GATTEFOSSÉ

Oral Drug Delivery

With Lipid Excipients

Oral | Topical | Rectal | Vaginal | Parenteral

People make our name

ABOUT GATTEFOSSÉ

Gattefossé is a leading provider of excipients and formulation solutions to healthcare industries worldwide. Our company history - of over 140 years - is built on a commitment to our customers to deliver the highest quality products and technical support. In parallel to developing innovative formulation applications, Gattefossé has worked diligently to guarantee the pharmaceutical qualification of its excipients.

GATTEFOSSÉ EXCIPIENTS

The lipids and fatty acids used in the production of Gattefossé excipients are derived strictly from raw materials of vegetable origin.

Excipients are obtained by the esterification of fatty acids with alcohols - glycerol, polyglycerol, propylene glycol and polyethylene glycol - and by the alcoholysis of vegetable oils and fats with glycerol, polyethylene glycol and propylene glycol.

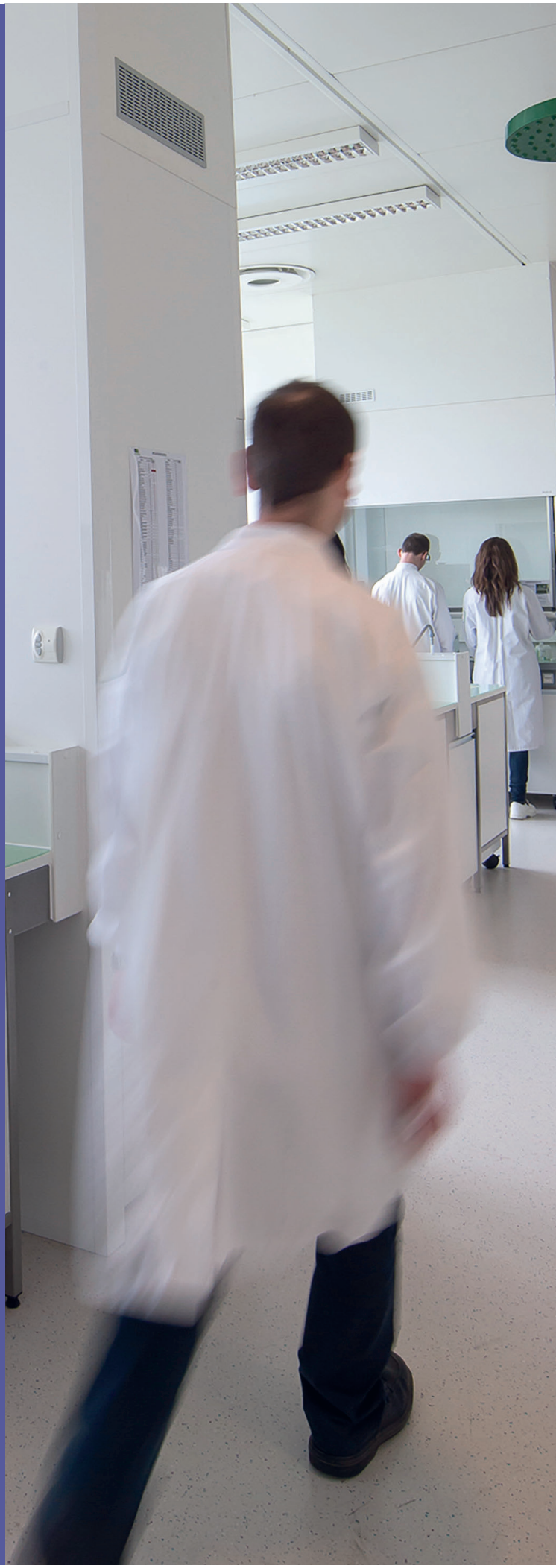
Expertise in oleo-chemistry has enabled the development of a range of functional excipients with different thermal, rheological and textural properties and a wide spectrum of solubility characteristics.

ORAL DRUG DELIVERY

Our functional excipients are designed to meet the most pressing formulation challenges in drug development. Challenges which include API solubility, permeability and low bioavailability; modified drug release; protection of sensitive API and taste-masking. In manufacturing, lipid excipients provide benefits in tablet lubrication and their versatility means they can be used in numerous processing techniques providing scope for innovation.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **Ch.P.:** Chinese Pharmacopoeia; **EP:** European Pharmacopœia; **HLB:** Hydrophilic Lipophilic Balance; **JPE:** Japanese Pharmaceutical Excipients; **LFCS:** Lipid Formulation Classification System Consortium; **USP-NF:** US Pharmacopœia-National Formulary; **S(M)EDDS:** Self (Micro) Emulsifying Drug Delivery System



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Excipients for sustained drug release

Modulating drug release by the formation of a matrix tablet is a popular approach since it provides dosage form flexibility and drug delivery efficacy. Matrices can be made by simple physical blending of ingredients followed by direct compression or by the formation of a solid dispersion and subsequent transformation into a dosage form.

Excipients have a proven history of use in simple sustained release (SR) matrix tablets and in more complex drug delivery systems such as dual API release systems, pulsed, timed and delayed release systems.

Modulation of drug release to achieve the target profile is readily achieved with glyceride matrices by modifying basic formulation and processing parameters. Lipophilic matrices are insoluble in aqueous systems, they do not swell, and diffusion is the principle mechanism of drug release.

High melting point, low HLB excipients have excellent plastic properties and matrix tablets can be produced by numerous standard processing techniques (see table 1). In addition, these excipients are chemically inert, neutral in flavor and odorless. They are compatible with standard excipients, including polymers for coating. However, coating is not always necessary.

Biopharmaceutical and manufacturing advantages including:

- Straightforward modulation of drug release profile
- Effective solutions for highly water soluble, short half-life APIs
- Resistance to pH changes and hydroalcoholic environment
- Non-hydroscopic matrix for improved stability on storage
- Solvent-free processing for cleaner and greener manufacturing

Table 1: Excipients for sustained drug release

Products	Chemical description	Form	HLB	Melting point (°C) (capillary tube)	Drop point (°C) (Mettler)	Techniques
Compritol® 888	Glycerol dibehenate EP Glyceryl dibehenate NF Glyceryl behenate Ch.P.	Powder* Pellets	2	65.0-77.0	69.0-74.0	Direct compression Wet granulation Solid dispersion/ granulation Extrusion (melt/partial melt) Spray cooling/prilling Melt coating
Precirol® ATO 5	Glycerol distearate (type I) EP Glyceryl distearate NF	Powder*	2	50.0-60.0	53.0-57.0	Extrusion (melt/partial melt) Melt coating Spray cooling/prilling Capsule molding
Geleol™ Mono and Diglycerides NF	Glycerol monostearate 40-55 (type I) EP Mono and diglycerides NF	Pellets	3	54.0-64.0	54.5-64.5	Extrusion (melt/partial melt) Melt coating Capsule molding

* Powder mean particle diameter 50 µm

Download our brochure on sustained release

Excipients for solubilization and bioavailability enhancement

Self emulsifying drug delivery systems provide an effective approach for poorly water soluble, lipophilic APIs. Surfactive, dispersible and oily excipients are known to improve oral bioavailability by a number of mechanisms including:

- Enabling higher drug loading by increasing the wettability/solubility of API in the formulation
- Maintaining the API in a solubilized state in gastro-intestinal fluid promoting increased absorption
- Facilitating selective absorption of certain APIs via the lymphatic transport system.

Gattefossé excipients can be used in self (micro) emulsifying formulations (SEDDS/SMEDDS), comprising single or multiple excipients. They cover a wide HLB range from 1 to 12 and deliver different properties in formulations (Tables 2 and 3).

- Higher HLB surfactants are frequently combined with water insoluble surfactants, oily vehicles and co-solvents
- Lower HLB water dispersible surfactants are formulated with higher HLB water dispersible surfactants.

Table 2: Gattefossé solubilizers and Lipid-based Formulation Classification System (LFCS)

Products	Functionality	LFCS	Solubility in water	HLB
Gelucire® 48/16	Water soluble surfactant	Type IV, micellar	Transparent micellar solution	12
Gelucire® 44/14 Labrasol® ALF	Water dispersible surfactant	Type III fine emulsion/ microemulsion	Translucent dispersion	10 - 12
Labrafil® (s)	Wetting agent	Type II formulation Coarse emulsion	Milky dispersion	7 - 9
Capryol® (s) Lauroglycol™ FCC	Water insoluble surfactant	Use in Type II/III	Dispersion	5 - 6
Lauroglycol™ 90 Plurol® Oleique CC 497	Water insoluble surfactant	Use in Type II/III	Insoluble	2 - 4
Maisine® CC Peceol™	Oily phase	Use in Type I	Insoluble	1

Further practical information can be found in our Formulation Guidelines: Developing Lipid based Formulations for Oral Bioavailability Enhancement

Table 3: Excipients for solubility and bioavailability enhancement

Products	Chemical description	HLB	Functionality
Gelucire® 48/16	Macrogol stearate (type I) EP Polyoxyl stearate (type I) NF	12	Water soluble surfactant
Labrasol® ALF	Caprylocaproyl macrogol-8 glycerides EP Caprylocaproyl polyoxyl-8 glycerides NF	12	Water dispersible surfactant
Gelucire® 44/14	Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF	11	
Gelucire® 50/13	Stearoyl macrogol-32 glycerides EP Stearoyl polyoxyl-32 glycerides NF	11	
Labrafil® M 1944 CS	Oleoyl macrogol-6 glycerides EP Oleoyl polyoxyl-6 glycerides NF	9	
Labrafil® M 2125 CS	Linoleoyl macrogol-6 glycerides EP Linoleoyl polyoxyl-6 glycerides NF	9	
Labrafil® M 2130 CS	Lauroyl macrogol-6 glycerides EP Lauroyl polyoxyl-6 glycerides NF	9	
Capryol® PGMC	Propylene glycol monocaprylate (type I) NF	6	Water insoluble surfactant
Capryol® 90	Propylene glycol monocaprylate (type II) NF	5	
Lauroglycol™ FCC	Propylene glycol monolaurate (type I) EP/NF	5	
Lauroglycol™ 90	Propylene glycol monolaurate (type II) EP/NF	3	
Plurol® Oleique CC 497	Polyglyceryl-3 dioleate NF	3	
Maisine® CC	Glycerol monolinoleate EP Glyceryl monolinoleate NF	1	Oily vehicle
Peceol™	Glycerol monooleate (type 40) EP Glyceryl monooleate (type 40) NF	1	
Labrafac™ PG	Propylene glycol dicaprylocaprate EP Propylene glycol dicaprylate/dicaprate NF	1	
Labrafac™ Lipophile WL 1349	Triglycerides medium-chain EP Medium chain triglycerides NF Medium chain fatty acid triglyceride JPE	1	
Transcutol® HP	Highly purified diethylene glycol monoethyl ether EP/NF	/	Co-solvent

Excipients for taste-masking and API protection

Certain excipients have excellent thermoplastic properties ideal for use in melt processes to deliver taste-masking and protect sensitive drug compounds.

High shear coating

A standard high shear mixer, without external heating or cooling, and a simple binary formulation consisting of 80% API and 20% Precirol® ATO 5 are used.

During mixing, friction is generated which induces sufficient heat to partially melt the lipid excipient. The molten excipient coats the drug particles and, upon cooling, solidifies, covering the drug particles and masking the unpleasant taste.

Hot melt coating

Molten excipient is sprayed on to solid drug particles in a fluid bed coating device. The lipid excipient produces a thin, homogeneous film coating which delivers improved tablet compaction and resolves API taste and compatibility problems. The process is quick, solvent-free and no drying step is required.

Excipients are compatible with flavoring agents, polymers, plasticizers and surfactants. For example, the combination of Compritol® 888 ATO with 20% Labrasol® ALF in a lipid film coating delivers API protection and can modulate drug dissolution properties.

The coated API can be used in tablets, hard and soft gelatine capsules and sachets.

Melt granulation

Excipients are used as binders to form liquid bridges with the powder particles (API and other ingredients) forming small granules under high shear mixing. Granules can be transformed into spheronized pellets by controlling the mixing conditions. Thermoplastic lipid excipients are typically used between 15% and 25% w/w depending on the fineness of the powder mixture. The process is simple (one-step) and solvent-free.

Excipients enable high drug loading 85% theoretically and up to 66% experimentally reported in the literature. Lipid granules and pellets can be used in tableting and capsule filling.

The choice of excipient depends on the formulation objective, please see table 4.

For more information on the use of our excipients in melt processes please ask your local Gattefossé representative

Table 4: Excipients for taste masking and API protection

Products	Chemical description	Form	HLB	Melting point (°C) (capillary tube)	Drop point (°C) (Mettler)	Techniques
Taste Masking						
Precirol® ATO 5	Glycerol distearate (type I) EP Glyceryl distearate NF	Powder*	2	50.0-60.0	53.0-57.0	Hot melt coating Melt granulation Extrusion (melt/ partial melt)
Geleol™ Mono and Diglycerides NF	Glycerol monostearate 40-55 (type I) EP Mono and diglycerides NF	Pellets	3	54.0-64.0	54.5-64.5	Melt granulation Extrusion (melt/ partial melt)
API protection / API compatibility						
Compritol® 888 ATO	Glycerol dibehenate EP Glyceryl dibehenate NF Glyceryl behenate Ch.P.	Powder*	2	65.0-77.0	69.0-74.0	Hot melt coating Melt granulation Extrusion (melt/ partial melt)
Gelucire® 43/01	Hard fat EP/NF/JPE	Pellets	1	/	42.5-46.0	Capsule molding

* Powder mean particle diameter 50 µm

Excipients as lubricants for tablets and capsules

Effective lubrication in tablet and capsule production has a major impact on manufacturing and the quality of the final dosage form in terms of the appearance and content homogeneity.

Gattefossé lubricants are often used to resolve problems associated with poor powder properties and being chemically inert, they are compatible with all types of active pharmaceutical ingredient and additional excipients.

Fine powder excipients of well-defined and controlled particle size deliver superior ingredient homogeneity and content uniformity for tabletting and capsule filling.

Lubricant performance is independent of mixing time and speed, making tablet and capsule manufacturing more straightforward.

- **Compritol® 888 ATO** is recommended for tabletting as it provides effective lubrication without compromising tablet properties. For dispersible tablets **Compritol® HD 5** is recommended.
- **Precirol® ATO 5** offers excellent anti-friction properties and is ideal for capsule filling.

Table 5: Gattefossé excipients for tablet and capsule lubrication

Products	Chemical description	Form	HLB	Drop point (°C) (Mettler)
Tablet lubricant				
Compritol® 888 ATO	Glycerol dibehenate EP Glyceryl dibehenate NF Glyceryl behenate Ch.P.	Powder*	2	69.0-74.0
Compritol® HD5 ATO	Behenoyl polyoxyl-8 glycerides NF	Powder*	5	60.0-67.0
Capsule lubricant				
Precirol® ATO 5	Glycerol distearate (type I) EP Glyceryl distearate NF	Powder*	2	53.0-57.0

* Powder mean particle diameter 50 µm

Download our brochure on lubricants

Technical support

Our applications laboratories in France, India, China and USA are at your service to provide technical support and formulation feasibility assessment.

We have many years of experience of formulating with our products with both experimental and model drugs. We are committed to answering your questions on formulation, regulatory, safety, scale-up issues and precedence of use as quickly and as comprehensively as we can.

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 API formulations.

If you need practical laboratory assistance, the services we are able to offer include solubility screening, basic formulation development, texture optimisation and sensorial analysis.

For more information, please contact your local Gattefossé representative

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www.gattefosse.com

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

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