GATTEFOSSÉ

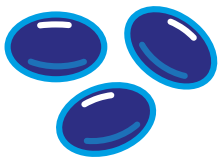
Lipid-based formulations

A winning strategy to overcome oral bioavailability challenges

People make our name

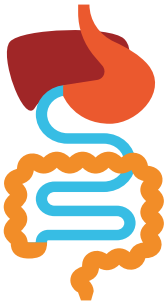
Lipid excipients offer a unique combination of benefits

Poor solubility, poor permeability, and pre-systemic elimination are factors that can limit absorption of some drugs. Lipid excipients have the capability to overcome these hurdles and enhance oral bioavailability through different mechanisms.



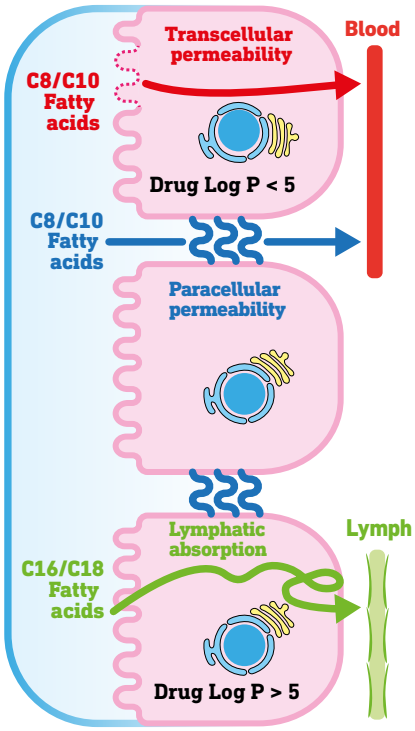
Increase drug solubility

Poorly water-soluble drugs are generally soluble in lipid excipients, as revealed by the abundant scientific literature on lipid-based formulations.



Maintain drug solubilization throughout digestion

Upon action of enzymes and bile salts, the lipid-based formulation is digested and transformed in a series of colloidal structures: vesicles, mixed micelles, and crystalline lipid phases. They contribute to maintaining the drug in solubilized state throughout the digestion process. Ultimately, fatty acids, monoglycerides and drug partition out of the micelles and are absorbed.



Increase intestinal permeability

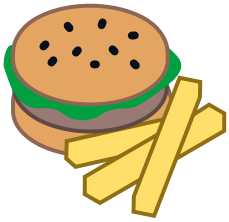
Medium-chain fatty acids (C8-C10) are known to facilitate intestinal absorption of poorly permeable drugs via:

- Transcellular uptake due to a membrane fluidization effect
- Paracellular uptake due to the reversible opening of tight junctions.

Target lymphatic transport

Two prerequisites to promote lymphatic absorption:

- As a general rule, the drug should be highly lipophilic (Log P > 5) and soluble in triglycerides (>50 mg/g)
- The formulation must contain unsaturated long-chain fatty acids (C16-C18:1, C18:2) known to facilitate lymphatic uptake via assembly of drug with lipoproteins in the chylomicrons.



Mitigate food effect

Ingestion of a lipid-based formulation is sufficient to trigger the release of bile and lipases, in the same manner and extent as it occurs with a fat-containing meal. The difference between fasted and fed state is minimized and food effect can be reduced or cancelled.

Overview of Gattefossé excipients for oral bioavailability enhancement

Our range of functional excipients includes oils, low HLB surfactants, high HLB surfactants and solvents. They can be combined to formulate all types of lipid-based formulations (LBF).

LBF TYPE			HLB
I	Oils	Maisine® CC	1
		Peceol™	1
		Labrafac™ Lipophile WL 1349	1
II	Water insoluble surfactants	Lauroglycol™ 90	3
		Plurol® Oleique CC 497	3
III		Capryol® 90	5
	Water dispersible surfactants	Labrafil® M 1944 CS	9
		Labrafil® M 2125 CS	9
		Gelucire® 44/14	11
		Gelucire® 50/13	11
		Labrasol® ALF	12
IV	Water soluble surfactant	Gelucire® 48/16	14
	Solvent	Transcutol® HP	

Our self-emulsifying excipients are all-in-one systems enabling the preparation of:

- Type II LBF: Labrafil® M 1944 CS or Labrafil® M 2125 CS
- Type III LBF: Gelucire® 44/14, Gelucire® 50/13 or Labrasol® ALF

Examples of marketed drug products formulated with lipid excipients

- Calcitriol
- Cyclosporine
- Dutasteride
- Enzalutamide
- Ibuprofen
- Nimesulide

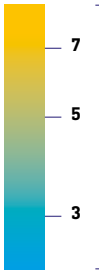
- Fenofibrate
- Ibuprofen
- Isotretinoin
- Omeprazole
- Piroxicam
- Telmisartan

Download our “Panorama Newsletter” for more information on the precedence of use of lipid excipients.

API and dosage form guide the excipient choice

This table gives comprehensive indications on excipient choice as a function of:

- API affinity for lipid excipients, and its physicochemical and pharmacokinetic properties;
- dosage form preference.

		Gattefossé recommendations for excipient selection	Labrafac™ lipophile WL 1349	Maisine® CC	Peceol™	Lauroglycol™ 90	Plurol® Oleique CC 497	Capryol® 90	Labrafil® M 1944 CS	Labrafil® M 2125 CS	Gelucire® 44/14	Gelucire® 50/13	Labrasol® ALF	Gelucire® 48/16	Transcutol® HP
API characteristics	 High lipophilicity	Use oils, or mixed mono, di-, and triglycerides	●	●	●										
	Medium lipophilicity	Use low HLB (≤ 9) surfactants				●	●	●	●	●					
	Low lipophilicity	Use high HLB (> 10) surfactants and hydrophilic solvents									●	●	●	●	●
	Heat sensitive	Prefer liquid excipients and room / low temperature handling	●	●	●	●	● [1]	●	●	●			●		●
	High first pass metabolism	Use unsaturated long chain fatty acids to promote lymphatic uptake		●	●		●		●	●					
	Low permeability	Use medium chain fatty acids (C8/C10) to increase intestinal permeability						●					●		
Dosage form	Soft gels	Prefer liquid / low viscosity formulation Check capsule shell compatibility[2]	●	●	●	●	●	●	●	●			●		●
	Hard capsules – liquid filled	Prefer liquid / low viscosity formulation Check capsule shell compatibility[2] Use special capsule shell to prevent leakage	●	●	●	●	●	●	●	●			●		●
	Hard capsules – solid filled	Use semi-solid / solid excipients as main components. Up to 20% liquid excipients is feasible Check capsule shell compatibility[2]									●	●		●	

[1] Plurol® Oleique CC 497 is a viscous liquid. Handling at 37°C is recommended

[2] Our excipients are compatible with gelatin and cellulose capsule shells at all concentrations, except:
- Transcutol® HP that should be used below 15%
- Labrasol® ALF is hygroscopic and may interact with some type of shells

Developing successful lipid-based formulations step by step

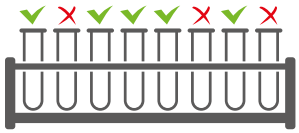
An optimized LBF enables solubilization of the entire therapeutic dose and maintains the drug in solubilized state throughout the digestion process.

To speed up LBF development, we have produced tools to guide you at each stage of development:

1 - methods for saturation solubility screening
2 - database of solubility of drugs in common pharmaceutical excipients
3 - methods for miscibility and dispersability testing
4 - miscibility table
5 - *in vitro* lipolysis procedure
6 - guideline for preclinical studies

Contact Gattefossé for more information

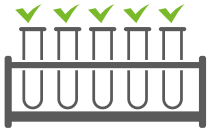
Solubility screening in individual excipients



A single excipient solubilizes the entire therapeutic dose

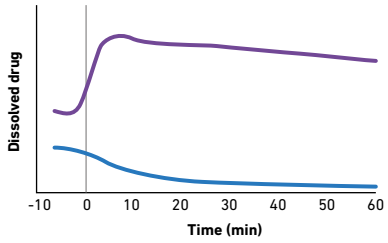
No

Select excipients with highest solubilizing capacity in various classes: oily vehicles, surfactants and solvents

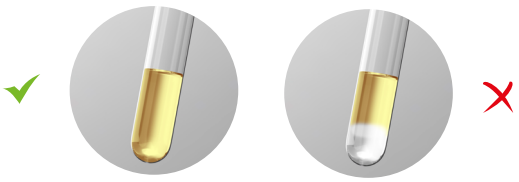


Yes

In vitro lipolysis test



Miscibility screening of binary mixtures of excipients



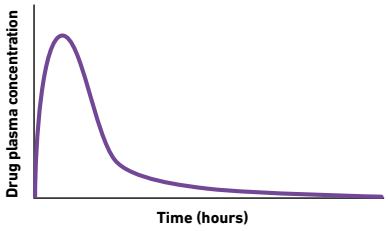
The formulation maintains the drug in solubilized state throughout digestion

No

Dispersability testing of mixtures of excipients without and with API

Yes

In vivo testing



Define formulations with good solubilizing capacity, miscibility and dispersability

GATTEFOSSÉ

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