

Transcutol® P

For efficient drug solubilization
and skin penetration



ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **DEGEE:** Diethylene glycol monoethyl ether; **DMF:** Drug Master File; **DMSO:** Dimethyl sulfoxide; **FDA:** US Food and Drug Administration; **INCI:** International Nomenclature of Cosmetic Ingredients; **PG:** Propylene glycol; **Ph. Eur.:** European Pharmacopœia; **SC:** Stratum corneum; **UNII:** Unique Ingredient Identifier; **USP-NF:** US Pharmacopoeia National Formulary; **W/W:** Weight / Weight

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Product description: a safe solvent

Transcutol® P is a high purity grade of diethylene glycol monoethyl ether (DEGEE) (Figure 1) manufactured by the condensation of ethylene oxide and ethanol, followed by distillation. The presence of an ether and an alcohol function explains the exceptional solubilizing capacity of this solvent.

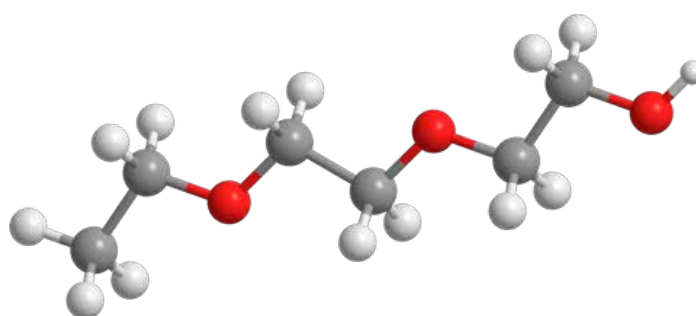


Figure 1: DEGEE molecular structure

Transcutol® is the highest purity pharmaceutical grade DEGEE available. Gattefossé implements a proprietary distillation process to ensure the lowest level of impurities in all Transcutol® grades, well below the Pharmacopoeia limits. For topical formulations Gattefossé recommends the use of Transcutol® P grade for human medicines and Transcutol® V for veterinary medicines. Note that Transcutol® HP is the highest purity grade and is preferred for oral medicines and for highly sensitive APIs.

Transcutol® P is a protic solvent; a colorless limpid liquid (viscosity = 4.1 mPa.s at 25°C), with a faint odor. It is miscible in most of the excipients commonly used in topical formulations (Table 1). In standard laboratory conditions (20 - 25°C; 35 - 50% RH), Transcutol® P is relatively stable to humidity. However, above 60% RH, Transcutol® P is hygroscopic (Figure 2).

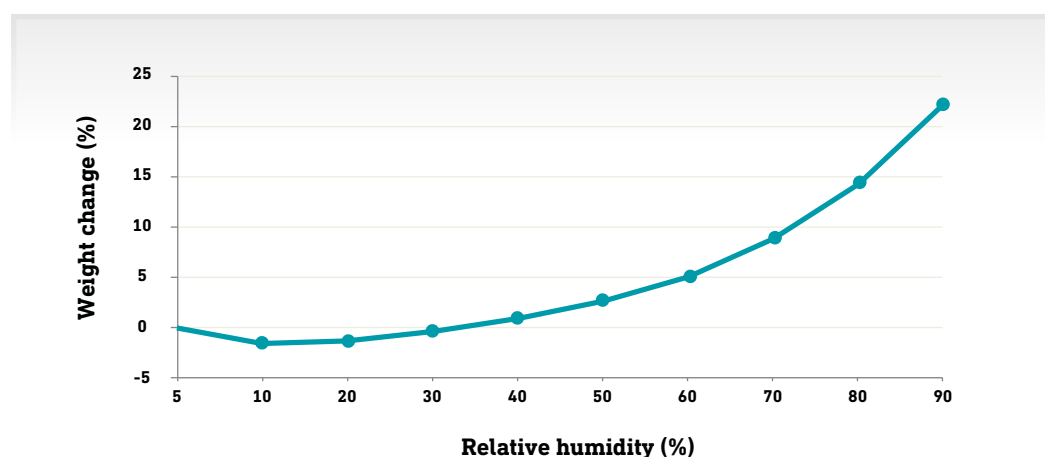


Figure 2: Transcutol® P water sorption isotherm at 25°C

Table 1: Main physicochemical properties of Transcutol® P compared to common topical solvents

	Transcutol® P	Propylene glycol	Ethanol	PEG 400	Water
	$C_6H_{14}O_3$	$C_3H_8O_2$	C_2H_6O	$C_{2n}H_{4n+2}O_{n+1}$ n = 8.2 to 9.1	H_2O
Molar mass (g/mol)	134.175	76.1	46.07	380 - 420	18
Density (g/cm ³ at 20°C)	0.989	1.038	0.789	1.128	0.998
Viscosity (mPa.s at 20°C)	4.8	58	1.2	120	1
Log P (Octanol:Water)	-0.43	-0.92	-0.18	-4.8	-0.5
Melting point (°C)	-76	-59	-114	4-8	0
Boiling point (°C)	196 - 200	187 - 188.2	78.5	290	100
Vapor pressure (Pa)	16	9	5950	1.33	3130
Flash point (°C)	96	99	13	238	NA
Dielectric constant (25°C)	14.1	32.1	24.3	NA	80.4
Surface tension (mN/m at 25°C)	31.3	40.1	21.8	NA	72.8
Miscibility at 25°C of solvents (above) in main topical excipients (below)					
Capryol® 90	Miscible	Miscible	Miscible	Miscible	Immiscible
Capryol® PGMC	Miscible	60%	Miscible	Miscible	Immiscible
Isopropyl myristate	Miscible	Immiscible	Miscible	Immiscible	Immiscible
Labrafil® M 1944 CS	Miscible	Immiscible	50%	10%	Immiscible
Labrasol®	Miscible	Miscible	Miscible	Miscible	Miscible
Lauroglycol™ 90	Miscible	Miscible	Miscible	Miscible	Immiscible
Lauroglycol™ FCC	Miscible	20%	Miscible	30%	Immiscible
Mineral oil	Immiscible	Immiscible	Immiscible	50%	Immiscible
Sweet almond oil	30	Immiscible	Immiscible	Immiscible	Immiscible
Plurol® Oleique CC 497	Miscible	20%	Miscible	Immiscible	Immiscible

Examples to explain how to read the miscibility table:
 Transcutol® P is miscible with sweet almond oil up to 30% and above 90% solvent in oil. From 40 to 80% it is immiscible.
 10% PEG 400 are miscible in 90% Labrafil® M 1944 CS.

Handling: measures to ensure product integrity



Transcutol® P is sensitive to oxidation and hydrolysis; exposure to oxygen and humidity should be limited during handling and storage.

Control exposure to oxygen

- Minimize aeration of the excipient
- Minimize and control the degree of exposure to heat and light
- Use N₂ blanket

Control exposure to humidity

- Minimize and control relative humidity when opening the packaging
- Seal the container tightly after use

A safe solvent to handle

Transcutol® P evaporation is reduced compared to ethanol due to a higher boiling point and a lower vapor pressure.

Transcutol® P has a flash point of 96°C, therefore exposure to external (or potential) sources of ignition at or above this temperature should be avoided. Gattefossé recommends avoiding heating above 85°C.

Detailed information is available in the Handling Sheet and the Material Safety Datasheet

Product functionality



A powerful solubilizer

A key feature of Transcutol® P is its solubilization capacity for both lipophilic and hydrophilic APIs. Figure 3 gives saturation solubility data of a wide set of APIs used in topical drug delivery.

Increasing drug solubility in the vehicle, and thereby the thermodynamic driving force, provides higher diffusion and better skin permeation. Formulating with Transcutol® P ensures sufficient drug solubilization and subsequent delivery of an adequate concentration at the target site.

An efficient penetration and permeation enhancer

The mechanism of action of Transcutol® P for penetration and permeation enhancement can be explained as follows:

- Increasing drug solubility in the vehicle
- Decreasing drug charge by a solvent effect
- Increasing drug solubility and partitioning in the stratum corneum
- Maintaining hydrated dynamics in the stratum corneum without disturbing the lipid bilayer structures

The effect of chemical permeation enhancers on skin structure and how they interact with the lipid bilayer is well characterized (Gwak, 2002; Hirata, 2014; Moghadam, 2013; Salimi, 2015; Trommer, 2006).

A qualitative ranking of the common permeation enhancers can be established (Figure 4). With no effect on lamellar structure, Transcutol® P appears to be as gentle as water on the skin.

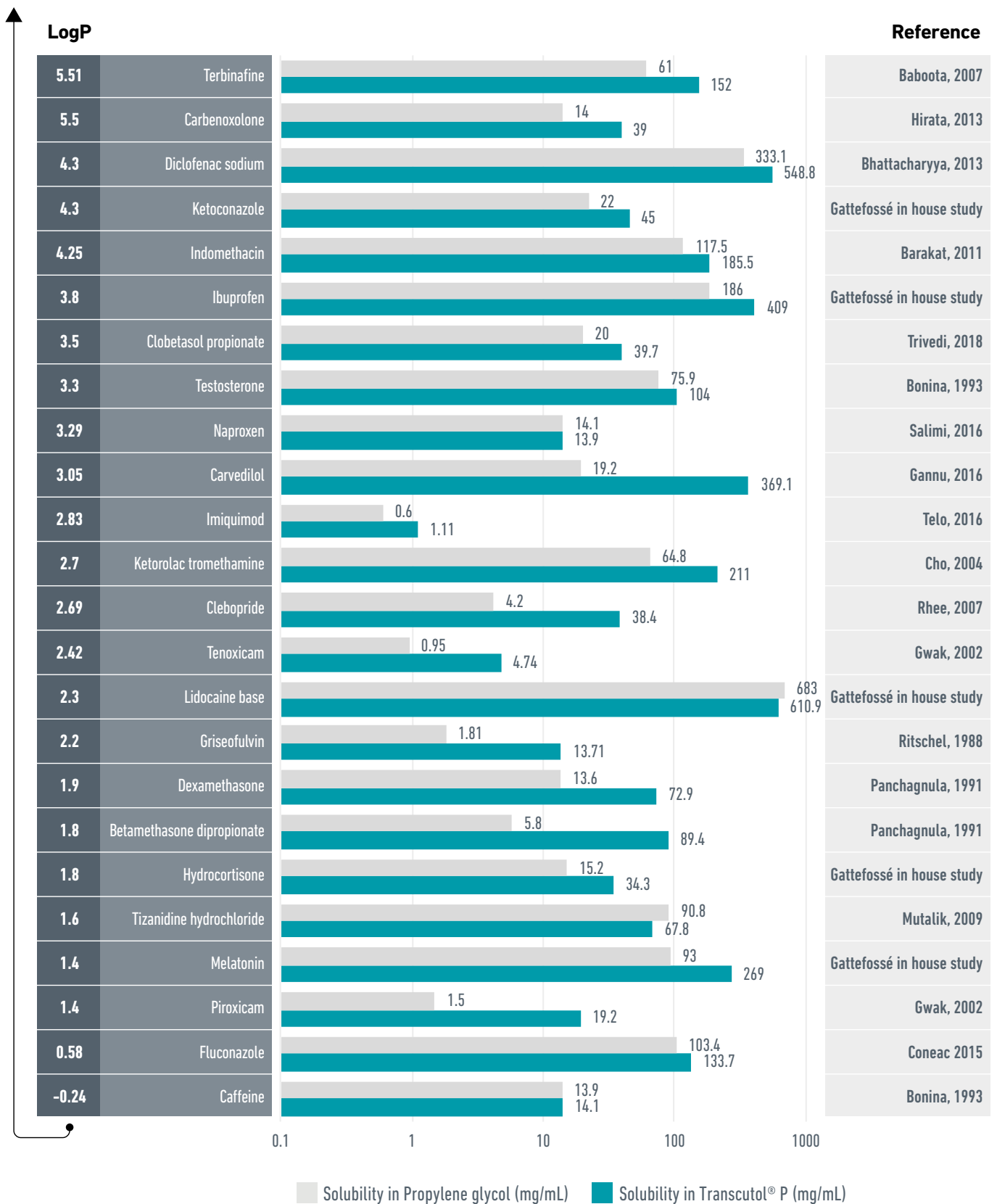


Figure 3: Solubility data in Transcutol® P and propylene glycol for selected APIs

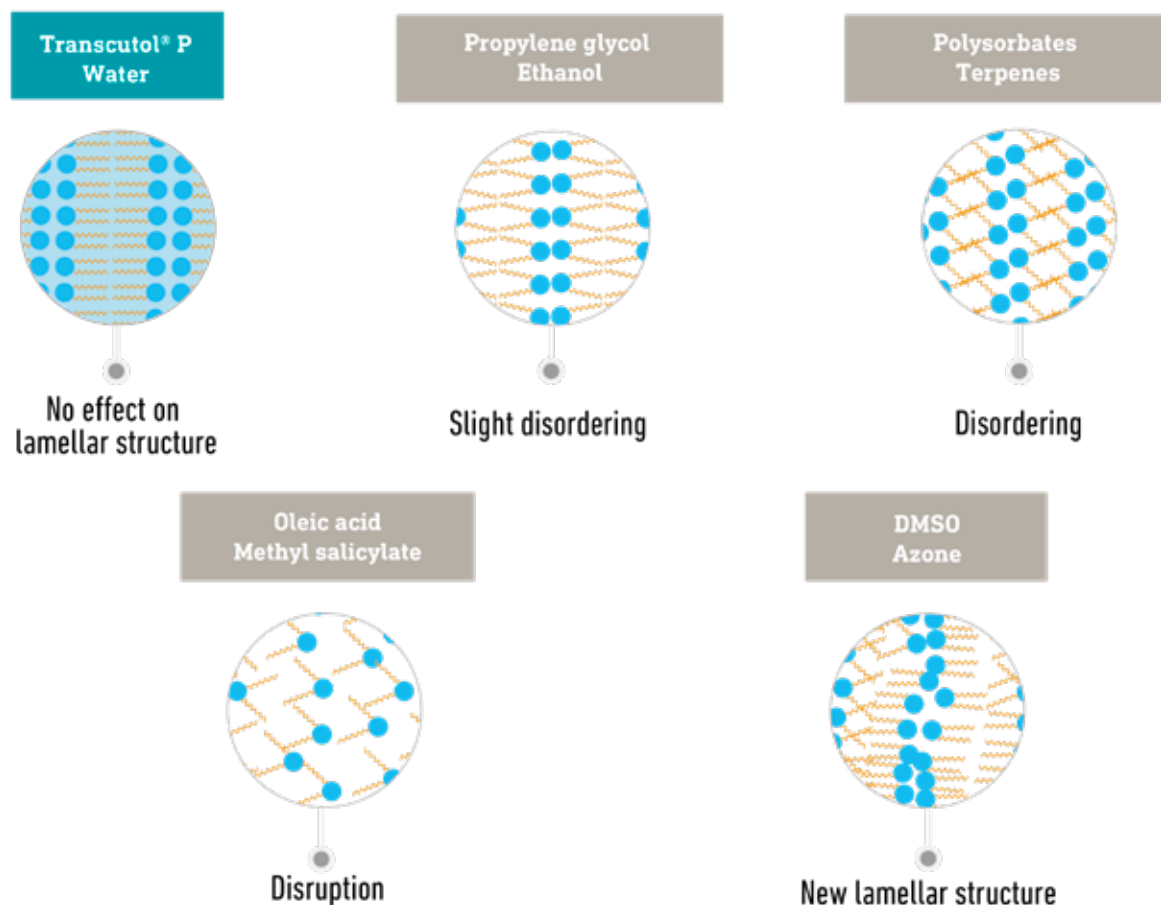


Figure 4: Qualitative ranking of the effect of permeation enhancers on skin lamellar structure

Translating functionality into practical tips

- ✓ A good solubilization of API in a solvent does not necessarily correlate with good permeation.
- ✓ Screening of various solvents for solubility and permeation capacity is a compulsory step in formulation development to determine the most appropriate solvents and their ratio as a function of the target (topical or transdermal) and the drug properties.
- ✓ Water is a key solvent. Formulated with Transcutol® P, good solubilization and permeation are obtained, while maintaining skin hydration dynamics.
- ✓ Enhanced permeation resulting from the combination of Transcutol® P with different permeation enhancers i.e. a synergistic effect has been reported, notably with Capryol® and Lauroglycol™.

Formulating with Transcutol® P

Transcutol® P has been referenced in all types of dosage forms, including creams, emulgels, foams, and gels. Moreover, it is a widely used enhancer in the preparation of micro/nano emulsions and vesicular / liposomal drug delivery systems for transdermal delivery.

General recommendations

In most cases, the API is dissolved in Transcutol® P at ambient temperature, although if necessary, heating to 50 - 60°C is possible.

Addition of common antioxidant for topical formulation is recommended.

Emulsions

Transcutol® P may be included in the aqueous or oily phase. Typically, it is gradually added after emulsification during the cooling step when the temperature is around 40°C to avoid API degradation.

Stable anhydrous and hydrous creams containing as high as 40% Transcutol® P can be obtained (Dave, 2018).

Stable emulgels have been formulated with up to 25% Transcutol® P.

Gels

Transcutol® P can be used in aqueous and hydro-alcoholic gels. High levels of Transcutol® P are achievable without altering the clear gel structure or its stability, whatever the gelling agent (carbomers, hydroxyethylcellulose and hydroxypropylcellulose).

Stable, clear gels (viscosity \approx 5000 mPa.s) are obtained with:

- 2% hydroxyethylcellulose and up to 40% Transcutol® P
- 0.5% carbomer and up to 30% Transcutol® P
- 2.5% hydroxypropylcellulose and up to 25% Transcutol® P

Microemulsions

Transcutol® P has been extensively studied in microemulsion systems where it acts as a solubilizer (Kreilgaard, 2002). A comprehensive review summarizes the main microemulsion compositions with Transcutol® P (Ha, 2019).

Foams

Foams result from the conversion of a microemulsion or an emulsion with the use of a propellant-free or propellant device. In both cases, Transcutol® P is used as a solubilizer.

Patches

Transcutol® P is used as a permeation enhancer with the API in the pressure-sensitive-adhesive layer (Shen et al, 2018).



Case studies

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

- Solubility: the formulation must solubilize a sufficient amount of drug to deliver 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 and that maximum flux is obtained at saturation solubility.

The different processes for a drug to solubilize, partition and diffuse through the different layers of the skin are dependent on API intrinsic properties (molecular weight, melting point, solubility,) and on the formulation (Figure 5). As such, the choice of excipients is critical.

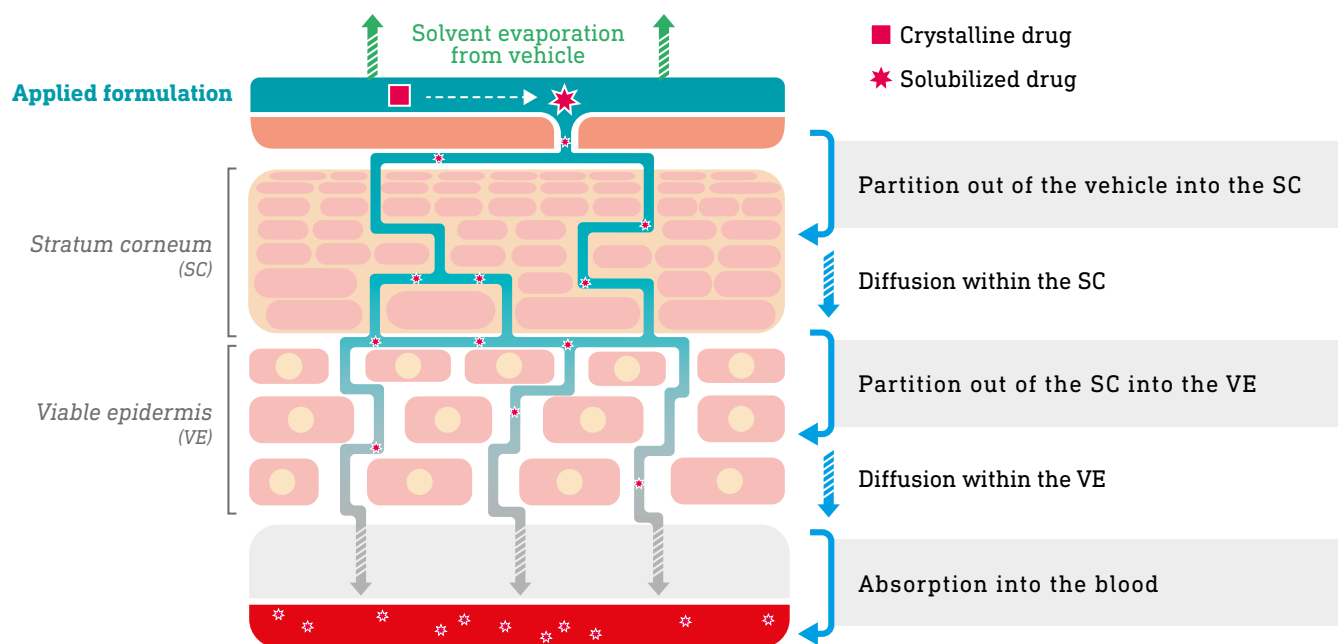


Figure 5: Schematic representation of skin delivery (adapted from Lane, 2013)

To illustrate the role of Transcutol® P and the importance of formulation, several case studies are described.

CS #1: Achieving the right balance between solubility and thermodynamic force

CS #2: Transcutol® P is suitable for a wide range of active ingredients

CS #3: Benefiting from synergy between Transcutol® P and Lauroglycol™ FCC

CS #4: Leveraging solvent evaporation for increased efficacy

CS #1: Achieving the right balance between solubility and thermodynamic force

The art of the formulator consists in choosing the appropriate vehicles and determining their correct ratio to maximize drug solubility in the formulation and partition in the skin. Since no general rule can be established, screening of the API in different vehicles is a necessary step.

Two examples are provided below to show how different APIs behave in Transcutol® P and the importance of using a mixture of solvents, keeping in mind water is an essential solvent in topical formulations.

Clonazepam

Drug properties	Impact on skin penetration
Molecular weight: 316 g/mol	Suitable for topical delivery
Log P \approx 2.4	Low lipophilicity
Water solubility: 0.1 mg/mL	A major hurdle for drug partitioning in the hydrophilic regions past the SC
Solubility in Transcutol® P: 38.7 mg/mL	Soluble

The gel formulation consisted of 1.5% of clonazepam, 1% Carbopol 934 as gelling agent, 97% vehicle (different Transcutol® P:water ratios) and 0.5% triethanolamine as neutralizer. Two hundred milligrams of the gel formulation were applied on rabbit ear skin and permeation of the drug was assessed *in vitro* (Figure 6).

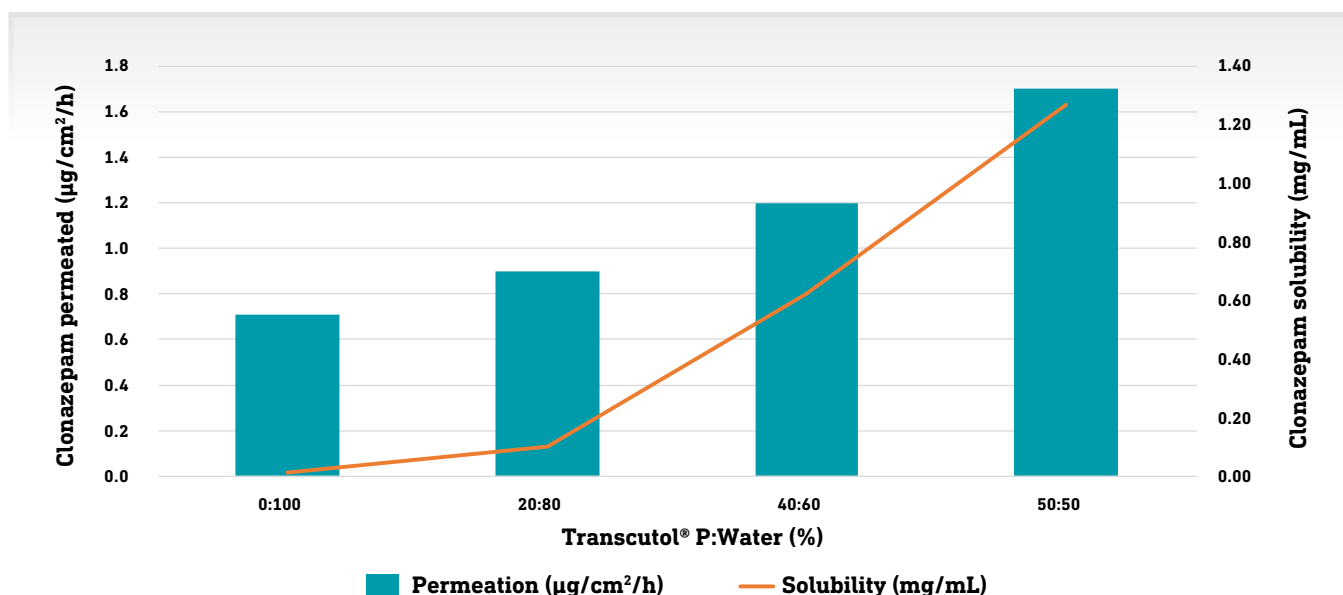


Figure 6: Clonazepam permeation for different ratios Transcutol® P:water solutions (adapted from Mura, 2000)

With rising Transcutol® P concentration both the flux and solubility of clonazepam increase. At 50% Transcutol® P concentration, the right balance between solubility and permeation is achieved.

Ibuprofen

Drug properties

Molecular weight: 206 g/mol

LogP \approx 4

Water solubility: 0.021 mg/mL

Solubility in Transcutol® P: 400 mg/mL

Impact on skin penetration

Suitable for topical delivery

Medium lipophilicity

A major hurdle for drug partitioning in the hydrophilic regions past the SC

Freely soluble. Ibuprofen has a strong affinity for Transcutol® P

Ibuprofen formulations (50 mg/mL) were prepared at different ratios of Transcutol® P:water and the permeation rate through human skin was assessed *in vitro* (Bialik, 1993). Comparing solubility and permeation rates of ibuprofen (Figure 7) suggests that there is an inverse relationship between flux and solubility.

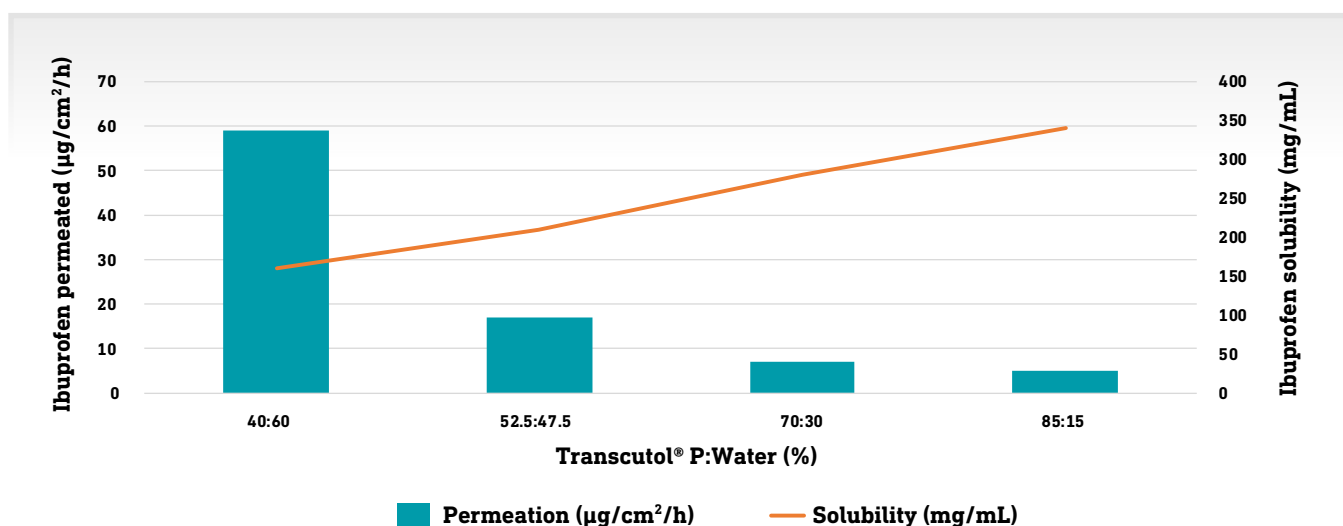


Figure 7: Ibuprofen permeation from Transcutol® P:water solutions (adapted from Bialik, 1993)

At 85:15 Transcutol® P:water ratio, limited permeation is observed, whereas at 40:60 ratio highest permeability is obtained. Due to its strong affinity for Transcutol® P, ibuprofen has little tendency to partition out when the vehicle contains more than 50% Transcutol® P.

The addition of water, in which ibuprofen is less soluble, increases the thermodynamic activity of ibuprofen, thus increasing its rate of permeation. The presence of water in the mixture maintains the skin hydration levels needed for a faster permeation rate. In this example, 40% Transcutol® P in water provides adequate solubility with the highest flux ratio.

Conclusion

For hydrophilic or low lipophilic API, the SC is the sole barrier to the API. Therefore, good solubilization of the API is necessary to facilitate skin penetration. For API with medium or high lipophilicity, the barriers are the SC and the difficulty to partition into the hydrophilic layers beneath the SC.

Hydration capacity of the skin and the vehicle impact skin permeation. Thus, the relationship between solubility and permeation may be linear or inverse, depending on the quantity of solvent as well as water in the formulation.

CS #2: Transcutol® P is suitable for a wide range of active ingredients

Lipophilic, hydrophilic, cationic or anionic... whatever the API, Transcutol® P is a powerful solubilizer and penetration/permeation enhancer.

Highly lipophilic drug: tetrahydrocannabinol (LogP \approx 7)

Fabin et al (1991) measured the penetration of tetrahydrocannabinol in rat skin from three different formulations: neat Transcutol® P, PEG 400 and a 7:3 blend of propylene glycol:ethanol. Among the different solvents tested, the highest cumulative permeation was observed for Transcutol® P (Figure 8).

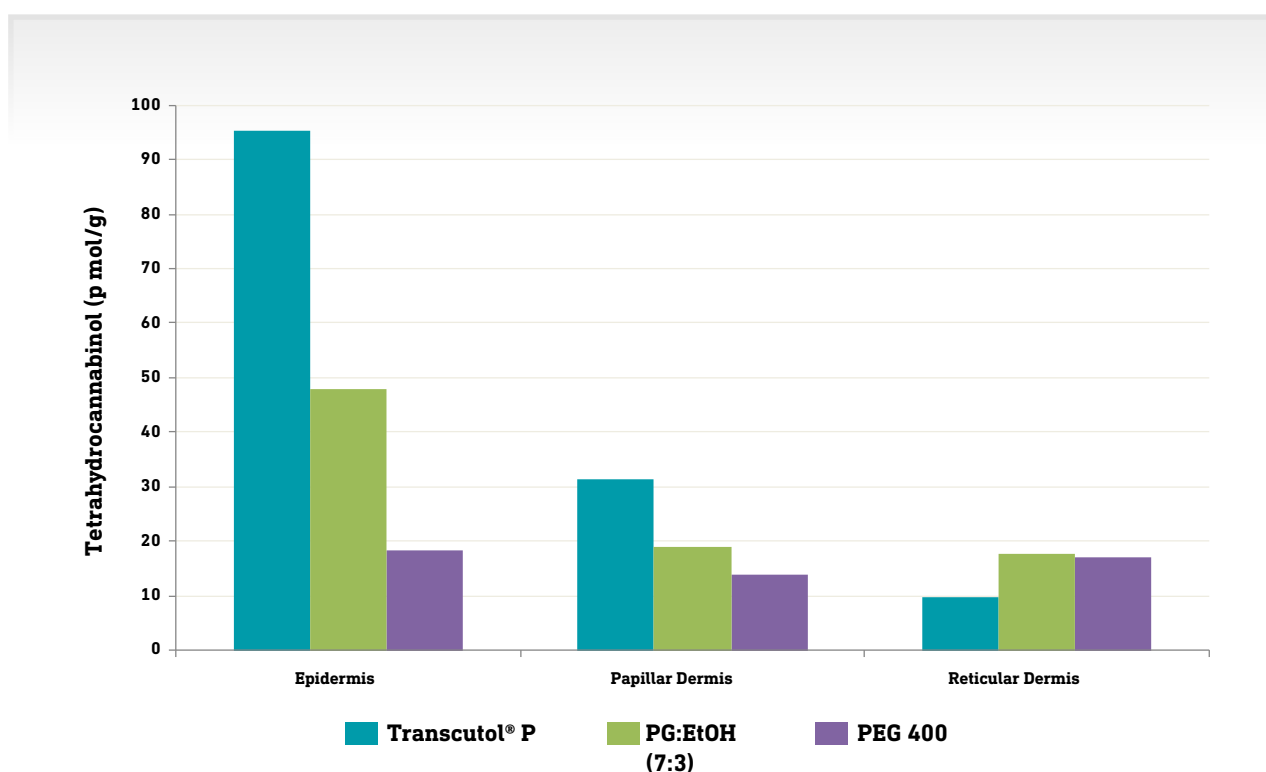


Figure 8: Distribution of tetrahydrocannabinol across rat skin (adapted from Fabin et al, 1991)

Low lipophilic drug: dexamethasone (LogP \approx 1.8)

Panchagnula et al (1991) observed a marked increase in dexamethasone solubility in Transcutol® P compared to other solvents: 0.445 mg/mL in water, 13.60 mg/mL in propylene glycol and 72.9 mg/mL in Transcutol® P.

The penetration of dexamethasone as a function of skin depth for the tested solvents showed a tremendous increase in permeation with Transcutol® P (Figure 9).

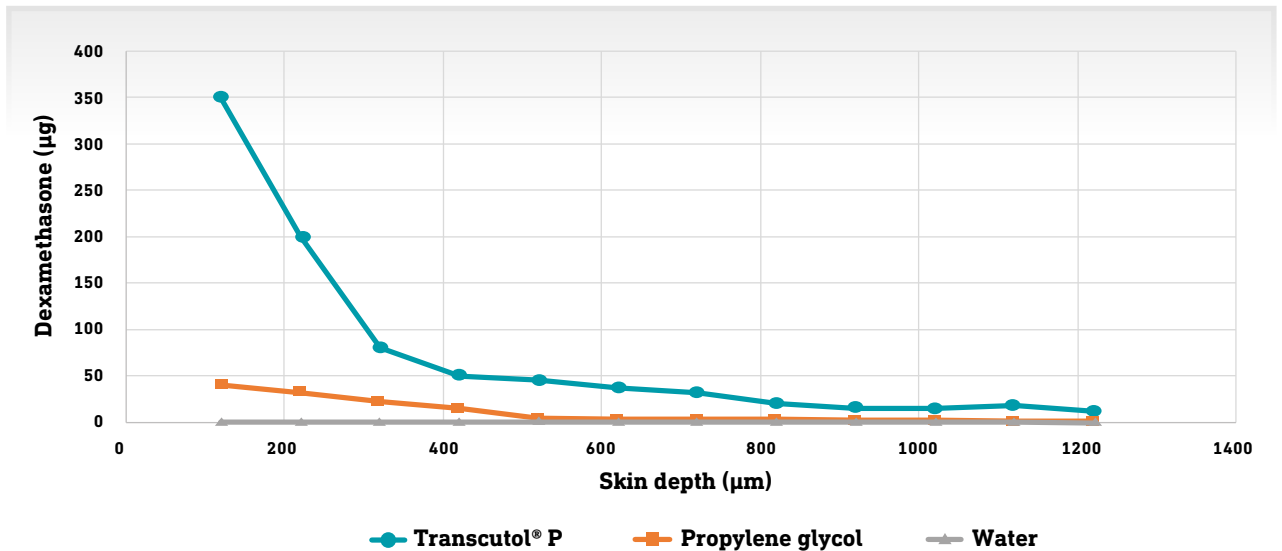
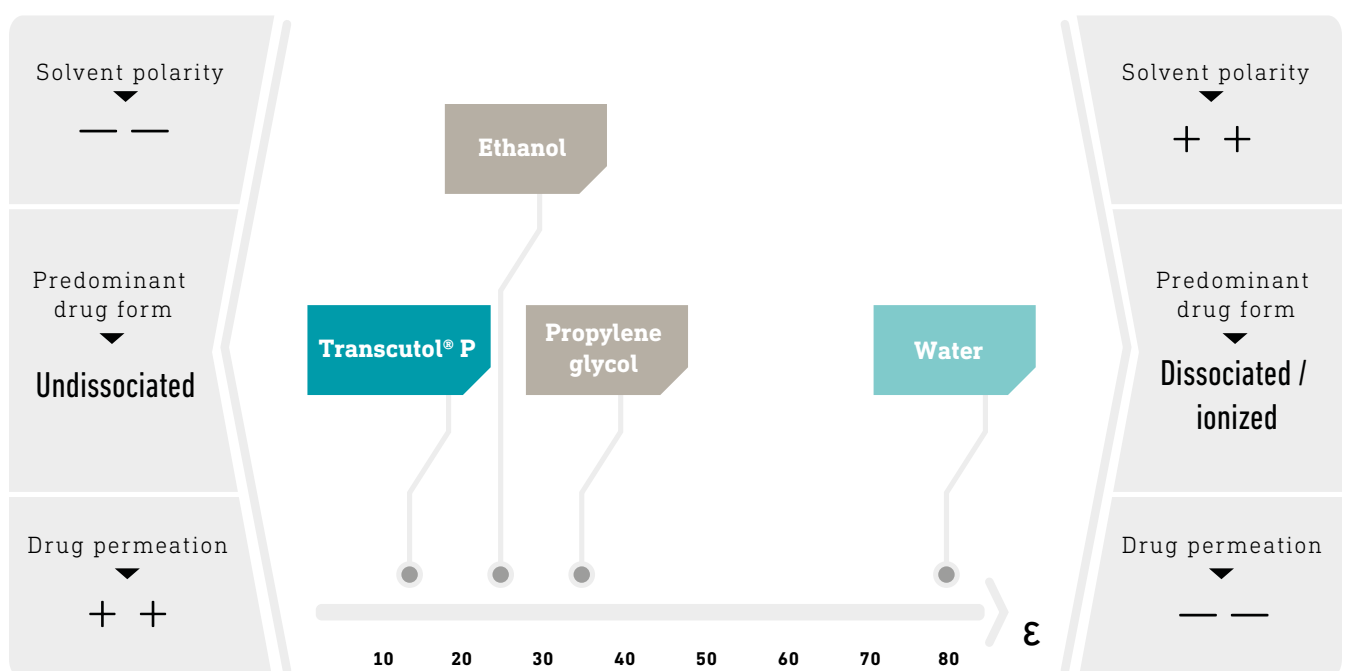


Figure 9: Distribution of dexamethasone in rat skin layers (adapted from Panchagnula, 1991)

Ionizable drugs

Ionized, drug molecules are poorly absorbed across the skin barrier. Moreover, slight changes in pH in the formulation or in the skin can cause large variations in permeability (Cázares -Delgadillo, 2005).

Owing to a lower dielectric constant (ϵ), Transcutol® P is much less polar than water. Therefore, ionizable drugs will dissociate to a lower extent in Transcutol® P than in water, which favors increased permeation.



CS #3: Benefiting from synergy between Transcutol® P and Lauroglycol™ FCC

The synergistic use of penetration enhancers to increase skin delivery is a well-established practice, abundantly described in the literature (Dragicevic, 2015; Karande, 2009; Lane, 2013). The synergy of Transcutol® P with penetration enhancers has been more specifically reviewed (Osborne, 2018) and its association with Lauroglycol™ FCC highlighted (Morin, 2019; Dauphin-Chanard, 2019).

Lauroglycol™ FCC is a propylene glycol monolaurate (Type I, >45% monoesters), with ≥95% lauric acid (C₁₂), a fatty acid known to enhance skin permeation (Aungst, 1986).

Lidocaine hydrochloride solubility was assessed in various solvents and penetration enhancers, either alone or in combination (Table 2). In neat excipients, highest solubility was obtained for water, followed by Transcutol® P, whereas Lauroglycol™ FCC exhibited a limited solubility.

Table 2: Solubility of lidocaine HCl in various penetration enhancers (adapted from Dauphin-Chanard et al. 2019)

Permeation enhancer	Solubility at 32°C (mg/mL)
Water	796.2 ± 16.7
Transcutol® P	379.0 ± 14.8
Transcutol® P / Lauroglycol™ FCC (7/3)	271.0 ± 8.4
Transcutol® P / Lauroglycol™ FCC (5/5)	143.4 ± 9.6
Lauroglycol™ FCC	5.4 ± 0.3

Permeation of lidocaine hydrochloride was assessed in Franz cells (Strat-M membrane) for Transcutol® P and Lauroglycol™ FCC, alone or in combination (Figure 10).

In neat excipient, highest permeation rate was obtained for Transcutol® P, followed by water and Lauroglycol™ FCC. This shows that although water is the best solubilizer for lidocaine hydrochloride, it is not the best permeation enhancer.

When combining Lauroglycol™ FCC and Transcutol® P at different ratios, a faster onset of drug diffusion was observed demonstrating a synergistic effect. Transcutol® P increased drug solubility in the formulation, whereas Lauroglycol™ FCC pushed the drug to partition into the membrane.

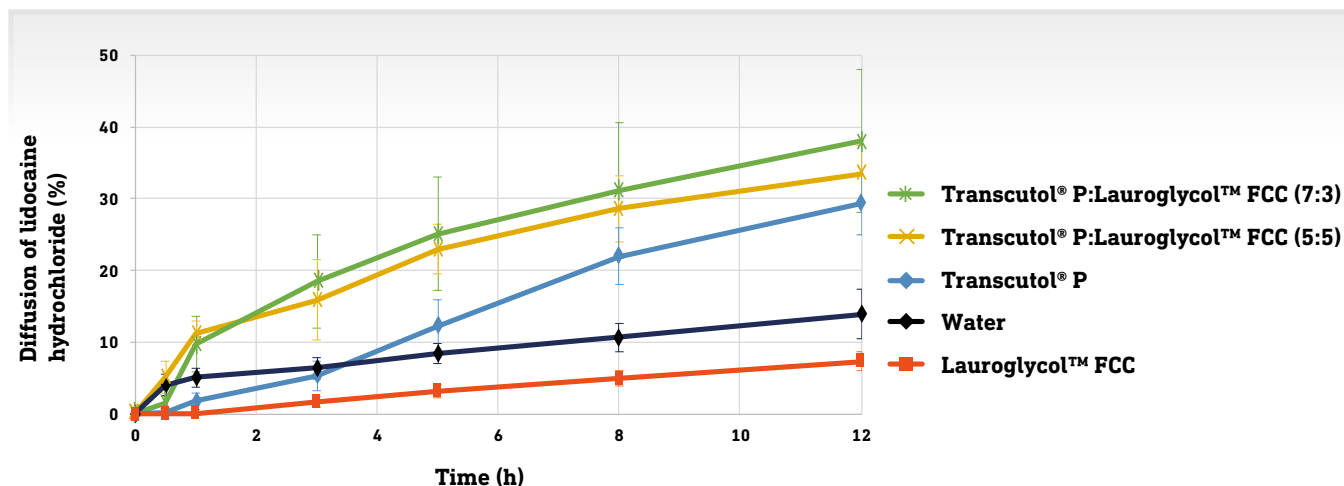


Figure 10: Diffusion of lidocaine HCl in Transcutol® P and Lauroglycol™ FCC (adapted from Dauphin-Chanard et al. 2019)

CS #4: Leveraging solvent evaporation for increased efficacy

Aczone® gel was first approved by the FDA in 2005. The original commercial product contained 5% dapsone and 25% DEGEE.

Dapsone has poor aqueous solubility and high solubility in DEGEE (Figure 11). Therefore, about 25% of the API is dissolved in the gel, the remaining being suspended in the gel.

Interestingly, the efficacy of the product relies on the subtle equilibrium between solubilized and crystalline API, which is driven by water evaporation after application of the gel.

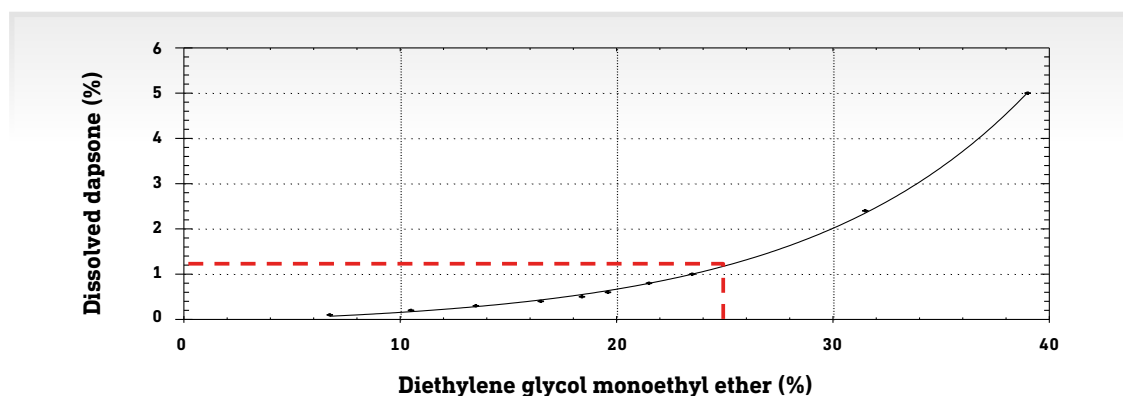


Figure 11: Dapsone solubility as a function of DEGEE concentration (adapted from Osborne, 2011)

Dapsone is used to treat acne due to its dual efficacy as anti-microbial and anti-inflammatory agent:

- The anti-microbial activity is targeted in the pilosebaceous follicle in the upper part of the stratum corneum where sebum accumulates and bacteria can develop.
- To reach the systemic circulation and reduce inflammation, dapsone must be solubilized and penetrate through the stratum corneum.

During rub-in, dapsone penetrates and accumulates in the hair follicle openings, where it acts as anti-microbial. Rubbing in the gel onto the skin also helps deposit any suspended drug particles into the pilosebaceous units, creating a reservoir for subsequent dissolution in sebum over time, becoming a secondary formulation.

Another factor significantly impacting the efficacy of the formulation is the relative volatility of water compared to Transcutol® P. The evaporation of water after application of the gel translates to a higher ratio of Transcutol® P in the dose, helping to further solubilize the undissolved dapsone. The relative increase in DEGEE concentration in the gel enables a higher drug solubilization and penetration across the skin, providing a higher efficiency. Since DEGEE is the stronger solvent and less volatile there is no drug precipitation on the surface of the skin, and consequently no residue after application.

In this gel formulation, DEGEE and water act as solvent partners, enabling optimization of the ratio of crystallized /solubilized drug to obtain an efficient formulation for acne.

Regulatory information, precedence of use and safety

Transcutol® P is a well-identified, safe excipient which conforms to the EP and USP-NF pharmacopoeias (Table 3). Diethylene glycol monoethyl ether is registered in the FDA Inactive Ingredient Database and its use level in topical and transdermal skin delivery is provided in Table 4.

Diethylene glycol monoethyl ether safety is established via numerous toxicological studies reviewed by Sullivan et al, 2014. Gattefossé main studies on Transcutol® P in dermal route are listed in Table 5, all demonstrate the safety of Transcutol® P. For further information about the extensive toxicological and safety data available to support the use of Transcutol® P please contact Gattefossé.

DEGEE has been used for decades in numerous market references for topical and transdermal deliveries, some examples are listed in Table 6.

Table 3: Transcutol® P regulatory summary

USP-NF Name	Diethylene glycol monoethyl ether
Ph. Eur. name	Diethylene glycol monoethyl ether
CAS number	111-90-0
UNII Code (FDA)	A1A1I8X02B
INCI name	Ethoxydiglycol
Handbook of Pharmaceutical Excipients	Diethylene glycol monoethyl ether
Drug master file	US DMF 5718; Canada MF 2005 - 108

Table 4: US FDA inactive ingredient database references for diethylene glycol monoethyl ether

Route	Dosage form	Use level
Topical	Cream	15%
Topical	Gel	49.91%
Topical	Lotion	1%
Topical	Ointment	5%
Transdermal	Gel	5%
Transdermal	Patch	430 mg

Table 5: Safety studies for the dermal route performed by Gattefossé on Transcutol® P

Study type	Species	Transcutol® P concentration	Conclusion
Acute Irritation (JORF)	Rabbit	50% in water	Non-irritant
Acute Irritation (Patch test)	Human	Pure	Well tolerated
Sensitization (HRIPT)	Human	Pure	Non-irritant Non-sensitizing

Detailed information is available in
our Regulatory Datasheet

Table 6: Market references using diethylene glycol monoethyl ether in topical dosage forms

Dosage form	Indication	API	Country
Cream	Anesthetics	Lidocaine	South Korea
	Anti-acne	Erythromycin	Ghana
		Tretinoin	Ghana
	Antibiotics	Fusidic acid	Pakistan
	Antibiotics; Antifungals	Mupirocin; Clotrimazole	Columbia
	Antibiotics; Cicatrizants; Antihistaminic	Sulfadiazine; Zinc oxide; Diphenhydramine	Taiwan
	Antifungals	Terbinafine	Taiwan
	Anti-inflammatory; Anesthetics; Analgesics and antipyretics	Diclofenac; Menthol; Methyl salicylate	India
	Antivirals	Aciclovir	South Korea
	Cicatrizants	Dexpanthenol	Syria
	Corticosteroids	Fluocinonide	USA
		Halobetasol	Brazil; India
	Corticosteroids; Hyperpigmentation; Anti-acne	Fluocinolone acetonide; Hydroquinone; Tretinoin	Pakistan
	Hyperpigmentation; Anti-acne; Corticosteroids	Hydroquinone; Tretinoin; Mometasone	India
Vitamins; Emollients and protectives	7-Dehydrocholesterol; Saccharide isomerate	Malaysia	
Vitamins	Vitamin C	Indonesia	
Gel	Analgesics and antipyretics; Anesthetics	Diethylamine; Myrtecaine	Germany
	Anesthetics	Lidocaine, Lidocaine hydrochloride	South Korea
		Tetracaine	USA
	Anti-acne	Dapsone	Canada; USA
		Anti-inflammatory	Diclofenac
	Ibuprofen		Spain
	Ketoprofen		South Korea
	Naproxen		Italy
	Nimesulide		Brazil; Italy; Turkey
	Piroxicam		South Korea; Taiwan
	Anti-inflammatory; Analgesics and antipyretics; Anesthetics		Nimesulide; Methyl salicylate; Menthol; Capsaicin
	Anti-neoplastics	Mechlorethamine	USA
	Anti-varicose	Organo-heparinoid	Brazil
	Drugs for urinary frequency and incontinence	Oxybutynin	USA
	Improves the microcirculation; Analgesics and antipyretics	Escin; Diethylamine salicylate	Italy
	Hormones	Estradiol	Europe; Tunisia; Chile, USA

Dosage form	Indication	API	Country
Lotion	Anti-inflammatory	Piroxicam	South Korea
	Antiseptics and disinfectants	Menthol	USA
	Corticosteroids	Desoximethasone	South Korea
Ointment	Blood substitutes; Anti-inflammatory	Dextran; Phenylbutazone	France
Patch	Analgesics and antipyretics; Anti-inflammatory	Paracetamol; Diclofenac	Taiwan
	Anesthetics	Capsaicin	USA; Europe
	Anti-inflammatory	Piroxicam	South Korea
	Antiseptics and disinfectants	Menthol	South Korea
	Hormones	Estradiol; Levonorgestrel	UK
Solution	Anesthetics; Antiseptics and disinfectants	Benzocaine; Butoforme; Oxyquinoleine	France
	Antifungals	Terbinafine	South Korea
	Antiseptics and disinfectants	Benzalkonium	Italy
		Triclosan	France
	Antiseptics and disinfectants	Benzalkonium; Chlorhexidine	France
	Corticosteroids	Hydrocortisone	France
	Corticosteroids; Antifungals; Antibiotics	Clobetasol; Clotrimazole; Neomycin	India
	Erectile dysfunction	Alprostadil	Brazil
	Insecticides and repellents	Esdepallethrine; Piperonyl butoxyde	France; Germany; Eastern Europe; Morocco; Tunisia
	Peripheral vasodilators	Minoxidil	South Korea
Expectorants	Guethol nicotinate; Guaifenesin; Eucalyptol; Pinus	France	

Technical support

Gattefossé range of excipients for topical drug delivery include solubilizers, emulsifiers and viscosity modifying agents. Emulsifiers are designed for challenging formulations and deliver excellent texture and sensorial properties. Solubilizers provide skin penetration enhancement and viscosity agents stabilize formulations. Our excipients are used in creams, emulgels, lotions, foams, microemulsions and gels. Gattefossé can provide technical support to help you with the selection of excipients for topical drug delivery.

Please contact your local Gattefossé representative



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Bibliography

1. Aungst B. J., Rogers N. J. and Shefter E. (1986). Enhancement of naloxone penetration through human skin in vitro using fatty acids, fatty alcohols, surfactants, sulfoxides and amides. *International journal of pharmaceuticals*, 33(1-3), 225-234.
2. Baboota S., Al-Azaki A., Kohli K., Ali J., Dixit N. and Shakeel F. (2007). Development and evaluation of a microemulsion formulation for transdermal delivery of terbinafine. *PDA Journal of pharmaceutical Science and technology*, 61(4), 276-285.
3. Barakat N. and Fouad E. (2014). Enhancement of skin permeation and anti-inflammatory effect of indomethacin using microemulsion. *Asian Journal of Pharmaceutics* 5(3).
4. Bhattacharyya A. and Bajpai M. (2013). Development and oral bioavailability of self-emulsifying formulation of ketoconazole. *Int J Pharm Sci Nanotechnol*, 5(4), 1858-1865.
5. Bialik W., Walkers K.A., Brain K.R., Hadgraft J. (1993). Some factors affecting the in vitro penetration of ibuprofen through human skin. *Int J Pharm.* 92:219-23.
6. Bonina F. P., Carelli V., Di Colo G., Montenegro L. and Nannipieri E. (1993). Vehicle effects on in vitro skin permeation of and stratum corneum affinity for model drugs caffeine and testosterone. *International Journal of Pharmaceutics*, 100(1-3), 41-47.
7. Cázares-Delgadillo J., Naik A., Kalia Y.N., Quintanar-Guerrero D., Ganem-Quintanar A. (2005). Skin permeation enhancement by sucrose esters: a pH-dependent phenomenon. *Int J Pharm.* 297 (1-2):204-212.
8. Cho Y. A. and Gwak H. S. (2004). Transdermal delivery of ketorolac tromethamine: effects of vehicles and penetration enhancers. *Drug development and industrial pharmacy*, 30(6), 557-564.
9. Coneac G., Vlaia V., Olariu I., Muț A. M., Anghel D. F., Ilie C. and Vlaia L. (2015). Development and evaluation of new microemulsion-based hydrogel formulations for topical delivery of fluconazole. *AAPS PharmSciTech*, 16(4), 889-904.
10. Dauphin-Chanard E., Forest A., Deleglise C., Ducros M., Marchaud D. (2019). Synergising excipients to boost skin delivery. A case study with lidocaine hydrochloride. *Poster Skin Forum*.
11. Dave M. and Le Pree J. (2018). A systematic approach to formulate and evaluate the stability of topical creams with high concentrations of Transcutol® HP. *Poster AAPS PharmSci* 360.
12. Dragicevic N. and Maibach H.I. (2015). *Percutaneous penetration enhancers chemical methods in penetration enhancement* (Springer-Verlag GmbH Berlin Heidelberg).
13. Fabin B., Touitou E. (1991). Localization of lipophilic molecules penetrating rat skin in vivo by quantitative autoradiography. *Int J Pharm.* 74(1):59-65.
14. Gannu R., Vishnu Y. V., Kishan V. and Rao, Y. M. (2008). In vitro permeation of carvedilol through porcine skin: effect of vehicles and penetration enhancers. *PDA journal of pharmaceutical science and technology*, 62(4), 256-263.
15. Gwak H. S. and Chun I. K. (2002). Effect of vehicles and penetration enhancers on the in vitro percutaneous absorption of tenoxicam through hairless mouse skin. *International journal of pharmaceuticals*, 236(1-2), 57-64.
16. Gwak H.S., Kim S.U., Chun I.K. (2002). Effect of vehicles and enhancers on the in vitro permeation of melatonin through hairless mouse skin. *Arch Pharm Res.* 25(3):392-6.
17. Ha E. S., Lee S. K., Choi D. H., Jeong S. H., Hwang S. J. and Kim M. S. (2019). Application of diethylene glycol monoethyl ether in solubilization of poorly water-soluble drugs. *Journal of Pharmaceutical Investigation*,
18. Hirata K., Helal F., Hadgraft J. and Lane M. E. (2013). Formulation of carbenoxolone for delivery to the skin. *International journal of pharmaceuticals*, 448(2), 360-365.

19. Hirata K., Mohammed D., Hadgraft J. and Lane M.E. (2014) Influence of lidocaine hydrochloride and penetration enhancers on the barrier function of human skin. *Int J Pharm.* 477(1–2):416–20.
20. Karande P. and Mitragotri S. (2009). Enhancement of transdermal drug delivery via synergistic action of chemicals. *Biochimica et Biophysica Acta-Biomembranes*, 1788(11), 2362-2373.
21. Kreilgaard M. (2002). Influence of microemulsions on cutaneous drug delivery. *Advanced drug delivery reviews*, 54, S77-S98.
22. Lane M.E. (2013) Skin penetration enhancers. *Int J Pharm.* 447(1–2):12–21.
23. Moghadam S.H., Saliq E., Wettig S.D., Dong C., Ivanova M.V., Huzil J.T. and Foldvari M. (2013). Effect of chemical permeation enhancers on stratum corneum barrier lipid organizational structure and interferon alpha permeability. *Molecular pharmaceutics*. 10(6). 2248-2260.
24. Morin C. and Marchaud D. (2019). Synergising excipients to boost skin delivery. *OndrugDelivery Magazine*. Issue 99, pp 54-58.
25. Mura P., Faucci M.T., Bramanti G., Corti P. (2000). Evaluation of Transcutol® as a clonazepam transdermal permeation enhancer from hydrophilic gel formulations. *Eur J Pharm Sci.* 9(4):365–72.
26. Mutalik S., Parekh H. S., Davies N. M., & Nayanabhirama U. (2009). A combined approach of chemical enhancers and sonophoresis for the transdermal delivery of tizanidine hydrochloride. *Drug delivery*, 16(2), 82-91.
27. Osborne D.W. (2011). Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products. *Journal of cosmetic dermatology*. 10(4). 324-329.
28. Osborne D.W. and Musakhanian J. (2018). Skin penetration and permeation properties of Transcutol®- neat or diluted mixtures. *AAPS PharmSciTech*, 19(8), 3512-3533.
29. Panchagnula R. and Ritschel. WA (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. *Journal of pharmacy and pharmacology*, 43(9), 609-614.
30. Rhee Y. S., Huh J. Y., Park C. W., Nam T. Y., Yoon K. R., Chi S. C. and Park E. S. (2007). Effects of vehicles and enhancers on transdermal delivery of clobopride. *Archives of pharmacal research*, 30(9), 1155.
31. Ritschel W. A. and Hussain A. S. (1988). Influence of selected solvents on penetration of griseofulvin in rat skin, *in vitro*. *Pharmazeutische Industrie*, 50(4), 483-486.
32. Salimi A. and Fouladi M. (2015). Effect of the various penetration enhancers on the *in vitro* skin permeation of meloxicam through whole rat skin. *Eur. J. Bio. Pharm. Sci*, 2(3), 1282-1291.
33. Salimi A., Hedayatipour N., Moghimipour E. (2016). The effect of various vehicles on the naproxen permeability through rat skin: a mechanistic study by DSC and FT-IR techniques. *Adv Pharm. Bull.* 6(1):9–16.
34. Shen M., Liu C., Wan X., Farah N. and Fang L. (2018). Development of a daphnetin transdermal patch using chemical enhancer strategy: insights of the enhancement effect of Transcutol® P and the assessment of pharmacodynamics. *Drug Dev Ind Pharm.* 44(10):1642-1649.
35. Sullivan D.W., Gad S.C. and Julien M. (2014). A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether used as a pharmaceutical excipient. *Food and chemical toxicology*, 72, 40-50.
36. Telò I., Pescina S., Padula C., Santi P. and Nicoli S. (2016). Mechanisms of imiquimod skin penetration. *International journal of pharmaceutics*, 511(1), 516-523
37. Trivedi K., Shaikh N., Ravikumar P. (2018). Development of novel microemulsion based topical formulation of clobetasol propionate and salicylic acid for the treatment of psoriasis. *Int. Res. J. Pharm.* 9 (5)
38. Trommer H. and Neubert R.H.H. (2006). Overcoming the stratum corneum: the modulation of skin penetration. *Skin pharmacology and physiology*, 19(2), 106-121.



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