or a local area beneath the skin. Others target the systemic circulation, often for a sustained delivery. Therefore, good knowledge of the skin's physiology and the proper role of excipients is essential in formulating effective topical treatments.

Dosage Forms

In certain cases, cannabinoids need to be applied locally on the skin for various purposes such as **anti-acne**, **anti-psoriatic**, **anti-fungal**, **analgesics** and **anti-inflammatory** applications. These may be in topical dosage forms having various sensorial properties / textures, and a range of viscosities.

Other possibilities include ointments, foams, and gels. The choice of dosage form will largely depend on the intended use conditions such as spreadability over a given surface area of the skin, frequency of use, and the intended cannabinoid concentration to be delivered. Additionally, enhancers may be added to improve the rate of drug penetration and permeation into the dermis. Another important consideration is whether the formulation is to remedy a brief episode or a lingering ailment. Proven safety and absence of irritation potential become essential for chronic treatments.



Excipients for Topical Formulations

An overview of Gattefossé emulsifiers, consistency agents, and solubilizers suitable for topical preparations is provided in Figure 3. With excellent tolerance / safety profiles and long history of use, these are products of choice for developing stable and luxurious textures.

Each product listed below has unique advantages. Emulsifying bases are ready-to-use formulation systems designed to simplify and to drastically reduce cost/time for development and production; **Tefose® 63** is a very mild base with precedence of use in vaginal preparations for many decades; **Gelot™ 64** can help emulsify high levels of polar oils; **Labrasol®** and **Labrafil®** are permeation

enhancing emulsifiers that can be incorporated in all formulations. Likewise, **Transcutol® P**, a hydroalcoholic solubilizer and enhancer is suitable for a wide range of dosage forms. Microemulsions on the other hand are unique in their transparency, low viscosity and superior permeation enhancing capacity.

Table 3. Excipients by function, category, and suitability for topical dosage forms

		Ointment	Cream	Foam	Microemulsion	Gel
Excipient Functionality	Oily Vehicles / Carriers	Labrafac™ WL 1349, Pluro® Oleique CC 497				
	Emulsifying bases for sensitive drugs	Tefose® 63, Gelot™ 64, Sedefos™ 75, Tefose® 1500				
	Consistency, viscosity agents	Compritol® 888, Geleol™, Monosteol™				
	Liquid O/W Surfactants	Labrasol®, Labrafil® M 1944, Labrafil® M 2125				
	W/O Emulsifiers	Pluro® Diisostearique				
	Solvent	Transcutol® P				

Penetration and Permeation Enhancers - Transcutol® P

A number of excipients such as the **Labrasol®** and **Labrafil®** series, **Pluro® Oleique CC 497**, **Lauroglycol™** series, **Capryol™** series, and **Transcutol® P** are solubilizers as well as skin penetration and permeation enhancers. They are often used in combination to modulate drug delivery to/or across the skin.

Transcutol® P is globally known to solubilize and enhance the penetration of many drugs, notably THC and delivery across skin layers. Using quantitative autoradiography methods, an independent study (Fabian, 1991) measured the penetration of THC in rat skin from three different enhancing formulations: neat Transcutol® P, PEG 400, and a 7:3 blend of propylene glycol/ethanol. The neat Transcutol® P formulation showed the highest and the most stable THC distribution profile across the skin layers. The results for 24 hours of application (Figure 3) show that the THC concentration delivered from neat Transcutol® P was significantly higher than from the other systems.

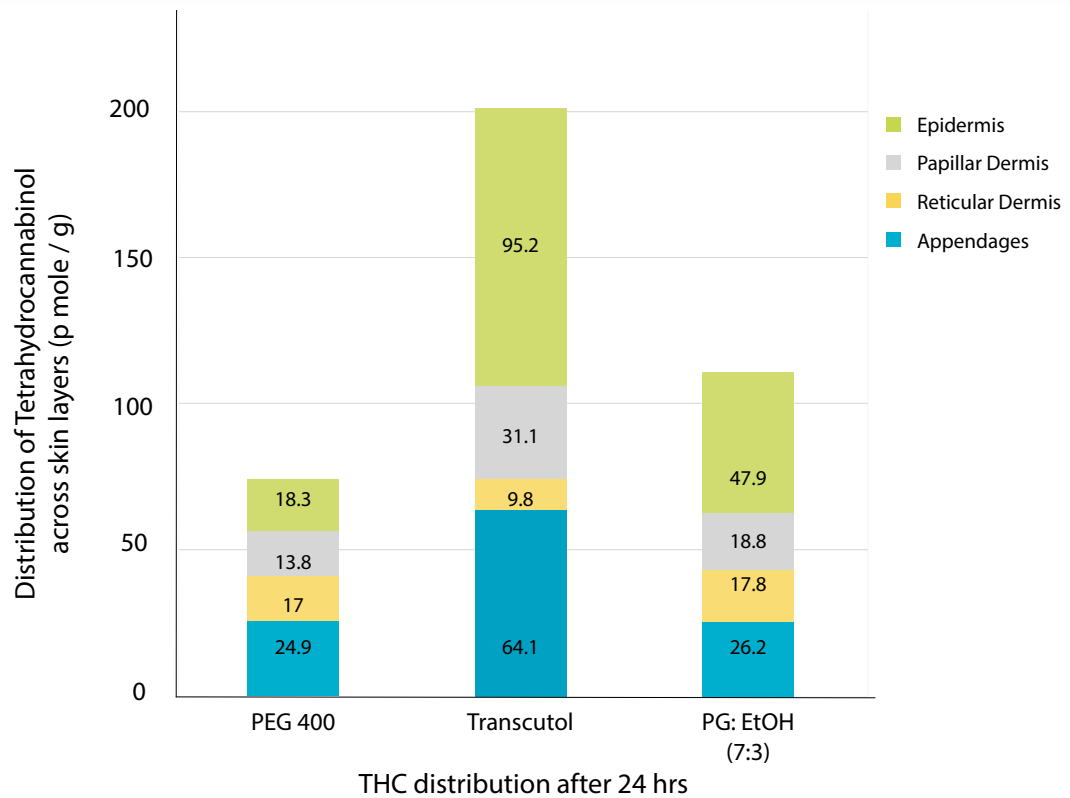


Figure 3. Effect of formulation on the skin distribution of THC from PEG 400, Transcutol® P and propylene glycol:ethanol formulations

Transcutol® P is a safe and effective solubilizer of both hydrophilic and lipophilic compounds. It acts as an enhancer by inducing a transient swelling of the hydrophilic regions of the stratum corneum, rendering it permeable similar to fully hydrated skin. By diffusing into the skin layers, Transcutol® P improves the drug solubility in the skin and its partitioning into the deeper hydrophilic regions of the dermis (Osborne, 2018).

More information is provided in our *Dermacare* and *Topical Drug Delivery* brochures, available on request.

Additionally, we offer:

- ✓ Regulatory, safety, and precedence of use assistance
- ✓ Enhancing formulation efficacy
- ✓ Expertise in sensorial properties

The Benefits of Lipid Excipients in Alternative Drug Delivery Routes

A highly effective and yet unexploited approach to difficult drugs is mucosal delivery. The possibilities include **nasal**, **buccal**, **rectal**, and **vaginal** routes of administration. In addition to circumventing exposure to the GI tract where drug degradation may occur by digestive enzymes, bile salts and/or pH related effects, this approach helps eliminate any first pass (hepatic elimination) risks for drugs like cannabinoids.

Mucosal Delivery

Mucosal delivery is a unique alternative for administration of drug to patients with special needs. Examples include children suffering from recurring seizures, patients unable to take oral medication, and those in palliative care who may receive medicine as nasal sprays or suppositories.

Mucosal delivery is the fastest route of delivery, next to injectable / parenteral routes administration. Compared to oral delivery, the benefits for incapacitated patients include:



- ✓ Rapid drug absorption and onset of action
- ✓ By-passing the hostile GI tract
- ✓ No risks of hepatic elimination
- ✓ No taste issue or emesis

Nasal or Buccal Sprays and Tinctures

Several products listed in Table 1, including Gattefossé solubilizers such as **Lauroglycol™**, **Labrafac®**, **Lipophile WL 1349**, **Labrafil® M 1944** and **Capryol™** series may be used alone or in combination, to obtain drug solutions or dispersions in aqueous or microemulsion systems for use as sublingual drops or nasal sprays.

Rectal and Vaginal Delivery

Solid lipid excipients, known in pharmacopoeia as “Hard fat” commonly constitute the “base” or the medium for delivery of drugs in suppository (rectal) or pessary (vaginal). In order to meet the formulation needs for different drugs, dose variations, mold types, and manufacturing speeds, Gattefossé has developed a wide range of bases: namely the **Suppocire®** product line for rectal and the **Ovucire®** line of excipients for vaginal routes of administration (Table 4).

The Suppocire® bases consist of safe, well characterized, and globally referenced excipients which are primarily composed of glycerol esters of fatty acids with varying chain length, degree of esterification, hydrophilicity, and rate of crystallization. Within the Suppocire® line of products, there are unique series, each designed to meet a specific set of formulation and manufacturing conditions. As an example the **Suppocire® M** series are multipurpose vehicles for a wide range of drugs; the **Suppocire® N** series are applied in high speed manufacturing environments; and **Ovucire®** are appropriate for the hydrophilic vaginal environments.

Table 4. Rectal and vaginal product series

Product Series	Applications
Suppocire® M	Multipurpose bases offering a range of melting points and hydroxyl values
Suppocire® N	Bases with for sensitive actives and high speed manufacturing processes
Suppocire® P	Amphiphilic bases for poorly soluble drugs
Ovucire®	Bases optimized for vaginal drug delivery

The drug properties, intended dose, and mode of absorption are among the critical considerations when selecting an appropriate base that will deliver the optimal physiochemical stability, dispersion and release profile.

Having helped develop hundreds of marketed references over a 60-year span, our group has significant and in-depth knowledge to share with the customers.

Advantages of Suppocire® and Ovucire® Series

- ✓ Drug delivery in high concentrations
- ✓ Faster absorption for a rapid onset of action
- ✓ Alternative for niche patient populations
- ✓ Bypassing the hostile GI tract



Detailed information and complete list of product series are available upon request.

References

Charman W & Stella V (1991)

Transport of lipophilic molecules by the intestinal lymphatic system.

Advanced Drug Delivery Reviews 7(1):14.

Fabin B & Touitou E (1991)

Localization of lipophilic molecules penetrating rat skin in vivo by quantitative autoradiography.

International Journal of Pharmaceutics 74(1):59-65.

Hauss DJ, et al. (1998)

Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB₄ inhibitor.

J Pharm Sci 87(2):164-169.

O'Driscoll CM (2002)

Lipid-based formulations for intestinal lymphatic delivery.

Eur J Pharm Sci 15(5):405-415.

Osborne DW & Musakhanian J (2018)

Skin Penetration and Permeation Properties of Transcutol®-Neat or Diluted Mixtures.

AAPS PharmSciTech.

Paudel KS, Hammell DC, Agu RU, Valiveti S, & Stinchcomb AL (2010)

Cannabidiol bioavailability after nasal and transdermal application: effect of permeation enhancers.

Drug Dev Ind Pharm 36(9):1088-1097.

Zgair A, et al. (2016)

Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines.

Am J Transl Res 8(8):3448-3459.

Zgair A, et al. (2017)

Oral administration of cannabis with lipids leads to high levels of cannabinoids in the intestinal lymphatic system and prominent immunomodulation.

Sci Rep 7(1):14542.

Technical Support

We can reduce your development time by providing straightforward formulation guidelines for oral, dermal, rectal and vaginal dosage forms as well as access to extensive databases comprising hundreds of validated placebo or model drug formulations. **Our application laboratories in France, India, China and the United States are at your service to provide technical support and formulation feasibility assessment.**

We have decades of formulation experience with both experimental and model drugs. We are committed to answering your questions on formulation, regulatory, safety, precedence of use, and scale-up issues.

Please contact your local Gattefossé representative



Compritol[®], Gelucire[®], Maisine[®], Labrafac[®], Labrafil[®], Labrasol[®], Plurol[®], Precirol[®], Tefose[®], Transcutol[®], Suppocire[®] are registered trademarks of Gattefossé.

The information included in this brochure is presented in good faith and we believe that it is correct, but no warranty as to accuracy of results or fitness for a particular use is given, nor is freedom from patent infringement to be inferred. It is offered solely for your consideration, investigation and verification. The user shall determine under his responsibility, the use and the security conditions of the information, and will remain the only one responsible in case of damageable consequences. Before using a Gattefossé product, or any other product mentioned in this literature, read, understand and follow the information contained in most recent Material Safety Data sheet.



Canada Regional Office

GATTEFOSSÉ Canada, Inc.
190 Attwell Drive, Suite 600
Toronto, Ontario M9W 6H8
Tel: +1 416 243 5019
service@gattefosse.ca



USA Regional Office

Gattefosse Corporation
Plaza I, 115 West Century Road, Suite 340
Paramus, New Jersey 07652
Tel: +1 201 265 4800
info@gattefossecorp.com

www.gattefosse.com



Corporate Headquarters

36 chemin de Genas - CS 70070
69804 Saint-Priest Cedex - **France**
+(33) 4 72 22 98 00