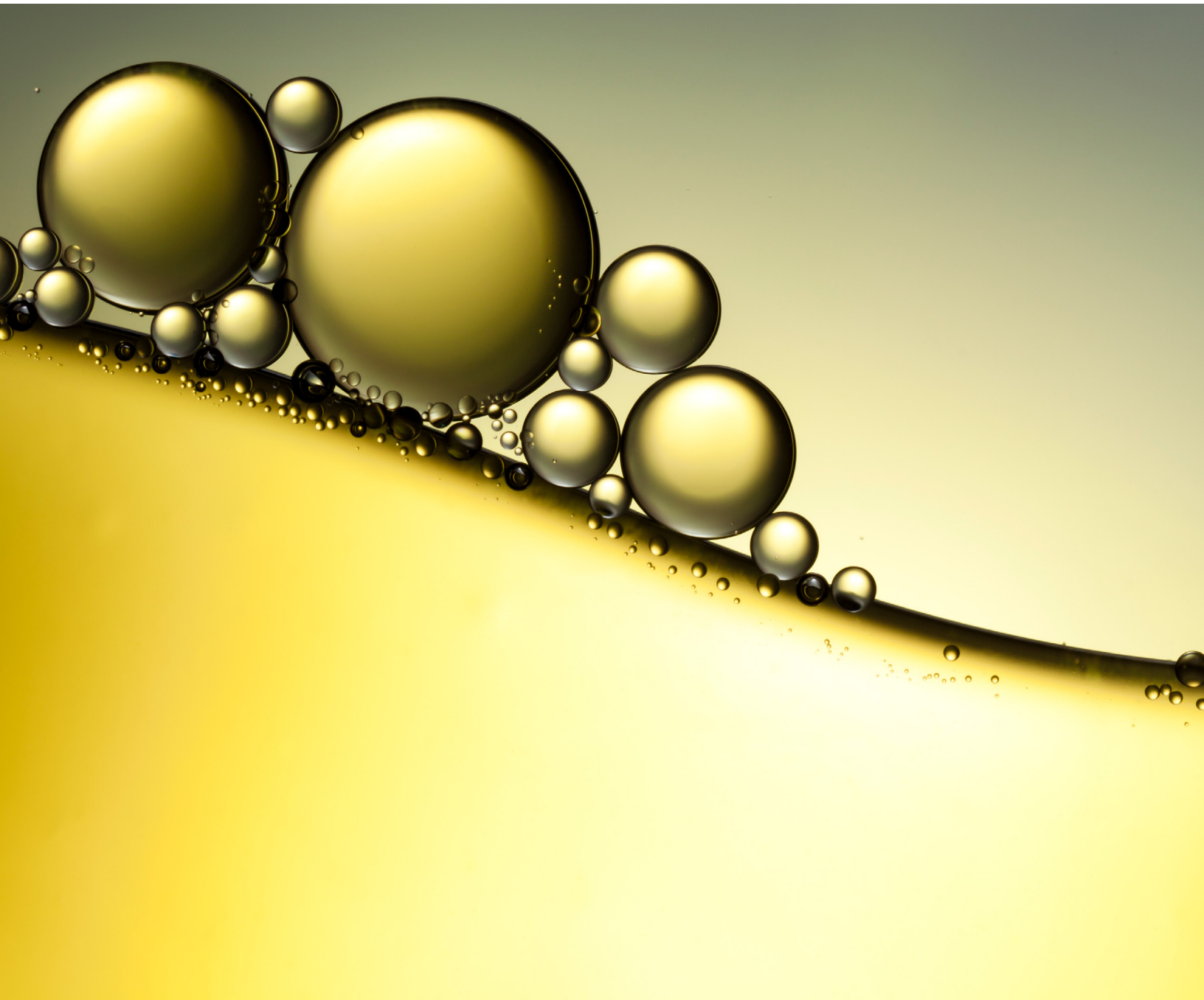
GATTEFOSSÉ

ADM

Refined Soybean, Sesame, and Olive Oils for the Pharmaceutical Industry

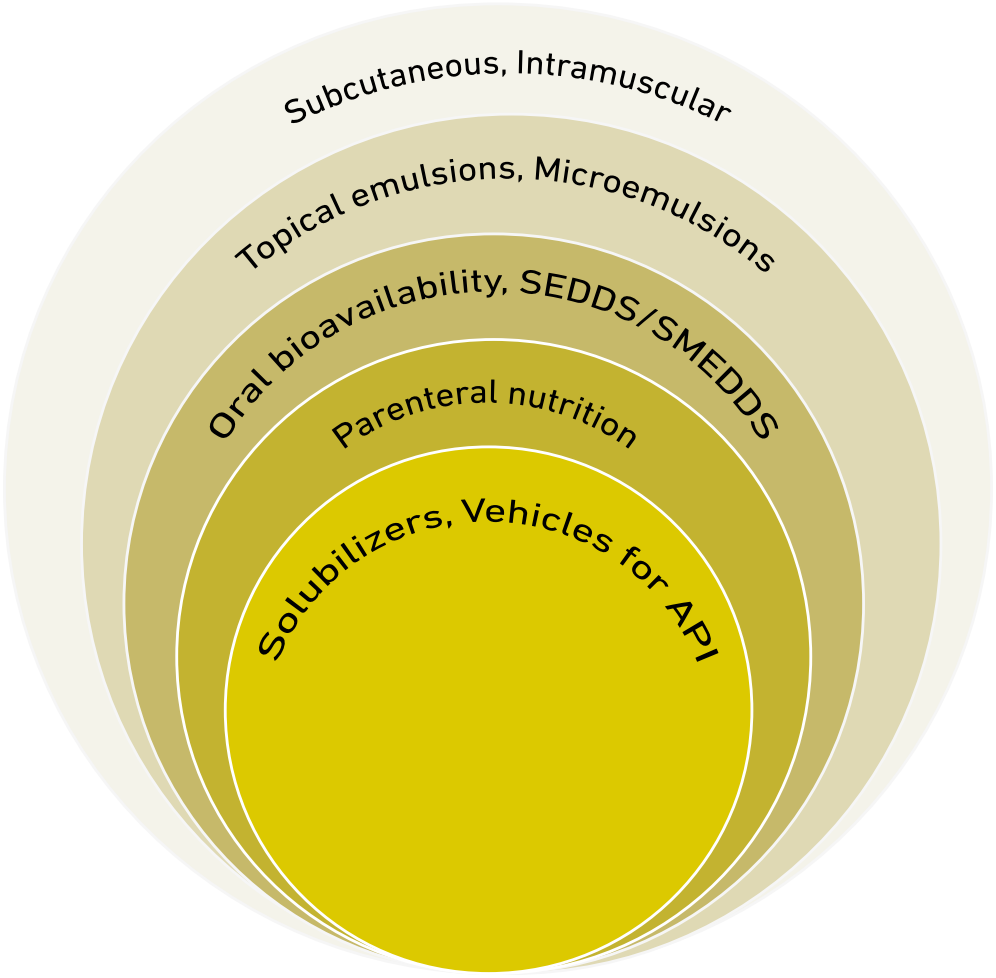


Gattefossé

The Gattefossé Group is a leading innovator and provider of excipients. Focusing on oleochemistry and drug delivery solutions for the health industries worldwide, the Group has subsidiaries and agents in more than 60 countries around the globe. The North American subsidiaries of the Gattefossé Group, Gattefossé USA and Gattefossé Canada, are responsible for the marketing and distribution of the group's products in the region.

ADM-SIO

Société Industrielle des Oléagineux (SIO) is a subsidiary of Archer Daniel Midland (ADM), a global supplier of highly purified pharmaceutical grade oils. ADM is the first manufacturer to have employed an enzymatic process in North America for interesterification of oils commercially. The ADM-SIO Refined Soybean Oil IV, Refined Olive Oil IV, and Refined Sesame Oil IV-1 are designed for highly sensitive applications in oral, injectable, and other routes of administration.



Functions and areas of application for highly purified oils

Partners in North America

The North American affiliates of the Gattefossé Group are in partnership with ADM-SIO to bring highly purified soybean, sesame and olive oils to the pharmaceutical markets in Canada, Mexico, and the United States. Complementing the joint expertise from both companies is the formulation support provided by the Gattefossé North America Technical Center of Excellence.

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Acronyms

ADM	Archer Daniel Midland Corporation
API	Active Pharmaceutical Ingredient
EP	European Pharmacopoeia
FDA	Food and Drug Administration
HLB	Hydrophilic/Lipophilic Balance
ICH	International Council for Harmonisation
LAI	Long-Acting Injectables
PUFA	Polyunsaturated Fatty Acids
SEDDS	Self-emulsifying Drug Delivery System
SIO	Société Industrielle des Oléagineux
SMEDDS	Self-micro Emulsifying Drug Delivery System
SNEDDS	Self-nano Emulsifying Drug Delivery System
USP-NF	US Pharmacopoeia-National Formulary

Regulatory status and precedence of use

Refined soybean, sesame, and olive oils constitute the bulk of vegetable oils used in medicinal preparations. They are used as sources of nutrition in parenteral delivery; as solubilizers and carriers for poorly soluble drugs; and/or bioavailability enhancers in oral, intravenous, intramuscular, subcutaneous, and topical dosage forms.

To be used in medicinal preparations, the vegetable oil must, at the minimum, comply with the standards set forth by regulatory bodies. The ADM-SIO oils summarized in Table 1 meet the USP-NF and EP pharmacopoeias.

Table 1. Pharmaceutical grade oils by ADM-SIO

	Conformity to compendia	
Refined Soybean Oil IV	USP-NF	EP
Refined Sesame Oil IV-1	USP-NF	EP
Refined Olive Oil IV	USP-NF	EP

The FDA Inactive Ingredients Database (IID) reports the precedence of use for dozens of medical references for these oils. For the oral route of administration, the highest reported amounts per dose are 283 mg, 162 mg, and 425 mg/mL respectively for soybean, sesame, and olive oils.

Table 2. Select references from Inactive Ingredients Database for various oils

Oil	Administration route	Dosage form	Amount per unit dose of up to
Soybean	Intravenous	Emulsion; Injection	200 mg/mL
Soybean	Intravenous (infusion)	Emulsion; Injection	10%
Soybean	Oral	Capsule; Soft gelatin	283.53 mg
Soybean	Topical	Solution	5.82% W/W
Sesame	Intramuscular; Subcutaneous	Injection; Sustained action	QS
Sesame	Intramuscular	Injection	70% V/V
Sesame	Oral	Capsule	162.5 mg
Olive	Oral	Solution	425 mg/1mL
Olive	Topical	Cream	27.75% W/W

Refined olive oil has been used up to 27.75% in topical cream; soybean and sesame oils are listed for injectable dosage forms at levels of 10% and 70% respectively; and purified soybean oil has been incorporated in non-pyrogenic emulsions of propofol, an injectable used in general anesthesia.

Sesame oil has been referenced as an excipient in long acting injectables such as doramectin for the treatment of parasitosis for veterinary applications. Sesame oil is also referenced in cannabinoid drugs: Marinol® (of 2.5 mg, 5 mg, or 10 mg dronabinol in soft gelatin capsules) and Epidiolex® (100 mg/mL oral solution of cannabidiol).

Chemistry and composition

Vegetable oils consist of triglycerides, molecules consisting of three fatty acid chains of varying length attached to glycerol. The type, size, and repartition of the fatty acids vary significantly from one to another oil, each seed or fruit oil extract having its own natural footprint of compositional distribution. Table 3 shows the similarities and differences found in soybean and olive oils by their respective fatty acid compositions, as defined by the USP-NF and EP monographs.

Table 3. Soybean and olive oil compositions

		USP-NF/EP specifications (%)	
Fatty acid	Chain (*)	Soybean oil	Olive oil
Caprylic	8	≤0.1	≤0.1
Capric	10		
Lauric	12		
Myristic	14	≤0.2	
Palmitic	16:0	9.0–13.0	7.5-20.0
Palmitoleic	16:1	≤0.3	≤3.5
Stearic	18:0	2.5–5.0	0.5-5.0
Oleic	18:1	17.0–30.0	56.0-85.0
Linoleic	18:2	48.0–58.0	3.5-20.0
Linolenic	18:3	5.0–11.0	≤1.2
Arachidic	20:0	≤1.0	≤0.7
Gondoic	20:1	≤1.0	≤0.4
Behenic	22:0	≤1.0	≤0.2
Erucic	22:1	≤0.3	-
Lignoceric	24:0	≤0.5	≤0.2

(*) Number of carbons: number of unsaturated bonds

The USP-NF and EP monographs for sesame oil go beyond the description of the fatty acid profile and delve into the triglycerides' composition (Table 4).

Table 4. Triglycerides(*) composition of sesame oil defined by USP-NF

	LLL	OLL	PLL	OOL	POL	OOO	SOL	POO
Composition (%)	7.0-19.0	13.0-30.0	5.0-9.0	14.0-25.0	8.0-16.0	5.0-14.0	2.0-8.0	2.0-8.0

(*) P = Palmitic; S = Stearic; O = Oleic; L = Linoleic

Quality and stability

Product monographs define the oil identity while allowing wider specification ranges to accommodate variabilities in crops, seasonality, and geography. The exigencies of the pharmaceutical product development however demand much stricter limits and reliable consistency from the oil manufacturer.

ADM-SIO purified soybean, sesame and olive oils are obtained through advanced processes that preserve the oil's integrity while removing undesirable constituents like elemental impurities and oxidative species. Applying strict controls over raw materials, analytical capabilities, and proprietary processes help guarantee the highest consistency for the oils' quality and composition.

Owing to the sophisticated refining processes that also preserve the natural antioxidants, the ADM-SIO purified oils can remain stable under environmental stress factors like heat and humidity. The shelf stability of ADM-SIO purified soybean oil for example has been confirmed under ICH test conditions (Table 5). It has a stability of 3 years from the date of manufacture.

Table 5. Stability study of ADM-SIO soybean oil

	Temperature	Relative humidity	Result
Long term (36 months)	30°C±2°C	65% RH ±5%	Stable
Accelerated (12 months)	40°C ±2°C	75% RH ±5%	Stable

Oils are scrutinized for other attributes, notably for presence of oxidative species (peroxide value), degree of unsaturation (iodine value), and amount of free fatty acids (acid value). Figure 1 shows the natural variability in acid value for the raw soybean oil (black line) and the final acid value of ADM-SIO refined soybean oil (yellow line) from 67 consecutive production batches compared to the USP limit of 0.2 for acid value (red line).

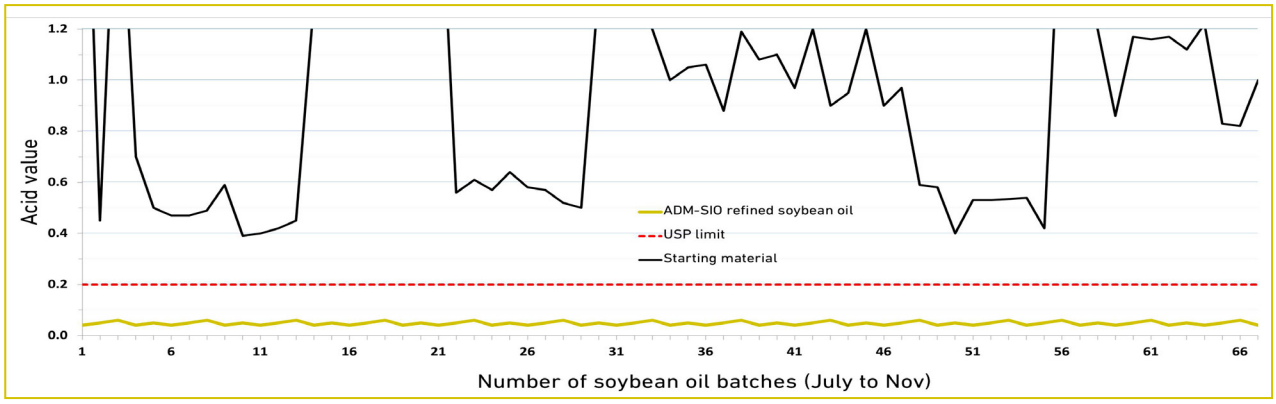

Figure 1. ADM-SIO controlling acid value for soybean oil batches

The ADM-SIO has proven capabilities in meeting customer specific, quality-by-design initiatives. As an example, ADM-SIO can provide refined olive oil with linoleic acid content in the range of 9 to 13%. The blue bar in Figure 2 shows the company's ability to successfully accommodate much narrower specification ranges while complying with multiple regulatory standards and customer requirements.

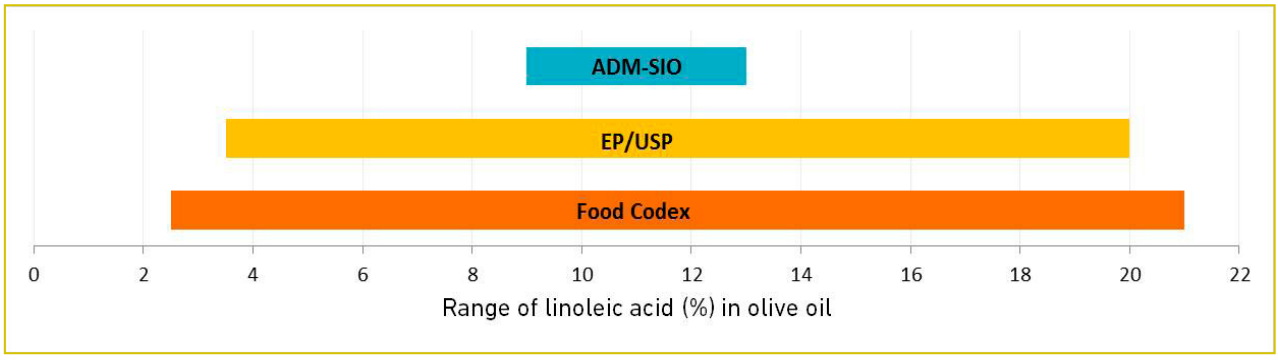

Figure 2. Controlling linoleic acid value in olive oil

Role in drug delivery

Parenteral nutrition

In parenteral nutrition, aside from caloric value, vegetable oils provide essential nutrients like linoleic and linolenic acids. The beginnings of oils in parenteral nutrition is marked by the first lipid emulsion, Intralipid®, approved in Europe in the early 1960's and later in the USA in 1975 [1]. Among the current USA references, two consist of 100% soybean oil (Intralipid® and Liposyn III®).

The fatty acid chain length, degree of saturation, and positioning of the unsaturated bonds on the polyunsaturated fatty acids (PUFA) can have significant impact, among other things, on the release and absorption of the intravenously administered drugs.

Advances in the field point to the importance of achieving a balance among the nutrients by reducing the proportion of α-linolenic relative to linoleic acids. Such is the example of the lipid emulsion in Olimel, consisting of refined olive and soybean oils (ratio 80:20) with approximate distribution of 15% saturated fatty acids , 65% monounsaturated fatty acids, and 20% polyunsaturated essential fatty acids. Another example is SMOF lipid emulsion obtained by mixing soybean oil with medium chain triglycerides, olive oil , and fish oil - at the ratios provided in Table 6.

Table 6. Balanced fatty acid composition based on 100g oil blend in 500 mL formulation

	Oil composition (%)
30% Purified soybean oil	30
30% Medium-chain triglycerides	30
25% Purified olive oil	25
15% Fish oil	15

	Fatty acid composition (%)
18.5 Linoleic acid (C18:2 w-6)	18.5
2.5% alpha Linolenic acid (C18:3 w-3	2.5
2.4% Eicosapentaenoic acid (C20:5 w-3)	2.4
2.2% Docosahexaenoic acid (C22:6 w-3)	2.2

Intravenous emulsions

Oils may be used alone or in combination with other excipients to form oily solutions, suspensions, and/or emulsions. Drugs with octanol/water partition coefficients (LogP) ranging from 1.7 to 5.8 have been successfully formulated in emulsions with improved pharmacokinetics relative to solutions[1]. The drug release rate from lipid emulsions may vary by the affinity of the drug for the system components – i.e. partitioning into the oil phase or at the surfactant interface. Ultimately, the entire drug from the formulation is released by the metabolism of the oil phase in the liver.

A global reference, Diprivan® (propofol), is an example of an intravenous emulsion. It is used for inducing and maintaining general anesthesia and for sedation of patients that are mechanically ventilated. Due to its poor solubility in aqueous media, propofol is formulated in an opaque oil-in-water emulsion consisting of soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL), and disodium edetate (0.005%), with sodium hydroxide to adjust pH. Other examples of soybean oil/egg lecithin emulsions are clevidipine butyrate, dexamethasone palmitate, diazepam, and liposoluble vitamins A, D, E, K.

Long-acting injectables

Commonly administered by subcutaneous (SC) or intramuscular (IM) routes, long-acting injectables (LAI) form a reservoir following injection and subsequently release the drug at a predetermined rate over days or months. The API may be dispersed in a blend of pharmaceutical oil and/or a high melting point solid lipid; a polymer that can swell and jellify after injection; and possibly a non-ionic surfactant[2].

Examples of LAI are found in psychotropic injections with lasting effects of 6 or 12 weeks. There is also an established history of oils in veterinary such as doramectin, indicated for the treatment of parasites (worms, lice, mites) in food producing animals. This poorly soluble API is formulated in a combination of oils, including sesame oil. Sesame oil is viscous, resists spreading, and is slowly absorbed (digested) by the lymphatic route. Surfactant lipids on the other hand help spread the oil. An intramammary LAI indicated for lactating dairy cattle is a suspension of Ceftiofur HCl encapsulated in microcrystalline wax and polyoxylglyceryl-oleate (Labrafil® M1944 CS). The latter provides solubilizing and wetting properties.

Oral absorption

In addition to solubilization of the API, oils have an important biopharmaceutical role to play. The presence of a small amount of fatty acid (e.g. oil or lipid excipient droplet) in the stomach triggers the release of bile into the duodenum, thus creating fed-state conditions which are amenable to further solubilization and absorption of drugs[3]. Lipid digestion is a very rapid and efficient process; it begins in the stomach with gastric lipase and continues in the duodenum. During digestion (lipolysis) in the presence of bile salts and lipases, these vegetable oils take part in the emulsification and micellization of other nutrients (e.g. vitamins) or poorly soluble drugs, hence enhancing their solubility and absorption via the gastrointestinal tract (GIT).

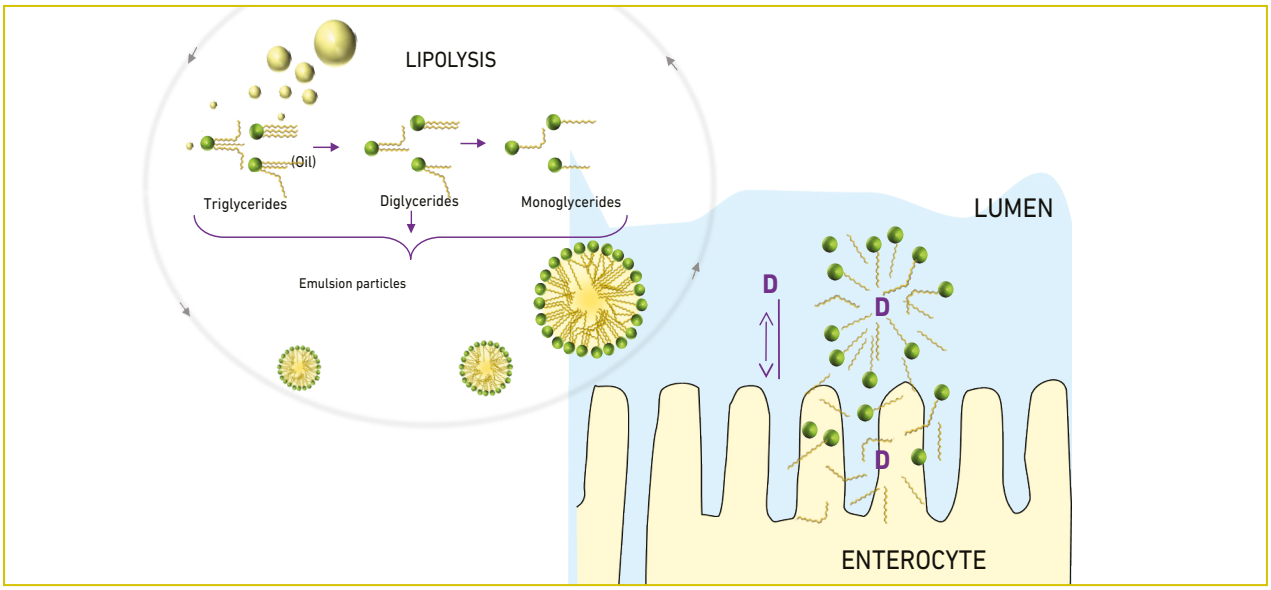

Figure 3. Digestion and absorption of oils in the presence of lipases and bile salts

As lipolysis continues and finer emulsion particles are formed, the digestion products are rapidly absorbed through the intestinal epithelial cells. Alongside, the absorption of a nutrient or drug (D) may significantly be improved if it is soluble in the oil or dispersible in the oil digestion products[3]. Figure 3 illustrates the dispersion of oil into fine droplets as lipases cleave the triglycerides, resulting in the formation of amphiphilic species like free fatty acids, monoglycerides, and diglycerides. While free fatty acids are rapidly absorbed, the diglycerides and monoglycerides behave as mild surfactants and help reduce the oil droplet size while creating emulsion particles.

Route of absorption

The fatty acid chain length and unsaturation influence their fluidity; solubilization capacity; and the rate of permeation across the GIT enterocytes. Studies have shown that the absorption efficiency of unsaturated fatty acids is greater than those of saturated fatty acids, and in the latter case it decreases with increasing chain length[5,6]. Moreover, fatty acid chain length influences the route of absorption by the systemic (hepatic) and the lymphatic routes of uptake.

Generally, the fatty acids with 12 or fewer carbon atoms are more hydrosoluble and passively diffuse across the epithelial cells lining. They are subsequently taken up by the blood stream through the portal vain, and transferred to the liver. Fatty acids with 14 or more carbons however, tend to be subject to lymphatic transport (Table 7). Being more hydrophobic, they are substrates for transporters that import them into the epithelial cell where they are re-synthesized into lipoproteins (known as chylomicrons) for lymphatic uptake. Unsaturated long-chain fatty acids in particular, which are abundant in soybean, sesame, and olive oils are known to stimulate chylomicron secretion and increase the lymphatic uptake.

Table 7. Fatty acid permeation and absorption routes

Fatty acids		Primary route of uptake after crossing the enterocytes	
Name	Chain length		
Caprylic	8	PORTAL	Passed through the liver before reaching the systemic circulation.
Capric	10		
Lauric	12		
Myristic	14	LYMPHATIC	Transformed in enterocytes into chylomicrons for delivery by the lymph. Absorbed by systemic circulation before metabolization by the liver.
Palmitic	16:0		
Stearic	18:0		
Oleic	18:1		
Linoleic	18:2		
Arachidic	20:0		
Behenic	22:0		
Lignoceric	24:0		

Formulations with unsaturated long-chain fatty acids serve as a promising strategy for improving the oral bioavailability of drugs which are extensively metabolized in the liver. Danazol, saquinavir, ontazolast, and halofantrine[7-9] are among the drugs that have been shown to benefit from lymphatic route of absorption mediated by long chain unsaturated fatty acids. Recent examples of this approach relate to cannabinoids (THC, CBD). Sesame oil is the vehicle of choice for dronabinol soft gelatin capsules (Marinol®) and for cannabidiol (Epidiolex®).

Highly lipophilic drugs (LogP>5) with high solubility of >50mg/mL in triglycerides are ideal candidates for lymphatic absorption.

Synergy with Gattefossé excipients

The ADM-SIO vegetable oils can be used effectively in combination with Gattefossé lipid excipients for a variety of drug delivery systems in oral, topical, and other routes of administration.

Gattefossé excipients are also esters of fatty acids but differ from the discussed oils in several ways: by fatty acid composition, degree of esterification, and type of hydrophilic moieties to which the fatty acids are esterified. The hydrophilic moieties used in the synthesis of the Gattefossé excipients include glycerol, PEGs of varying molecular size, propylene glycol, and polyglycerol.

Figure 4 illustrates the schematic differences and the range of functionalities of Gattefossé excipients on an HLB (Hydrophilic/Lipophilic Balance) scale. HLB is a numeric index, indicative of an excipient's ability to disperse and/or solubilize in water. Triglycerides (oils) typically have an HLB of 1 to 2, whereas PEG esters of the same fatty acids have much higher HLB values.

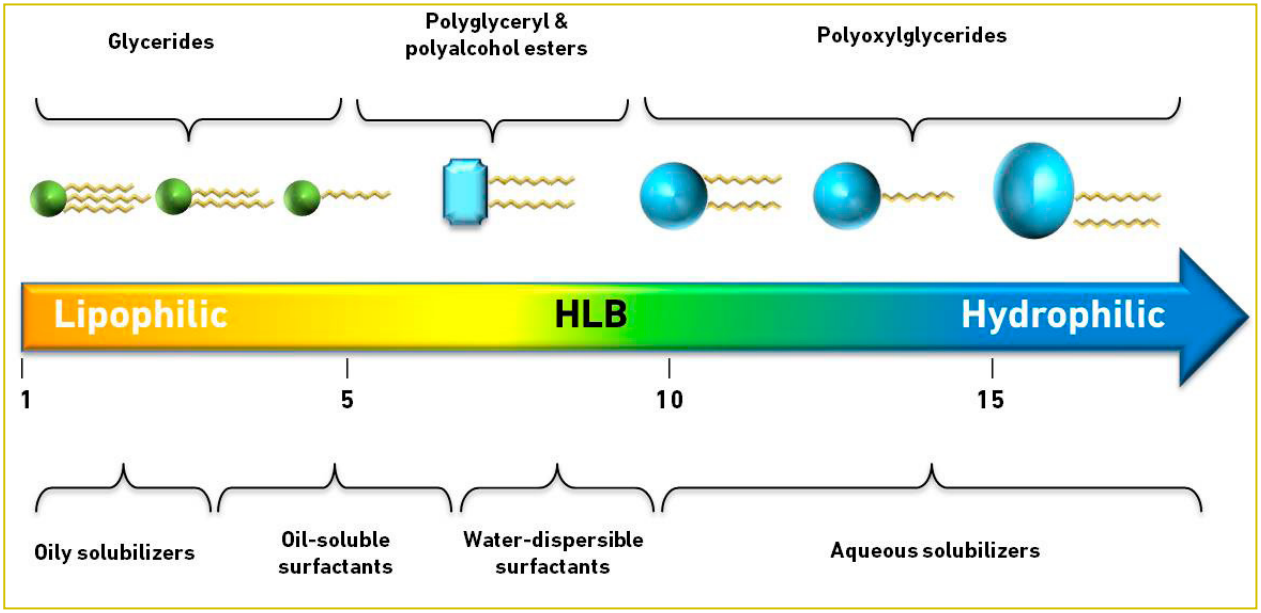

Figure 4. Schematic representation of excipients based on HLB scale

The unique chemistry of lipid excipients provides a wide range of solubility properties and allows for the formation of spontaneous dispersions in aqueous media (Figure 5) ranging from <10nm (micellar solutions) to >500nm (colloidal dispersions).

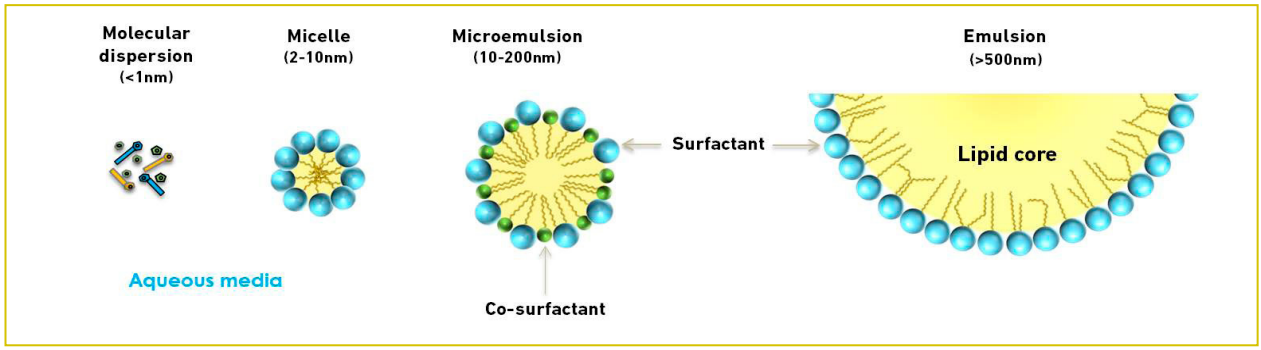

Figure 5. Various emulsion sizes by molecular size (nm)

Self-emulsifying drug delivery systems

Self-emulsifying drug delivery systems (SEDDS) typically consist of three primary components: an oil fraction, a co-surfactant, and a primary surfactant. They spontaneously form fine emulsion particles in aqueous media of the GIT. A SEDDS forming dispersion in the sub-micron (<150 nm) range is referred to as self-micro emulsifying (SMEDDS) or self-nano emulsifying (SNEDDS) drug delivery system which are interchangeable terms.

The interest in liquid and/or solid SEDDS as an enabling technology has greatly increased over the past decades. The trend is partly reflected in the number of market references involving Gattefossé products between 2005 and 2016 (Figure 6).

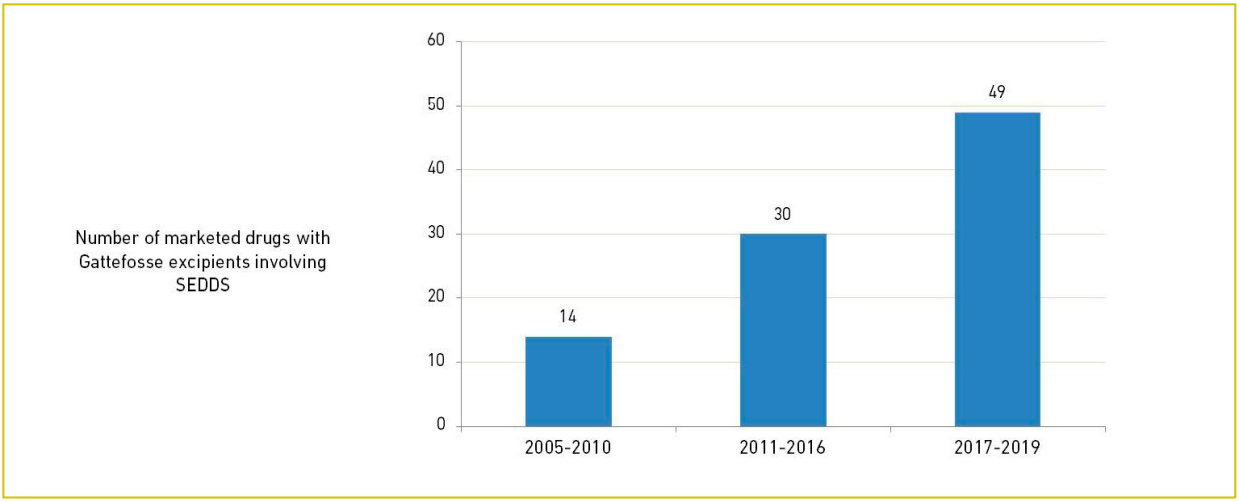

Figure 6. Prevalence of SEDDS in solubility and bioavailability enhancement

Like oily formulations, SEDDS are subject to digestion processes but form emulsion particles and disperse instantaneously in the GIT environment without the initial help from lipases. With superior wetting and solubilization power, SEDDS maintain the drug in solubilized / dispersed states in the GIT, long enough for absorption. The subsequent breakdown and digestion of SEDDS follow the fate of the vegetable oils illustrated in the previous section.

These systems enable also the development of poorly soluble drugs into solid and semi-solid dosage forms. This is achievable by formulation techniques such as capsule molding, high shear granulation, and melt extrusion.

Excipient selection

Generally, low-medium HLB lipid excipients like soybean oil (HLB 1) serve as suitable carriers for highly lipophilic, high logP APIs. However, many APIs are soluble neither in oils nor in aqueous media and need mid-high HLB excipients or self-emulsifying systems that will maintain their dispersion in aqueous conditions. Depending on the solubility of the API in one or more excipients, it is possible to obtain customized combinations that will not only maintain solubility, but also effectively deliver the intended dose of the poorly soluble API *in vivo*.

Excipient selection is the most important step in designing lipid formulations and begins with solubility and miscibility screening. Detailed guidelines for solubility screening methods pertaining to oils/lipids are available upon request.

Miscibility testing

At times, a single oil/excipient may not provide sufficient solubilization for the given API. To achieve the desired dose/solubility, it is necessary to identify combinations of two or more excipients which are miscible with one another at the desired ratios. Figure 7 shows how soybean oil may be miscible with different excipients at different amounts.

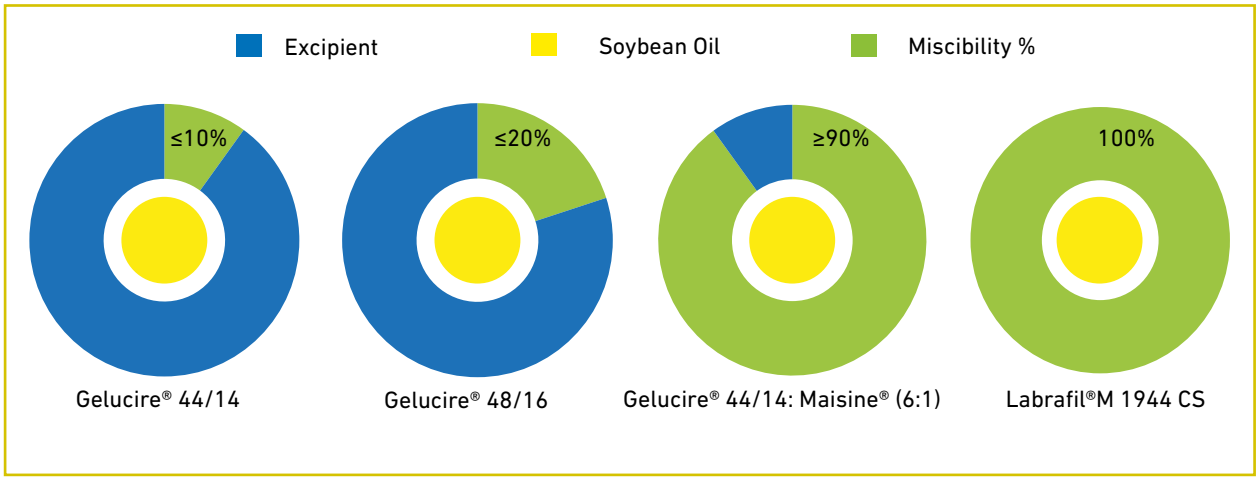

Figure 7. Soybean oil miscibility with various excipients

Additional information on binary mixtures with various excipients is provided in Table 8.

Table 8. Miscibility of soybean oil in Gattefossé excipients

Excipient	Soybean oil miscibility in listed excipients
Gelucire® 44/14	10% ≤ miscible
Gelucire® 48/16	20% ≤ miscible
Capryol™ 90, Capryol ™ PGMC	Completely miscible
Lauroglycol™ 90, Lauroglycol™ FCC,	
Labrafil® M1944 CS, Labrafil® M2125 CS	
Labrafac® Lipophile WL 1349	
Maisine® CC	
Peceol™	
Plurol® Oleique CC 497	
Transcutol® HP	10% ≤ and ≥ 70% miscible

Topical formulations

Vegetable oils and lipid-based excipients are commonly used in topical rubs, ointments, creams and lotions. These systems consist of oils, solubilizers/surfactants, and/or consistency agents. Often, oily components like soybean, olive, or sesame oil have two or more functions within a formulation: solubilizing the drug; enhancing drug penetration; providing sensorial or emollient properties; and/or acting as building blocks for microemulsions.

Topically applied microemulsions can significantly increase the cutaneous absorption of both lipophilic and hydrophilic drugs compared to conventional vehicles[11-13]. Their biggest area of interest however, is in the transdermal delivery of poorly soluble drugs like steroids, ketoconazole, aceclofenac, and celecoxib amongst others.

Microemulsions require little or no energy to produce. With low viscosity, they may be presented as sprays or gels by adding appropriate viscosity agents. Microemulsion development follows the very principles discussed above for SMEDDS except, water is present. As with SMEDDS, it requires solubility screening, miscibility testing, and ternary diagramming (Figure 8) to identify the optimal combinations of the excipients in the presence of water to achieve micro/ nano dispersions.

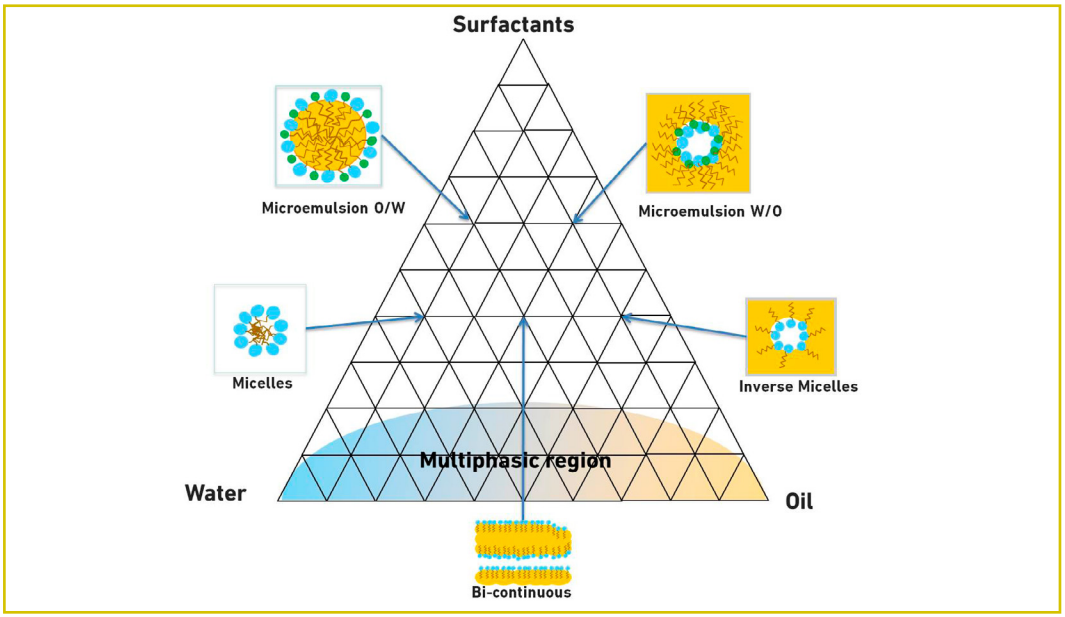

Figure 8. Existence of different lipid assemblies within a ternary diagram

Gattefossé offers a range of emulsifiers for topical delivery and especially for stabilization of olive, soybean, and sesame oil emulsions. Our Technical Center of Excellence in NJ provides assistance in the selection and design of all types of formulations.

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Formulation assistance

Our highly trained scientists at the Technical Center of Excellence located in Paramus, NJ can assist you with a wide range of product and formulation support services to advance your projects.

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Refined Soybean Oil IV, Refined Sesame Oil IV-1, and Refined Olive Oil IV are manufactured by ADM-SIO.

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