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REVIEW ARTICLE

Skin Penetration and Permeation Properties of Transcutol® in Complex Formulations

Jasmine Musakhanian[1] · David W. Osborne[2] · Jean-David Rodier[3]

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Abstract

Percutaneous delivery is explored as alternative pathway for addressing the drawbacks associated with the oral administration of otherwise efficacious drugs. Short of breaching the skin by physical means, the preference goes to formulation strategies that augment passive diffusion across the skin. One such strategy lies in the use of skin penetration and permeation enhancers notably of hydroxylated solvents like propylene glycol (PG), ethanol (EtOH), and diethylene glycol monoethyl ether (Transcutol®, TRC). In a previous publication, we focused on the role of Transcutol® as enhancer in neat or diluted systems. Herein, we explore its' role in complex formulation systems, including patches, emulsions, vesicles, solid lipid nanoparticles, and micro or nanoemulsions. This review discusses enhancement mechanisms associated with hydroalcoholic solvents in general and TRC in particular, as manifested in multi-component formulation settings alongside other solvents and enhancers. The principles that govern skin penetration and permeation, notably the importance of drug diffusion due to solubilization and thermodynamic activity in the vehicle (formulation), drug solubilization and partitioning in the stratum corneum (SC), and/or solvent drag across the skin into deeper tissue for systemic absorption are discussed. Emphasized also are the interplay between the drug properties, the skin barrier function and the formulation parameters that are key to successful (trans)dermal delivery.

Keywords Transcutol · Skin · Percutaneous absorption · Permeation · Mechanism · Transdermal

Abbreviations

DEGEE (TRC)	Diethylene glycol monoethyl Ether NF (Transcutol®)
DiPG	Dipropylene glycol
DPPG	Propylene glycol dipelargonate
EtOH	Ethanol
GMO	Glyceryl monooleate
IVPT	In vitro permeation testing
IPM	Isopropyl myristate
HPMC	Hydroxypropyl methyl cellulose
HPC	Hydroxypropyl cellulose
LBSL	Caprylocaproyl polyoxyl-8 glycerides NF (Labrasol®)
NLC	Nano lipid carriers
OA	Oleic acid
PEG	Polyethylene glycol
PEV	Penetration enhancing vesicle
PG	Propylene glycol
PGMC	Propylene glycol monocaprylate (Type I) NF (Capryol™)
PGML	Propylene glycol monolaurate type II NF (Lauroglycol™)
POCC	Polyglyceryl-3 dioleate NF (Plurol™ Oleique CC497)
PS80	Polysorbate 80 (Tween 80)
SLN	Solid lipid nanoparticles
SC	Stratum corneum

✉ Jasmine Musakhanian
jasmine.musa@videotron.ca

[1] Senior Scientific Director, Paramus, USA

[2] President of David W. Osborne, PhD Consulting Inc., Fort Collins, USA

[3] R&D Director Oleochemistry, Gattefossé Group, Saint-Priest, France

Introduction

Enhancement of drug delivery to/via the skin has been guided by universally recognized strategies which include i) maximizing the thermodynamic activity of the drug in its vehicle; ii) raising the solubility of the drug in the stratum

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corneum (for local delivery); and/or iii) enhancing drug diffusivity across the stratum corneum for transdermal delivery [1–3]. These seemingly simple guidelines envelope complexities that arise from concomitant interactions of the formulation components with the skin structures. Maximization of thermodynamic activity in itself is a balancing act of achieving the right degree of drug solubilization relative to drug's saturation solubility in the vehicle. Moreover, the drug and the formulation constituents (solvents, cosolvents, emulsifiers, oils) including water can interact with the skin to different degrees and rates in synergistic or competitive manner. Meanwhile, "the most innocuous of vehicles may change the nature of the stratum corneum" when hydration occurs in the membrane [2, 4]. Thus, understanding the mechanism by which an excipient exerts its function vis-à-vis the formulation and the skin can be critical to the development process.

Percutaneous absorption is governed by the physical chemical properties of the drug and the physiology of the healthy or diseased skin. A non-invasive approach to these immovables lies in formulation optimization, including the incorporation of solubilizers and one or more penetration / permeation enhancers. Hundreds of chemical entities have been described as enhancers for having shown some type of penetration / permeation enhancing effect – irrespective of the mechanisms in play. However, not all of the revealed chemical entities have pharmaceutical acceptance due to concerns over their safety / innocuity. As for enhancers with precedence of use, published reviews provide useful information on their properties which is largely based on simple, neat, or diluted experimental models. In fact, there are fewer reviews discussing their role in complex formulation systems where they may exert multiple effects [1, 5, 6]. Meanwhile, the commonly used excipients (oils, surfactants, cosolvents) and water are known to exert one or another effect on drug penetration and permeation and therefore behave as "enhancers". The interplay between the formulation constituents and the resulting effect on penetration and permeation is yet another confounding factor to consider.

The aim of this review is to explore hydroalcoholic solvents in general and the function of Transcutol® (TRC) in particular for their effects in a variety of formulation systems, in multi-component settings alongside other solvents and enhancers. Following an overview of enhancer categories and the basic concepts about skin penetration and permeation enhancement, the effects of TRC and other hydroalcoholic solvents are discussed in the context of gels, emulsions, ointments, patches, as well as complex formulation systems like vesicles, solid lipid nanoparticles, and micro and nanoemulsions. Where possible, the factors influencing the outcome of the studies, relative to therapy objectives, and the possible interplay among the constituents are highlighted.

Skin Penetration and Permeation Enhancers

Hundreds of chemical entities have been dubbed as skin penetration enhancers for having exhibited some type of enhancing effect [7, 8]. By general chemistry, enhancer categories include fatty acids [9], solvents [10], terpenes [11], lactams [12, 13] as well as ethers, alcohols, polyols, and amides [1, 6, 14–17]. Table I provides a condensed list of the more commonly reviewed enhancers.

In the simplest terms, an enhancer may carry the permeant along as it permeates the stratum corneum (SC) and/or induce changes to the SC structure to facilitate the penetration of the permeant molecule. It may do so by enhancing the solubility of the drug molecule in the SC and/or perturbing the intercellular lipid bilayers, leading to improved partitioning

Table I Commonly investigated enhancers [1, 7, 8, 16–18]

Chemical category	Example(s)
Alcohols	Ethanol, isopropyl alcohol
Esters	Isopropyl myristate; glyceryl oleate; glyceryl monolaurate
Ether	Diethylene glycol monoethyl ether
Fatty acids	Capric; caprylic; lauric; oleic
Glycol	Propylene glycol; polyethylene / polyoxyethylene glycol
Inorganic	Water
Lactams	Caprolactam; Azone® derivatives; morpholine; pyrrolidine; laurocapram
Pyrrolidone	N-methyl-1–2-pyrrolidone (NMP); 2-pyrrolidone
Sulfoxides	Dimethyl sulfoxide
Surfactant, ionic	Dodecyl methyl sulfoxide cetyltrimethylammonium
Surfactant, nonionic	Polysorbates; polyoxylglycerides; sucrose esters, propylene glycol esters
Terpenes	Menthol; thymol; carvone
Miscellaneous	Amines; amides (n,n-dimethyl-m-toluamide); hydrocarbons (squalene); cyclodextrin; urea (1;3-diphenyl-urea); essential oils (eucalyptus)

and diffusion of the permeant. Some enhancers interact with intracellular proteins to create channels for diffusion. The greater the interaction between the enhancer and the skin structures, the higher is the irritation potential [1, 7, 8, 19]. In the extreme, the interactions may result in irreversible changes to the integrity of the skin and its barrier function. To help a brief discussion of enhancers by type of chemistry (Fig. 1) and interaction with skin structures, a set of commonly studied enhancers have been qualitatively sorted into groups A, B, and C and tabulated (Table II) in order of increasing ability to impact the skin structures, i.e. a < b < c, as discussed below.

Listed in group A are hydroxylated solvents PG, EtOH, and diethylene glycol monoethyl ether (DEGEE, TRC). With distinct physical–chemical properties these solvents have in common the ability to disrupt the hydrogen bonding network between the water molecules due to their small hydrophobic hydrocarbon regions. They facilitate penetration and permeation by modification of drug-vehicle properties, i.e., enhanced solubilization, change in thermodynamic force, and/or reduction of charge for ionizable drugs. Meanwhile they have hydrophilic hydrogen-bonding groups (hydroxyl function) that ensure miscibility with water, therefore being capable of reducing the overall intermolecular attraction of water molecules [20, 21]. TRC and PG diffuse into the skin and alter the solubility of the permeant in the skin [22]. PG is not known to interact with SC lipid bilayers and is considered to exert a "carrier-solvent" effect [6]. Much like PG, TRC does not perturb the skin bilayers, or the keratin and its effect is similar to that of water on the skin [23]. Ethanol on the other hand, although a great solvent, is known for its capacity for extraction of skin lipids and SC dehydration due to its rapid evaporation [1]. Overall, in the presence of alcohols and glycols, lipophilic drugs may penetrate the SC with greater ease because their solubility in the lipid bilayers is increased [24].

Among the enhancers listed in group B are mid-to-low HLB esters like PG esters or sucrose esters which are known for their significant enhancing role as cosolvents and cosurfactants in ternary and quaternary systems. Their effect on the skin may be similar but milder than those of the high HLB surfactants like Tween® 80, Span® 80, Labrasol® ALF, or Kolliphor® EL. Surfactants perturb the lipid bilayers by solubilization of the SC lipids and by interacting with keratin [1] to different extents—depending on the size of their polar headgroup and their levels of use. Also in group B are free fatty acids. Most commonly studied is oleic acid (OA) which is reported to induce its effect by migrating into intercellular lipid bilayers, altering their packing order, and thereby reducing the diffusional resistance of the SC [2, 13, 25]. While perturbing the SC bilayers, OA may also improve epidermal permeability by formation of new lipid phases or lacunae within the SC bilayers [1].

Sulfoxides, pyrrolidones, laurocapram, and terpenes (in group C) can effectively alter the diffusivity of the skin but at the expense of disrupting skin structures. Their use levels are therefore comparatively low. Terpenes like eugenol, thymol,

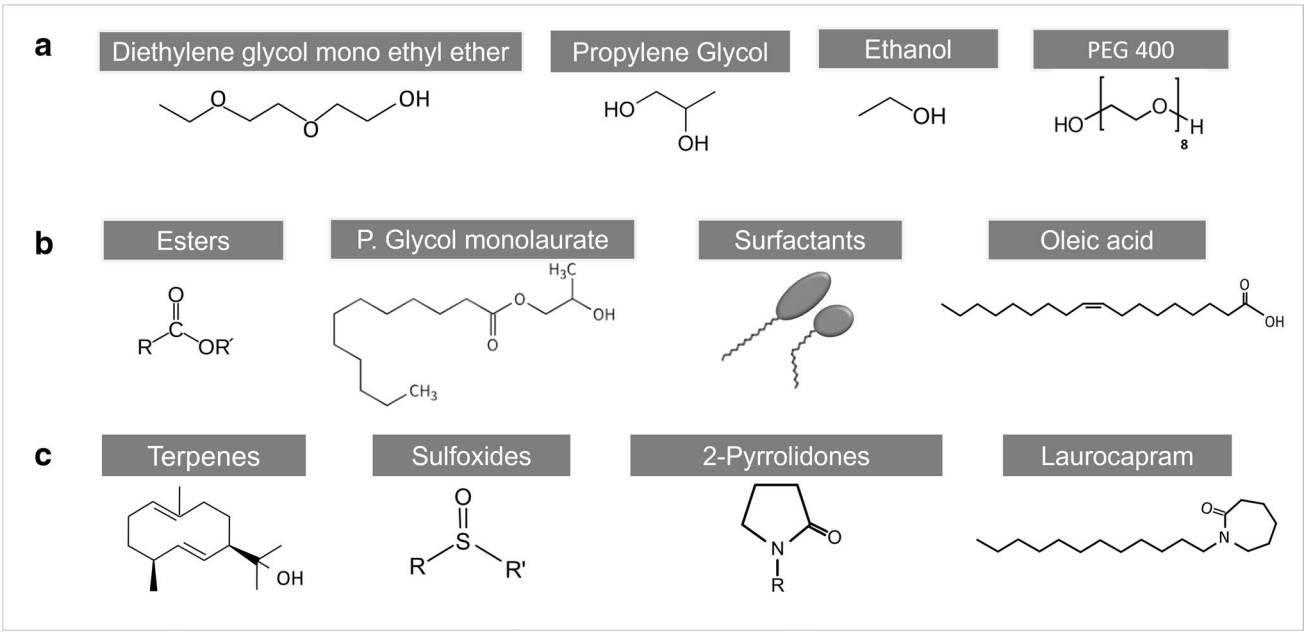

Fig. 1 Chemical structure of select enhancers in three groups: **a** hydroalcoholic solubilizers and cosolvents; **b** fatty acids, esters of fatty acids, and surfactants; **c** miscellaneous skin barrier modifiers

Table II Enhancers, grouped by chemical categories and examples in increasing order of interaction with the skin structures [1, 7, 8, 16–18]

Group	Description	Chemical Category	Example(s)	Brief description of known interactions
A	Hydroxylated solvents	Ether Alcohol	DEGEE (Transcutol®)	Enhance drug solubility in the dose; modify drug solubility in the stratum corneum; alter the drug's thermodynamic activity; interact mainly with the aqueous regions of the skin, having slight and reversible disordering of lamellar lipid structures; partitioning and diffusion assisted also by solvent drag effect.
		Glycols	Propylene glycol (PG)	
			Polyethylene glycol 400	
		Alcohol	Ethanol	Similar to propylene glycol but capable of extracting skin lipids; evaporates rapidly, affecting drug solubility and diffusion.
B	Lipophilic solvents and surfactants	Lipophilic esters	IPM, ethyl oleate	Lipophilic vehicles / solubilizers; help drug penetration and deposition within the lipid bilayers.
		Mid-low HLB esters	PG monolaurate	Precise mechanism unclear; contributes to drug solubility, partitioning / diffusion; potential synergistic effect when paired with another enhancer.
		Fatty Acids	Oleic acid	Interacts with lipid domains; improves drug diffusion across the SC by disrupting lipid bilayers.
		Surfactants (nonionic)	Kolliphor®; Labrasol®; Plurol®; Tween®	Improve drug solubility by micellization; interaction with and disordering of lipid bilayers depending on size of polar head groups; drug partitioning and diffusion.
		Surfactants (ionic)	Cetyltrimethylammonium bromide (CTAB)	Interacts strongly with the skin; disrupt lipid lamellar organizations, damage proteins; form new lamellar aggregates; compromise the skin barrier function; cause irritation.
C	Miscellaneous skin barrier modifiers	Lactam	Laurocapram (Azone®)	Highly lipophilic, interacts with lipid domains; induces fluidity by forming solvation shells in the SC lipids; not used in any topical products currently approved in the US.
		Terpenes	L-menthol; 1,8-cineole; d-limonene	Strongly interact with lipid domains; cause destabilization of the lamellar lipid structures.
		Pyrrolidone	N-methyl-1–2-pyrrolidone	Induces fluidity by forming solvation reservoirs in the skin lipids; limited clinical use due to adverse effects; may cause erythema, swelling, irritation, and skin thickening.
		Sulfoxides	Dimethyl sulfoxide (DMSO)	Aprotic solvent; interacts with lipid domains and keratin causing protein denaturation at high concentrations; DMSO absorbed through the skin is metabolized to DMS that is excreted in the breath to produce a characteristic garlic-like odor.

and d-limonene are volatile compounds used at 1–5% [18]. Laurocapram (Azone®) use levels are in the range of 1–3% [26]. High levels of sulfoxides are known to extract lipids, and to induce changes in the keratin conformations / protein denaturation [1, 2, 24, 27, 28]. In the extreme, localized channels or pores created by "pooling" phenomenon have been reported for OA, laurocapram, terpenes, and sulfoxides [1, 13, 16, 17, 28].

Expectedly, the enhancing effects depend not only on chemical structure and concentration of the enhancer [29, 30], but also the nature of the drug [31], and the constituents of the delivery system [32]. As discussed in the subsequent sections, two or more enhancers may be incorporated into the delivery system to achieve an appropriate level of drug solubilization and rate of delivery to / via the skin, while keeping the concentration of each component within the established limits of use.

About Transcutol

The tradename Transcutol® refers to highly purified (≥ 99%) cosmetic grade (CG), veterinary injectable grade (V), and the pharmaceutical P and HP grades of DEGEE. Transcutol® P and Transcutol® HP, referred to simply as TRC in this manuscript, have guaranteed purities of ≥ 99.7% and ≥ 99.9% respectively [21]. The elimination of impurities is critical to the safety of the product. For example, impurities like ethylene glycol and diethylene glycol may have contributed to cell culture viability outcomes in a 2019 publication [33] where a reagent grade of DEGEE (Millipore sigma) was used.

TRC is globally approved for topical and transdermal use (30, 31) at concentrations of up to 49.9%. Marketed dermal products in Europe have not produced contra-indication/ adverse effect linked to pregnant women. There are topical references for adolescents (US/Canada) and orally administered products for adult and children under 6 years of age in Europe. Full safety / tox data on TRC is available from the manufacturer, the FDA drug master file, and published works [34–38] indicating it can be administered safely to humans. The proposed permissible daily exposure limits, with 100-times safety factored into the calculations are 20 mg/Kg/day for dermal and 10 mg/Kg/day for oral administration, translating respectively to 1400 and 700 mg/day for a 70 kg man. The FDA Inactive Ingredients Database cites a significantly higher daily exposure limit of 1720 mg/day in a topical product. TRC is currently referenced in veterinary and human injectables outside the USA. The suitability of TRC in parenteral applications is in evidence by a study that quantitatively analyzed the effect of eighteen different excipients on human hemoglobin, including eleven which are approved for parenteral use by the FDA [35]. The results pointed to the non-hemolytic nature of TRC in the ranks of medium chain triglycerides (Labrafac® WL 1349).

Table III compares the physic-chemical properties of TRC to those of PG, ETOH, and water. TRC is an optically clear, transparent, and odorless protic solvent/cosolvent. It is biocompatible, biodegradable and compatible with polar and non-polar substances. It is soluble in ETOH, PG, small molecular weight PEGs, and glycerin; miscible with medium chain triglycerides, polyoxylglycerides, methylene chloride, and chloroform; and insoluble in mineral oils and dimethicone. TRC permeates into the more hydrophilic strata in the dermis and as such, its' skin penetration properties resemble those of PBS, urea, and glycerol [23]. The permeation rate of TRC across the skin was found to be 55 ± 10 µg/cm^2 and 231 ± 40 µg/cm^2 respectively from 5 and 30% TRC in PBS.

The ability of TRC to enhance the quantity and rate of drug permeation is often correlated with its' solubilization capacity, in a concentration dependent manner [23, 30, 39]. Its' enhancing effect is most significant when formulated with suitable surfactants, cosolvents, and/or water [3, 40, 41]. Certain publications have ascribed an HLB value to TRC [21, 24, 42]. Nevertheless, TRC is a hydrotropic solvent with a hydrophobic (ethyl) tail which is too short to be capable of forming micelles.

Penetration and Permeation Mechanisms

Skin's Reservoir Function and Sustained Delivery

Highly lipophilic molecules have high affinity for the SC lipids and therefore do not readily partition out of the SC into the viable epidermis. It has been proposed that a high degree of retention, also called "drug depot" effect may be the result of swelling in the SC bilayers especially with solvents like PG or more so with TRC [39, 43]. However, a swollen SC may be a small contributor to drug retention, an occurrence which is largely a function of drug chemistry and vehicle/skin partitioning [3]. Intracutaneous depot occurs when the drug's affinity for the skin lipids exceeds that of its affinity / solubility in its vehicle [40]. Curcumin for example, is a highly lipophilic molecule and its partitioning in the SC can result in a higher retention [44]. An unexpected drug retention in the SC may be an artifact of poor experimental design when sink conditions in the receptor are inadequate during the *in vitro* permeation testing (IVPT). Also, drug retention may be attributed to the dehydrating effect of very hygroscopic vehicles, including surfactants and hydroxylated solvents including TRC [40, 45–47]. Therefore, consideration must be given to dehydration potential, when surfactants and solvents are used neat or at high concentrations.

The reservoir function of the SC may be viewed as a challenge but also an opportunity for sustained action. It has been successfully exploited for the topical delivery of roflumilast, a lipophilic molecule (LogP of 3.53) with high affinity for protein binding [48]. Approved for the treatment of chronic plaque psoriasis, a 0.3% roflumilast cream provides sustained plasma levels and helps avoid the drawbacks (diarrhea, nausea) of oral roflumilast, providing skin concentrations that are 126 times higher than those achievable with oral dosing. The cream consists of a relatively simple formulation: 50% water; 25% TRC P; 15% moisturizers; and 10% other excipients including emulsifier [48].

Solubility and Thermodynamic Activity

The rate of a drug's penetration or permeation across the skin is directly correlated with its' concentration or more accurately the degree of saturation in its' vehicle, translating to a higher driving force for the drug to diffuse across the SC [16, 18]. Moser [49] demonstrated the effect of thermodynamic force on the permeation of LAP, an experimental molecule across porcine skin. LAP was solubilized in combination of PG and water at four levels of saturation (Fig. 2). The results indicated that LAP permeation correlated with drug concentration and not due to change in diffusivity or partitioning effects in the porcine epidermis.

Table III Physical chemical properties of Transcutol® (TRC), propylene glycol (PG), ethanol (EtOH), and water

Property	TRC	PG	EtOH	Water
Molar mass g/mole (Da)	134.18	76.1	46.07	18
Density g/cm^3 (at 20 °C)	0.989	1.038	0.789	0.998
Melting point (°C)	-76	-59	-114	0
Boiling Point (°C)	196—200	187—188.2	78.5	100
Vapor pressure (Pa)	16	9	5950	3130
Flash point (°C)	96	99	13	-
Viscosity (mPa.s, at 20 °C)	4.8	58	1.2	1
Dielectric Constant (ε at 20 / 25 °C)	14.1	32.1	24.3	80.4
Log P (octanol:water)	-0.43	-0.92	-0.18	-0.5
Surface tension (Nm/m, at 25 °C)	31.34	40.1	21.8	72.8

Screening excipients for drug solubility is a critical step in the development of any (trans)dermal delivery system. In the process, the tendency is to opt for excipients demonstrating the highest capacity for drug solubilization. Since very high drug solubilization can lead to diminished thermodynamic force, it is important to aim for a balance between drug concentration and its solubility in the eventual formulation. For example, the solubility of ibuprofen was reported to be 0.021 mg/mL in water and 400 mg/mL in TRC [50]. At 5% concentration, being fully dissolved in neat TRC, ibuprofen exhibited no measurable flux across human skin. Diluting TRC with 30% water led to ibuprofen cumulative permeability (Q_{48h}) of 17 µg/cm^2. Addition of 60% water to TRC further increased ibuprofen permeability, to 139 µg/cm^2 within the same period. Therefore, when comparing various vehicles that have similar drug concentrations, the vehicle having the lowest solubility will provide the highest thermodynamic/driving force [2, 51].

In a comparative study of penetration enhancers, Balazs [52] selected TRC (at 10%), sucrose esters (at 2.64%), and combinations thereof to solubilize ibuprofen at 5% before incorporation into various Carbomer gels. The study did not measure (or report) the ibuprofen solubility differences in the excipients or in their combinations. The results for IVPT across human cadaver skin pointed to a potential synergy, for the TRC-sucrose myristate gel which produced the highest cumulative permeation (Q_{16h}) and rate of permeation (J) of ibuprofen. In contrast, the lowest permeability values were associated with TRC. This was despite the authors' expectation that a great "enhancer" like TRC should have resulted in higher permeation values. No mention was made of potential differences in thermodynamic activity among the tested vehicles. The paper went on to suggest that the gravely diminished permeation of ibuprofen from the TRC gel was likely due to drug retention in the skin due to TRC, even though drug retention in the skin was not measured. Unfortunately, the said drug depot effect of TRC is inaccurately perpetuated. A powerful solvent like TRC can have a dramatic effect on the thermodynamic activity of the drug, lowering its tendency to escape its vehicle [53]. Moreover, when the permeant's affinity for the SC is higher than that of its' vehicle, the likely outcome is an intracutaneous drug deposit [40]. Without consideration to such effects, it may appear that TRC retards drug penetration. For these reasons, even the proposed synergy between TRC and sucrose ester proposed by Balazs [52] becomes a mere speculation.

Solvent Drag Effect

Zhang Q and colleagues [54–56] have demonstrated that enhanced drug solubility in the SC depends on the amount of drug being dissolved in the vehicle and the amount of the vehicle absorbed into the SC. A well-known outcome of drug solubilization in the vehicle is the alteration of drug's solubility in the skin layers and therefore the modification of its partitioning and diffusivity in the skin. A less obvious and infrequently discussed phenomenon is a "drag" or "convection" effect resulting from simultaneous permeation of the drug alongside its vehicle [57, 58]. The existence of a solvent drag effect was first postulated by Bendas [59] in a permeation study of three glucocorticoids having varying degrees of lipophilicity. The solubility of betamethasone 17-valerate (BMV), hydrocortisone 17-butyrate (HCB), and hydrocortisone (HC) in PG was determined to be 3.1 mg/mL, 8.9 mg/ml, and 13.4 mg/mL respectively. The study found improved partitioning conditions for all three molecules due to solubilization by PG. At PG concentrations of up to 40%, there was a linear relationship between permeation rate and the thermodynamic activity of BMV and HCB. However, the reverse relationship was observed with HC because flux decreased with increasing thermodynamic force (lowering amount of PG). Reportedly, the flux of HC

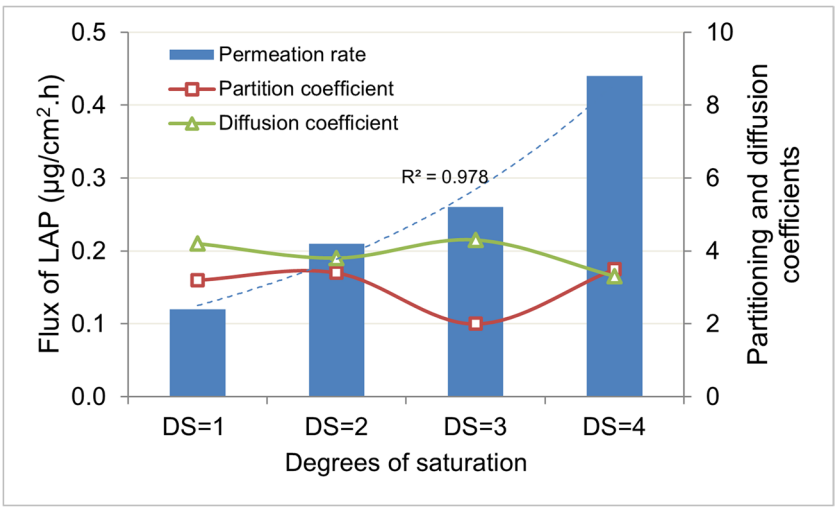

Fig. 2 Permeation rate (Flux) of LAP as a function of its degree of saturation (DS) in the vehicle while permeation parameters i.e., diffusion and partitioning coefficients remain relatively unchanged. Adapted from Moser [49]

increased with increasing amounts of PG (40–80% range), and that more than proportionally, within 15 min of application to the skin. The authors proposed the existence of an additional effect, masking the thermodynamically controlled penetration of HC by PG. Put differently, the migration of the solute, HC in this case, was modulated by PG as solvent, mediating its' transport across the membrane. Such solvent mediated transport of drugs has been associated with TRC [57, 58].

A study that helps demonstrate the interplay of solvent properties with respect to drug solubilization, permeability, and transport is that of anthramycin by Haque [39]. Anthramycin is a potent cytotoxic agent with potential use in the management of skin cancer. Permeation studies across viable epidermis separated from female abdominal skin were carried out with saturated solutions of anthramycin in various hydrophilic and lipophilic vehicles. The list included PG, 1,3-butanediol (BD), dipropylene glycol (DiPG), propylene glycol monocaprylate (PGMC), propylene glycol monolaurate (PGML), and isopropyl myristate (IPM). The study measured the amount of vehicle and drug remaining on the skin surface, penetrating into the epidermis, and permeating across to the receptor compartment. The amount of anthramycin found in the epidermis varied by type of vehicle, somewhat independent of the solubility values(Fig. 3a). The epidermis values detected with IPM, TRC, and PGMC were significantly different from the other vehicles but not statistically different from each other($p > 0.05$). TRC permeated across the skin at the highest quantity (57% by 48h). The second most permeable vehicle was PG (22% by 48h) having reached a plateau at 27 h. Combined, the solvent retention and permeation values were 65.3% for TRC and 24% for PG. The cumulative permeation of anthramycin over 48 h followed (mirrored) the penetration of TRC and to a lesser degree that of PG or PGML (Fig. 3b). Aside from the critical role of drug solubility within the vehicle, this work underlines the potential for the active, anthramycin

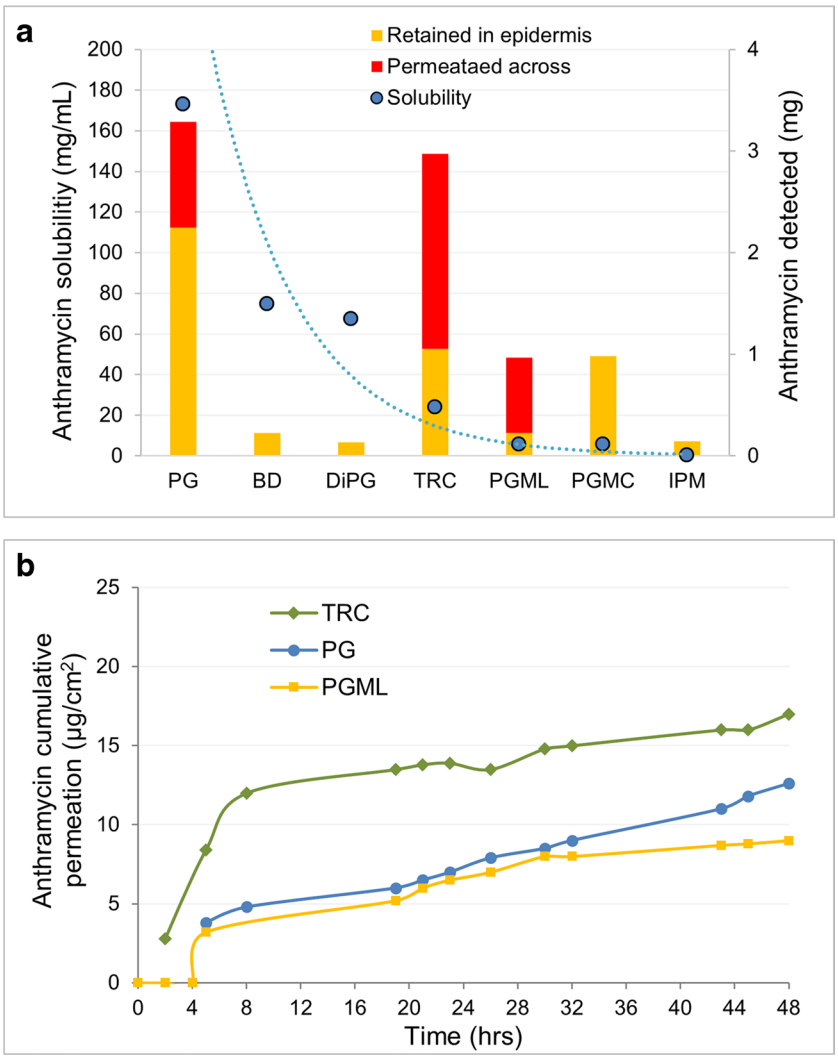

Fig. 3 **a** Anthramycin detected in epidermis or permeated across human abdominal skin as a function of vehicle (propylene glycol, dipropylene glycol, 1,3-butanediol, Transcutol, propylene glycol monolaurate, propylene glycol monocaprylate, and isopropyl myristate); **b** Cumulative permeation of anthramycin over 48 h. Haque 2017 [39]

in this case, tracking the skin penetration of its' vehicle. Lastly, sorption studies to evaluate the evaporation tendencies of the vehicles indicated that penetration of anthramycin also mirrored the evaporation of PG and TRC. Few published works have tracked the effect of solvent evaporation despite the significant effect it may have on drug permeability (see solvent volatility below).

Cosolvency

When an organic cosolvent which is less polar than water is combined with water, the polarity in the aqueous medium is reduced, thus creating favorable conditions for increased solubilization of a hydrophobic solute [20]. For comparison purposes, the dielectric constant values of common solvents in decreasing order are water (80.4), MeOH (32.70), PG (32.10), EtOH (24.30), isopropyl alcohol (19.92) and TRC (14.1). In a complex formulation, the primary function of the hydroxylated solvent is enhancing drug solubilization by cosolvency in aqueous media by decreasing the self-association forces between water molecules [20, 21, 60, 61]. As an example, addition of EtOH to progesterone solubilized in polysorbate 80(PS80):PG mixtures, resulted in a drastic increase in the solubilization of progesterone, with an optimal ratio of PS80:PG:EtOH (4:1:5) [61]. The net effect of the cosolvency is an increased solubility for weak electrolytes and nonpolar drugs by up to several orders of magnitude – an effect that is observed with TRC [21].

Cosolvency and Ionizable Drugs

The picture becomes more complex with ionizable drugs. Charged molecules may not readily penetrate the SC, except when the pH conditions are optimized [62] or when they form ion pairs in the presence of alcohols and glycols which have a significantly lower dielectric constant (ε) values than water [63, 64]. In this context, a commonly cited study is that of Minghetti [63] where saturated solutions of diclofenac salts (sodium, potassium, diethylamine, and epolamine) were incorporated into four different solvents: water, TRC, PG, and OA. The aim was to demonstrate that solvents having low dielectric constant could improve the permeability of the diclofenac salts by preventing ionic dissociation and facilitating ion-pair formations. Contrary to the expectation, the permeation rate (flux) of the salts across human skin did not correlate with the dielectric constant of the solvents used. The permeation rates were inversely proportional to the solubility of the diclofenac salts, resulting in higher permeation rates from the water and OA, significantly higher than that observed with PG or TRC (Fig. 4). Not considered was the absence of water from the saturated salt solutions in the neat PG and TRC. Moreover, the possibility of thermodynamic force differences among the preparations was dismissed because the test samples were saturated with diclofenac salts.

A different picture emerges when water is present in diclofenac sodium formulations. Hamed[65] aimed to investigate the effect of hydroxylated solvents TRC, PG, and EtOH on the viscoelasticity of Carbopol-based gels and subsequent impact on permeability using diclofenac sodium as model drug. The permeation of diclofenac Na (1%) gels with 10%, 30%, or 40% enhancer (PG, EtOH, or TRC) was evaluated across Strat-M as barrier for IVPT. The permeation rates obtained for diclofenac sodium correlated directly with the amount of EtOH and more so with TRC in the gels but not with PG. The results were presumed to be due to the effect of these solvents on the viscoelastic properties of the Carbopol gels. The possible effect(s) of vehicle polarity, notably the differences in dielectric constant and cosolvency power on diclofenac permeability however were not in the

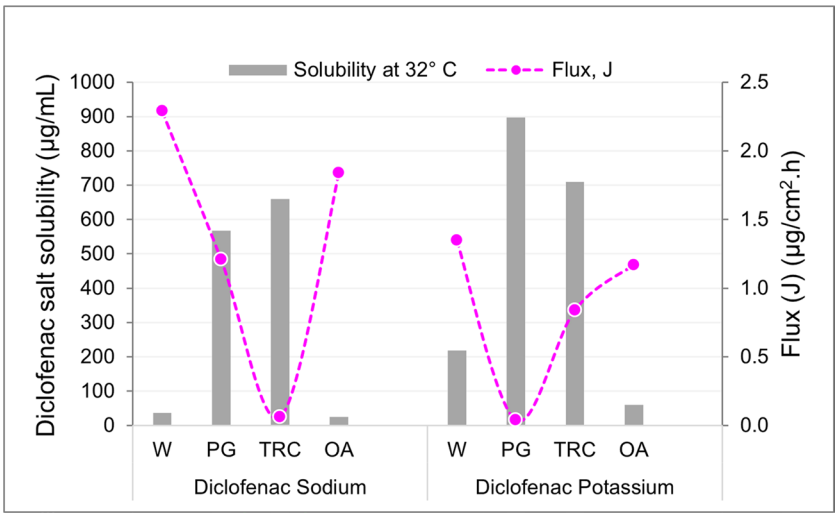

Fig. 4 Inverse relationship between solubility and flux (J) for diclofenac sodium and diclofenac potassium in neat solvents, water (W), propylene glycol (PG), Transcutol (TRC), and oleic acid (OA). Adapted from Minghetti [63]

purview of this investigation. Considering the results from this [65] work and that of the aforementioned Minghetti [63] study, one could speculate that the effect of alcohols and glycols as enhancing solvents for charged drugs becomes more apparent when they are combined with water.

Synergies Among Binary and Ternary Systems

Combination of enhancers can have a significant effect on cutaneous permeability. Synergistic effect of two or more vehicles on drug penetration and permeation has been cited by numerous works [41, 45, 46, 66, 67] indicating highest flux or highest total drug permeation especially when TRC is diluted with water / PBS, or used in combinations with IPM, PEG 400, or PG. Examples of such findings on binary systems [3] are melatonin [68] and tenoxicam [69] where significantly higher drug flux values were associated with the presence of TRC in the 20% to 40% range. The optimal range may be different in complex systems (discussed below) suggesting that enhancer function is context and concentration dependent; that the presence of another solvent (or enhancer) can dramatically alter the permeability properties of the drug-vehicle. In the same vein, is a study that investigated the effect of enhancers on the organizational structure of the human SC lipids using X-ray scattering (small-angle and wide-angle) techniques [19]. Among the enhancers investigated were four solvents, six surfactants, and four terpenes. OA was grouped with EtOH, PG, and TRC as solvent; among the terpenes were menthol, nerol, camphor, and methyl salicylate; and in the surfactants category were Kolliphor RH40, Tween 80, plus two anionic and two cationic surfactants. As expected, the highest degrees of lipid organization disturbance was found with surfactants and terpenes. For the solvents (EtOH, PG, TRC, OA) however, the comparison was on unequal terms. EtOH and PG were evaluated neat (hence found to be innocuous), but TRC and OA were tested each at 10% in PG resulting in minor but detectable levels of disturbance. Such comparisons ignore the possible synergies when the solvent is diluted with water or combined with another solvent [45, 46, 50, 66, 68, 69].

To investigate the effect of ternary combinations on the permeation of highly lipophilic diarylheptanoids (LogP 4.4–4.9), another study [29] identified the optimal binary combinations before introducing the third solvent. First, binary systems of EtOH-water, PG-water, or PEG-water were screened for solubilization capacity and permeation performance for diarylheptanoids. The highest solubility and cumulative (Q24h) permeation across porcine skin was observed with the EtOH-water, being 7-times that obtained with the PG-water combination. Next, the addition of 10% or 20% TRC to the EtOH-water combination helped further increase the cumulative permeation of diarylheptanoids by 25-times and 14-times respectively. In parallel, the deposition of diarylheptanoids in the skin increased by up to 14-times. Based on the findings, the paper proposed synergy, likely a combination of improved drug diffusivity combined with enhanced thermodynamic activity. The enhanced skin deposition also indicated potential for 24h sustained percutaneous absorption – a positive finding because the highly lipophilic diarylheptanoids have an oral half-life of 2–3 h.

An earlier work that points to the potential benefits of combining vehicles with varying properties is that of Rojas [70] involving morphine base as model drug. Neat, binary, and ternary combinations of three excipients namely TRC as cosolvent, Labrasol® (LBSL) as surfactant, and propylene glycol dipelargonate (DPPG) either neat or in combination were supersaturated with morphine (specific activity of 75 KG q/g or 2 uCi/g) and then gelled by addition of ethyl cellulose. Table IV provides the solubility of morphine in each of the vehicle / combinations subjected to IVPT in rat skin and the respective permeation parameters. Noteworthy is the large differences in morphine solubility in individual solvents—being 39mg/mL, 3 mg/mL, and 0.2 mg/mL in TRC, LBSL, and DPPG respectively. The longest lag

Table IV Solubility and permeation parameters of morphine from neat, binary, and ternary solvent gels [70]

Solvent System	Solubility (mg/g)	Partition (Kp)	Lag time (h)	Flux ($\mu g/cm^2.h$) × 100	Diffusion Coeff (cm^2/h) × 10^4)
TRC	39.0	3.5	47.0	0.8	0.0
LBSL	3.0	9.6	23.0	3.6	0.7
DPPG	0.2	20.0	1.3	4.2	0.7
DPPG:LBSL (1:1)	0.4	11.2	0.9	10.4	13.6
TRC:LBSL:DPPG (2:1:1)	8.0	0.7	5.0	10.4	11.1
TRC:DPPG (3:7)	4.7	2.1	3.4	13.0	7.9
TRC:LBSL:DPPG (1:2:1)	6.8	1.1	4.3	14.9	8.0
TRC:LBSL:DPPG (1:1:2)	4.8	3.5	1.8	4.8	1.7
TRC:LBSL:DPPG (1:1:1)	6.8	1.1	5.2	9.6	7.7
TRC:LBSL (1:1)	9.0	1.2	21.4	6.6	3.5

time coincided with the highest solubility, i.e. neat TRC, accompanied with minimal diffusion coefficient i.e., the lowest mobility in the skin, hence with the highest morphine concentration in the skin. In contrast, the LBSL:DPPG (1:1) mixture provided the reverse effect – with the highest diffusion and shortest lag time (0.9 h). Depending on the objective of the treatment, an optimal compromise may fall anywhere between these two extreme findings or perhaps the combination of TRC: LBSL: DPPG (at 1:2:1 ratio) where highest permeation rate was achieved. This study exemplifies the potential possibilities in optimization of drug solubility, partitioning, and diffusivity by combining compatible solvents having different physical chemical properties.

An interesting extract of the aforementioned work [70] is the general relationships drawn among permeation parameters for the TRC:DPPG binary combinations. Expressed as normalized values to neat DPPG in Fig. 5, it is evident that partitioning of the morphine base has an opposite relationship with drug solubility and that a change in the drug concentration is reflected in the partition coefficient. Drug mobility expressed by the diffusion coefficient is interconnected to the rate of permeation (flux), but the shapes of these curves compared to the solubility curve (inversely proportional) show that more than thermodynamic activity is influencing the *in vitro* permeation of morphine base from this binary mixture.

Minding Solvent Volatility

It is known that addition of a volatile solvent to a non-volatile vehicle or formulation can drastically change the drug solubility and increase the thermodynamic activity of the solute [71]. Evaporation of the solvent, be water or EtOH from the applied dose following application on the skin can leave a saturated residue of the drug in the non-volatile vehicle increasing its' drive to penetrate and permeate the skin. The relative volatility of the formulation constituents can be critical, especially for treatments that target the shunt pathway, via the sebaceous glands (anti-acne) and hair follicles (hair growth). Capitalizing on the differentials in solvent volatility, is a commercialized treatment for acne, involving dapsone (5%). This formulation was developed with water:TRC at a ratio such that only a third of the dapsone would be solubilized (due to TRC) and the remaining drug suspended in the aqueous gel [72]. Since water evaporates quickly after application of the gel to the skin, the remaining TRC can further solubilize the suspended drug in the sebaceous glands. In the example of a hair growth stimulant, bimatoprost, Subedi [73] developed a topical formulation with volatile and nonvolatile co-solvents and spreading agents. The optimal formulation consisted of 55% EtOH, 27% TRC, 8% water, and 5% cyclomethicone loaded with 5% bimatoprost. When compared to the same amount of bimatoprost in ethanol, the optimized formulation had a 4.6-fold higher human skin flux, 5 times the drug deposited into the skin, and tenfold greater cumulative permeation over 10 h. Moreover, the formulation provided 585% higher hair regrowth in androgenic alopecia mice within 10 days of treatment when compared with the blank vehicle. The remarkable results were explained by the immediate infiltration of the drug into the deep dermal layers to activate dermal papilla cells.

Formulation Development

Transcutol® (TRC) has been referenced in a diverse range of pharmaceutical preparations – including solutions, gels, suspensions, emulsions, vesicles, solid lipid nanoparticles, microemulsions, and self-microemulsifying delivery systems [21, 48, 72, 74, 75]. Its' adaptability to different formulation systems and effects on drug penetration and permeation in various settings are discussed in the section below.

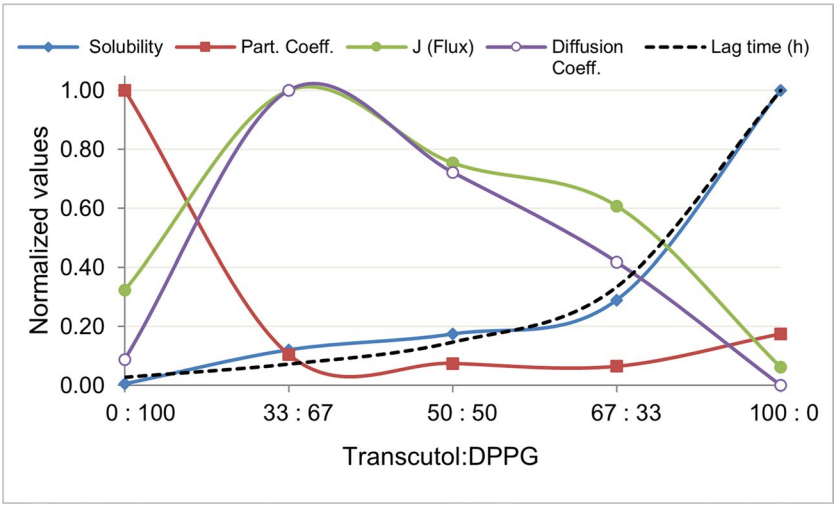

Fig. 5 Relationship between morphine solubility and permeation parameters in binary combinations of Transcutol® and DPPG. Rojas [70]

Gels

Gelling agents are often used to impart viscosity and sensorial consistency to topical solutions, suspensions, emulsions, and microemulsions. A most recent publication provides an in-depth review of nanoemulgels involving various skin cancer drugs [76]. Among the commonly used gelling agents are Carbomers [52, 77–79], celluloses [80], poloxamers [81, 82], chitosan [82, 83], and alginates [84]. The suitability of the gelling agent varies by the type of consistency, formulation pH, and the visual aspect of the intended product. A key consideration in the selection process is whether the performance of the gelling agent is pH independent. Most grades of Carbomers require pH adjustment by addition of NaOH or triethanolamine, whereas cellulosic polymers like hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), and acrylamide block copolymers like sodium acryloyl dimethyl taurate (SAMT) perform independent of pH. The compatibility of the gelling agent with the formulation and particularly the presence of hydroxylated solvent(s) needs to be considered. In the case of TRC, there are no known incompatibilities with pH dependent or pH independent gelling agents. Commercialized gel products like Viractin® and Aczone® demonstrate that the consistency of TRC gels remains constant for two or more years. Viractin®, an over-the-counter treatment for cold sores with tetracaine as the active, was formulated with 42% TRC and used HPC as the gelling agent. Aczone® on the other hand has been commercialized with two different gelling agents. It was initially launched as 5% dapsone (twice daily dosing) and later as 7.5% dapsone (once daily dosing) for the treatment of acne, having 25% and ~ 35% TRC respectively in a gel suspension. The consistency agents for the 5% and 7.5% Aczone® respectively were Carbopol® 980 [72] and SAMT [85]. In a more recent study of dapsone for cutaneous leishmaniasis, Moreno [86] opted for a Pluronic-lecithin-based organogel. More specific examples of different gel systems are provided below.

Cinnarizine Hydrogels with HPMC

To evaluate the skin permeability of the highly lipophilic cinnarizine (LogP 5.8, MW 368.6), three types of formulations with varying hydrophilicity / lipophilicity were developed by Damgali [80]. These included an HPMC-based gel, an O/W emulsion, and an anhydrous, lipophilic (oleaginous) cream as base formulations, to which enhancers like OA, PG, glycerin, and TRC were added at 5%. The combination of TRC in the oleaginous base was excluded from the study due to loss of homogeneity and phase separation (see ointments and anhydrous systems below). No incompatibility was noted with the O/W emulsion or the hydrogel base, which contained 3.15% HPMC. Overall, the hydrogel formulations provided the highest cumulative permeation of cinnarizine irrespective of the enhancer, suggesting that permeability of this lipophilic molecule increased with decreasing lipophilicity of the formulation. Among the hydrogels however, performance varied with the type of enhancer. Relative to the control formulation, the cumulative permeation of cinnarizine over 6 h from the PG and OA hydrogels were 1.4-fold and 1.7-fold respectively. The highest activity, i.e. 2.8-fold increase in cumulative permeation was obtained with the TRC hydrogel. This formulation was recommended as an alternative to the oral administration of cinnarizine for the treatment of Meniere's disease and motion sickness.

Testosterone Gel with Film Forming Polymers

To develop a film forming testosterone gel, Zeng [87] experimented with various polymers including poly vinyl alcohol, carboxymethylcellulose (CMC-Na), and carbomers. Ultimately, an optimized testosterone (0.5%) gel (patch) with good uniformity and *in vitro* release of nearly 100% drug was developed. The incorporation of 1%, 3%, or 5% TRC in the optimized patch resulted in significant improvements in the *in vitro* and *in vivo* results. The pharmacokinetic parameters of the testosterone in film forming gels obtained *in vivo* over 28 h in rabbits were compared to those of a marketed reference Androderm patch. The results indicated a 40%-80% increase in AUC, significant increases (up to 2.8-fold) in the C_{max}, alongside reduction in T_{max} from 21 min to as low as 5 min with the gel/patch having 3% TRC. Skin irritation and histopathology studies further confirmed the innocuity of the optimized gel.

Caspofungin in Chitosan-Pluronic Gels

Indicated for treatment of invasive and resistant candidiasis, caspofungin was the subject of permeation studies across human skin. Perez-Gonzales [82] developed a chitosan-Pluronic gel without enhancers and the same gel with TRC and laurocapram at 5% each as enhancers. Whereas both gels produced similar quantities of cumulative drug permeation their effects on skin retention were significantly different. Caspofungin retention from the gel with enhancers (and lower water content) resulted in 80 μg/cm^2, about 2.5 times the amount observed with the control gel without an enhancer (33 μg/cm^2). The latter could be a desirable outcome for an antifungal topical treatment. However, there was no mention of differences in the formulations for drug solubility or availability of water molecules for interaction with formulation and drug partitioning. The paper suggested that laurocapram and TRC together had increased the partitioning of the drug between the formulation and the skin while limiting its diffusion to the receptor fluid.

pH Responsive Nanoparticles in Gel

Sahu *et al*. [83] developed a capecitabine nanosized gel system designed to trigger passive targeting of the acidic media found in the leaky, disordered endothelial cell layers of the tumor vasculature. The formulation consisted of cationic chitosan-based pH responsive gel obtained by adding the dried nanoparticles of chitosan-capecitabine to an aqueous mixture of Pluronic 127 (22%) and TRC (24%). This preparation provided a three-fold increase in drug penetration and retention in porcine skin, relative to the free solution as control. This same approach and same concentrations of Pluronic F127 and TRC were used in a subsequent study [88] for delivery of temozolomide, which is also indicated for skin cancer (aggressive skin papilloma). *In vitro* analysis of the nanogel confirmed that temozolomide was effectively encapsulated in the nanogel; that it provided an accelerated but sustained release of the drug in mildly acidic (pH 6) conditions and that it effectively displayed potent tumor accumulation and suppression of metastasis in carcinogenic mice.

Pressure Sensitive Adhesive Patch

Drug release from pressure sensitive adhesive (PSA) patches may be influenced by a number of factors, including drug-PSA interactions. As part of a study with daphnetin as model drug, Shen [89] investigated the effect of seven different enhancers on drug release from PSA patches. TRC was selected for providing the highest drug release. Next, the permeation of daphnetin (1%) from the patches with varying concentrations of TRC was evaluated. An optimized PSA patch with 10% TRC was chosen for further investigations including FTIR, DSC, and IVPT to elucidate the mechanisms in play. The results indicated that there was a strong intermolecular interaction between daphnetin and the PSA; that daphnetin release from the patch was facilitated by a significant reduction of its' association with the PSA, due to TRC competitively interacting with the ester group in the PSA, hence improving its mobility. Lastly, the *in vivo* effect of the said patch was confirmed with significant anti-inflammatory and analgesic effects in Wistar rats.

Cubic *vs.* Lamellar Phase Gels

The morphology of the vehicle (the delivery system) such as cubic or lamellar phases obtained with lipid and water is known to significantly increase the permeation of drugs across the skin. One example involves glyceryl monooleate (GMO), an amphiphilic lipid, that is known to spontaneously form thermodynamically stable cubic or lamellar phases in water. Using varying ratios of GMO, water, and TRC Zhang [78] developed cubic and lamellar gels for dermal delivery of baicalin, a compound with low aqueous solubility. The cubic phase gel systems were isotropic, viscous, and transparent without flow properties whereas the lamellar phase gels were anisotropic and had the viscosity of a flowing gel. Figure 6 provides the formulation compositions having different GMO:TRC ratios and varying amounts of water (10, 20, 30, or 60%). Included in the experiments was a hydrogel consisting of 30% PEG 400 solution gelled by 0.4% Carbopol® 980 as control. The cumulative permeation (Q_{12h}) and flux (J) of baicalin from the said formulations, shown in dotted lines were significantly greater than those of the control hydrogel. The lamellar gel formulations provided up to 20-fold enhancements in cumulative absorption and permeation rates. The values from the cubic gel systems were incredibly greater, representing 21-, 91-, and 200-fold increases relative to the control hydrogel. Worth noting is that the cubic gel providing the highest values (GMO:TRC at 9:1 ratio) consisted simply of 4% TRC, 36% GMO, and

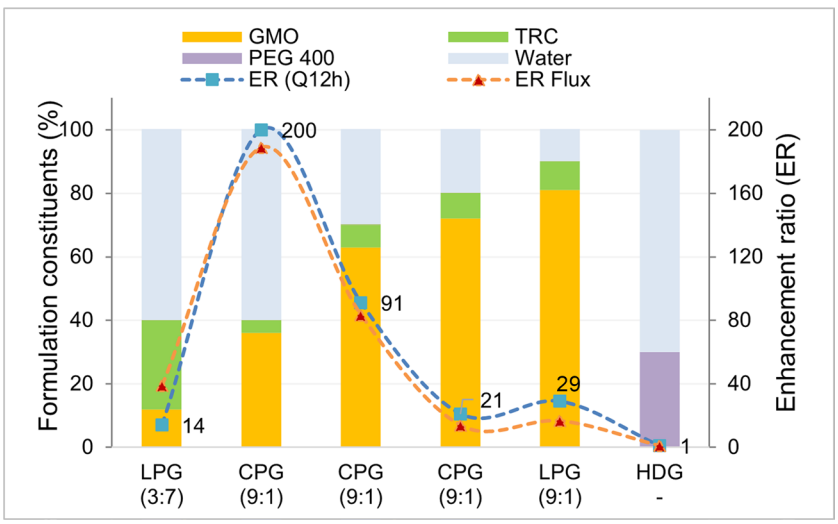

Fig. 6 Cubic phase gel (CPG) and lamellar phase gel (LPG) formulations at varying ratios of glyceryl monooleate (GMO) and Transcutol (TRC). The dotted lines represent the enhancement ratios (ER) for flux and cumulative permeation (Q) of baicalin after 12 h across rat skin relative to the control hydrogel (HDG). Adapted from Zhang 2015 [78]

60% water. Also reported was the ability of these gel systems to preserve the stability of baicalin.

Aqueous Acyclovir Gel

Acyclovir is indicated for the treatment of herpes simplex viruses. To be effective, it must penetrate the depth of the epidermis/dermis and to be available to the tissue for extended time. To this effect, Schwagerle [90] developed acyclovir formulations, incorporating TRC, PEG400, and or PG into various types of gels, at acyclovir concentrations ranging between 0.2% and 5% before subjecting them to *in vitro* and *in vivo* analysis. A commercialized cream (Zovirax®) served as reference in the experiments that included pharmacokinetic evaluations in pigs using dermal open flow microperfusion. Figure 7a compares the composition of an optimized 0.2% acyclovir aqueous gel (50% TRC, and 10% PEG 400) to that of the reference 5% acyclovir cream (1% of sodium lauryl sulphate and ~ 40% PG). The relative permeation of acyclovir from the said formulations into the dermis and epidermis of pig skin is shown in Fig. 7b—expressed as enhancement ratio (ER) for acyclovir concentration in skin layers. Normalizing the results for the 25 times difference in drug concentrations (dose), the aqueous gel outperformed the reference product by seven times higher drug amount in the dermis, eight times greater C_{max}, and ten times greater cumulative amount of acyclovir recovered from the epidermis (Fig. 7b). More importantly, the dermal concentration of acyclovir achieved by the optimized formulation was similar to that attained by the oral route.

Ointments and Anhydrous Systems

As indicated above, incorporation of 5% TRC in an anhydrous oleaginous cream resulted in loss of homogeneity and eventual phase separation [80]. The said cream consisted of > 75% Vaseline, 12% liquid paraffin, and 12.5% stearic acid, indicating immiscibility and insolubility of TRC in such a combination. With this incompatibility in mind, TRC

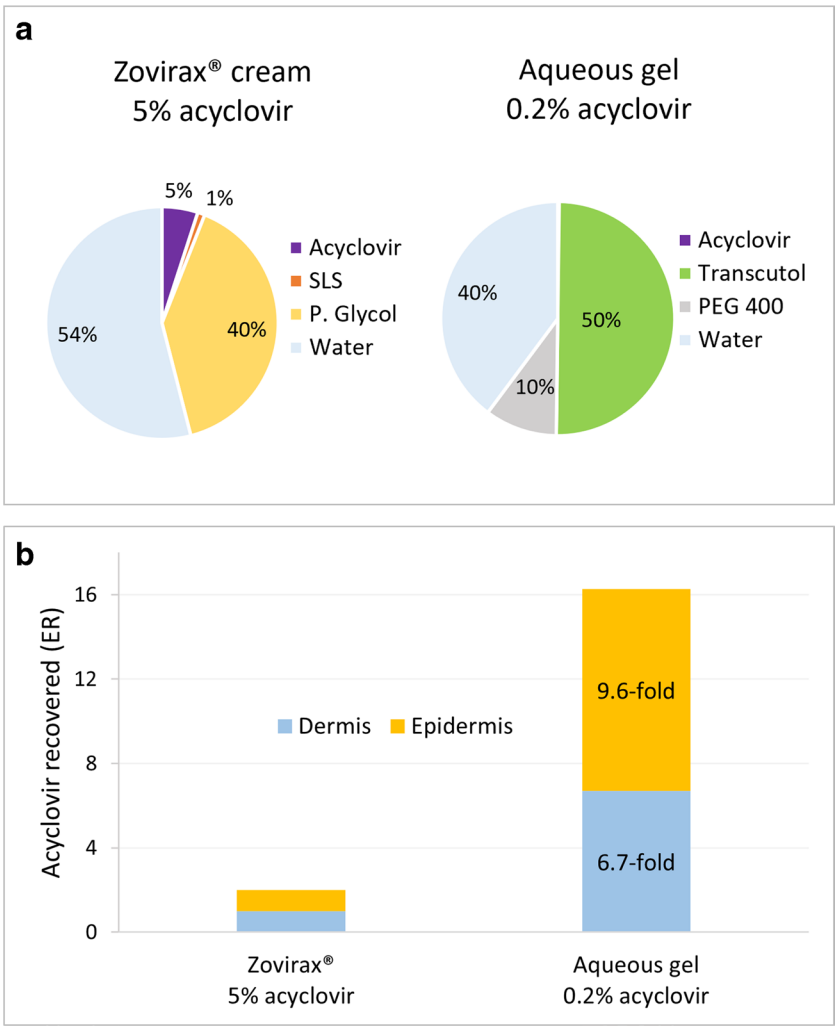

Fig. 7 **a** Compositions of Zovirax and optimized aqueous gel formulations; **b** Enhancement ratio (ER) of acyclovir concentration in skin layers from aqueous gel relative to Zovirax. Schwagerle 2023 [90]

has been successfully applied in other anhydrous systems as solvent/enhancer. In the example below, incorporation of TRC drastically improved the permeability of itraconazole (MW 705.6). Orally administered itraconazole at doses of 200-400mg/day is associated with nephrotoxicity, hepatic damage, and reproductive complications [91]. To obtain topically administered alternatives, Subedi [91] developed formulations with EtOH as solvent, benzyl alcohol as non-volatile solubilizer, TRC as permeation enhancer, and cyclomethicone as wetting agent. IVPT across full thickness human skin was carried out. Select itraconazole (1%) formulations are presented in a decreasing order of EtOH concentration in Fig. 8a where significant enhancements in cumulative permeation of itraconazole are denoted by a dotted line. Relative to the EtOH-benzyl alcohol binary system (ITZ1), the permeation enhancement, expressed as ER was 12.6 times greater with the incorporation of TRC and again by up to 30 times after the addition of cyclomethicone. The highest permeation was obtained with ITZ11, a formulation consisting of 39% EtOH, 30% benzyl alcohol, 15% TRC, and 8% cyclomethicone. Three formulations (ITZ6, ITZ8, and ITZ11) were next analyzed for permeation across full thickness human skin. The concentration of itraconazole was found to be highest in the SC, followed by epidermis and dermis (Fig. 8b), likely due to the lipophilic nature of itraconazole. The most significant finding of this work however was the *in vivo* efficacy of the optimized emulsion (ITZ 11) for antifungal activity that was achieved at a dose identical to that of a commercially available oral itraconazole in the mouse model. This formulation was deemed as a superior alternative to orally administered itraconazole in the treatment of superficial mycosis.

Itraconazole was also the topic of permeability investigation in anhydrous creams consisting of glycerides and OA as lipid phase, waxes as consistency agents, and 1:1 ratio of PEG 200:PEG 400 as the hydrophilic phase [92]. TRC was incorporated at 5%, 10%, or 15% in the anhydrous creams and itraconazole (0.5%) dissolved in a 1:1 mixture of PEG 200 and PEG 400 solution served as control. IVPT experiments across human cadaver skin confirmed that both the

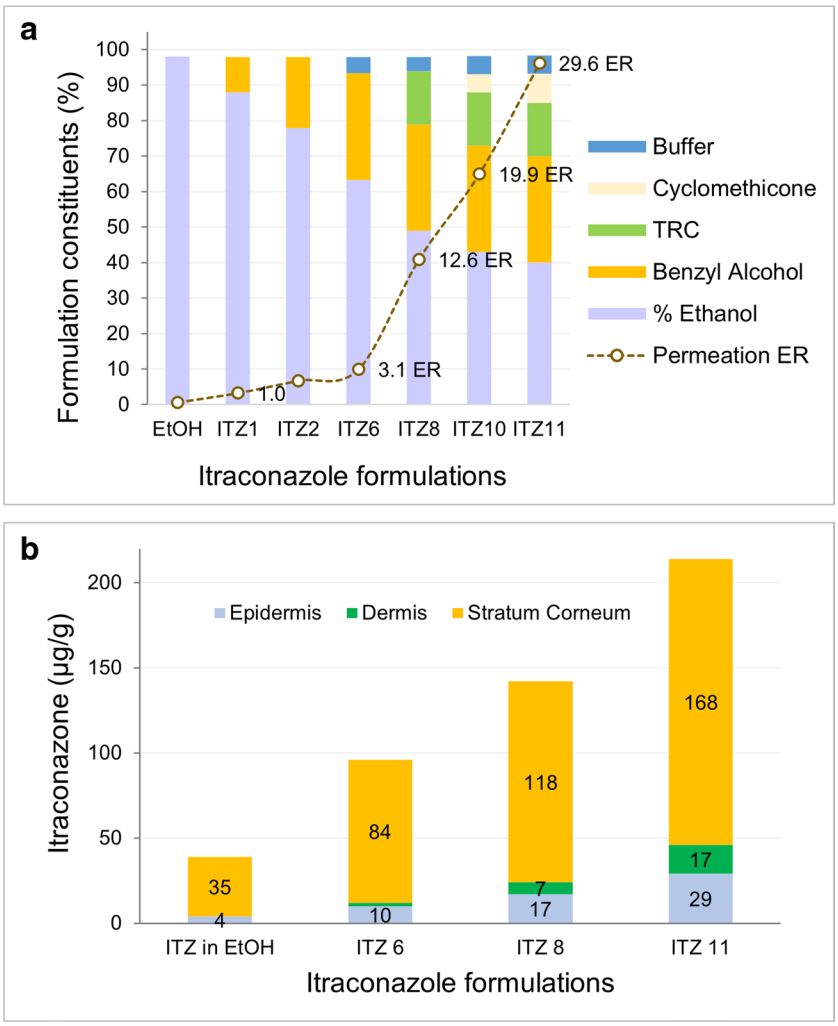

Fig. 8 **a** Formulation compositions and permeability of itraconazole across artificial skin; **b** Distribution of itraconazole in different layers of full thickness human skin. Adapted from Subedi 2021 [91]

amount of itraconazole permeated and the amount found in the skin increased with the increasing concentration of TRC (Fig. 9). Relative to the control formulation, the findings were significant, representing 3-, 5-, and tenfold enhancements with the 5%, 10%, and 15% TRC creams respectively. These creams were deemed superior alternatives to other routes of administration for itraconazole in the treatment of skin fungal infections.

Emulsions and Foams

The use of TRC at elevated concentrations, especially upwards of 30% may lead to loss of consistency in anhydrous systems [92] regular emulsions [93], and in foams [94]. To elucidate the mechanisms behind such loss of emulsion consistency, Hernandez [93] developed a base emulsion consisting of 28% solid phase and 72% water. An emulsifier (Brij®), medium chain glycerides (Miglyol®), PG, and cetostearyl alcohol represented the solid phase. Four creams were obtained from the base formulation by substituting the water with 20%, 25%, 30%, or 40% of TRC as cosurfactant (Fig. 10a). Analysis of the creams by DSC indicated that the melting onset temperature of the creams dropped significantly, from 53 °C to 33 °C with increasing amounts of TRC. Also determined was an inverse relationship between TRC concentration and the interfacial tension observed for the emulsions (Fig. 10b). This trend, notably the drop in viscosity at > 25% TRC was explained by a reduction in droplet volume density as observed by microscopy. To compensate for the loss in emulsion consistency the paper suggested the use of higher melting point-lipids and surfactants.

Three-Phase Aerosol Foam

Three-phase pharmaceutical aerosol foams contain a two-phase (usually oil-in-water) foam concentrate emulsion in the cannister that is in equilibrium with a third phase liquid propellant (often a hydrocarbon propellant). Upon shaking the cannister prior to dispensing, the liquid propellant is emulsified with the product concentrate. When the valve is actuated, this combined emulsion is forced through the nozzle and the propellant entrapped in the internal oil phase of the combined emulsion reverts to the vapor phase to form a foam when it reaches the atmosphere. An FDA approved three-phase aerosol 0.3% roflumilast foam for the treatment of seborrheic dermatitis, per the product (ZORYVE) package insert [95] contains TRC, an alkyl phosphate emulsifier blend, hexylene glycol, moisturizers, preservatives, and water dispensed from an aluminum can pressurized with propellant blend of butane, isobutane, and propane. According to US patent application 2023/0190651 increasing TRC above 35% destabilized the emulsion and caused creaming of the combined emulsion oil phase within the canister. This destabilization of the combined emulsion resulted in unacceptable drug content uniformity in the expressed foam [94].

Liposomes and Penetration Enhancing Vesicles

Vesicles are hollow liposomal (colloidal) formations that entrap water within concentric unilamellar bilayers. They are called liposomes if their bilayers consist mainly of lipids or referred to as niosomes if they are made entirely of non-ionic surfactants [96]. With the incorporation of enhancers, they become penetration enhancing vesicles (PEVs) gaining elasticity and greater ability to traverse the skin while carrying along the encapsulated drug entity [97–99]. Manconi [98] prepared PEVs by adding TRC at 10%, 20%, and 30% to a phospholipid-PBS liposomal system for delivery of diclofenac sodium across porcine skin. Analysis of the liposomal base and the PEVs by confocal laser scanning microscopy confirmed the presence of unilamellar and multilamellar vesicles. The rate of permeation (*J*) increased by 2 and 3

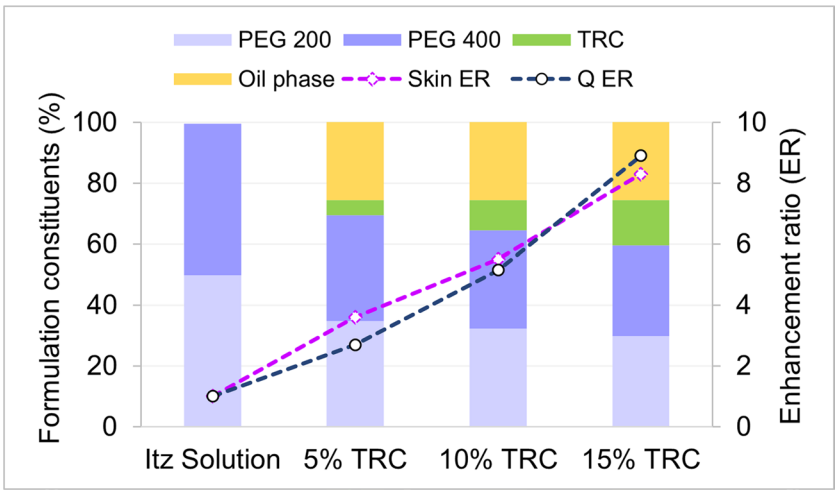

Fig. 9 Ex vivo permeation of itraconazole across human cadaver skin and its deposition in the skin from anhydrous systems. Adapted from Kolimi 2022 [92]

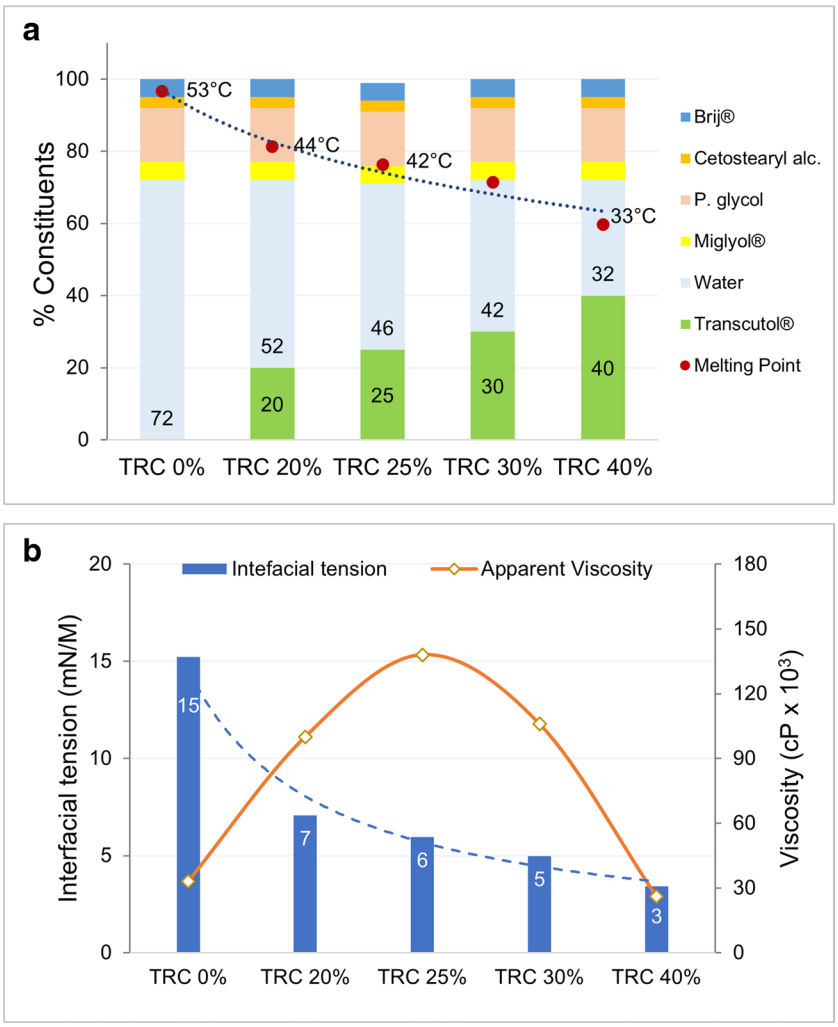

Fig. 10 **a** Effect of Transcutol® concentration on the melting onset temperature of cream formulations; **b** Interfacial tension and viscosity of O/W emulsion as a function of Transcutol® concentration. Hernandez 2019 [93]

times with the PEVs having 20% and 10% TRC respectively. The cumulative permeation of diclofenac sodium was also significantly greater by 7 and 9 times that of the liposomal base when TRC was present at 20% and 10% respectively. In a subsequent publication, the said PEVs were the subject of extensive evaluations for permeation and accumulation of diclofenac acid into pig skin structures [99]. Figure 11 compares the results obtained from PEVs with 0, 10, 20, and 30% TRC, showing the distribution of diclofenac acid in the receptor and the amounts retained in the skin structures after 8 h of IVPT. The permeation and distribution profiles indicated the possibilities for both immediate release and sustained release formulations. Moreover, the TRC containing vesicles were closely packed and capable of being internalized by the 3T3 fibroblasts. To explain the underlying mechanisms, the authors pointed to the ability of TRC to improve the fluidity of PEV bilayers leading to improved permeability and diffusion across the skin.

The type of organic solvent used in the preparation of liposomal systems is critical to the efficiency of the process and can also impact the quality, stability, and safety of the vesicles being formed. Lopez [100] investigated the effect of four different solvents on the characteristics and stability aspects of liposomes. In a decreasing order of polarity, methanol > ethanol > isopropanol > diethylene glycol monoethyl ether (TRC) were each used in the liposomal preparations obtained by in a periodic disturbance mixer. The resulting systems were characterized by dispersion size, size distribution, and zeta potential. Among the solvents tested, TRC yielded the finest dispersion sizes, ranging from 80 to 160 nm with the lowest polydispersity index. Moreover, these results were reproduced under different temperatures and lipid concentration conditions. Given that process temperature and lipid concentration had no influence on the liposomal zeta potential, the authors strongly recommended TRC as an alternative to replace conventional alcohol-based solvents in order to avoid filtration steps due to its low toxicity.

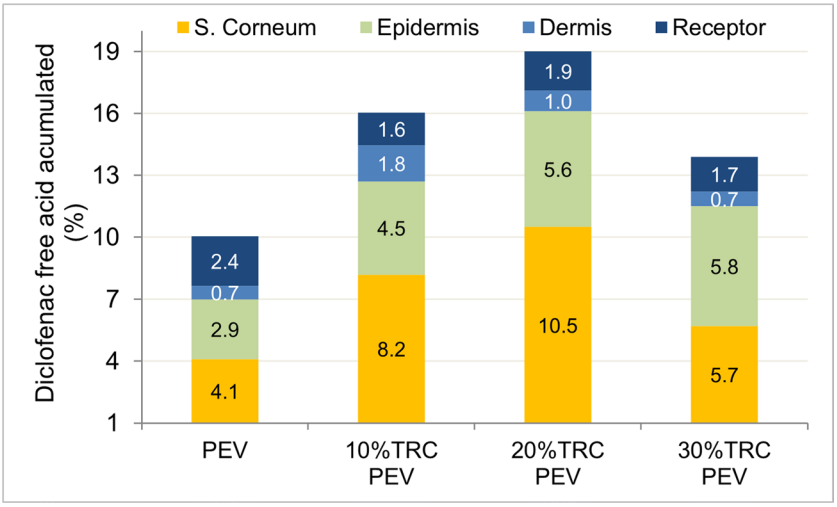

Fig. 11 Permeation and accumulation of diclofenac acid into pig skin from liposomal preparations with 0, 10, 20, and 30% Transcutol® after 8 h of treatment. Adapted from Manca 2013 [99]

Lipid Nanoparticles and Nano-Lipid Carriers

Solid lipid nanoparticles (SLN) and nano lipid carriers (NLC) are encapsulation technologies of interest for enhancing drug permeation across biological membranes. Among the benefits of encapsulation are protection of photosensitive actives against light, reducing skin irritation, targeting of the follicular route, and controlled (sustained) drug release [101]. The main difference between SLN and NLC lies in the inclusion of liquids or liquid lipid(s) into the solid lipid scaffolding of the conventional SLN to obtain NLC [102] in order to generate a larger space for loading of the active substances. Key considerations in SLN/NLC development are entrapment efficiency (EE) and the integrity of the nanoparticles for modulating drug release. Solid lipids may undergo polymorphic changes that delay the release of the active. Alternately the presence of enhancers with high solubilization capacity may compromise the nanoparticles' integrity, leading to the expulsion of the active substance from the solid lipid matrix during prolonged storage [103]. Hence, the use of enhancers and hydroxylated solvents like TRC in SLN/NLC requires additional mechanistic discussion.

By "entrapping" the active in the SLN/NLC, the formulator is intentionally blocking the active from crossing the skin by the intercellular path in favor of triggering the release of active by the follicular route e.g. for hair growth stimulation or delivery via the pilosebaceous unit [104] in targeting the tumor sites. Since TRC is a good solvent for most substances, dilution of nanoparticles with an aqueous blend or TRC may partially dissolve the SLN or extract the active from the SLN (leakage). If leakage occurs during product storage, then dosing may be dependent on the time elapsed since manufacture of the final SLN dosage form. As a counter measure, solid lipids with melting points above 45°C, like glyceryl dibehenate (Compritol®) or glyceryl palmitostearate (Precirol®) are needed for development of SLN/NLC [103] accompanied with TRC [105–107]. Combinations of TRC and ethyl oleate [102] or OA [108] with solid lipids as the SLN/NLC matrix have been reported. Among the examples, is the work of Pitzanti [105] developing SLN consisting of Compritol® 888 ATO as solid lipid matrix, Pluronic F68 as stabilizer, and TRC at 2% or 4% as solvent/enhancer. The active entrapped in the SLN was 8-methoxypsoralen (8-MOP), a photosensitizing agent with aqueous solubility of ~ 47 mg/mL at 30°C. The entrapment efficiency for all SLN formulations (97–99%) appeared to be independent of the TRC concentration. The distribution of 8-MOP within the skin layers, expressed as percent of the applied dose in Fig. 12 could be correlated with the amount of TRC present in the formulations. The higher skin uptake (vs. permeated) was a desired effect for the objective of the drug – i.e. local treatment of psoriasis with potentially reduced side effects due to diminished systemic exposure.

Micro and Nanoemulsions

Microemulsions and nanoemulsions are a powerful approach for enhancing the (trans)dermal delivery of poorly soluble drugs. Among the defining aspects of micro and nanoemulsions are their high solubilization capacity and fine dispersion size (< 200 nm in diameter). Dispersion size is known to vary by small changes in the proportion of the system constituents defined as oil, surfactant, cosurfactant/cosolvent, and the aqueous phase [109–111]. Hydroxylated solvents, notably TRC, are frequently used in the development of micro and nanoemulsions for their role as solvent, cosolvent, cosurfactant and/or enhancer. An in-depth review of the subject is in progress (in press). Meanwhile, the examples below can be demonstrative of their utility in (trans) dermal applications.

Almost invariably, the incorporation of TRC in micro / nanoemulsions facilitates a dramatic reduction in the

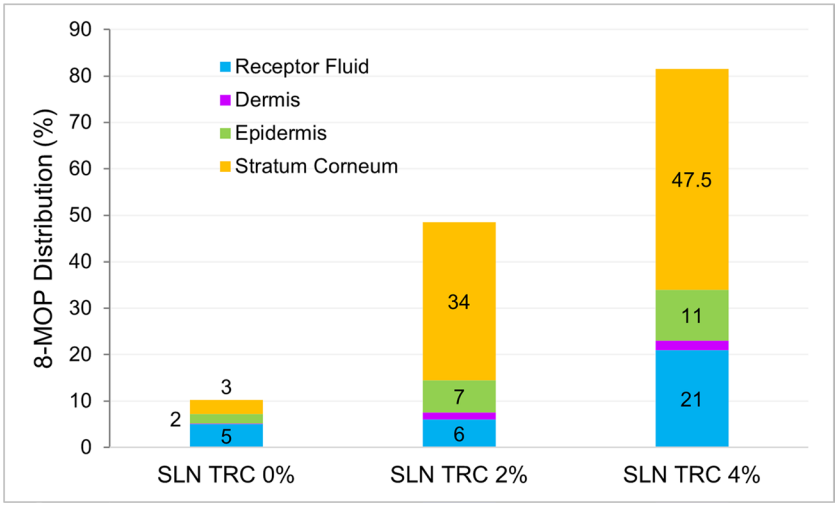

Fig. 12 Formulation dependent deposition, distribution, and permeation of 8-MOP from solid lipid nanoparticles (SLN) with varying concentrations of Transcutol®. Pitzanti 2020 [105]

surfactant levels needed, reduced dispersion size, and improved delivery [112]. Also demonstrated by pseudo-ternary phase diagrams is a uniquely larger dilution capacity with the aqueous phase when TRC is present [112–114]. The microemulsion fields (zones) obtained with TRC are typically two to three times larger than those achievable with EtOH or PG. The key role of TRC in micro / nanoemulsions is found in the examples of ibuprofen [115–117]; ketoprofen [31, 113], indomethacin [79, 118–120], piroxicam [121] and quercetin [47].

Having established a direct correlation between indomethacin solubility in the microemulsion and its diffusion across the skin, Spaglova [79] deemed TRC to be the most suitable solubilizer and penetration enhancer for indomethacin. Similar results were reported by Virani [110] for permeability of oxcarbazepine. Among publications that report TRC helps enhance or modulate drug permeation from microemulsions, a noteworthy example involves imiquimod, an immunostimulant used in the treatment of neoplastic skin diseases [58]. Imiquimod is poorly absorbed by the skin and is very poorly soluble. Following screening of solubilizers and based on results of skin uptake experiments, Telo [58] established that imiquimod accumulation in the skin is correlated with skin solvent uptake. Aiming to increase the retention of imiquimod in the skin, an optimized microemulsion consisting of 10% OA, 35% TRC, 35% PS80 and 20% water was developed. This optimized preparation helped accumulate the same amount of drug as the commercial formulation but with much greater efficiency at 12 times lower quantity of imiquimod in the dose.

In the case of aceclofenac, a non-steroidal anti-inflammatory drug, the drawbacks are very poor oral bioavailability (first pass elimination) and adverse effects. With MW of 354.2 Da and high LogP (4–5), it could be a candidate for transdermal delivery. An optimized O/W nanoemulsion (NE1) with an average droplet size of 35 nm was identified as the best performing combination for aceclofenac determined by IVPT and *in vivo* paw edema model in rats [122]. In a subsequent study [123] NE1 and its gelled version, NE1 Gel (Fig. 13a) were subjected to *in vivo* study in rats, against an orally administered tablet dose of aceclofenac. The pharmacokinetic profile obtained for both formulations was significantly higher than the orally administered aceclofenac tablet (Fig. 13b), representing bioavailability enhancements of 295% and 260% as well as a delayed Cmax for the nanoemulsion F1 and F1-Gel respectively.

Summary

Passive diffusion across the SC is largely influenced by the properties of the permeant (the drug), the affinity of the drug for the skin, and the solubility/concentration relationship between the drug and its vehicle. In this context, the quintessential tool at the scientist's disposal is the vehicle or so called the drug delivery system, which is to be adapted to the properties of the drug and the treatment objectives. Incorporation of one or another type of skin penetration enhancer in the delivery system is an attractive proposition which has been extensively explored over the past decades. The search for an ideal enhancer has revealed hundreds of chemical entities that may not have pharmaceutical relevance. In the meantime, entities like terpenes, sulfoxides, and amides which strongly alter drug permeability across the skin can also damage the skin barrier function. In parallel, an improved knowledge of the skin's barrier function and the emergence of new analytical tools have helped develop consensus on far less invasive formulation strategies which combine two or more less invasive enhancers. Hydroxylated solvents are such an alternative. TRC for example is minimally engaged with the skin structures and manifests its effects by altering drug/formulation properties, including drug

a

	% Composition	
	NE 1	NE 1-Gel
Aceclofenac	2.00	2.00
Carbopol® 940	-	1.00
Labrafil® M1944	10.00	10.00
Triacetin	5.00	5.00
Tween® 80	35.33	35.33
Transcutol® P	17.66	17.66
Water	30.01	29.01

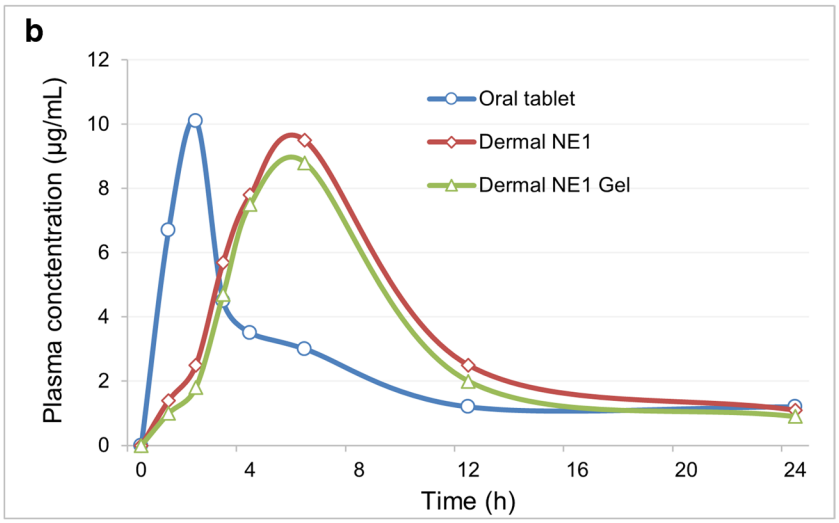

Fig. 13 **a** Composition of aceclofenac nanoemulsion E1 and its gelled version; **b** *In vivo* performance of aceclofenac nanoemulsion and its gel compared to a tablet form in Wistar rats. Shakeel 2009 [118], [122], [123]

solubilization in the dose, altering thermodynamic activity, and improved drug solubility in the skin. Other attributes discussed above were cosolvency, solvent mediated transfer or drag effect, and evaporation post application which impact the drug trajectory while crossing the skin structures.

On the formulation possibilities, the adaptability of TRC in hydrogels, cubic and lamellar mesophases, liposomal vesicles, and pH responsive nanoparticles were indicated. The ability of TRC to dissolve significant amounts of hydrophilic and lipophilic substances makes it suitable in hydrogels, anhydrous gels, and emulsions. When incorporated at high levels in emulsions it can lead to loss of emulsion viscosity (not stability) which is explained by its action as cosolvent, thus lowering both surface tension and formulation melting point. In such cases, emulsion viscosity may be adjusted with an appropriate consistency or gelling agent. For the same reasons, incorporation of TRC in in SLN or NLC would require characterization of the system entrapment efficiencies upon storage. Highlighted was also the critical role of TRC in microemulsions, a topic which deserves an in-depth review elsewhere. The distribution and retention of the drug in the SC, epidermis, or dermis is highly relevant to drugs that have very short half-life if administered orally. Examples emphasizing the significant potential for sustained delivery by the dermal route have been provided.

Overall, each component of a complex formulation can contribute to (modify) the rate and quantity of active substance being deposited into the various skin layers and/or crossing it for systemic absorption. Within the limitations of a drug's solubility and permeability, it is possible to modulate its release, retention, and permeation by capitalizing on the inverse relationship between solubility and permeability. This is because very high drug solubilization in the vehicle can translate to improved drug penetration or permeation only if the vehicle itself is capable of traversing the skin. The studies reviewed demonstrate that TRC is one such vehicle. Dilution with water or another excipient can help strike a balance between drug concentration in the vehicle relative

to its saturation solubility limit, and therefore its tendency to partition out of the vehicle.

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Declarations

Conflict of Interest The authors declare no direct competing interests.

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