Efficient skin delivery: no compromise with Transcutol®

Skin barrier property is the main obstacle for skin delivery. Many different techniques have been developed to facilitate drug passage through the skin as reviewed by Morrow, 2007. Among the non-invasive techniques, chemical penetration enhancers have been classically used in dermatological products (Lane, 2013).

Transcutol®, Diethylene Glycol monoethyl Ether (DEGEE), is a penetration enhancer that merits special attention. It is a powerful solvent renowned for its non-irritant properties that has been used in various topical dosage forms for decades. The reasons for its success lie in its acknowledged efficiency as solvent and skin penetration enhancer, its exceptional safety as it is a non skin irritant solvent and its versatility of use in all types of dosage forms.

This white paper explains the remarkable skin penetration properties of Transcutol®, a solvent more powerful than ethanol but with exceptional safety as non irritant. This paper also sets out the precedence of use of Transcutol®. Practical information is also given for the formulation of Transcutol® in many topical dosage forms.

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Transcutol®, the highest purity DEGEE

Transcutol® P is Gattefossé's trade name for highly purified diethylene glycol monoethyl ether (DEGEE) for topical uses. This product is commercially available as a clear liquid with a mild flavor. It is produced by condensation of ethylene oxide and alcohol, followed by purification steps. Purification is a critical step in the process to eliminate impurities, such as 2-methoxyethanol, ethylene glycol and diethylene glycol. High purity grades have been shown to be non irritant for skin delivery (Osborne, 2011). Gattefossé conducts a purification step to guarantee a minimum 99.8% purity for Transcutol® P for safe use in skin drug delivery.

A safe excipient

Transcutol® safety is established via numerous toxicological studies recently reviewed by Sullivan et al, 2014. **The main studies related to dermal route are gathered in Table 1. They all demonstrate the safety of Transcutol®.** The toxicological overview is available upon request at www.gattefosse.com. Transcutol® has been used for decades in dermal applications without adverse effects being reported. Osborne identified more than 500 cosmetic products using DEGEE in 2011 (Osborne, 2011).

Study type	Route	Species	Transcutol® concentration	Conclusion
Acute Irritation (JORF)	Dermal	Rabbit	50% in water	Non-irritant
Acute Irritation (Patch test)	Dermal	Human	Pure	Well tolerated
Acute Irritation (JORF)	Ocular	Rabbit	30% in water	Slightly irritant
Acute Irritation (OECD405)	Ocular	Rabbit	Pure	Slightly irritant
Sensitization HRIPT	Dermal	Human	Pure	Non-irritant Non-sensitizing

Table 1: Safety studies performed by Gattefossé on Transcutol®

An approved excipient

Transcutol® P conforms to the diethylene glycol monoethyl ether monograph of European and USP/NF pharmacopeias. This excipient has a US drug master file (n° 5718).

The **US FDA Inactive Ingredient Guide has recently been updated**, and new reference of use has been added for diethylene glycol monoethyl ether (Table 2). DEGEE has been used in concentrations up to 50% (reference FDA IIG – topical gel); however, this is not a limit on its use level. Based on available toxicological data, literature and history of use, Gattefossé suggests a Permissible Daily Exposure of 20 mg/kg/day for the dermal route.

Route	Dosage Form	Level of use (% W/W)
Topical	Gel	49.91
Topical	Cream, Emulsion, Sustained release	15
Topical	Lotion	1
Transdermal	Gel	5

Table 2: DEGEE use level referenced in US FDA Inactive Ingredient Guide

An effective solvent

DEGEE is an acknowledged solvent (Table 3) and is part of the solvents routinely tested by formulators.

Drug	Log P	Solubility (mg/mL)			Reference
		Ethanol	Propylene Glycol	Transcutol® DEGEE	
Aceclofenac	3.9	na	na	292.4	Shakeel
Betamethasone dipropionate	1.8	42.1	5.8	89.4	In house
Celecoxib	4.0	na	na	125	Baboota
Curcumin	4.1	6.0	na	140.6	Wang
Diclofenac sodium	4.2	113.4	333.1	459.6	In house
Fluconazole	0.6	120	147	146	Ayub
Ibuprofen	3.8	398.7	185.5	395.7	In house
Ketoprofen	3.1	na	na	425	In house
Lidocaine base	2.1	774.0	683.0	610.9	In house
Lorazepam	3.0	10.1	na	180.9	Yao
Piroxicam	1.4	1.5	1.5	19.2	In house
Quercetin	1.8	2	na	296	Censi
Terbinafine	5.5	30	61	152	Baboota

Table 3: Solubility of APIs in Transcutol® (na: not available)

Transcutol® has better physicochemical characteristics than ethanol (Table 4).

Ethanol has a higher **vapor pressure** than Transcutol® and therefore evaporates more easily and diffuses more easily in the atmosphere. This has two major drawbacks. On a process point of view, the laboratories and production facilities have to be equipped to avoid open evaporation. On a formulation point of view, once evaporated from the topical dosage form upon application on the skin, the solvent is no longer present for effective drug solubilisation.

Ethanol has a lower **boiling point**, restricting its processing temperatures. Therefore it offers less flexibility in use than Trancutol® which has a higher boiling point.

Transcutol® offers great flexibility of use in the formulation and in the process.

Solvent	Boiling point (°C)	Vapor pressure (Pa at 20°C)	Density (g/cm^3)	Log P
Transcutol®	198 - 201	16	0.988	-0.54
Ethanol	78	5850	0.789	-0.18
Propylene glycol	188	9.33	1.04	-0.92

Table 4: Physicochemical properties of common pharmaceutical solvents

Call out box 1: Drug absorption into the skin by passive diffusion

The rate of drug transport across the *Stratum corneum* follows Fick's laws of diffusion (Förster, 2009) and can be expressed at steady state and under sink conditions by equation (1):

$$J_{ss} = \frac{D\ K_m\ C_v}{h} = K_p C_v \qquad (1)$$

with:

- J_{ss} ($g/m^2/s$): Flux at steady state
- D (m^2/s): Diffusion coefficient
- K_m (-): Vehicle – membrane partition, usually estimated via the $K_{oct/water}$ partition coefficient of the drug
- Kp (m/s): Permeability coefficient, which is a function of both the partitioning and the diffusion
- C_v (g/m^3) : Concentration of the drug in the vehicle
- h (m): length of diffusion pathway (skin thickness)

An efficient skin penetration enhancer

Skin penetration enhancement with Transcutol® is mainly described as a "push and pull effect" reported to increase the percutaneous passage of the API.

The **"push" effect** is primarily due to the strong solubilizing capacity of DEGEE. A higher solubility of the API in Transcutol® increases its concentration in the vehicle. This is the parameter C_v in equation (1).

The **"pull" effect** is related to the skin penetration effect of Transcutol®. As it interferes with the lipid bilayer structure, it facilitates the diffusion of the drug. This is the parameter D in equation (1).

Some examples from literature are given in Table 5 to illustrate the penetration enhancer effect of Transcutol®. In these studies, measures of flux, permeability coefficient and/or diffusion constant were carried out to demonstrate the penetration enhancer effect of Transcutol® in the tested formulations.

API/substance	Dosage form	Reference
Aceclofenac	Nanoemulsion	Shakeel, 2007
Hydrocortisone acetate	Microemulsion	Fini, 2008
Polyunsaturated fatty acids	Microemulsion	Puglia, 2008
Dapsone	Gel	Osborne, 2011
Methotrexate	Gel	Javadzadeh, 2011

Table 5: Examples of skin penetration enhancing effect of Transcutol®

A **drug depot** has also been described for certain drugs and attributed to Transcutol®. Panchagnula, 1991, observed an intra-cutaneous depot of dexamethasone and hydrocortisone in topical delivery systems containing 50% Transcutol®. Ritschel, 1991, described the depot effect in hydrocortisone gels containing 50% Transcutol®. Ivermectin was also shown to accumulate in the skin with DEGEE (Yazdanian, 1995). Osborne in 2011 described the use of Transcutol® in gels to increase the skin permeation of dapsone due to a combination of penetration and depot effects.

Precedence of use

DEGEE has a long history of use in many dosage forms (Table 6).

Dosage form	Active ingredient	Country
 **Gel**	Dapsone	USA
	Diclofenac	Argentina, Uruguay
	Escin, Diethylamine salicylate	Italy
	Ibuprofen	Spain
	Ketoprofen	Korea
	Lidocaine	Korea
	Mucopolysaccharide polysulfate	Brazil
	Naproxen	Italy
	Nimesulide	Brazil, Ireland, Italy, Turkey
	Nimesulide, Methyl salicylate, Menthol, Capsaicin	India
	Estradiol	USA
	Oxybutynin	USA
	Piroxicam	Korea
	Tetracain HCl	USA
 **Cream**	Bee venim	New Zeland
	Ciclopirox olamine	Ghana
	Diclofenac, Methyl salicylate	India
	Erythromycin	Ghana
	Fluocinonide	USA
	Halobetasol propionate	Brazil, India
	Hydroquinone, Tretinoin, Mometasome furoate	India
	Lidocaine	Korea
	Sulfadiazine, Zinc oxide, Diphenhydramine hydrochloride	Taiwan
	Tretinoin	Ghana
Ointment	Dextran, Phenylbutazone	France
Solution/spray/lotion	Benzalkonium chloride	Italy
	Clobetasol propionate, Clotrimazole, Neomycine sulfate	India
	Minoxidil	Korea
	Esdepallethrine, Piperonyle butoxyde	Europe, Morocco, Tunisia
	Water of rose petals	Spain
	Desoxymethasone	Korea
	Menthol	USA
Transdermal patch	Capsaicin	Europe, USA
	Estradiol, Levonorgestrel	UK
	Panadol, Diclofenac	Taiwan
	Piroxicam	Korea

Table 6: Precedence of use of DEGEE for skin delivery

Transcutol® in gels

Topical gels are transparent or translucent semi-solid formulations (Figure 1). They present a high interest in dermatology because a high ratio of solvents can be included in the formula while maintaining a high viscosity/stability. They are also appreciated for their sensorial properties, with less greasy feeling compared to ointments and creams.

Figure 1: Clear gel containing 25%Transcutol®

Transcutol® can be used in aqueous and hydro-alcoholic gels. It is compatible with all types of gelifying agents (Carbomers, hydroxyethylcellulose and hydroxylpropylcellulose).

With Transcutol®, high levels of use are achievable without altering the clear gel structure or its stability.

Transcutol® is miscible in aqueous phase and is easily dispersible in viscous gels at room temperature. When formulating a poorly soluble drug, it is recommended to solubilize the API in Transcutol® first – eventually with other solvents – and then add the solution into the gel as illustrated in Figure 2.

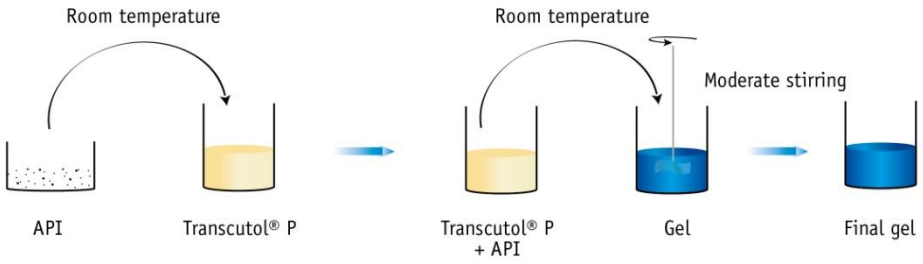


Figure 2: Gel preparation protocol with Transcutol®

1% Diclofenac sodium gel

Formula

Ingredient	% W/W
Phase 1	
Diclofenac sodium	1.00
Transcutol® P	10.00
Labrasol®	5.00
Benzyl alcohol	1.00
Phase 2	
Demineralized water	81.00
Natrosol 250 HHX Pharma	2.00

Process

Solubilize diclofenac sodium into phase I, under stirring at 250 rpm.
Disperse Natrosol into demineralized water while stirring at 1000 rpm (Phase II).
Add phase I into phase II.
Decrease stirring down to 350 rpm.

Properties

Transparent gel
pH = 7.7
Viscosity (50 s^{-1}; 25°C): 5520 Pa.s
12 months stability (40°C/75% RH and 25°C/60% RH)

Transcutol® in creams

Emulsions - like creams - are also widely developed for dermatological treatments. Their oily phase provides a soft and moisturized sensation, bringing skin comfort. However, emulsions are more difficult to prepare, their stability over time being difficult to achieve. Their formulation requires at least a good emulsifier that will prolong the stability of one phase dispersed into another (Water-in-Oil or Oil-in-Water). Solvents can reduce the stability and are therefore not used at high level (<15%).

Transcutol® can be used in emulsion. It is however recommended to add it in the external phase, when the process temperature has cooled down to room temperature (Figure 3).

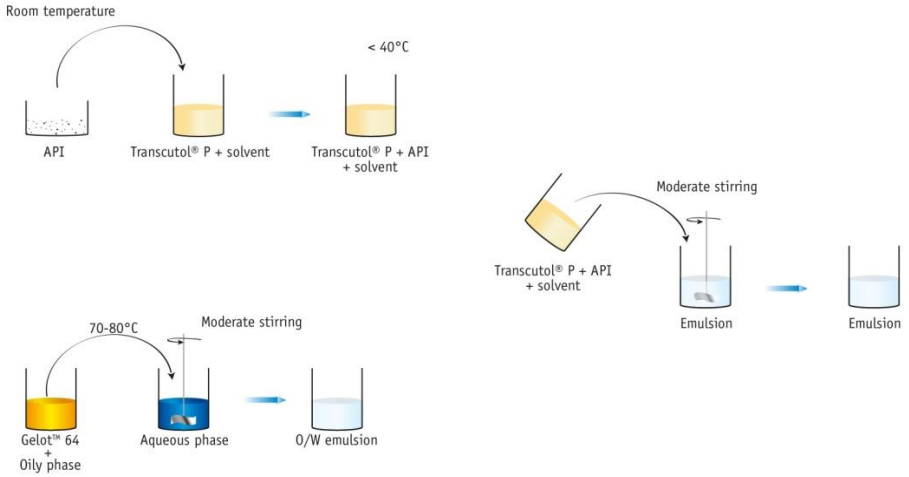


Figure 3: Cream preparation protocol with Transcutol®

Gattefossé recommends using Transcutol® in combination with Gelot® 64/Emulcire® 61, a high-performance emulsifier/co-emulsifier system, to obtain a bright, shiny and creamy texture, stable over time.

1% Diclofenac sodium cream

Formula

Ingredient	% W/W
Phase 1	
Gelot® 64	3.00
Emulcire® 61	3.00
Vaseline oil	10.00
Cetyl alcohol	3.00
Labrafil® 1944 CS	2.00
Phase 2	
Demineralized water	67.85
Sorbic acid	0.10
Paraben	0.05
Phase 3	
Transcutol® P	10.00
Diclofenac sodium	1.00

Process

Mix all ingredients of Phase I and heat up to 75-80°C.
Solubilize preservatives in water at 75-80°C (Phase II).
Solubilize diclofenac sodium into Transcutol (Phase III), under stirring at 250 rpm.
Add phase II into phase I under stirring at 250 rpm for 5 min. Then cool down.
Add phase III at 35°C.
Cool down to room temperature.

Properties

White compact cream
pH = 7.4
Viscosity (50 s^{-1}; 25°C): 4775 Pa.s
12 months stability (40°C/75% RH and 25°C/60% RH)

Transcutol® in solutions and micro-emulsions

Microemulsions are thermodynamically stable dispersions of oil and water phases with a surfactant/co-surfactant system. They differ from conventional emulsions by their physical properties: transparency, liquid, small particle size (< 200 nm). The other specificity of this system is that surfactant or solvent can represent the majority of the formulation. **Transcutol® is therefore well adapted for microemulsion when it is associated with a surfactant.**

The pseudo-ternary phase diagram (Figure 4) shows an example of microemulsion domains that are obtained by mixing Labrafac™ lipophile WL1349, Labrasol®/Capryol™ PGMC, Transcutol® and water. The composition A could be a good starting point for formulation development.

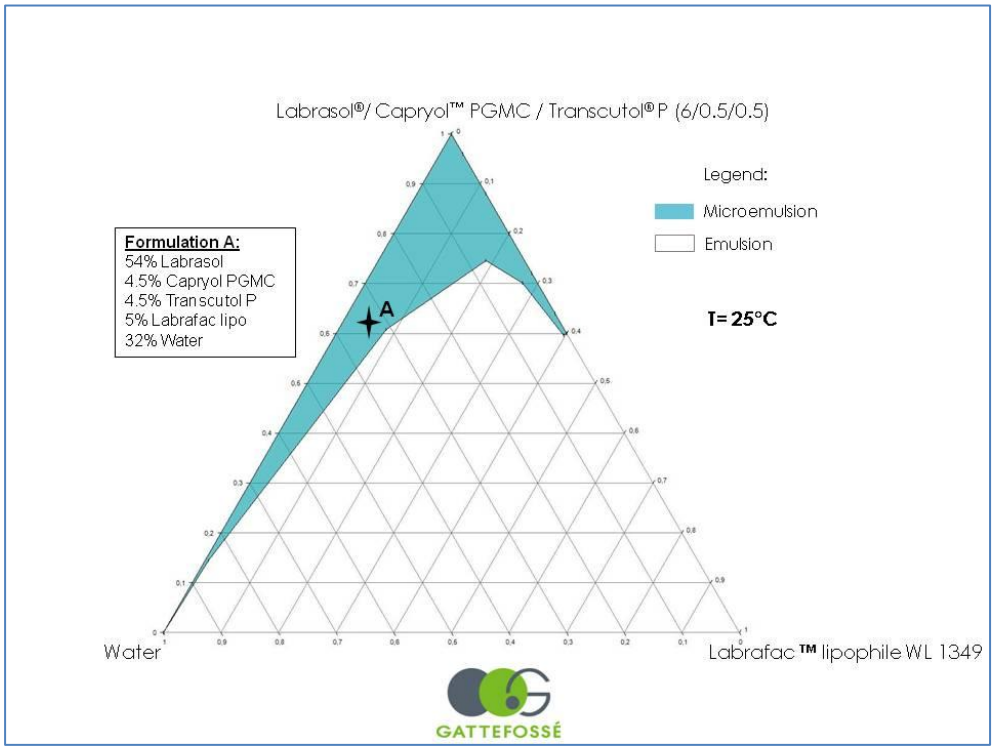


Figure 4: Pseudo-ternary diagram: Labrasol® - Capryol™ PGMC - Transcutol® P - Labrafac™ Lipophile WL1349 - Water

The preparation of the microemulsion requires only a simple mixing of liquid ingredients at room temperature. The API can be solubilized in solvents (Labrasol®/Capryol™ PGMC/Transcutol®) prior to mixing or directly in the microemulsion.

Transcutol® in patches

These transdermal delivery systems are intended to stay in contact with the skin for a certain period of time and drug is released slowly from the reservoir in the patch to and through the skin (Wiedersberg, 2014). As Transcutol® is non-irritant, an effective solubilizer and skin penetration enhancer, it presents the ideal performance properties required in patch formulations.

Clonazepam has been included in patch using DEGEE as a penetration enhancer and solubilizer (Mura, 2000). More recently, sibutramine has been included in patches combined with micro-needles, and improved transdermal delivery was observed with Transcutol® (Serrano, 2013).

Transcutol® in liposomes and analogues

Liposomes are microscopic spheres with an aqueous core surrounded by one or more outer shells consisting of lipids arranged in a bilayer configuration. Liposomes are having ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. Liposomes are attractive for their capacity to penetrate deeper into the skin. Liposomes can be formulated in creams or gels.

Publications have described the use of Transcutol® in liposomes containing minoxidil (Mura, 2007) and diclofenac (Manconi, 2009), in ethosomes (Somwanshi, 2015).

Conclusions

Transcutol® is a remarkable solubilizer and chemical penetration enhancer, suitable for both lipophilic and hydrophilic drugs. Compared with ethanol, currently the most widely used solvent, it offers the dual advantage of being less volatile and less irritant. This acknowledged safety and efficiency make Transcutol® an ideal candidate in many topical formulations.

Transcutol®, Diethylene glycol monoethylether, has a long history of use in cosmetic and pharmaceutical applications, especially for skin delivery. Different commercial products have been authorized and marketed worldwide, using DEGEE in a variety of dosage forms, such as lotion, creams, gels, ointments and patches.

Transcutol® range also includes:

- Transcutol® HP for oral, parenteral and nasal applications
- Transcutol® V for veterinary applications such as spot-on, pour-on, spraying solutions, creams, ointments and shampoos.

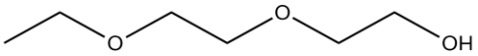
Gattefossé
36 chemin de Genas CS70070
69804 Saint Priest, France
Email: infopharma@gattefosse.com
www.gattefosse.com

Call out box 2: Transcutol®'s identity card

Names

Commercial name: Transcutol® P
Highly purified diethylene glycol monoethyl ether EP/NF
INCI (PCPC): Ethoxydiglycol
CAS: 111-90-0
EINECS: 203-919-7

Description



Colorless liquid
Empirical formula: $C_6H_{14}O_3$
Molecular weight: 134.17 $g.mol^{-1}$

Regulatory

Product conforms to EP, USP/NF pharmacopeias
US DMF Type IV N° 5718
Canadian DMF Type III n° 2005-108

FDA Inactive Ingredient Guide recommended use level:

Topical (gel)	49.91%
Topical (cream, emulsion, sustained release)	15%
Transdermal (gel)	5%

Functions:

Solubilizer
Chemical penetration enhancer for topical application

Properties

Boiling point	198 - 201 °C
Vapor pressure	16 Pa at 20°C
Freezing point	-105 to -103°C
Flash point	90 - 96.1°C
Density	0.988 $g.cm^{-3}$
Log P	-0.54

Soluble in water and in ethanol
Miscible in acetone, benzene, chloroform, ethanol (95%)
Partially soluble in vegetable oils
Insoluble in mineral oils

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