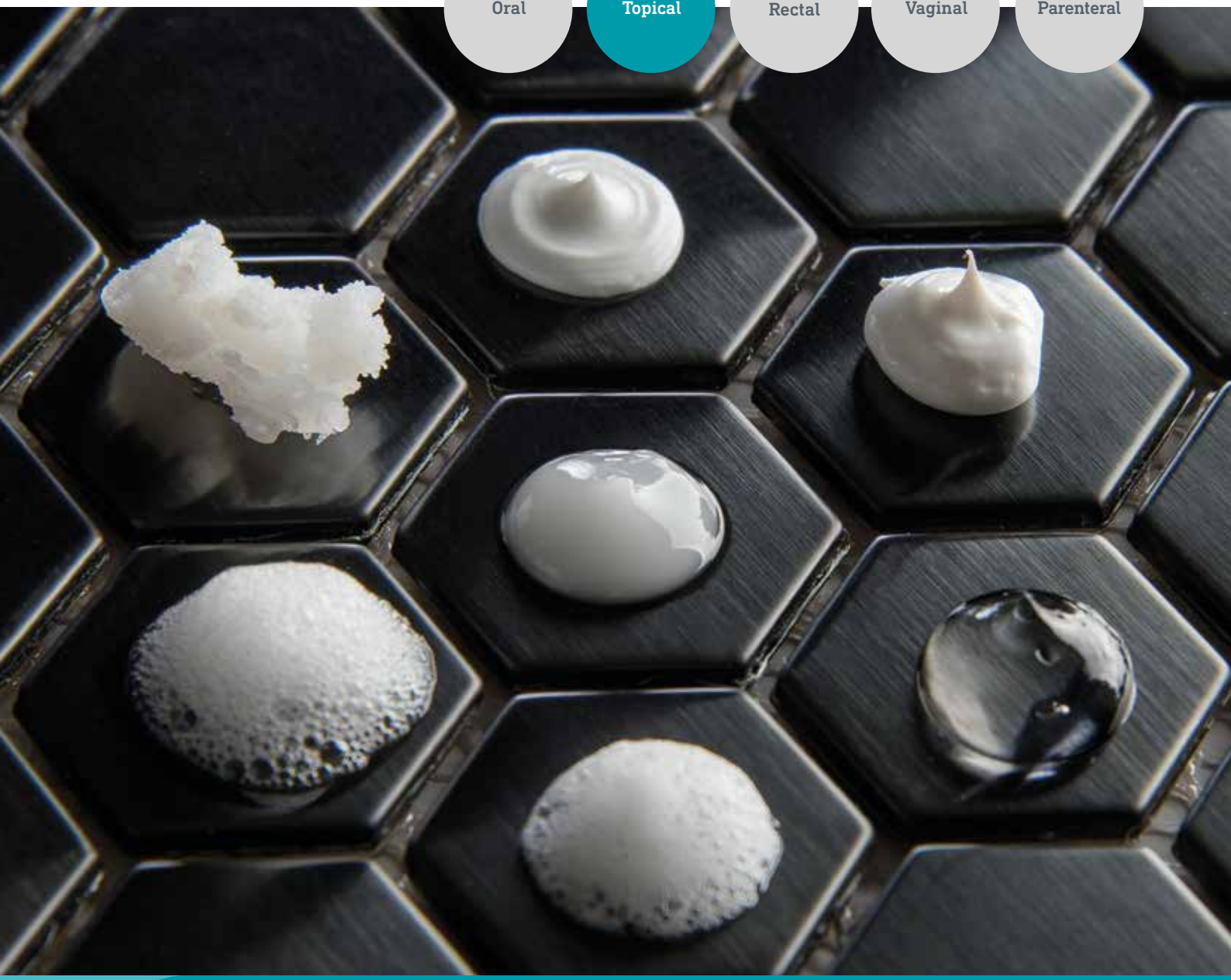
GATTEFOSSÉ

Topical Drug Delivery

With Lipid Excipients

Oral | **Topical** | Rectal | Vaginal | Parenteral



People make our name

ABOUT GATTEFOSSÉ

Gattefossé is a leading provider of excipients and formulation solutions to healthcare industries worldwide. Our company history - of over 130 years - is built on a commitment to our customers to deliver the highest quality products and technical support. In parallel to developing innovative formulation applications, Gattefossé has worked diligently to guarantee the pharmaceutical qualification of its excipients.

GATTEFOSSÉ LIPID EXCIPIENTS

The lipids and fatty acids used in the production of Gattefossé excipients are derived strictly from raw materials of vegetable origin.

Excipients are obtained by the esterification of fatty acids with alcohols - glycerol, polyglycerol, propylene glycol and polyethylene glycol - and by the alcoholysis of vegetable oils and fats with glycerol, polyethylene glycol and propylene glycol.

Expertise in oleo-chemistry has enabled the development of a range of functional excipients with different thermal, rheological and textural properties and a wide spectrum of solubility characteristics.

TOPICAL DRUG DELIVERY

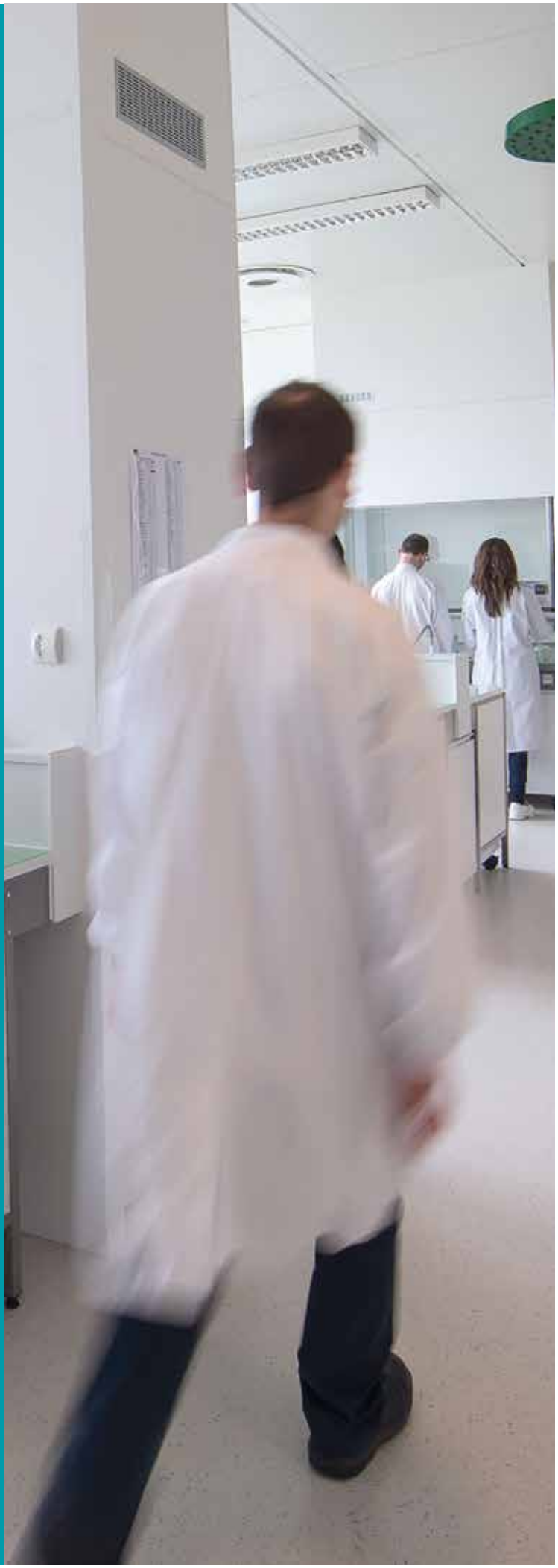
Lipid excipients can be used to formulate creams, ointments, oily and aqueous gels and foams.

Gattefossé excipients are associated with improved skin drug delivery. The stability, texture and sensorial qualities of a topical product can be optimized by selection of the right combination of Gattefossé excipients.

Our excipients are extremely safe and many are used in internationally approved and marketed products.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **Ch.P.**: Chinese Pharmacopœia; **DMF:** Drug Master File (Type IV); **DSHEA:** Dietary Supplement Health & Education Act; **EP:** European Pharmacopœia; **FCC:** Food Chemical Codex; **FDA:** Food and Drug Administration; **GRAS:** Generally Recognized As Safe; **HLB:** Hydrophilic Lipophilic Balance; **IID:** FDA Inactive Ingredient Database; **JPE:** Japanese Pharmaceutical Excipients; **JSFA:** Japanese Standard of Food Additives; **NSAID:** Non Steroidal Anti Inflammatory Drug; **O/W:** Oil in Water; **PEG:** Polyethylene Glycol; **ROW:** Rest of the World; **USFA:** US Food Additive; **USP-NF:** US Pharmacopœia-National Formulary; **W/O:** Water in Oil



Contents

Lipid excipient emulsifiers for challenging formulations

Our emulsifiers are particularly useful for resolving challenges associated with API insolubility, heat sensitivity, extremes of pH, and the incorporation of alcohols and essential oils. The right emulsifier can also greatly improve the texture and sensorial qualities of a product and offer the patient an improved experience on application.

Candidate emulsifiers are routinely selected based on several criteria:

- Characteristics of the API: solubility, physico-chemical properties and chemical stability
- Type of emulsion required: oil in water or water in oil
- The amount of emulsifier required to obtain the desired appearance and consistency of the final product

Use the table below to identify which emulsifier corresponds to your application need...

Products	Chemical description	Appearance	HLB	Melting point °C (Drop point)
Emulsifier O/W				
Apifil®	PEG-8 beeswax	Pellets	9	67.5
Emulcire™ 61 WL 2659	Mixture of Cetyl alcohol EP/NF and ethoxylated fatty alcohols (Ceteth-20, Steareth-20) EP/NF	Pellets	10	48.5
Gelot™ 64	Mixture of Glycerol monostearate EP/NF and PEG-75 stearate (Type I) NF	Pellets	10	59
Sedefos™ 75	Mixture of Tricetereth-4 phosphate (and) ethylene glycol stearate EP/NF/JPE (and) diethylene glycol stearate EP/NF/JPE	Pellets	10	47.5
Tefose® 63	Mixture of PEG-6 stearate (Type I) NF (and) ethylene glycol stearate EP/NF/JPE (and) PEG-32 stearate (Type I) NF	Waxy solid	9.5	48
Tefose® 1500	Mixture of PEG-6 stearate (Type I) NF (and) PEG-32 stearate (Type I) NF	Waxy solid	10	43
Emulsifier W/O				
Plurol® Diisostearique	Triglycerol diisostearate EP Polyglyceryl-3-diisostearate NF	Viscous liquid	4.5	Liquid

Our emulsifiers have excellent skin tolerance profiles and their safety is substantiated by worldwide use in both well-established and recently approved pharmaceutical products.

They enable the development of a variety of dosage forms ranging from thick creams to sprayable fluid emulsions.

There is precedence of use of these excipients in marketed products: anti-acne, anti-psoriatics, anti-fungal, anti-inflammatory, analgesics...

Key benefits	Market reference*
Ideal for emulsions incorporating a high volume of oil and lipophilic API. Forms creams with firm texture and glossy appearance (use 7 to 15%).	ASIA, EU
An ideal co-emulsifier with Gelot™ 64 (ratio 1: 1) to improve texture and with Apifil® (ratio 2: 1) to improve heat stability.	ASIA, EU, INDIA
Ideal for difficult-to-formulate API including alcohol extracts or essential oils. Forms a firm texture cream over a wide range of pH (use 6 to 20%).	ASIA, CANADA, EU, INDIA, ROW
Ideal for emulsions containing solvents or large amount of oily phase, for hydrosensitive API requiring PEGs or glycerine as hydrophilic phase. Forms a firm texture cream (use 6 to 20%). Use a simple one-pot formulation process (≥ 9%).	EU
An ideal emulsifier for anti-fungal treatments due to excellent mucosal tolerance. Forms elegant creams with firm texture (use 8 to 20%). Use a simple one-pot formulation process (≥ 12%).	ASIA, EU, ROW, USA
A polyvalent emulsifier compatible with all types of oils and ideal for lotions. Forms light and soft creams (use 8 to 12%). Forms fluid to very fluid lotions (use below 8%).	EU, USA
A PEG-free emulsifier ideal for heat-sensitive API when used in a cold process. Forms elegant creams with firm texture (use 3 to 6%).	USA

* Market reference refers to the current or historic existence of a pharmaceutical product authorized for use following the approval of a Market Authorization Dossier type NDA or ANDA or equivalent.

Lipid excipient solubilizers for improved drug delivery

Lipid excipients provide high solubilizing power and amphiphilic properties, both of which are associated with mechanisms that can modulate the penetration of API into the *stratum corneum* and drive API flux.

Gattefossé offers a range of high performance liquid solubilizers that can be used to improve drug delivery in a variety of topical formulation types.

All the excipients in the table below can be used to formulate emulsions, microemulsions and lipophilic ointments. Aqueous gels and foams can be formulated using hydrodispersible excipients such as Labrasol® and Transcutol® P.

Products	Functionality	Abridged chemical description	HLB	Market reference
Solubilizer				
Labrasol®	O/W surfactant	Caprylocaproyl macrogol-8 glycerides EP/NF	12	ASIA, EU, INDIA, USA*, ROW
Labrafil® M 1944 CS	O/W surfactant	Oleoyl macrogol-6 glycerides EP/NF	9	ASIA, EU, ROW, USA
Labrafil® M 2125 CS	O/W surfactant	Linoleoyl macrogol-6 glycerides EP/NF	9	EU, ROW, USA
Labrafil® M 2130 CS	O/W surfactant	Lauroyl macrogol-6 glycerides EP/NF (semi-solid)	9	EU, ROW*, USA*
Capryol® PGMC	W/O surfactant	Propylene glycol monocaprylate (type I) NF	6	EU*
Capryol® 90	W/O surfactant	Propylene glycol monocaprylate (type II) NF	5	ASIA, EU, USA
Lauroglycol™ FCC	W/O surfactant	Propylene glycol monolaurate (type I) EP/NF	5	EU, ROW*, USA*
Lauroglycol™ 90	W/O surfactant	Propylene glycol monolaurate (type II) EP/NF	3	ASIA, INDIA*
Plurol® Oleique CC 497	W/O surfactant	Polyglyceryl-3 dioleate NF	3	EU*, ROW, USA*
Labrafac™ PG	Oily vehicle	Propylene glycol dicaprylocaprate EP/NF	1	ASIA, EU*
Labrafac™ Lipophile WL 1349	Oily vehicle	Triglycerides medium-chain EP/NF/JPE	1	ASIA, EU, ROW, USA
Transcutol® P	Solvent	Highly purified diethylene glycol monoethyl ether EP/NF	/	ASIA, CANADA, EU, ROW, USA

*Oral dosage form

The functional properties of Gattefossé excipients and their role in dermal drug delivery are widely studied and reported in the scientific literature. The following table describes the functional properties of our excipients with a range of APIs in microemulsion, emulsion, gel or ointment and pure excipient API solutions.

API	Solubilizer, penetration modulator	Reference
Microemulsion formulations		
Aceclofenac (NSAID)	Labrafil® M 1944 CS and Transcutol® P	Shakeel, 2007
Caffeine (stimulant)	Labrasol® and Labrafac™	Zhang, 2011
Curcumin (prevention Alzheimer disease)	Transcutol® P, Labrasol® and Capryol® 90	Wang, 2012
Dehydroepiandrosterone (steroid)	Labrasol®, Plurol® Oleique and Transcutol® P	Ceschel, 2005
Doxepin, Imipramine (anti-depressant)	Transcutol® P, Labrasol® and Plurol® Oleique CC 497	Sandig, 2013
Fluoxetine (anti-depressant)	Labrasol®, Lauroglycol™ FCC and Transcutol® P	Parikh, 2005
Hydrocortisone acetate (corticosteroid)	Labrafil® M 1944 CS, Labrasol®, Lauroglycol™ 90, Plurol® Oleique CC 497, Transcutol® P	Fini, 2008
Ketoprofen (NSAID)	Labrasol®	Rhee, 2001 Zhang, 2011
Lidocaine (anaesthesic)	Labrasol®	Kreilgaard, 2002 Zhang, 2011
Lorazepam (sedative)	Transcutol® P, Labrafil® M 1944 CS and Lauroglycol™ FCC	Yao, 2009
Terbinafine (anti-fungal)	Labrafil®, Plurol® Oleique CC 497 and Transcutol® P	Baboota, 2007
Gel formulations		
Dexamethasone (corticosteroid)	Transcutol® P	Panchagnula, 1991
Dapsone (anti-acne)	Transcutol® P	Osborne, 2011
Genistein (anti-neoplastic agent)	Lauroglycol™ 90 and Transcutol® P	Chadha, 2010
Hydrocortisone (corticosteroid)	Labrafil® M 1944 CS and Transcutol® P	Ritschel, 1991
Methotrexate (anti-psoriatics)	Transcutol® P	Javadzadeh, 2011
Emulsion or ointment formulations		
Coumarin (lymphoedema treatment)	Labrafil® M 1944 CS	Ritschel, 1988 [b]
Ketoprofen (NSAID)	Labrafil®, Labrasol® and Transcutol® P	Kim, 2002
Thymidylate synthase inhibitor (anti-psoriatics)	Labrafil® M 2130 CS, Labrasol® and Transcutol® P	Pavliv, 1994
Excipient - API solutions		
Dexamethasone, Hydrocortisone (corticosteroid)	Labrafil® and Transcutol® P	Panchagnula, 1991
Diclofenac diethylammonium (NSAID)	Labrafil® M 2125 CS, Lauroglycol™ FCC and Labrafac™ Lipophile WL 1349	Kweon, 2004
Fluconazole (anti fungal)	Labrasol® and Transcutol® P	Ayub, 2007
Ibuprofen (NSAID)	Transcutol® P	Bialik, 1993
Ivermectine (anti-parasitic)	Transcutol® P	Yazdanian, 1995
Ketorolac tromethamine (NSAID)	Capryol® 90, Lauroglycol™ FCC and Transcutol® P	Cho, 2004
Quercetin (UV protective)	Capryol® 90, Labrasol® and Transcutol® P	Censi, 2011
Tenoxicam (NSAID)	Capryol® 90, Lauroglycol™ FCC and Transcutol® P	Gwak, 2002

Efficient skin delivery: no compromise with Transcutol® P

Transcutol® P is a hydrophilic/lipophilic high purity solubilizer, with broad API compatibility and a broad spectrum of use in creams and lotions to aqueous gels and foams. It is a well characterized, safe excipient associated with interesting drug delivery properties including drug penetration enhancement and a drug depot effect.

Skin penetration enhancement with Transcutol® P is widely studied and is described as a 'push and pull' effect reported to increase the percutaneous passage of API.

The 'push' effect via solubilizing power

API must be in a solubilized state to penetrate the *stratum corneum* via a passive transport mechanism driven by the concentration gradient between the formulation and the skin. The solubilizing power of Transcutol® P enables high drug loading and the generation of a steep concentration gradient down which the API is 'pushed' into the skin.

Solubility studies with common NSAIDs (ibuprofen, sodium diclofenac and ketoprofen) report a minimum API solubility of around 400 mg per gram of Transcutol® P.

The 'pull' effect via diffusion

Transcutol® P induces reversible structural deformations as it penetrates the *stratum corneum*. The disorganization of the intercellular space between corneocytes (composed of lipidic layers) facilitates the diffusion of the API.

This 'pull' effect has been widely observed for Transcutol® P in association with many drugs and is particularly apparent for lipophilic compounds which penetrate the *stratum corneum* by diffusion through these intercellular spaces.

Transcutol® P – Performance for localized drug delivery

Effective localized drug delivery relies on bioavailability and the prevention of permeation and eventual systemic absorption. Studies have shown that the inclusion of Transcutol® P can increase drug retention in the skin, thereby improving localized drug delivery (Ritschel, 1988 a).

In addition, the intracutaneous depot effect, associated with the swelling of lipid bilayer structures which subsequently act as a depot for drug-solvent complexes, then enables the slow and localized diffusion of the API over time.

Transcutol® P – Non irritant solvent

Transcutol® P is also noted for its non-irritant properties compared with alternative co-solvents (Papakostantinou, 2007). Transcutol® safety is established via numerous toxicological studies recently reviewed by Sullivan et al, 2014.

Transcutol® P – Power and synergy

Used alone, Transcutol® P is widely reported to be a highly effective solubilizer for a wide range of APIs, enabling high drug loading leading to improved skin permeation.

API	Dosage form	Reference
Transcutol® P alone		
Atenolol (anti-hypertensive)	O/W emulsion	Puglia, 2008
Griseofulvin (antibiotic)	Excipient – API solution	Ritschel, 1988 [a]
Clebopride (anti-emetic)	Aqueous gel	Rhee, 2007
Dapsone (antibiotic)	Aqueous gel	Osborne, 2011
Dexamethasone, hydrocortisone (corticosteroid)	Aqueous gel	Ritschel, 1991
Methotrexate (anti-psoriatics)	Aqueous gel	Javadzadeh, 2011
Ivermectin (anti-parasitic)	Excipient – API solution	Yazdanian, 1995

Used in combination with other standard dermal drug delivery excipients (solubilizers and co-solvents), several studies report a further increase in the percutaneous passage of API, described as the synergistic effect of Transcutol® P.

Transcutol® P in synergistic combination		
Transcutol® P and oleic acid		
Caffeine (Stimulant)	Aqueous solution (PEG base)	Touitou, 1994
Carvedilol (cardiovascular)	Nanoemulsion	Dixit, 2008
Nimesulide (NSAID)	Gel	Gungor, 2004
Theophylline (Bronchodilatator)	Ointment	Papakostantinou, 2007
Theophylline (Bronchodilatator)	Gel, cream, ointment (PEG base)	Touitou, 1991
Transcutol® P and propylene glycol		
Dehydroepiandrosterone (steroid)	Patch	Minghetti, 2001
Clonazepam (anti-convulsant)	Gel	Mura, 2000

Lipid excipients for optimizing stability and sensorial properties

The most basic topical emulsion utilizes an emulsifier, mineral oil and water only.

However, the majority of APIs require more complex formulation with the use of additional excipients to produce a stable product with high tolerability and excellent textural properties. Gattefossé can help you to select the right combination of excipients to improve the stability, texture and sensorial properties of a formulation.

Formulating for high stability

An emulsion is, by nature, a thermodynamically unstable system and spontaneous coalescence of droplets can occur leading to phase separation. Instability is most frequently caused by ageing or adverse environmental conditions including excessive heat.

Consistency agents (thickeners) are often used for oil-rich formulations to control the final product viscosity and consistency. They improve and stabilize product consistency at elevated temperatures. In emulsion systems, the addition of a lipid-based thickener may be necessary to prevent coalescence and phase separation.

Some difficult to formulate systems require the use of a secondary emulsifier (co-emulsifier), which is used at a lower concentration to improve stability. Gattefossé has characterized numerous effective associations between its products and can provide recommendations and many examples of validated formulations on request.

Products	Abridged chemical description	Appearance	HLB	Melting point °C (Drop point)	Formulation type	Market reference
Consistency agent						
Compritol® 888 Pellets	Glycerol dibehenate EP/NF/Ch.P.	Pellets	1	72.5	Emulsion Ointment	ASIA*, EU, ROW*, USA
Geleol™ mono and diglycerides NF	Glycerol monostearate 40-55 (type I) EP/NF	Pellets	3	57.5	Emulsion Ointment	ASIA, EU, USA
Monosteol™	Propylene glycol monopalmitostearate EP	Waxy solid	4	36.5	Emulsion Ointment	ASIA, EU, USA
Gelucire® 43/01	Hard fat EP/NF/JPE	Waxy solid	1	43.0	Emulsion Ointment	USA*

* Oral dosage form

Improving the texture of ointments

Developing a homogeneous mixture with high viscosity and stability at elevated temperature is often a challenge with ointments. Lipid excipients facilitate the application of lipophilic API to the skin and also provide a degree of protection and occlusion.
Gelucire® 43/01 is recommended to optimise viscosity and as an alternative to hard paraffin, providing a smoother texture.

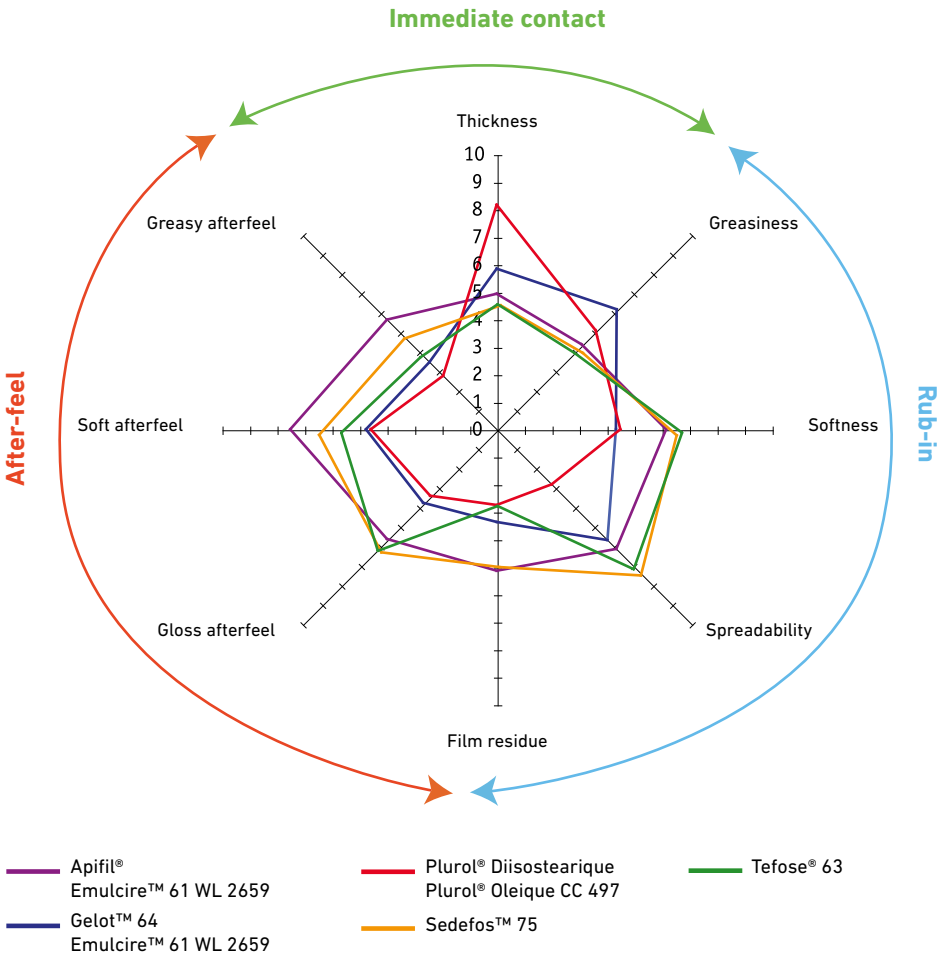
Improving patient sensorial experience

The choice of excipients in a formulation will affect its texture and sensorial properties. Gattefossé has developed validated methods to evaluate and measure these properties. This type of analysis - called sensorial mapping (see diagram below) - enables the fine optimization of a formulation not only for its 'drug delivery' properties but also to improve the patients' sensorial experience.

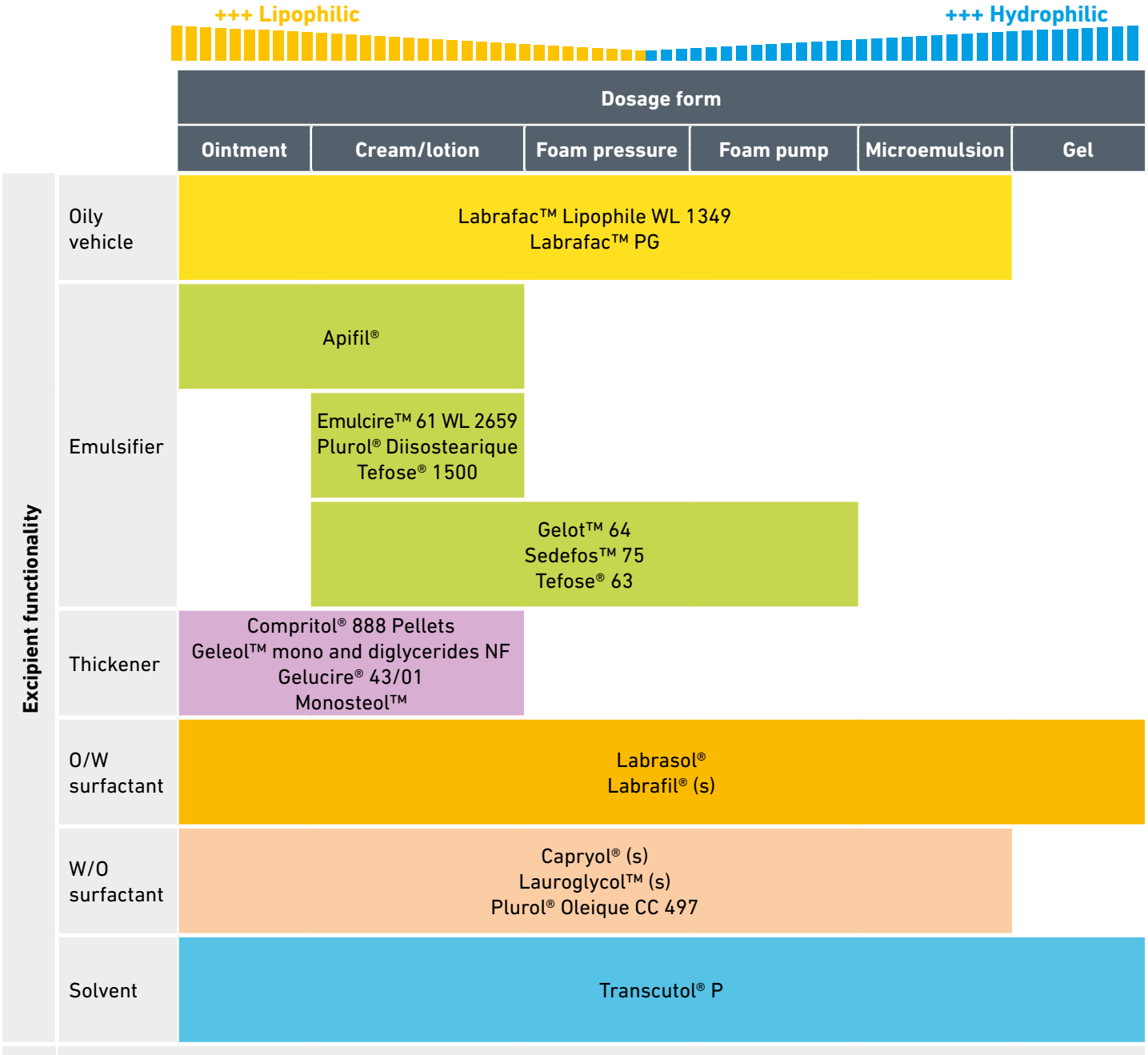
The symptoms that accompany dermatological diseases and disorders include extremely dry, sensitive and sore skin which require formulations that are easy to spread, rapidly absorbed and moisturizing, with a soft and soothing texture.

Gattefossé Dermacare kit has been developed to provide a range of 'model' placebo creams optimized for their sensorial qualities incorporating our functional emulsifiers.
For further information please contact Gattefossé.

Sensorial Map



Quick guide to formulating with lipid excipients



Pharmaceutical qualification

Gattefossé is committed to the manufacture of high quality products which conform to the relevant European, United States of America and Japanese Pharmacopœia monographs. Many of our products have been used in internationally approved and marketed pharmaceutical products. Gattefossé has undertaken relevant toxicological studies to assess the tolerability and safety of its products. Further information can be provided on request.

Product Name	Full chemical description	Additional regulatory information
Apifil®	PEG-8 beeswax	DMF
Capryol® 90	Propylene glycol monocaprylate (type II) NF	DMF
Capryol® PGMC	Propylene glycol monocaprylate (type I) NF	DMF
Compritol® 888 Pellets	Glycerol dibehenate EP Glyceryl dibehenate NF Glyceryl behenate Ch.P.	DMF/IID/GRAS/ FCC/JSFA
Emulcire™ 61 WL 2659 Pellets	Mixture of Cetyl alcohol EP/NF and ethoxylated fatty alcohols (Ceteth-20, Steareth-20) EP/NF	DMF/IID
Geleol™ Mono and Diglycerides NF	Glycerol monostearate 40-55 (type I) EP Mono and diglycerides NF	DMF/IID/E471/ FCC/GRAS/JSFA
Gelot™ 64	Mixture of Glycerol monostearate EP/NF (and) PEG-75 stearate (Type I) NF	DMF/IID
Gelucire® 43/01	Hard fat EP/NF/JPE	DMF/IID
Labrafac™ Lipophile WL 1349	Triglycerides medium-chain EP Medium-chain triglycerides NF Medium chain fatty acid triglyceride JPE	DMF/IID/ DSHEA/JSFA
Labrafac™ PG	Propylene glycol dicaprylocaprate EP Propylene glycol dicaprylate/dicaprate NF	IID
Labrafil® M 1944 CS	Oleoyl macrogol-6 glycerides EP Oleoyl polyoxyl-6 glycerides NF	DMF/IID
Labrafil® M 2125 CS	Linoleoyl macrogol-6 glycerides EP Linoleoyl polyoxyl-6 glycerides NF	DMF/IID
Labrafil® M 2130 CS	Lauroyl macrogol-6 glycerides EP Lauroyl polyoxyl-6 glycerides NF	DMF/IID
Labrasol®	Caprylocaproyl macrogol-8 glycerides EP Caprylocaproyl polyoxyl-8 glycerides NF	DMF/IID
Lauroglycol™ 90	Propylene glycol monolaurate (type II) EP/NF	DMF/IID
Lauroglycol™ FCC	Propylene glycol monolaurate (type I) EP/NF	DMF/IID
Monosteol™	Propylene glycol monopalmitostearate EP	IID
Plurol® Diisostearique	Triglycerol diisostearate EP Polyglyceryl-3-diisostearate NF	DMF/IID
Plurol® Oleique CC 497	Polyglyceryl-3 dioleate NF	DMF/IID/E475/ FCC/JSFA/USFA
Sedefos™ 75	Mixture of Tricetearet-4 Phosphate (and) ethylene glycol stearate EP/NF/JPE (and) diethylene glycol stearate EP/NF/JPE	DMF/IID
Tefose® 63	Mixture of PEG-6 stearate (Type I) NF (and) ethylene glycol palmitostearate EP/NF/JPE (and) PEG-32 stearate (Type I) NF	DMF/IID
Tefose® 1500	Mixture of PEG-6 stearate (Type I) NF (and) PEG-32 stearate (Type I) NF	DMF/IID
Transcutol® P	Highly purified diethylene glycol monoethyl ether EP/NF	DMF/IID

Technical support

Our applications laboratories in France, India and China are at your service to provide technical support and formulation feasibility assessment.

We have many years of experience of formulating with our products with both experimental and model drugs. We are committed to answering your questions on formulation, regulatory, safety, scale-up issues and precedence of use as quickly and as comprehensively as we can.

We can reduce your development time by providing straightforward formulation guidelines for oral, dermal, rectal and vaginal dosage forms as well as access to extensive databases comprising hundreds of validated placebo or model API formulations.

If you need practical laboratory assistance, the services we are able to offer include solubility screening, basic formulation development, texture optimisation and sensorial analysis.

Please contact your local Gattefossé representative
or email us at:
infopharma@gattefosse.com

Bibliography

Ayub A. C. et al (2007) Topical delivery of fluconazole: *in vitro* skin penetration and permeation using emulsions as dosage forms. Drug Development and Industrial Pharmacy 33[3]. 273-280.

Baboota S. et al. (2007) Development and evaluation of a microemulsion formulation for transdermal delivery of terbinafine. PDA journal of pharmaceutical science and technology 31 (4): 276-285.

Bialik, W. et al. (1993). Some factors affecting the *in vitro* penetration of ibuprofen through human skin. International journal of pharmaceutics, 92(1), 219-223.

Censi R. et al. (2011) Permeation and skin retention of quercetin from microemulsions containing Transcutol® P. Drug Development and Industrial Pharmacy 38[9]. 1128-1133.

Ceschel G. et al. (2005) Solubility and transdermal permeation properties of a dehydroepiandrosterone cyclodextrin complex from hydrophilic and lipophilic vehicles. Drug Deliv. 12 (5): 275-280.

Chadha G. et al. (2010) *In vitro* percutaneous absorption of genistein from topical gels through human skin. Drug Development and Industrial Pharmacy 37[5]. 498-505.

Cho Y. A. et al. (2004) Transdermal delivery of ketorolac tromethamine: effects of vehicles and penetration enhancers. Drug Dev. Ind. Pharm. 30 (6): 557-564.

Dixit N. et al. (2008) Nanoemulsion system for the transdermal delivery of a poorly soluble cardiovascular drug. PDA journal of pharmaceutical science and technology 62 (1): 46-55.

Fini A. et al. (2008) Control of Transdermal Permeation of Hydrocortisone Acetate from Hydrophilic and Lipophilic Formulations. AAPS Pharm. Sci. Tech. 9 (3): 762-768.

Gungor S. et al. (2004) Effect of penetration enhancers on *in vitro* percutaneous penetration of nimesulide through rat skin. Pharmazie 59 (1): 39-41.

Gwak H. S. et al. (2002) Effect of vehicles and penetration enhancers on the *in vitro* percutaneous absorption of tenoxicam through hairless mouse skin. Int. J. Pharm. 236 (1-2): 57-64.

Javadzadeh Y. and Hamishehkar, H. (2011) Enhancing percutaneous delivery of methotrexate using different types of surfactants. Colloids and surfaces B: Biointerfaces, 82 [2], 422-426

Kweon J. H. et al. (2004) Transdermal delivery of diclofenac using microemulsions. Archives of Pharmacal Research 27[3]. 351-356.

Kim J. H. et al. (2002) Effect of additives on the crystallization and the permeation of ketoprofen from adhesive matrix. Int. J. Pharm. 236 (1-2): 81-85.

Kreilgaard M. (2002) Influence of microemulsions on cutaneous drug delivery. Bull. Tech. Gattefossé (95): 79-100.

Minghetti P. et al. (2001) Development of Patches for the Controlled Release of Dehydroepiandrosterone. Drug Dev. Ind. Pharm. 27 (7): 711-717.

Mura P. et al. (2000) Evaluation of Transcutol® as a clonazepam transdermal permeation enhancer from hydrophilic gel formulations. Eur. J. Pharm. Sci. 9 (4): 365-372.

Osborne D. W. (2011) Diethylene Glycol Monoethyl Ether: An emerging solvent in topical dermatology products. J Cosmet Dermatol.10(4):324-9

Panchagnula R. et al. (1991) Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol® as a cosolvent: *in vitro*, *ex vivo* and *in vivo* rat studies. J. Pharm. Pharmacol. 43 (9): 609-614.

Papakostantinou E. et al. (2007) Efficacy of 2 weeks' application of theophylline ointment in psoriasis vulgaris. Journal of Dermatological Treatment 16 (3): 169-170.

Parikh D. K. et al. (2005) Feasibility of Transdermal Delivery of Fluoxetine. AAPS Pharm. Sci. Tech. 6 (2): E144-E149.

Pavliv L. et al. Topical (1994) Formulation development of a novel thymidylate synthase inhibitor for the treatment of psoriasis. Int. J. Pharm. 105 (3): 227-233.

Puglia C. et al. (2008) Effect of Polyunsaturated Fatty Acids and Some Conventional Penetration Enhancers on Transdermal Delivery of Atenolol. Drug Deliv. 15 (2): 107-112.

Rhee Y. S. et al. (2001) Transdermal delivery of ketoprofen using microemulsions. Int. J. Pharm. 228 (1-2): 161-170.

Rhee Y. S. et al. (2007) Effects of vehicles and enhancers on transdermal delivery of clebopride. Archives of Pharmacal Research 30 (9): 1155-1161.

Ritschel W. A. et al. (1988 a) Influence of selected solvents on penetration of griseofulvin in rat skin, *in vitro*. Pharm. Ind. 50 (4): 483-486.

Ritschel W. A. et al. (1988 b) Use of Sorption Promoters to Increase Systemic Absorption of Coumarin from Transdermal Drug Delivery Systems. Arzneim. Forsch. 38 (11-12): 1774-1777.

Ritschel W. A. et al. (1991) Development of an Intracutaneous Depot for Drugs Binding, Drug Accumulation and Retention Studies, and Mechanism of Depot. Skin Pharmacol. 4: 235-245.

Sandig A. G. et al. (2013) Transdermal delivery of imipramine and doxepin from newly oil-in-water nanoemulsions for an analgesic and anti-allodynic activity: Development, characterization and *in vivo* evaluation. Colloids and Surfaces, B: Biointerfaces 103. 558-565.

Shakeel F. et al. (2007) Nanoemulsions as Vehicles for Transdermal Delivery of Aceclofenac. AAPS Pharm. Sci. Tech. 8 (4): E1-E9.

Sullivan, D. W., Gad, S. C., & Julien, M. (2014). A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient. Food and Chemical Toxicology, 72, 40-50.

Touitou E. et al. (1991) Enhanced Permeation of Theophylline Through the Skin and Its Effect on Fibroblast Proliferation. Int. J. Pharm. 70 (1-2): 159-166.

Touitou E. et al. (1994) Modulation of Caffeine Skin Delivery by Carrier Design: Liposomes Versus Permeation Enhancers. Int. J. Pharm. 103 (2): 131-136.

Wang S. et al. (2012) Formulation and evaluation of microemulsion-based *in situ* ion-sensitive gelling systems for intranasal administration of curcumin. Journal of Drug Targeting 20[10]. 831-840.

Yao J. et al. (2009) Preparation of lorazepam-loaded microemulsions for intranasal delivery and its pharmacokinetics. Die Pharmazie 64[10]. 642-647.

Yazdanian M. et al. (1995) The effect of Diethylene Glycol Monoethyl Ether as a vehicle for topical delivery of Ivermectin. Vet. Res. Commun. 19 (4): 309-319.

Zhang J. et al. (2011) Investigation of microemulsion microstructures and their relationship to transdermal permeation of model drugs: Ketoprofen, lidocaine, and caffeine. International Journal of Pharmaceutics 421[1]. 34-44.

GATTEFOSSÉ

TOPICAL DRUG DELIVERY-GB-T8W-810-C (2061 BE) 2019

www.gattefosse.com

Corporate Headquarters
36 chemin de Genas - CS 70070 - 69804 Saint-Priest Cedex - **France**
+(33) 4 72 22 98 00

People make our name