GATTEFOSSÉ

People make our name

Labrasol® ALF
Premium bioenhancer

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Labrasol® ALF in a nutshell »

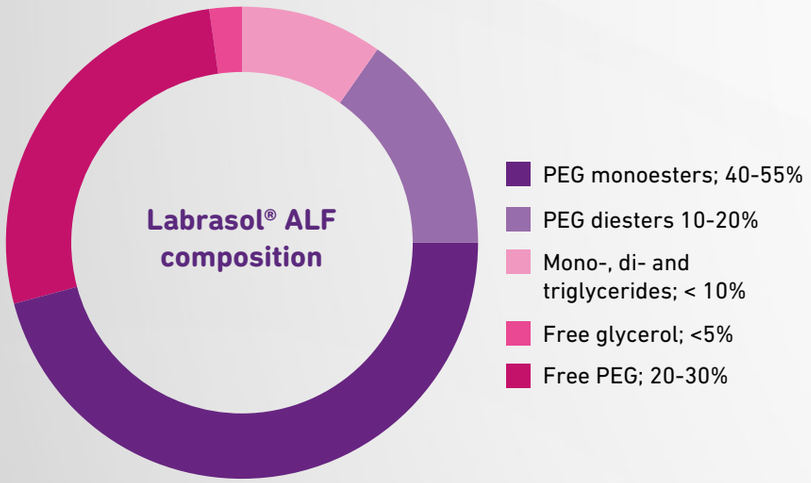
Product description

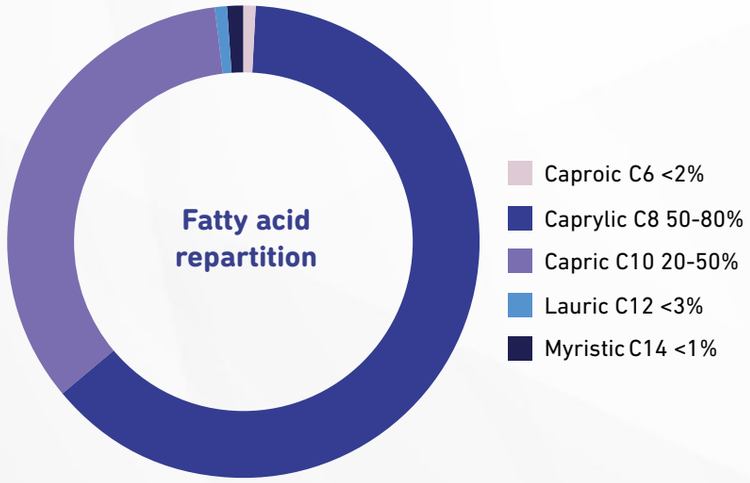
- Composition
- Physico-chemical properties
- Miscibility at 25°C with common excipients

Composition

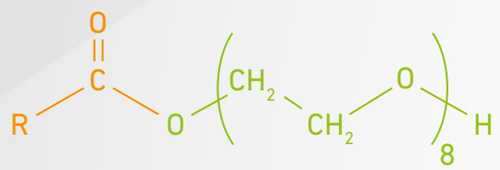
Medium chain triglycerides (C8-C10) + PEG-8 (MW 400) → Labrasol® ALF

Labrasol® ALF is issued from an alcoholysis reaction between PEG-8 and medium-chain triglycerides (C8 - C10) from vegetable oil. It is a well-defined multi-constituent substance composed of PEG-8 mono- and di- esters of caprylic/capric acids (C8 - C10) and mono-, di- and triglycerides.

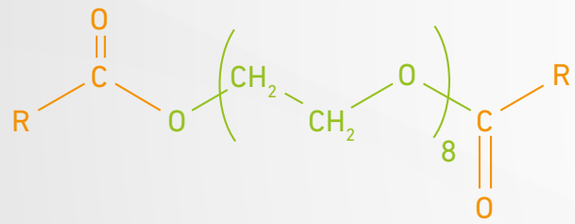




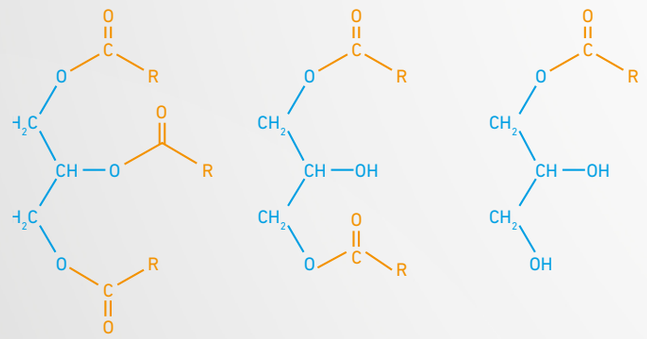
PEG monoester



PEG diester



Triglyceride *Diglyceride* *Monoglyceride*



R-COOH = caprylic acid and capric acid

Physico-chemical properties

Labrasol® ALF is a water dispersible surfactant with an HLB of 12 ± 1

HLB	12 ± 1
Viscosity at 20°C (mPa.s)	80-110
Critical Micellar Concentration (mg/L)	42 ± 24

Miscibility with solvents (25°C)	
Chloroform	Very soluble
Ethanol 96°	Very soluble
n Hexane	Insoluble

Labrasol® ALF has a very low aldehyde content for higher compatibility with capsule shell and other ingredients of the formulation.

Miscibility at 25°C with common excipients

Miscible Non-miscible

		% Labrasol® ALF									
		10	20	30	40	50	60	65	70	80	90
Oils	Maisine® CC										
	Peceol™										
	Labrafac™ Lipophile WL 1349										
Water insoluble surfactants	Capryol® 90										
	Labrafac™ MC60										
	Lauroglycol™ 90										
	Plurol® Oleique CC 497										
Water dispersible surfactants	Labrafil® M 1944 CS										
Solvents	Transcutol® HP										

Product functionality

- Self-emulsifying excipient
- Solubilizer of a wide range of molecules
- Intestinal permeation enhancer
- Oral bioavailability enhancer

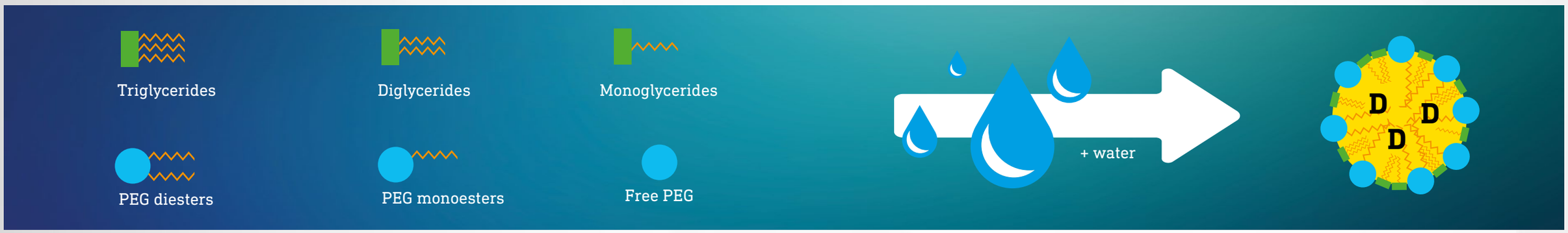
Self-emulsifying excipient

Labrasol® ALF is a self-emulsifying system: upon contact with aqueous / digestive media, it spontaneously forms a fine emulsion.

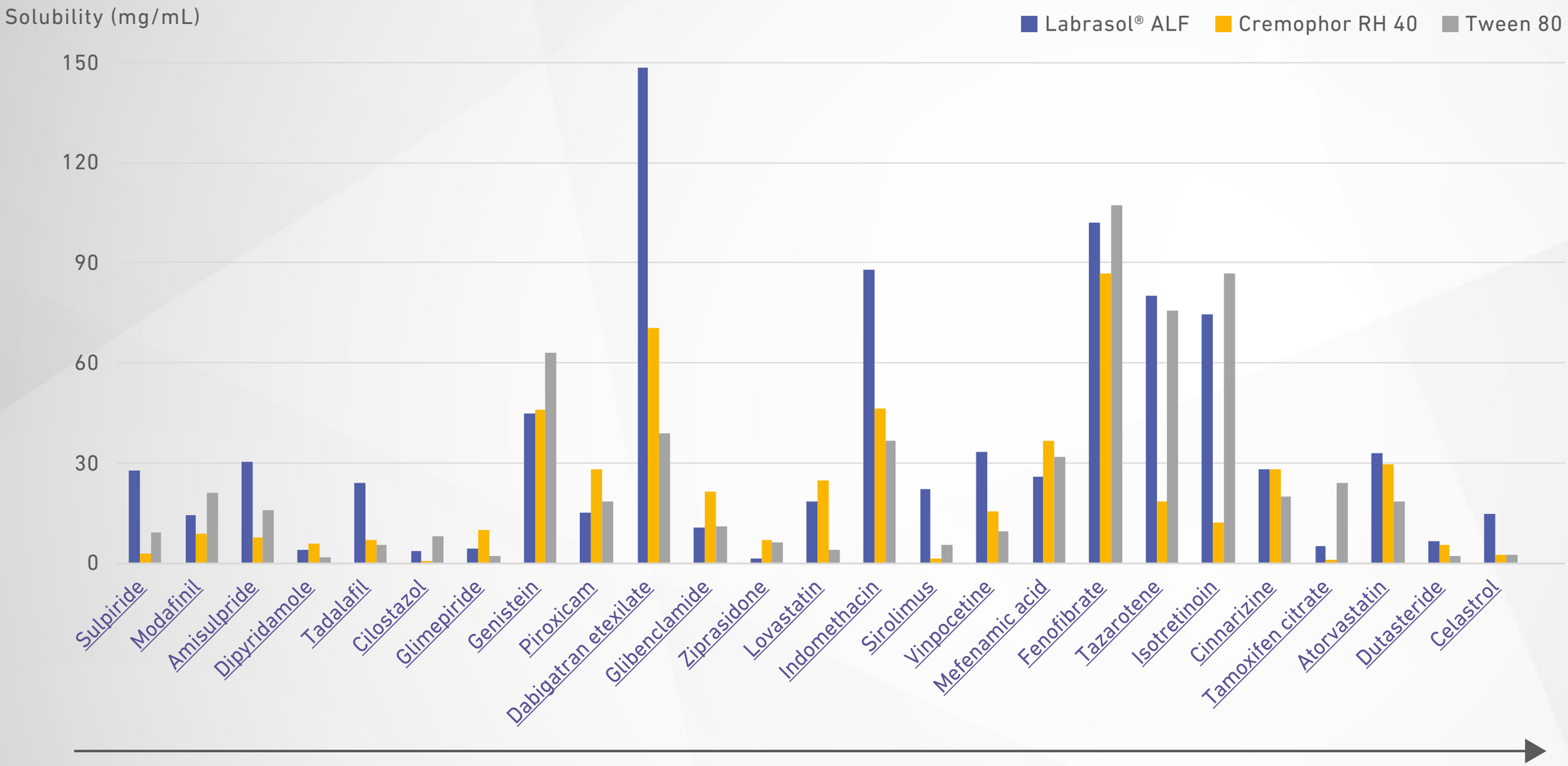
The different components self-assemble as a function of their affinity for water:

- PEGs are water-soluble
- PEG esters and monoglycerides are amphiphilic
- di- and triglycerides are hydrophobic.

Depending on the concentration used, Labrasol® ALF does not form micelles of the same size: 100 nm at low concentration (1-2 g/L), 450 nm for concentrations around 10 g/L to micellar solutions for concentration above 20 g/L.



Solubilizer of a wide range of molecules

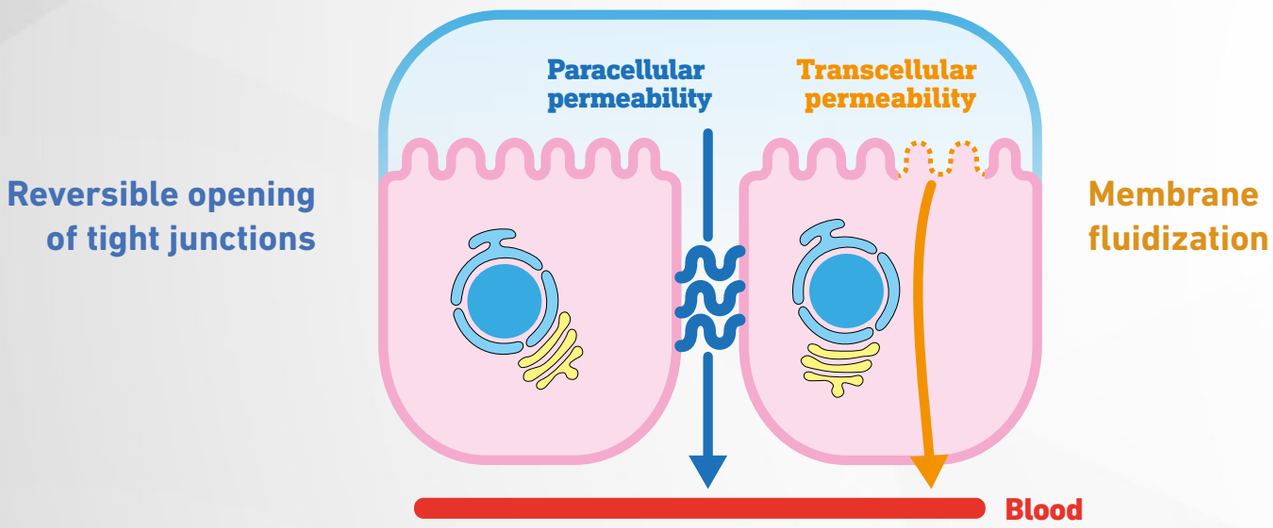


Intestinal permeation enhancer

Excipients containing medium chain acid derived salts are well-known for their intestinal permeation enhancing properties.

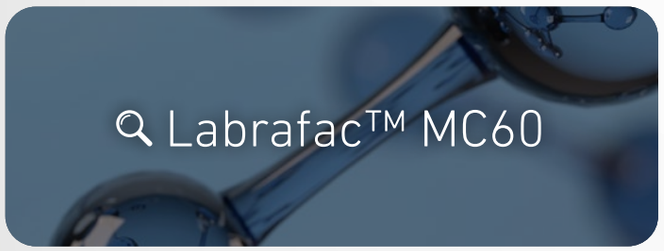
The proposed mechanism of action of C8/C10 fatty acids is a combination of:

- Paracellular transport with the reversible opening of enterocytic tight junctions
- Transcellular transport due to membrane fluidization



Brayden et al., 2014; Brayden et al., 2015; McCartney et al., 2016; Twarog et al., 2019

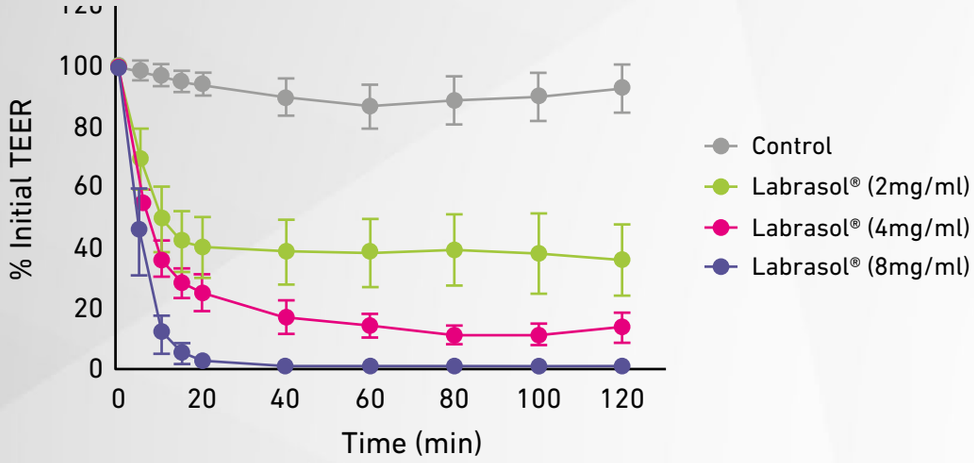
Gattefossé intestinal permeation enhancers

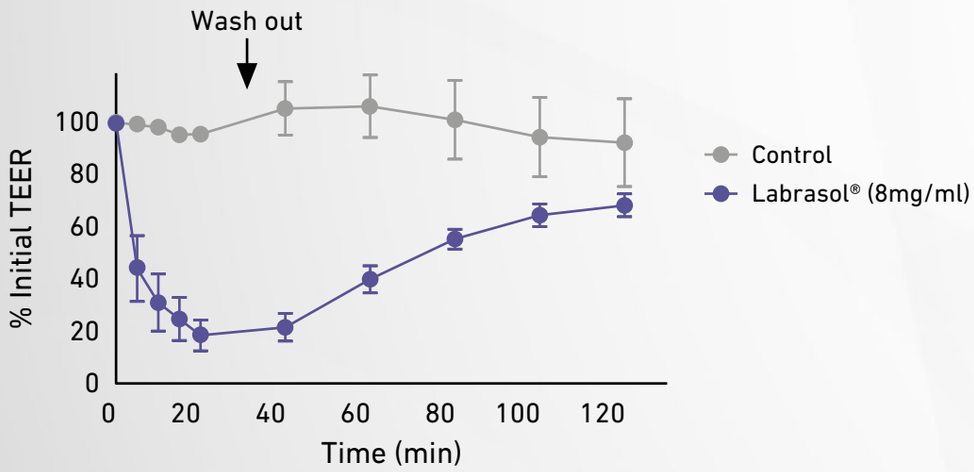


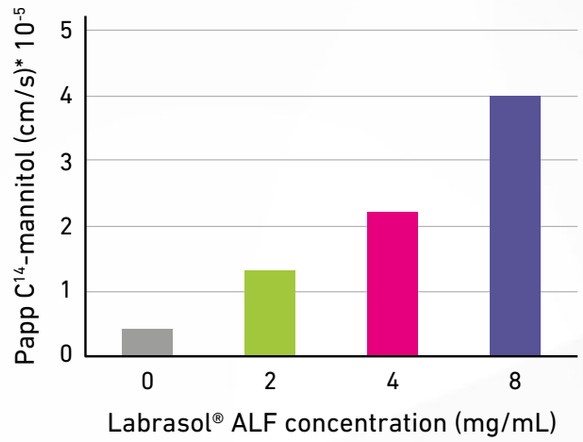
Labrasol® ALF transiently opens tight junctions

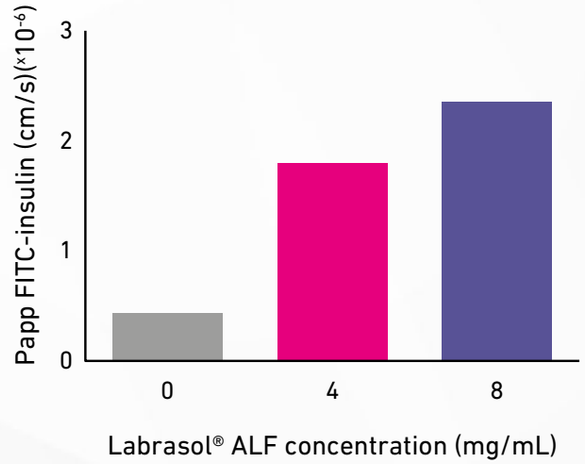
The decrease in the transepithelial electrical resistance (TEER) indicates that the tight junctions are open. And the recovery of the initial TEER level after wash out shows the reversibility of the opening.

The significant increase in apparent permeation of paracellular marker like C14-mannitol or model peptide like insulin confirms the tight junction opening.









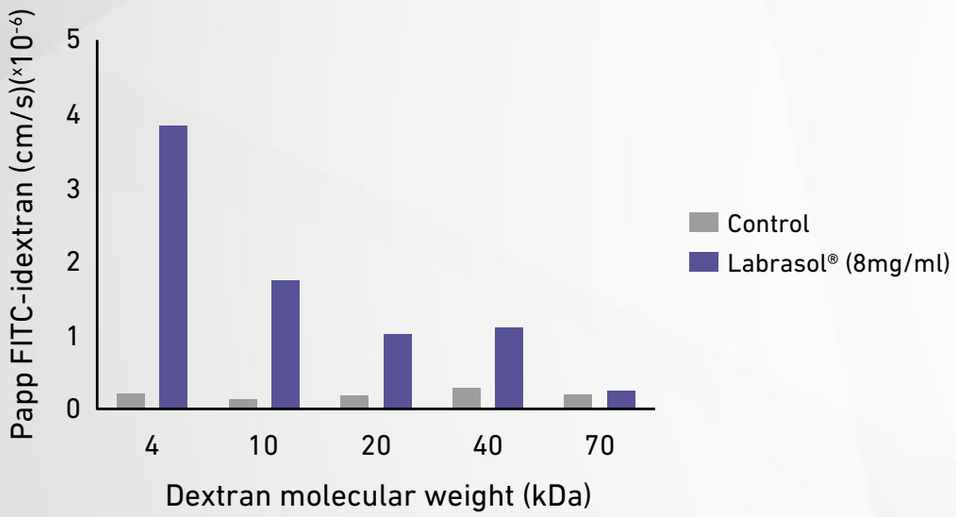
McCartney, 2019

Labrasol® ALF safely opens tight junctions

Permeation limited to low molecular weight compounds

The permeability of Fluorescein isothiocyanate-dextran of different molecular weights (4, 10, 20, 40 and 70 kDa) was tested in Ussing chamber on rat colon with or without the addition of 8mg/mL of Labrasol® ALF.

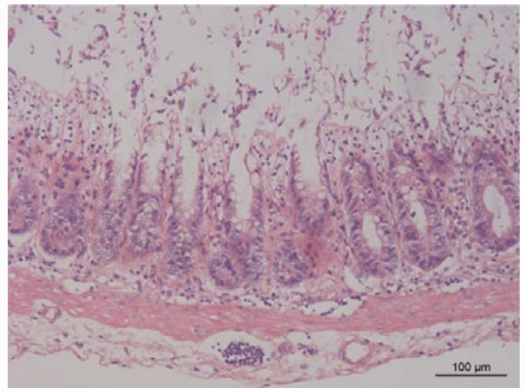
Labrasol® ALF permeation enhancement effect is limited to molecules with relatively low molecular weight (<40 kDa). Hence, the opening of tight junctions with Labrasol ® ALF will not allow the passage of large molecules like lipopolysaccharides or pathogens like viruses or bacteria.



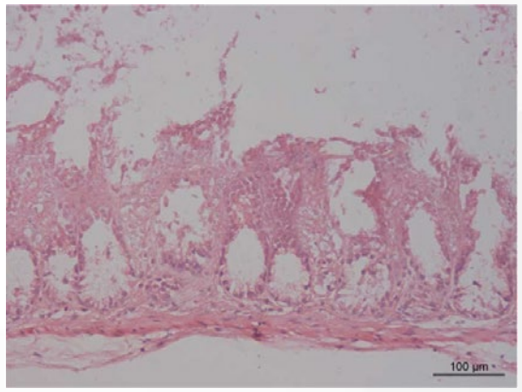
McCartney, 2019

Undamaged intestinal mucosae

Histological evaluation of rat intestinal mucosae treated with Labrasol® ALF reveals no damage unlike that observed with capric acid (C10).

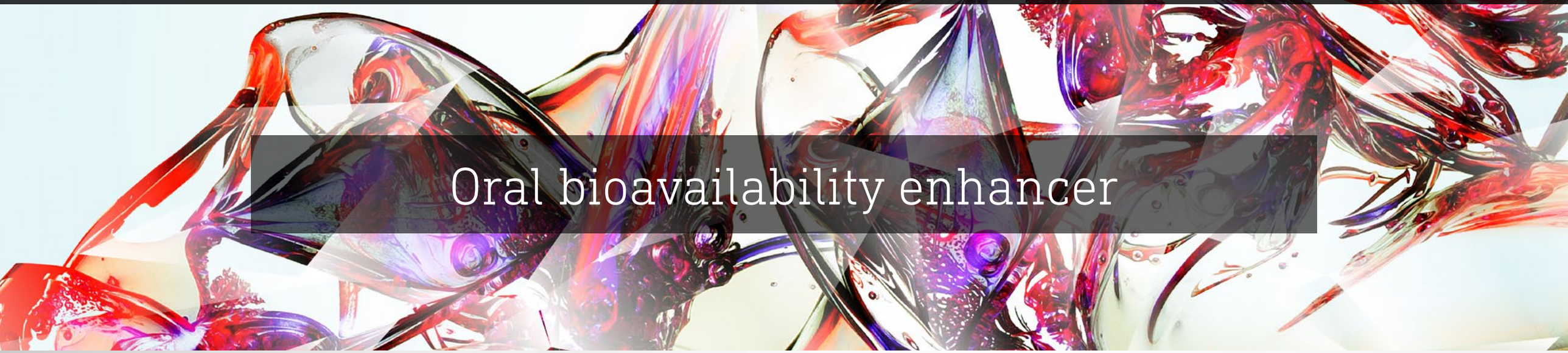


Labrasol® ALF



C10

Maher, 2018



Oral bioavailability enhancer

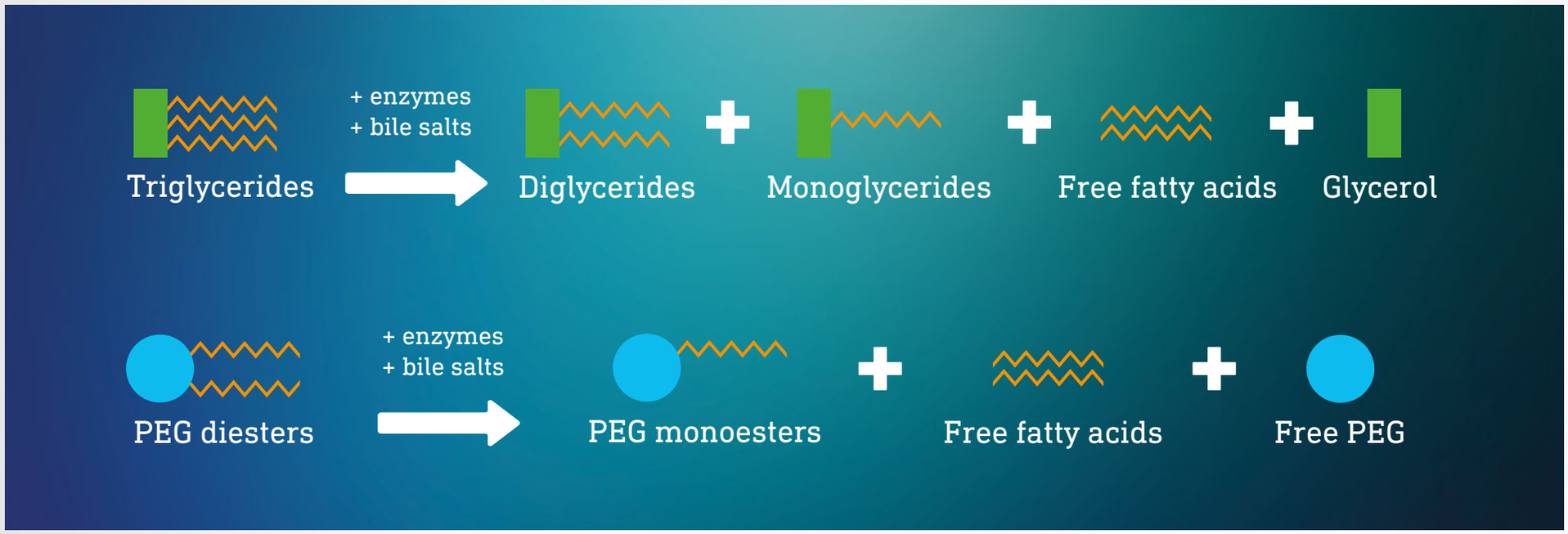
When entering the digestive system, the various components of Labrasol® ALF self-emulsifying excipient are hydrolyzed.

In the stomach

- Triglycerides are rapidly and almost completely digested into diglycerides, monoglycerides and free fatty acids.
- Diglycerides are partially digested into monoglycerides and fatty acids.

In the intestine

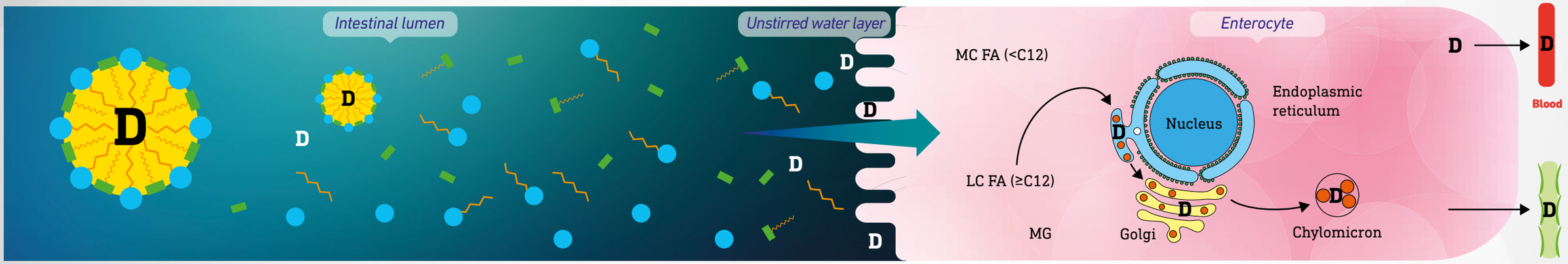
- PEG esters are partially digested releasing free fatty acids and free PEG.
- Free fatty acids and monoglycerides are absorbed via the enterocytes.



Oral bioavailability enhancer

The digestion products self-assemble into colloidal structures that maintain the drug in solubilized state until absorption.

The digestion of lipids stimulates the secretion of bile salts, phospholipids and cholesterol by the gall bladder. These amphiphilic compounds associate with the components of Labrasol® ALF digestion and self-assemble into different colloidal structures: multi-lamellar, vesicles, mixed micelles and micelles. These structures have variable solubilizing capacities and contribute to maintaining the drug in solubilized state throughout the on-going digestion process. Ultimately, the fatty acids, monoglycerides and drug partition out of the mixed micelles and are absorbed in the enterocyte.



D drug; MC FA medium chain fatty acid; LC FA long chain fatty acid; MG monoglyceride

Regulatory information and precedence of use

- A multi-compendial excipient
- Maximum potency per unit dose (IID)
- Examples of commercial products

A multi-compendial excipient

USP-NF	Caprylocaproyl polyoxyl-8 glycerides NF
European Pharmacopoeia	Caprylocaproyl macrogol-8 glycerides EP
FDA Substance Registration System	UNII: 00BT03FSO2

other names

Maximum potency per unit dose (IID)

FDA Inactive ingredient guide
(http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm)

CAPRYLOCAPROYL POLYOXYLGLYCERIDE 8 (UNII: 00BT03FSO2)

Administration route	Dosage form	Maximum Potency per unit dose	Maximum Daily Exposure (MDE)
ORAL	CAPSULE	274.7mg	/
	CAPSULE, LIQUID FILLED	/	3623mg
	SOLUTION	61.2mg/1ml	/

Examples of commercial products

Soft gelatine capsule	Hard capsule	Tablet	Solution (veterinary)
• Ciclosporin • Enzalutamide • Loratadine • Tocotrienol • Nimesulide	• Orlistat • Piroxicam	• Dexibuprofen • Glimepiride and metformin	• Moxidectin and triclabendazole

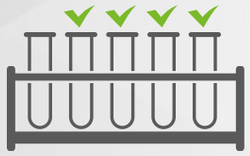
- SEDDS formulation development
- Case study with a small molecule: piroxicam
- Case study with a peptide: insulin

SEDDS formulation development

Due to its composition, Labrasol® ALF is a SEDDS on its own. Therefore, if a quantity corresponding to a reasonable unit dose size can solubilize the therapeutic dose of the API, there is no need to associate Labrasol® ALF with additional excipients. Alternatively, if the dose of API is not entirely solubilized, other standard SEDDS/SMEDDS excipients, such as oil, surfactant, co-surfactant and solvent, may be required.

Multi-excipient SEDDS and SMEDDS are developed in a stepwise approach following these main stages:

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

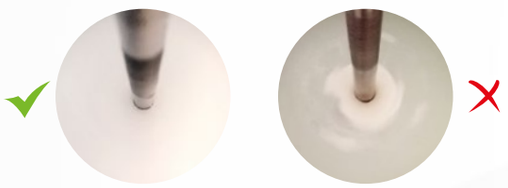


Assess API solubility in individual excipients (oils, surfactants and solvents) to select the excipients with highest solubilization capacity.

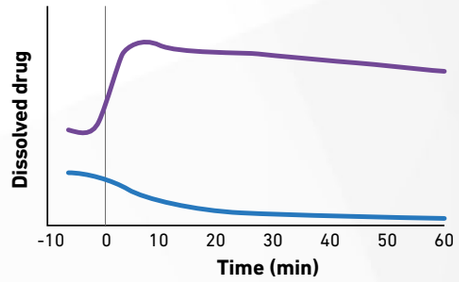
Miscibility screening of binary mixtures of excipients

Perform miscibility and dispersion testing to select the best excipient combination(s) and define ratios to develop the formulations.

Dispersability testing of mixtures of excipients without and with API



In vitro lipolysis test



Undertake in vitro lipolysis testing to assess if the drug is maintained in a solubilized state throughout the digestion process and select the best formulation for further development.

More information on SEDDS development

Case study with a small molecule: piroxicam

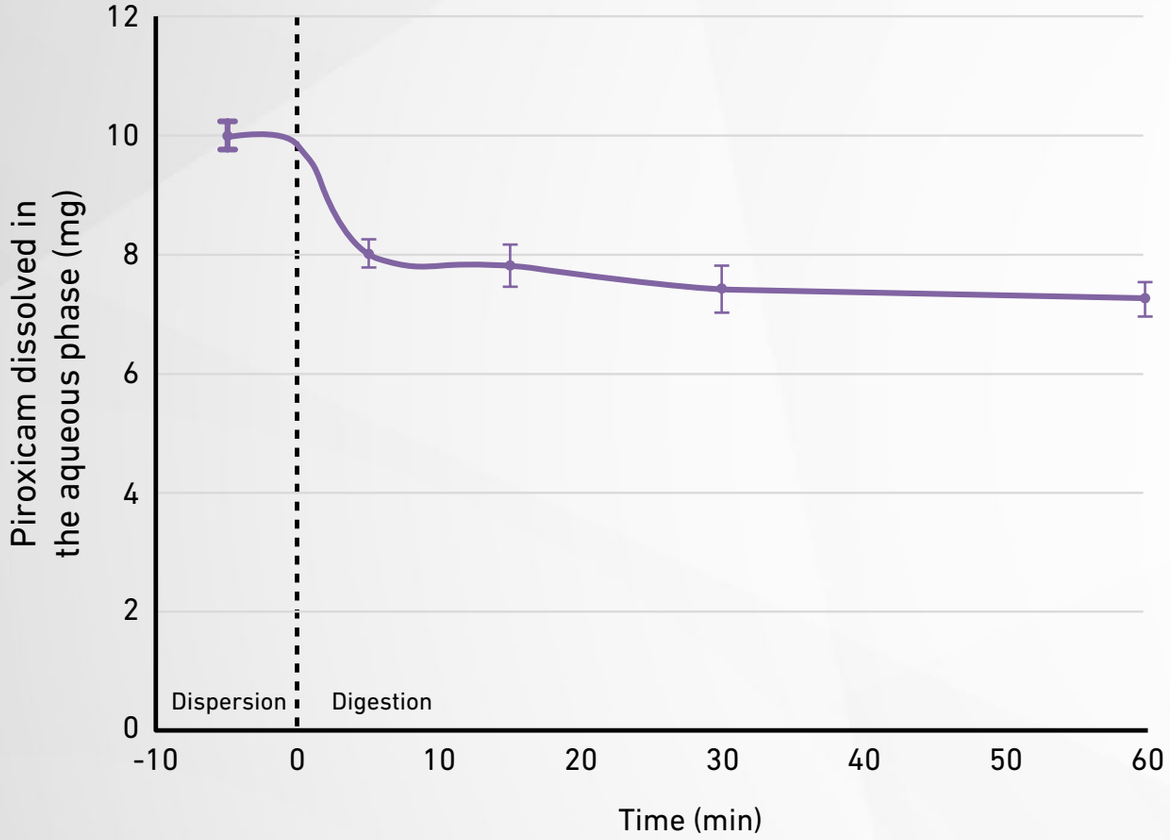
Drug characteristics

- Log P = 2.2
- Water solubility: 0.143 mg/mL
- Solubility in Labrasol® ALF: 15 mg/mL
- Commercial product strength: 10 to 20 mg

SEDDS formulation

- 1 mL Labrasol® ALF
- 10 mg of piroxicam

In vitro lipolysis test at 37°C



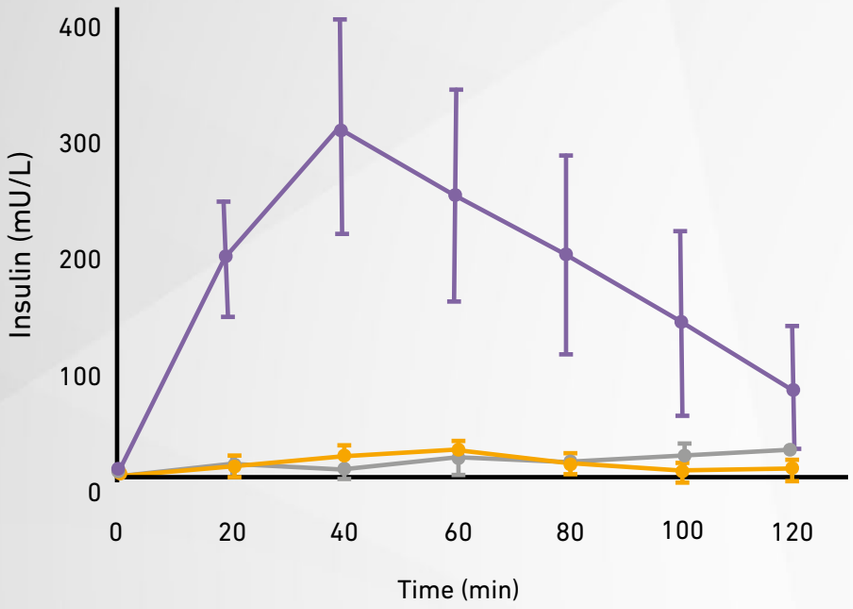
In this SEDDS formulation, Labrasol® ALF was able to maintain 80% piroxicam in solution during lipolysis.

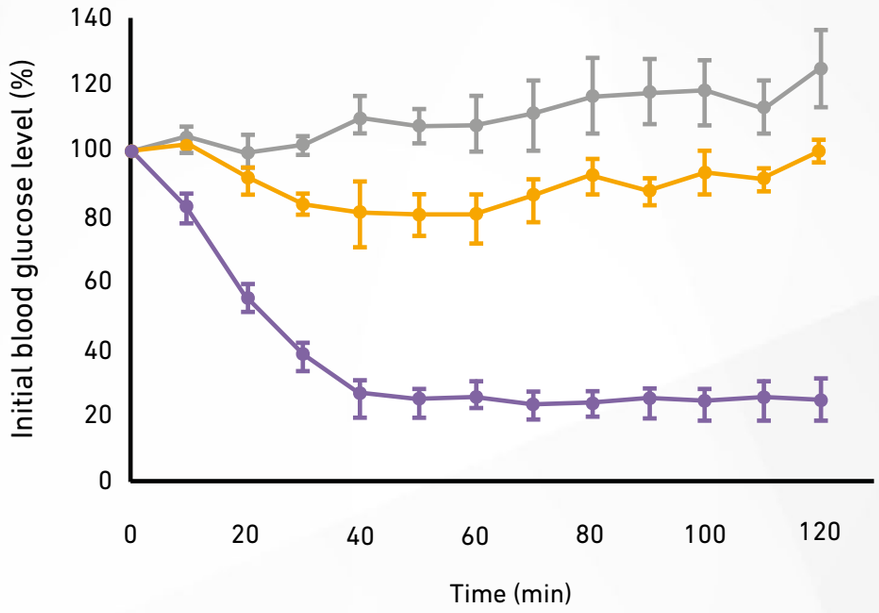
Jannin, 2013

Case study with a peptide: insulin

Rat in situ instillation

- Labrasol® ALF: 8 mg/mL
- Insulin solution 50 IU/kg





PBS — Insulin solution — Insulin + Labrasol®ALF (8 mg/mL)

This ex vivo rat study shows that Labrasol® ALF enables the intestinal permeation of insulin and an effective blood glucose decrease.

McCartney, 2018

Technical support

A long-established company

A pioneer in lipid-based formulations

A worldwide presence

A long tradition of knowledge sharing

High quality, functional excipients

A network of application laboratories

For technical support
and more information

www.gattefosse.com

Contact us

Labrasol® ALF in a nutshell

- A self-emulsifying excipient
- Liquid surfactant, HLB=12
- Oral bioavailability enhancer
- Solubilizer of a wide range of molecules
- Intestinal permeation enhancer
- Caprylocaproyl macrogol-8 glycerides EP/NF
- Worldwide precedence of use

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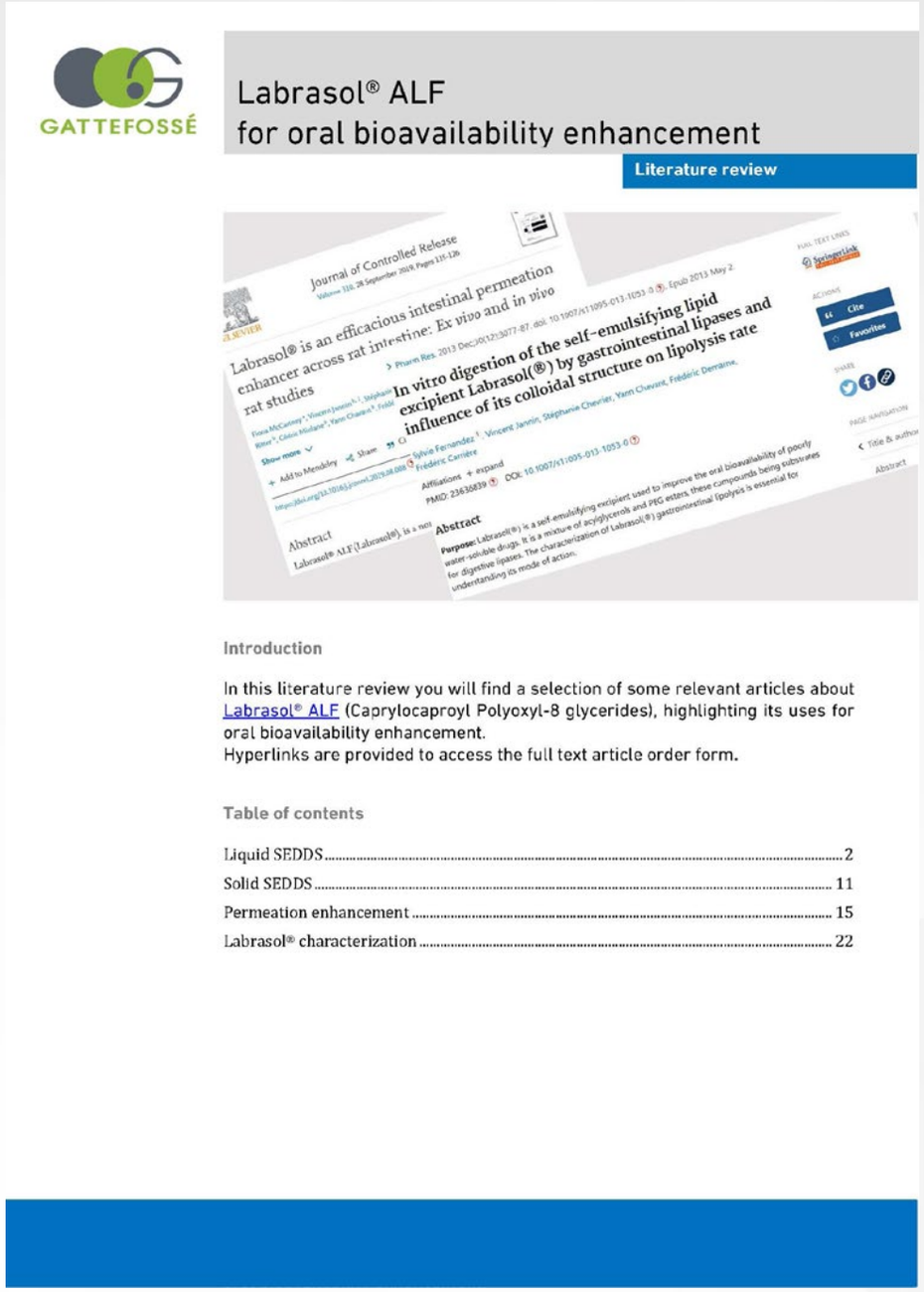
Labrasol® ALF is a well-known and widely studied excipient.
Ask for our Literature review to get a digest on relevant studies on the use of Labrasol® ALF for oral bioavailability enhancement



GATTEFOSSÉ

Labrasol® ALF
for oral bioavailability enhancement

Literature review

Introduction

In this literature review you will find a selection of some relevant articles about Labrasol® ALF (Caprylocaproyl Polyoxyl-8 glycerides), highlighting its uses for oral bioavailability enhancement.
Hyperlinks are provided to access the full text article order form.

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