GATTEFOSSÉ

Gelucire® 48/16 pellets

Solubility and oral bioavailability enhancement

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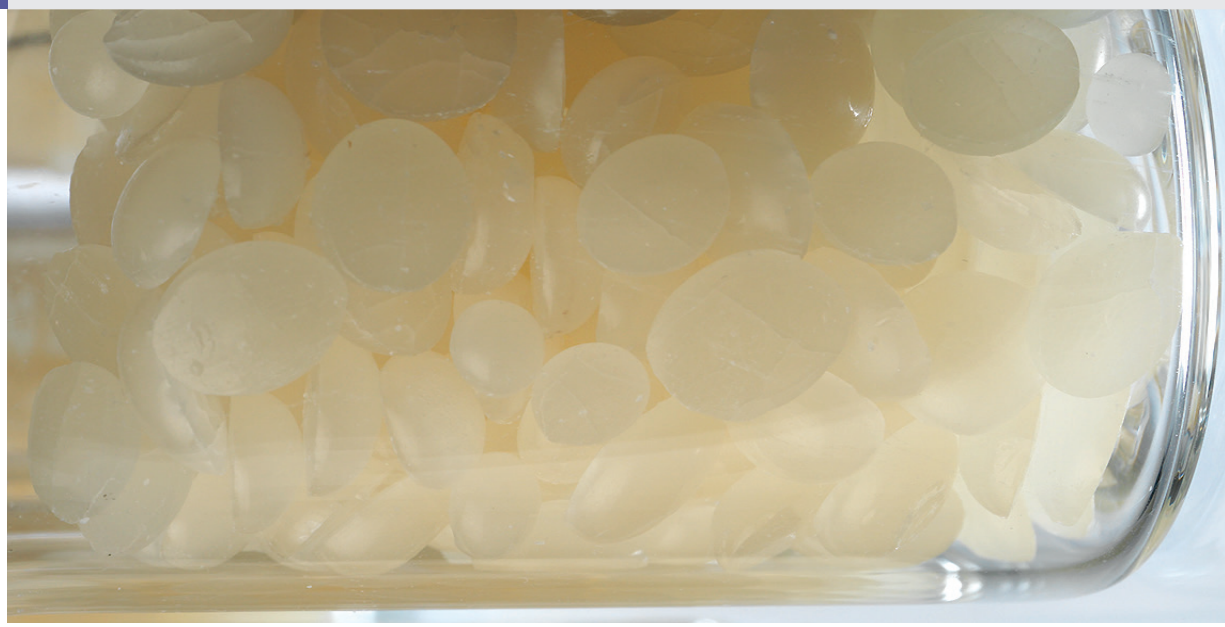
Contents



Product description

Gelucire 48/16 is a non-ionic surfactant recommended for use in Lipid-Based Formulations (LBFs) to increase aqueous solubility and oral bioavailability of poorly soluble active ingredients.

It is a PEG 32 ester lipid excipient comprising a mixture of stearic and palmitic acid monoesters and diesters.

Its high Hydrophilic-Lipophilic Balance (HLB) enhances the solubility of hydrophobic and lipophobic active ingredients.

It is solid at ambient temperature with a melting point of 48°C, making it suitable for capsule filling and melt processes.

Table 1: Physicochemical properties

Drop point (Mettler apparatus)	48.4 ± 0.1°C
Melting point (onset differential scanning calorimetry DSC)	45.4 ± 0.2°C
pH (10% in purified water)	5 ± 1
Calculated/practical HLB	16/12
Critical micellar concentration (CMC) at 25°C	153 ± 31 mg/L
Particle size (37°C, 1 g/200 ml water)	7 ± 1 nm

Product functionality

Gelucire 48/16 pellets in lipid-based formulations for solubility enhancement

Gelucire 48/16 is a pure water-soluble surfactant that can be used in different types of lipid-based formulations.

It forms a micellar solution when used alone in a simple binary formulation with an active ingredient or in combination with a low concentration (< 6%) of a miscible solvent, such as Transcutol HP. Micellar solutions are nanosystems (2-10 nm) which encapsulate the active ingredient within micelles. The size of micelles can change depending on the properties of the active ingredient.

Gelucire 48/16 can be combined with oils, surfactants and solvents, to form type III formulations, provided the excipients are miscible. Gelucire 48/16 is miscible with up to 18% Lauroglycol 90 and 14–30% Capryol 90, which are water insoluble surfactants available from Gattefossé.

A detailed physicochemical data sheet is available from Gattefossé.

Lipid-based formulations for solubility and oral bioavailability enhancement

Lipid-based formulations increase the solubility and oral bioavailability of poorly-water soluble active ingredients by:

- Providing adequate drug loading and solubilization of the therapeutic dose of the active ingredient in the dosage form unit.
- Maintaining the drug in a solubilized state in the gastrointestinal tract during dispersion and digestion.
- Presenting the solubilized drug to the unstirred water layer and brush border (apical) membrane of enterocytes for absorption.

Lipid-based formulations: composition and characteristics

The features and characteristics of LBFs are dependent on the excipient composition (see table 2). The Lipid Formulation Classification System (LFCS) was developed to categorize the different formulation compositions and behaviors in aqueous media[1].

Table 2: Lipid Formulation Classification System with indicative excipient composition for each type of formulation

Formulation	Composition		Formulation characteristics in dispersion
Type I	Oils	100%	Non-dispersible.
Type II	Oils	40-80%	SEDDS without water-soluble components. Opaque emulsion (200 nm-10 µm).
	Low HLB surfactants	20-60%	
Type III	Oils	< 20-80%	SEDDS/SMEDDS with water-soluble components. Ultrafine dispersion (10-200 nm).
	High HLB surfactants	20-50%	
	Hydrophilic cosolvents	0-50%	
Type IV	Low HLB surfactants	0-20%	Transparent micellar solution/nanosystem (2-10 nm).
	High HLB surfactants	30-80%	
	Hydrophilic cosolvents	0-50%	

SEDDS self-emulsifying drug delivery system
SMEDDS self-micro-emulsifying drug delivery system.

Type I formulations contain only lipophilic ingredients (oils) that are non-dispersible in aqueous media. The lipid excipients are digested *in vivo* forming mixed micelles.

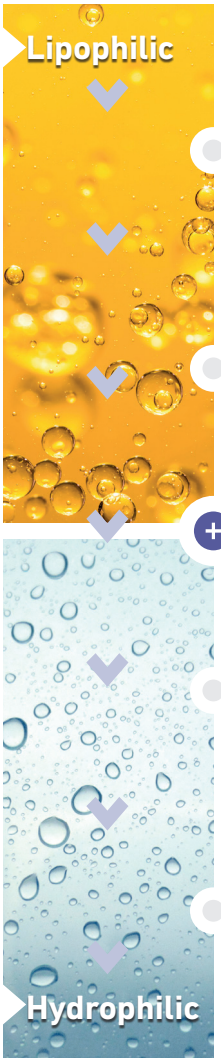
Type II and III formulations contain miscible excipients which form a homogenous dispersion on contact with aqueous media (ie. self-emulsifying system). The particle size and appearance of the dispersion (emulsion or micro/nano emulsion) depend on the properties of the surfactant and the oil phase concentration.

Type IV formulations contain hydrophilic components: water soluble surfactants and hydrophilic co-solvents. They form transparent micellar solutions on contact with aqueous media.

(1) Pouton, C.W. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur. J. Pharm. Sci. 29(3-4), 278-287 (2006)

Use of Gattefossé excipients in lipid-based formulations

Gattefossé excipients can be used in type I to type IV lipid-based formulations as explained below.



Type I (Oils)
Maisine/Peceol
Labrafac Lipophile WL 1349

Formulations with low HLB lipid excipients will be lipophilic, thus providing greater solubilizing potential for lipophilic (high LogP) active ingredients.

Type II (SEDDS)
Labrafil M 1944 CS
Labrafil M 2125 CS

Self-emulsifying excipients with medium HLB can be used to form type II and III formulations.

+ Co-surfactants & solvent used in Type II/III: Capryol 90, Lauroglycol 90, Plurol Oleique, Transcutol HP (6-10%)

These formulations will be more lipophilic or hydrophilic depending on the excipient composition. They are generally more suitable for active ingredients with medium logP.

Type III (SMEDDS)
Gelucire 44/14
Gelucire 50/13
Labrasol ALF

Type IV (Micellar)
Gelucire 48/16
Transcutol HP (< 6%)

Type IV formulations with high HLB excipients will be hydrophilic, containing mostly water soluble surfactants and are useful for active ingredients with low logP.

Guidelines for the development of lipid-based formulations for solubility and bioavailability enhancement are available from Gattefossé.

Excipient handling & processing

Gelucire 48/16 pellets are easy to sample and handle throughout drug development, from early formulation to industrial production.

The onset melting point of Gelucire 48/16 pellets is around 45°C with complete melting and liquefaction at around 48°C (table 1). Recrystallization occurs quickly on cooling, within a narrow temperature range; starting at 32°C the viscosity rapidly increases and the excipient solidifies as illustrated in the thermorheogram below (fig. 1).

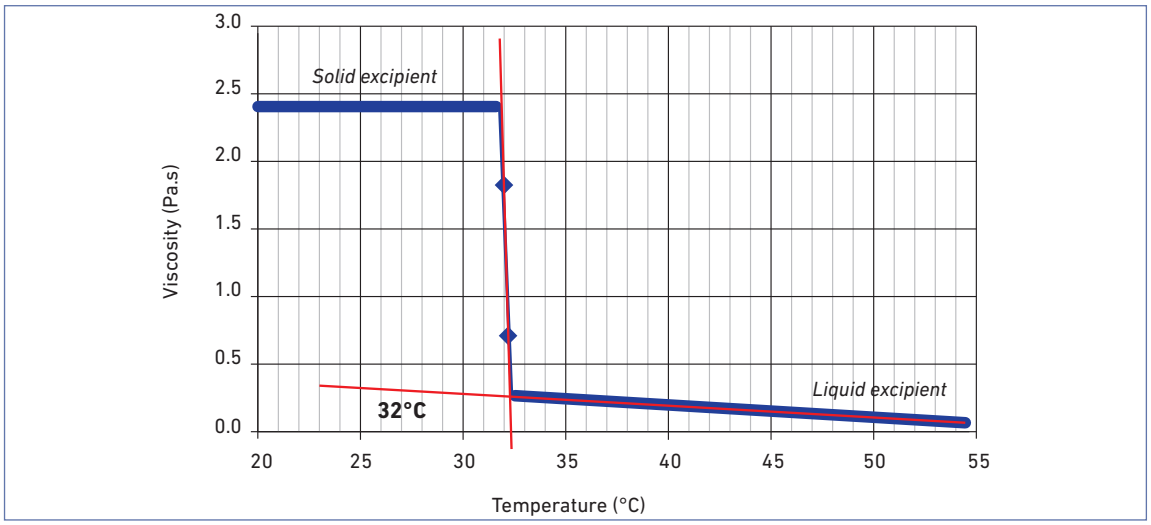


Figure 1: Thermorheogram of Gelucire 48/16 pellets.

The thermal behavior of Gelucire 48/16 makes it ideal for use in melt-processes, such as capsule filling (recommended filling temperature 37-40°C); melt granulation and extrusion without the need for specialized cooling equipment.

This processing flexibility provides scope for innovation in solid oral dosage form development.

Lipid formulation case studies

The following case studies with biopharmaceutical classification system (BCS) Class 2 compounds illustrate the solubilization properties of Gelucire 48/16 and its performance in *in vitro* dispersion and digestion.

Table 3: Physicochemical properties of BCS Class 2 compounds

Active pharmaceutical ingredient	Piroxicam	Curcumin
Water solubility (mg/L) 25°C	23	0.6
Melting point (°C)	198	183
LogP	3.06	3.0
pKa	1.87-6.3	7.8-8.5-9.0
Molecular weight (Da)	331	368

Measuring equilibrium solubility of the model drug compounds

The determination of drug solubility in the excipient is a critical step in lipid-based formulation. Drug solubility in solid Gelucire 48/16 was measured by differential scanning calorimetry (DSC) and the results were confirmed by polarized light hot-stage microscopy (HSM).

Table 4: Equilibrium solubility and dose concentration of drug compounds in Gelucire 48/16

	Piroxicam	Curcumin
Equilibrium solubility (mg/mL)	20	70
Therapeutic dose (mg/dosage unit)	10	30*
% drug saturation in Gelucire 48/16 (1 g capsule)	50	43
LFCS Type	IV	IV

*30 mg corresponds to the most frequently cited oral pharmaceutical dose in the literature for curcumin.

The equilibrium solubility values for both therapeutic compounds indicate that Gelucire 48/16 provides effective solubilization in the dosage form unit (1 g) and therefore no additional solvent is required.

Drug saturation of less than 80% is recommended in lipid-based formulations to reduce the risk of unstable dispersions forming, which can lead to drug precipitation in aqueous fluids.

Gelucire 48/16 enables effective solubilization of both piroxicam and curcumin with drug saturation levels remaining well below the recommended 80% level for lipid-based formulations.

Evaluating *in vitro* dispersion characteristics

The dispersions were evaluated for their appearance, particle size distribution, homogeneity (stability) and for drug precipitation (presence of particles). A 1 g capsule containing a solid dispersion of the formulation was stirred (100 rpm) in 200 ml of purified water at 37°C.

Table 5: Dispersion properties of model drug compounds in Gelucire 48/16

Formulation	Gelucire 48/16 + Piroxicam	Gelucire 48/16 + Curcumin
Size of dispersion (nm)	13 ± 5	10 ± 0
Drug precipitation	No	No
Homogenous dispersion	Yes	Yes

Gelucire 48/16 forms a micellar solution with piroxicam and curcumin. Encapsulation of active ingredient within micelles has little effect on the size of the dispersions which remain in the nanoscale.

The dispersions were homogenous and no drug precipitation occurred with either drug.

Gelucire 48/16 maintained the solubilization of both drugs in a thermodynamically stable micellar solution after dispersion in purified water at 37°C.

Gelucire 48/16 is suitable for solid dispersions. Drug loading can be high (i.e. the therapeutic dose can exceed the 100% drug saturation level) because Gelucire 48/16 is solid at ambient temperature and although the active ingredient may crystallize over time there is no risk of sedimentation.

Evaluating *in vitro* digestion performance

In vivo, gastrointestinal digestive fluid contains enzymes that hydrolyze ester bonds of lipids to form fatty acids and monoglycerides. This physiological process is known to affect the performance of lipid-based drug delivery systems due to their similar composition to that of food-derived lipids. It is therefore important to evaluate the impact of digestion on Gelucire 48/16 formulations using a lipolysis test.

In vitro lipolysis test

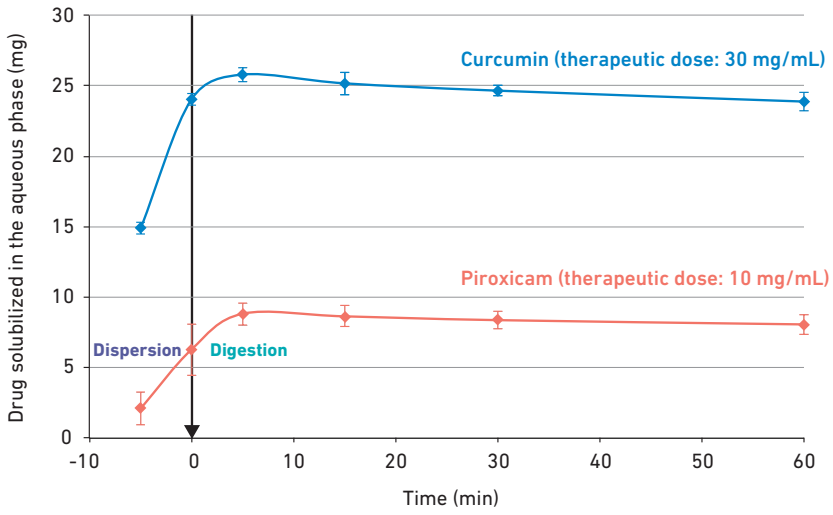
A capsule (1 g) containing the formulation was placed in bio-relevant media mimicking the fasted state conditions in the small intestine (36 ml). After a short dispersion period, pancreatic enzyme solution was added to simulate the *in vivo* digestive conditions. The detailed protocol is described in "Developing Lipid-Based Formulations for Oral Bioavailability Enhancement" available from Gattefossé.

Results and discussion (fig 2)

Hydration and erosion of the Gelucire 48/16 formulation occurred slowly on contact with an aqueous media during dispersion. Consequently, the solubility of piroxicam/curcumin in the aqueous media increased gradually over 5 to 15 minutes. Gelucire 48/16 continued to provide an increase in drug solubilization in the aqueous phase after the addition of the pancreatic digestive enzyme solution.

These results indicate that Gelucire 48/16 maintained its solubilizing power during digestion by pancreatic enzymes. Formulations with Gelucire 48/16 have a low propensity to precipitation because more than 75% of the drug is in micellar solution after 60 minutes of digestion.

Gelucire 48/16 maintains a high concentration of piroxicam and curcumin in solution during *in vitro* digestion for 60 minutes. This may favor enhanced *in vivo* absorption and bioavailability.



Dispersion phase

During the initial dispersion phase PEG chains hydrate forming viscous liquid crystalline mesophases which erode to form a micellar solution. The solubility of the active ingredient in the aqueous phase gradually increases due to the relatively slow hydration and micellization process. The risk of drug precipitation can be reduced by avoiding a sudden increase in drug solubility.

Digestion phase

The specific composition of Gelucire 48/16 helps to maintain the active ingredient in a solubilized state within the micellar solution. During digestion the diester composition provides a "reservoir" of surfactant which is digested to monoesters - a stronger surfactant component of Gelucire 48/16 - which replenishes the micellar system maintaining the drug in a solubilized state.

Figure 2: Evolution of the amount of piroxicam and curcumin (mg) solubilized in the aqueous phase (dispersed + digested).

These case studies illustrate how Gelucire 48/16 can be used in a straightforward lipid-based formulation to increase the aqueous solubility of BCS Class 2 compounds.

Regulatory and safety information

Gelucire 48/16 meets current specifications for the USP/NF monograph for polyoxyl stearate (type I) and the Japanese Pharmacopoeia (JPE) for polyethylene glycol monostearate.

Macrogol glycerides (polyoxyl stearate) have previously been used in authorized oral, topical, rectal and vaginal medicinal products. Polyoxyl stearates are listed in the US FDA Inactive Ingredients database for several administration routes and dosage forms.

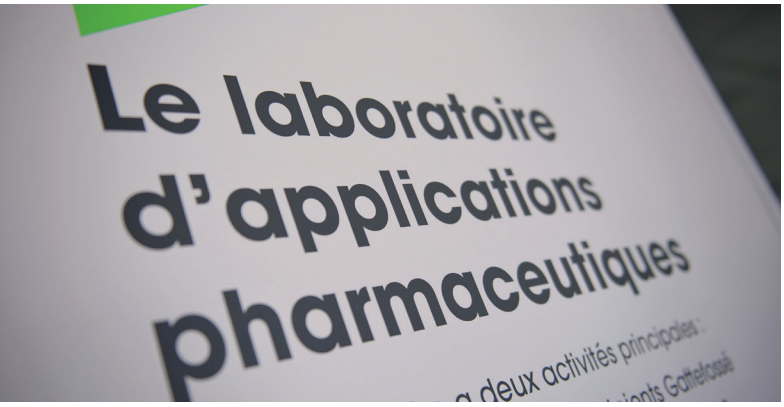
A type IV drug master file (DMF) is registered with the FDA in the US.

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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