Lipid-based formulations
Bio-enhancers by nature
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.

**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 overcome.

**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 transport 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.
Lipid-based formulations present the drug in a solubilized state in the gastro-intestinal tract. As such, the drug molecule solubility and stability in the excipients will dictate the formulation type. Formulation design and excipient choices are also influenced by considerations of other factors, such as emulsification capacity in the GI tract, behavior upon digestion, targeted route of drug absorption (lymphatic or systemic), and potential interactions of the drug with food. In all cases, careful selection of the lipid excipient(s) is necessary for increasing oral bioavailability.

Overview of Gattefossé excipients for oral bioavailability enhancement

LBF type II and III are known for enhanced solubilization capacity and auto-emulsification properties, hence referred to as Self Emulsifying Drug Delivery Systems (SEDDS).

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, Gelucire® 59/14 or Labrasol® ALF

Examples of marketed drug products formulated with lipid excipients
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.

<table>
<thead>
<tr>
<th>Log P</th>
<th>API characteristics</th>
<th>Gattefossé recommendations for excipient selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>High lipophilicity</td>
<td>Use oils, or mixed mono-, di-, and triglycerides</td>
</tr>
<tr>
<td>5</td>
<td>Medium lipophilicity</td>
<td>Use low HLB (≤ 9) surfactants</td>
</tr>
<tr>
<td>3</td>
<td>Low lipophilicity</td>
<td>Use high HLB (&gt; 10) surfactants and hydrophilic solvents</td>
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</tbody>
</table>

- **Heat sensitive**
  - Prefer liquid excipients and room / low temperature handling

- **High first pass metabolism**
  - Use unsaturated long chain fatty acids (C18:1, C18:2) to promote lymphatic uptake

- **Low permeability**
  - Use medium chain fatty acids (C8/C10) to increase intestinal permeability

**Dosage form**

- **Soft capsules**
  - Prefer liquid / low viscosity formulation
  - Check capsule shell compatibility

- **Hard capsules – liquid filled**
  - Prefer liquid / low viscosity formulation
  - Check capsule shell compatibility
  - Use appropriate 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

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

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**Gattefossé Pharmaceutical**
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 drug’s solubilities 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

Yes

In vitro lipolysis test

Dissolved drug

Time (min)

No

Yes

In vivo testing

Drug plasma concentration

Time (hours)

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

Miscibility screening of binary mixtures of excipients

Dispersability testing of mixtures of excipients without and with API

Define formulations with good solubilizing capacity, miscibility and dispersability