GATTEFOSSÉ

SYNERGISING EXCIPIENTS TO BOOST SKIN DELIVERY

In this article, Cécile Morin, Technical Communication Executive – Pharmaceuticals, and Delphine Marchaud, Marketing & Innovation Director – Pharmaceuticals, both of Gattefossé, discuss combining polar and apolar excipients in topical formulations in order to produce synergies that maximise the performance of the drug.

The skin constitutes a natural barrier to prevent loss of water from the body and penetration of exogenous substances into it. Understanding its constitution and organisation is essential when formulating efficient topical or transdermal dosage forms.

The "brick and mortar" representation is commonly used to describe the *stratum corneum* (SC), with the corneocytes being the "bricks" and lipids the intercellular "mortar". A gradient of decreasing lipophilicity is observed from the upper layer of the SC down to the dermis.

How vehicles in a formulation interact with the lipid structure significantly contributes to drug diffusion through the different layers of the skin. The major route of drug diffusion through the epidermis is the intercellular path[1] (Figure 1).

Three main steps govern drug diffusion from the formulation to the skin:

- **Solubility:** the formulation must solubilise a sufficient amount of drug to reach an effective concentration at the target site.
- **Partition:** the drug must partition out of the delivery vehicle into the upper layers of the SC.
- **Diffusion:** the drug molecule diffuses through the SC mainly via the intercellular path.

Fick's law applies for passive diffusion, meaning it is driven by drug concentration

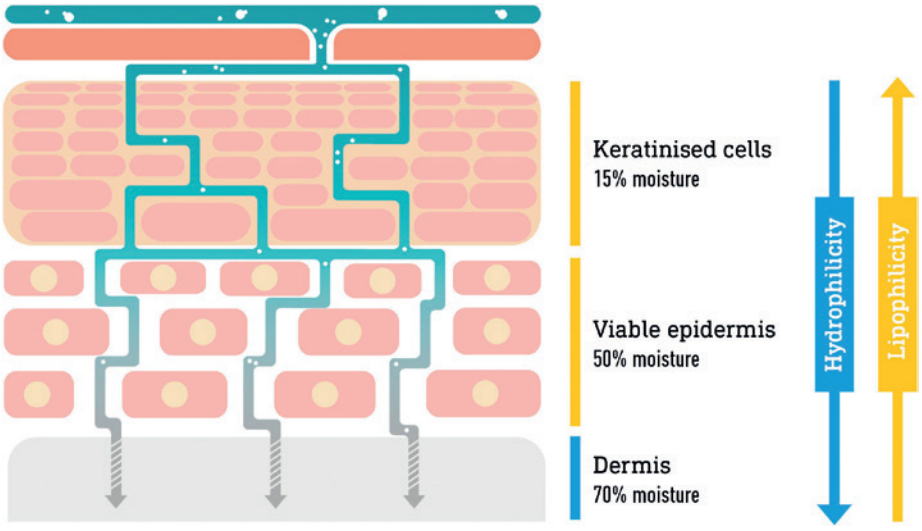

Figure 1: Schematic representation of the structure of the skin.

Cécile Morin
Technical Communication Executive – Pharmaceuticals
T: +33 4 26 04 19 82
E: cmorin@gattefosse.com

Delphine Marchaud
Marketing & Innovation Director – Pharmaceuticals
T: +33 4 72 22 98 41
E: dmarchaud@gattefosse.com

Gattefossé
36 chemin de Genas
69804 Saint Priest
France

www.gattefosse.com

and that maximum thermodynamic force is obtained at saturation solubility.

Therefore, the art of formulation consists of choosing the appropriate vehicles and determining their correct ratio to maximise drug solubility in the formulation and subsequent partition in the skin.

Gattefossé has a wide range of lipid excipients for skin delivery, some of which are described in Table 1. This article will focus on Transcutol® P, Capryol™ and Lauroglycol™ and the benefits that arise from their synergistic combination in topical formulations.

Tradename	Chemical Name	Practical Hydrophile-Lipophile Balance (HLB)
Capryol™ PGMC	Propylene glycol monocaprylate (type I, monoesters >55%) NF	6
Capryol™ 90	Propylene glycol monocaprylate (type II, monoesters >90%) NF	5
Lauroglycol™ FCC	Propylene glycol monolaurate (type I, monoesters >45%) EP/NF	5
Lauroglycol™ 90	Propylene glycol monolaurate (type II, monoesters >90%) EP/NF	3
Transcutol® P	Highly purified diethylene glycol monoethyl ether EP/NF	N/A

Table 1: Gattefossé's main excipients for dermal drug delivery (NF – Compliant with National Formulary monograph, EP – Compliant with European Pharmacopoeia).

LIPID EXCIPIENTS: NATURALLY ADAPTED TO THE SKIN

Lipid excipients, with their high solubilising power and amphiphilic properties, enable modulation of the penetration of the active pharmaceutical ingredient (API) into the SC, and drive API flux.

Transcutol® P is a safe and effective hydrophilic solvent widely used in skin delivery.[2] Transcutol® increases the solubility of both lipophilic and hydrophilic APIs. Furthermore, it can penetrate the SC and interact with the water in the intercellular space.[3]

Capryol™ and Lauroglycol™ are lipophilic solubilisers. They consist of fatty acid esters and can interact with the lipids in the intercellular space. The greatest permeation is observed with excipients containing caprylate (C10) and laurate (C12) fatty acid esters, whereas myristate (C14) and stearate (C18) favour skin-vehicle partitioning.[4]

Polar solvents (e.g. Transcutol®) increase drug solubility in the SC, whereas non-polar solvents (e.g. Capryol™, Lauroglycol™) increase the diffusion parameter of the drug in the SC. Their combination in a formulation has been reported to deliver higher efficiency.

Solubiliser	Permeation flux (µg/cm²/h)	Solubility (mg/mL)
Capryol™ 90	6.08 ±2.29	51.3 ±5.68
Lauroglycol™ 90	94.3 ±17.3	15.2 ±1.87
Transcutol® P	0.69 ±0.29	211 ±11

Table 2: Flux and solubility of ketorolac tromethamine with different solubilisers.[5]

A PROVEN SYNERGISTIC EFFECT

The combination of solubilisers is a common practice to maximise drug solubility, thermodynamic force and partition in the skin. Combinations of Transcutol® with other permeation enhancers have been reported in the scientific literature and reviewed by Osborne & Musakhanian (2018). Examples of synergistic combinations using Transcutol® and either Capryol™ or Lauroglycol™ are detailed hereafter.

Example One: Neat Solvents – Ketorolac Tromethamine – Rodent Skin

Cho *et al* (2004)[5] studied the transdermal delivery of ketorolac tromethamine. The study measured drug solubility and permeation through excised hairless mouse skin in various excipients, pure or in mixtures.

Permeation flux was highest for Lauroglycol™ and solubility highest for Transcutol® (Table 2). They then combined Transcutol® with either Lauroglycol™ or

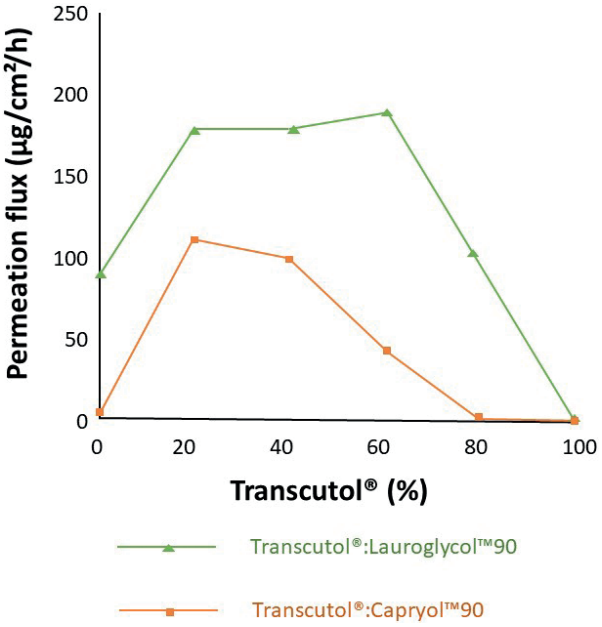

Figure 2: Ketorolac tromethamine flux in neat solvent and solvent mixtures (Adapted from Cho *et al,* 2004).[5]

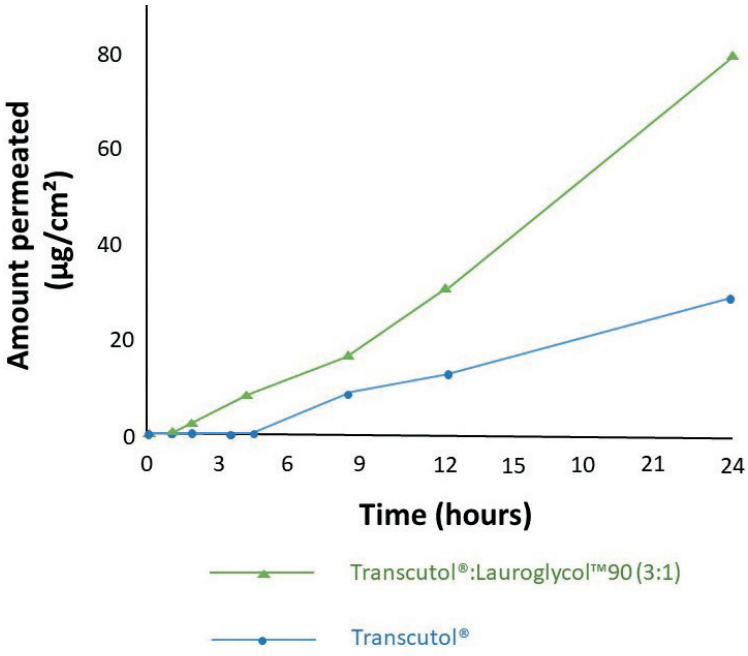

Figure 3: Genistein permeation from a gel containing 25% permeation enhancers (Adapted from Chadha *et al,* 2011).[6]

Capryol™ at different ratios (Figure 2). A 20% increase in permeability was observed for combined Transcutol® and Capryol™ in the ratios 80:20 and 40:60. A two-fold increase in permeation over Lauroglycol™ alone was observed for combined Transcutol®:Lauroglycol™ mixtures in the ratios 20:80, 40:60 and 50:50.

To the authors' knowledge, this study was the first to report a synergistic relationship between the polar solvent Transcutol® and apolar solvents such as Capryol™ and Lauroglycol™.

Example Two: Gel Formulation – Genistein – Human Skin

Chadha *et al* (2011)[6] formulated a gel with genistein and various permeation enhancers and assessed permeation across human skin (Figure 3). A three-fold increase in genistein solubility was observed with Transcutol® alone, whereas the combination Transcutol®:Lauroglycol™ 90 exhibited a 12-fold increase versus the control formulation with ethanol. Similarly, a significant five-fold increase in flux was achieved with Transcutol® alone and a 13-fold increase when combining Transcutol® and Lauroglycol™ 90 (ratio 3:1).

This study confirmed that the synergistic combination of Transcutol® and Lauroglycol™ is efficient when formulated in a gel and tested on human skin.

Example Three: Neat Solvents – Carbenoxolone – Human Skin

Hirata *et al* (2013)[7] tested various solvents, pure or in association, and assessed the skin permeability of carbenoxolone on human skin (Figure 4).

Dimethyl isosorbide (DMI), isopropyl myristate (IPM) and Transcutol® were tested as neat solvent, but permeation at 24 hours was below 0.3 µg/cm². In binary mixtures, synergies were observed, and permeation reached 16.0 and 14.0 µg/cm² at 48 hours for the binary systems Transcutol®:IPM and Transcutol®:Lauroglycol™ FCC, respectively.

Although binary mixtures of solubilisers significantly improved the permeation, the maximum synergy was observed with the ternary composition consisting

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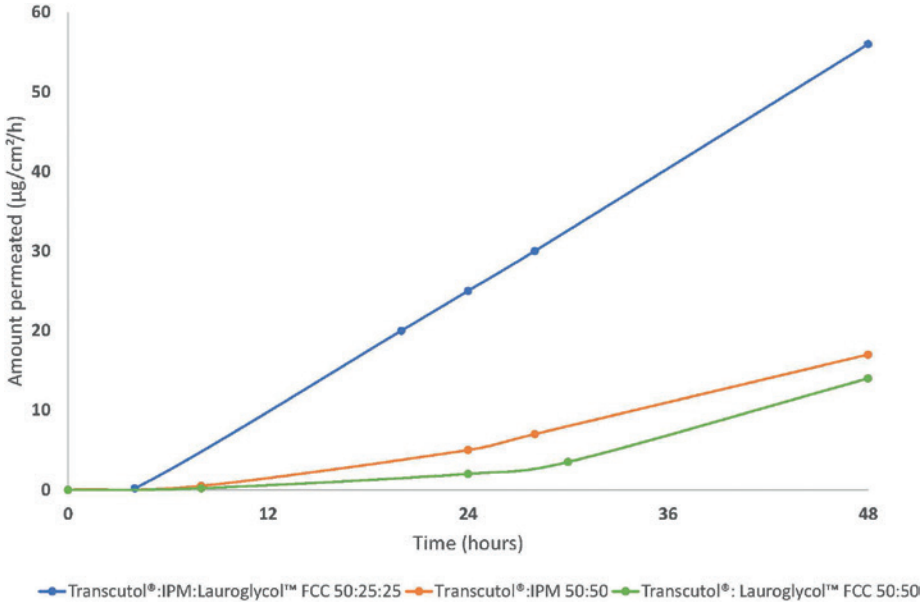

Figure 4: Carbenoxolone permeation from binary and ternary solvent mixtures (Adapted from Hirata *et al,* 2013).

"Each drug is specific and no general rule can be established. Therefore, a case-by-case approach is required to determine which solvents (polar and apolar) are best suited to the drug."

of Transcutol®:IPM:Lauroglycol™ FCC in the ratio 50:25:25, with flux reaching 56 µg/cm²/h.

This study highlights that for some actives, a ternary solubiliser system is needed to reach sufficient level of permeation.

Example 4: Gel Formulation – Diclofenac Sodium – Human Skin

At Gattefossé, diclofenac sodium was used as a model drug and formulated in gels for permeability studies on human skin (Figure 5). Although the permeation obtained with the binary system propylene glycol (PG):Lauroglycol™ FCC was quite high (about 100 µg/cm²), the best performance was achieved with a quaternary system consisting of Transcutol®P, IPM, PG and Lauroglycol™ FCC (Figure 5) and a permeation of about 120 µg/cm².

This study highlights the fact that some drugs are best served by multi-component solubiliser systems, with three to four excipients, to maximise drug delivery through the skin. The formulator has to determine the optimal ratio of polar and apolar solvents for the drug, and this can only be done on a case-by-case basis.

CONCLUSION

Drug delivery to the skin is a challenging process requiring solubilisation, partition and diffusion of the drug through the different dermal layers. Each drug is specific and no general rule can be established. Therefore, a case-by-case approach is required to determine which solvents (polar and apolar) are best suited to the drug. However, when developing a formulation, one has to keep in mind that even when permeation is low with individual excipients, combination can produce synergies, as was demonstrated with Transcutol® P in association with Lauroglycol™ or Capryol™.

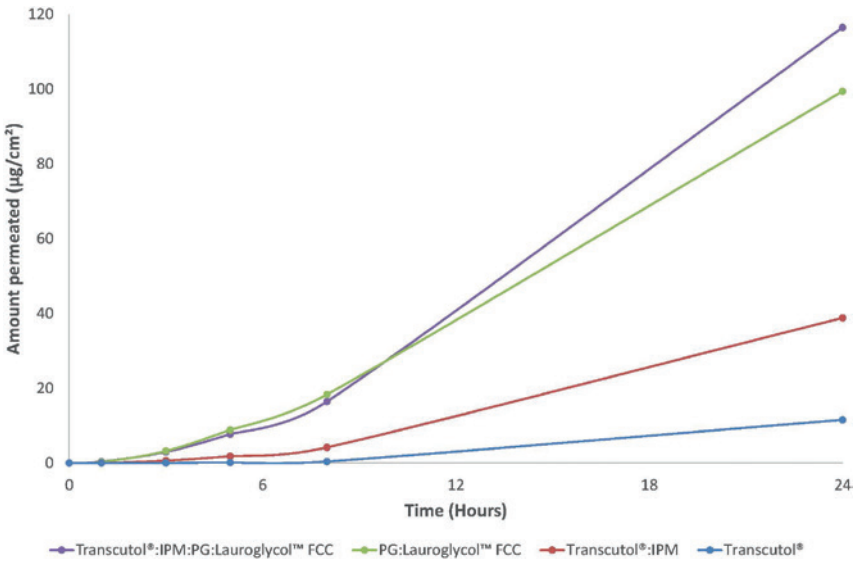

Figure 5: Diclofenac sodium permeation through human skin from various gel formulations (Gattefossé in-house study).

BOX 1: GATTEFOSSÉ'S DRUG DELIVERY OFFERING

ORAL DRUG DELIVERY

Functional lipid excipients that are designed to meet the most pressing formulation challenges in oral drug development:

- **Solubility/Bioavailability Enhancement:** Lipid-based drug delivery systems consisting of single or multiple excipients, forming oily formulations, self-emulsifying (SEDDS) and self-micro-emulsifying (SMEDDS) formulations or micellar solutions, for APIs with poor solubility, permeability or bioavailability.
- **Modified Release:** Lipid matrices that are water-insoluble and do not swell or erode when in contact with aqueous media. They form an inert matrix from which the drug diffuses slowly over time allowing for modified or sustained-release of API.
- **Protection and Taste Masking:** Excipients that form a film coating around the drug particle for taste-masking and protection of sensitive APIs when used in melt processes.
- **Lubrication:** Excipients that act as a lubricant for challenging tablets and capsules, with inert excipients eliminating drug-excipient incompatibility issues.

TOPICAL DRUG DELIVERY

Functional lipid excipients are used to formulate creams, lotions, ointments, foams and oily and aqueous gels:

- **Optimised Sensorial Experience:** Improved texture and sensorial properties positively impact the patient experience and adherence to treatment. Optimising stability, texture and sensorial qualities of a topical product can be achieved with the selection of the right combination of emulsifiers and consistency agents.
- **Solubilisers:** Transdermal drug delivery can be achieved by the selection of suitable solubilisers, skin penetration enhancers and solvents to enable passage through the skin.

RECTAL & VAGINAL DRUG DELIVERY

Functional lipid excipients are used to formulate suppositories, pessaries, creams, ointments and foams:

- Optimisation: Well-established hard fat bases for suppositories and pessaries optimise drug delivery for a wide range of APIs and manufacturing equipment.
- Emulsifiers: Alternative dosage forms for rectal or vaginal mucosal delivery can be formulated with safe, non-irritant emulsifiers and thickeners.

INTERNATIONAL TECHNICAL SUPPORT

With an international network of technical representatives and Technical Centers of Excellence in the US, France, India and China, Gattefossé provides bespoke technical and regulatory support to accelerate drug development.

ABOUT THE COMPANY

Gattefossé is a leading provider of lipid excipients and formulation solutions to healthcare industries worldwide, with an in-depth knowledge of lipid excipient physicochemical and functional properties. The company has an international network of technical representatives and Technical Centers of Excellence in the US, France, India and China. Gattefossé provides bespoke technical and regulatory support to accelerate drug development.

ABOUT THE AUTHORS

Cécile Morin is a food engineer with a long experience in communication concerning food, pharmaceutical and cosmetic ingredients. She is in charge of print and digital communication for Gattefossé Pharmaceuticals.

Delphine Marchaud graduated in 1996 from the School of Applied Sciences, University of Montpellier (France) in Physicochemistry and completed her training with a Master 2 in Pharmaceutical Technologies. In 1998, she joined Gattefossé, managing the Pharmaceutical Application Laboratory. From 2006 she took the lead of the Pharmaceutical Technical Division, with a team of scientists developing lipid based drug delivery platforms and novel applications. Since January 2014, Ms Marchaud is Director of the Marketing & Innovation department for pharmaceuticals at Gattefossé.

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