Review of Pharmaceutical Applications of Diethylene Glycol Monoethyl Ether

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ABSTRACT - Diethylene glycol monoethyl ether (DEGME) is a hydroalcoholic solvent that gained tremendous attention in the cosmetics, food, nanoformulations, and pharmaceutical industries. Due to its physicochemical features, it has been widely used as a penetration enhancer, surfactant, and solubilizer. Among numerous tradenames defined for DEGME -- Carbitol® (by Dow Chemical Co., USA), and Transcutol® HP, CG, and P. (by Gattefossé Co., France) -- are known to be employed in pharmaceutical industries. Transcutol® CG is utilized only in cosmetics; however, Transcutol® P and Carbitol® are both used in various pharmaceutical topical dosage forms such as creams, gels, etc. Additionally, Transcutol® HP is used in all administration routes. In view of this, the application of DEGME is highlighted in the areas of industry and pharmaceutical sciences. Moreover, in this review the prominent characteristics, pharmacokinetics, and toxicity of DEGME are examined and it is suggested that DEGME is a promising solvent/solubilizer with comparable assignments to other conventional excipients.

INTRODUCTION

Diethylene glycol monoethyl ether (DEGME) is the primary alcohol derived from diethylene glycol (Figure 1). It is a protic solvent/solubilizer, also known as 2-(2-ethoxy ethoxy) ethanol, ethoxydiglycol, and under the trade names, Carbitol® (by Dow Chemical Co., USA), Dioxitol® (by Shell Chemicals, UK), Dowanol® DE (by Dow Chemical Co., USA), Ektasolve® DE (by Eastman Chemical Co., USA), Cellosolve® (by Union Carbide Co., USA), Transcutol® HP, CG, and P. (by Gattefossé Co., France) (1-3). DEGME has been approved by the United States Food and Drug Administration (FDA) for use as an excipient and cosolvent in pharmaceutical formulation and the food industry. It has been used in solutions, ointments, sprays, capsules, and creams to deliver poorly water soluble drugs (4, 5). DEGME is listed on the United States Pharmacopeia (USP 24-NF 19) and European Pharmacopeia (4th edition) monographs. This work aims to review the features, toxicity, and application of DEGME as an invaluable excipient in food, cosmetics, and pharmaceutical formulations. Since diethylene glycol monoethyl ether, Carbitol®, and Transcutol® are three commonly termed names for this substance used in industry and research, we used them as keywords to search the databases.

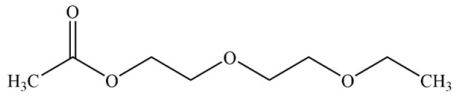

Figure 1. Diethylene Glycol Monoethyl Ether (DEGME)

PHYSICOCHEMICAL PROPERTIES

DEGME is a slightly viscous liquid that is miscible with most known cosolvents, surfactants, and oils in the liquid state. The physicochemical features of DEGME are listed in Table 1. DEGME can improve the solubility of various poorly water soluble drugs by playing the role of a surfactant (HLB 4.2) and solvent (5).

INDUSTRIAL AND PHARMACEUTICAL APPLICATIONS

DEGME is widely employed to deliver various classes of active pharmaceutical ingredients, e.g., hormones, anti-acne, antiinflammatory, anti-parasitic, anti-fungal, antiviral anesthetic, analgesic, antiseptic agents and immune suppressants (11, 12).

Table 1. Physicochemical Properties of DEGME

MP[1]	BP[2]	FP[3]	Solubility	Density	logP	ST[4] (dyn/cm)	Viscosity	VP[5]	MW
	(°F)		(g/L)	(g/cm^3)			(cPs)	(mm Hg)	(g/mol)
	(6)		(at 20 °C) (6)	(at 20 °C) (7)	(8)	(at 25 °C) (9)		(at 25 °C) (6)	(10)
-108	396	205	≥100	0.99	-0.54	31.8	3.85	0.13	134.17

[1]Melting Point, [2]Boiling Point, [3]Flash Point, [4]Surface Tension, and [5]Vapor Pressure

The first topical FDA-approved drug containing DEGME was ACZONE, the 5% dapsone (13). Carbitol® is another one of the known DEGME products that has made its way into the pharmaceutical industry. Various pharmaceutical topical dosage forms use Carbitol® as an excipient, including creams, gels, and other transdermal formulations (3). Moreover, four available products of DEGME manufactured by Gattefossé have been extensively used in pharmaceutical and nutraceutical products. They include Transcutol® highest-purity (HP), Transcutol® veterinary (V), Transcutol CG®, and Transcutol P®. DEGME acts as a strong solvent/solubilizer (due to its solubilizing ability compared to common solvents (propylene glycol, ethanol, etc.)) and as a penetration/permeation enhancer at non-toxic concentrations in these products (1). The differences between Transcutol® HP, V, CG, and P are defined by the level of impurities (impurities such as ethylene glycol (EG)). While Transcutol® P and HP have purity levels over 99.7% and 99.9%, respectively, EG concentration is less than 620 ppm in Transcutol® CG. Furthermore, Transcutol® V is an excipient used in livestock farming products. So, there is no reported maximum residual limit for DEGME in those products (3).

DEGME (as Transcutol® HP) is mainly a bioavailability enhancer for oral formulations such as lipid formulation classification system, type III and IV. Type III includes a self-micro emulsifying drug delivery system (SMEDDS), and type IV refers to micellar solutions (12). Moreover, DEGME (as Transcutol® HP) is used as a drug carrier in nasal and ophthalmic products. Besides, it has been developed to be used in the soft and hard capsule-filling processes. Lysanxiam, Pilosuryl, Natispray as oral products, and sodium diclofenac as injectable products are some of their reported applications in the pharmaceutical industry (11). DEGME (as Transcutol® V) has been used in oral (liquid and paste), transdermal (spot-on and pour-on solution, drops), and parenteral veterinary medicines. It has been stated as a penetration enhancer for topical formulations and a carrier in topical, parenteral, and auricular veterinary formulations (12). Tolfedine and vitamin E are two injectable products with DEGME as excipients (4). DEGME (as Transcutol® CG) is primarily used in cosmetics as a solubilizer and efficacy booster. The self-care products, including DEGME (as Transcutol® CG), are conditioners, hair dyes, anti-acne preparations, self-tanning products, antiperspirants, and soaps. DEGME (as Transcutol® P) is a solvent/solubilizer in topical dosage forms associated with skin penetration enhancement, such as topical gel, emulgel, emulsion, foam, microemulsion, and ointment (12).

DEGME IN DRUG DELIVERY SYSTEMS

Numerous pieces of literature investigate the application of DEGME in various drug delivery systems. Mangla *et al.* elucidated the effect of DEGME (as Transcutol® HP) in the formulation of tamoxifen and sulforaphane loaded into nanostructured lipid vehicles. Their results indicated that Transcutol® HP, as a liquid lipid and solubilizer with a negative log P, did not cause any toxicity in the heart, liver, kidney, or spleen. Besides, developed particles had better stability and efficiency than free drugs (14). Furthermore, Špaglová *et al.* investigated the solubility and improved penetration ability of DEGME in a topical indomethacin formulation. They indicated that DEGME is a potent solubility and penetration enhancer; however, the mechanism of its action could not be considered during *in-vitro* liberation studies (15).

Moreover, Lopez *et al*. considered the effect of ethanol, isopropyl alcohol, methanol, and DEGME on liposome features such as size, size distribution, and zeta potential. Their results imply that the average size of liposomes depends on the polarity of the solvent. They also stated that zeta potential changes are possibly independent of the organic solvent used, production temperature, and lipid concentration. As well they revealed that performing DEGME in comparison with ethanol leads to smaller liposome sizes and more content uniform particles even under various temperatures and lipid concentration conditions. Besides, they introduced DEGME as a potent replacement for conventional

alcohol-based solvents, which could be used without filtration steps (16).

Sahu and his colleagues developed capecitabine loaded in chitosan nanogel and considered their toxicity and penetration potential. DEGME was examined as a non-ionic penetration enhancer in this article. The optimum concentration, which leads to better penetration and diffusion, is reported to be 24% v/v (17). Abdel-Hafez *et al.* developed curcumin-loaded nanovesicles using DEGME as a penetration enhancer. Their assessment delineated the enhancing transdermal flux rate of DEGME. Oleic acid was superior to DEGME in the surging penetration issue (18). Hernandez *et al.* revealed an inverse relationship between the interfacial tension and the concentration of DEGME (as Transcutol® P), due to a surge in the miscibility of the oil and aqueous phases (19). Furthermore, Hosny and his colleagues established the features of isotretinoin-loaded nanoemulsions, which employed DEGME (as Transcutol®) as a cosurfactant. The results delineated higher hepatoprotective and improved permeation characteristics of developed nanoemulsions compared to free drugs and commercially marketed products (20).

Pitzanti *et al.* investigated the solid lipid nanoparticles for enhancing the skin permeation of 8-methoxy psoralen performing DEGME (as Transcutol® P). Their results indicated that the higher concentration of Transcutol P® could lead to the higher skin accumulation of 8-methoxy psoralen and cellular uptake of solid lipid nanoparticles. At the same time, it did not enhance their cytotoxicity on fibroblasts (21).

Zhang *et al.* developed a transdermal drug vehicle with DEGME (as Transcutol® P)/Cremophor®EL/ethyl oleate–formulated microemulsion loaded into the hyaluronic hydrogel to deliver ibuprofen. Their results revealed no significant difference in the rheology of the engineered system at skin surface temperature (25 °C and 32 °C) and higher drug transdermal flux and cumulative drug permeation compared to standard delivery systems. Based on their data, the DEGME effectively enhanced the transdermal permeation of ibuprofen in this drug delivery system (22).

Loo *et al.* prepared lyotropic liquid crystalline nanoparticles to improve Berberine's solubility and bioavailability profile. Their results indicated that the formulations with polyethylene glycol-400 and DEGME (as Transcutol® HP) had lower IC_{50} concentrations than free Berberine. Moreover, lyotropic liquid crystalline nanoparticles with DEGME exhibited higher cellular uptake (23). Singh *et al.* used microemulsion preconcentrates to enhance Canagliflozin's solubility and oral bioavailability. They denoted that the optimized preconcentrates formulation, including Lauroglycol FCC, Tween 80, and DEGME (as Transcutol® P), had increased *in-vivo* drug absorption, *in-vitro* dissolution rate, and drug release (24).

Venkatesan *et al.* considered cationic (water/DEGME/lecithin/M−812) green nanoemulsion to alter oxytetracycline's solubility and remove it from water. Their results represented the efficiency of DEGME formulation in decontaminating anionic oxytetracycline-in wastewater (25). Furthermore, Alghananim *et al.* developed a solid self-nano emulsifying carrier to deliver deferasirox. To improve the solubility of the system, Peceol, Kolliphor EL, and DEGME were selected as excipients. The results denoted that the developed formulation could improve the solubility and oral bioavailability profile of deferasirox (26). Shradha *et al.* reported that a porous silica-based lipid-solid formulation could lead to enhanced solubility and the dissolution rate of the nateglinide. They are used as Labrasol® and DEGME (as Transcutol® HP) as surfactants in silica lipid hybrid particles (27). Al-Tamimi *et al.* investigated a SMEDDS of tacrolimus to increase its oral bioavailability, dispersibility, and dissolution rate. DEGME was performed as a co-surfactant in this formulation. Results demonstrated enhanced *in-vitro* drug release profiles compared with pure tacrolimus (28). Besides, to improve the oral bioavailability of candesartan cilexetil, Raghuveer *et al.* investigated a self-nano-emulsifying drug delivery system. DEGME was used as a co-surfactant in the formulation of nanoemulsion. Based on the results, optimized formulations containing DEGME 64%w/w indicated an enhanced dissolution profile compared to that of the pure drug (29).

SOLUBILITY STUDIES

Ha *et al.* comprehensively reviewed the application of DEGME in improving the solubility of poorly water-soluble drugs. They indicated in their literature that, up to 2019, DEGME was utilized to enhance the solubility of 61 drugs (5). To include literature since 2019, with regards to DEGME application, we listed the drug solubility data at various temperatures in Table 2.

The following Equation 1 is an example of a generally trained version of the Jouyban-Acree

model for predicting drug solubility in DEGME and water combinations at different temperatures:

$$\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + \left(\frac{f_1 f_2}{T}\right)\left[792.4 - 1510.6(f_1 - f_2) + 1395.0(f_1 - f_2)^2\right] \quad (1)$$

where $X_{m,T}$, $X_{1,T}$, and $X_{2,T}$ denoted the mole fraction solubility of the solute in the solvent mixture, solvents 1 and 2 at temperature (T, K), respectively. Besides, f_1 and f_2 referred to the solute-free fractions of solvents 1 and 2. In this equation, the solute-solvent interactions for all investigated drugs are assumed equal and provide a relatively large prediction error (52). Furthermore, the trained model performing Abraham solute parameters is expressed as the Equation 2 below:

$$\begin{aligned}\log X_{m,T} = {} & f_1 \log X_{1,T} + f_2 \log X_{2,T} \\ & + \left(\frac{f_1 f_2}{T}\right)\left[-2789 - 2846E + 227S + 4033A + 6963B + 376V - 4146A \cdot B\right] \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)}{T}\right)\left[5691 - 5369E - 910S - 8789A + 15519B + 9140A \cdot B\right] \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)^2}{T}\right)\left[3444 - 5096E - 1880S + 5505A + 15745B - 8095A \cdot B\right]\end{aligned} \quad (2)$$

where E stands for the excess molar refraction, S denotes dipolarity/polarizability of the solute, A implies the solute's hydrogen-bond acidity, B conveys the solute's hydrogen bond basicity, and V expresses the McGowan volume of the solute. Based on the results of this study, the trained models were proficient in demonstrating the solubility of a drug in the mono-solvents and binary solvent mixtures of drugs in DEGME and water at various temperatures. As well, the log P value and the Abraham solvation parameters of the drug could be calculated using these models (54).

Romdhani *et al.* investigated the preferential solvation of trans-resveratrol in mixtures at various temperatures. Employing DEGME as a cosolvent led to higher solvation of trans-resveratrol in the mixtures with composition $0.14 < f_1 < 1.00$. They indicated the acid behavior of trans-resveratrol and the breaking of the ordered structure of water in front of DEGME molecules as a reason for this issue (55). Argade *et al.* analyzed the dissolution, permeation, and solubility of candesartan cilexetil byusing DEGME (as Transcutol® HP) as a solvent, Neusilin US2 as a carrier, and Aerosil as a coating substantial. The results indicated the improved features of the developed liquisolid compact tablet (32).

Delongeas *et al.* evaluated the effect of Labrasol®/Labrafil®/ DEGME (as Transcutol®) in delivering poorly water soluble drugs in Wistar rats. DEGME was used as a bioavailability enhancer and solubilizer absorption promoter. Their results denoted that Labrasol®/Labrafil®/Transcutol® with the ratio of 4/4/2, v/v/v at a 5 mL/kg/day dosing volume could reduce feed intake, as well as increase kidney and liver damage (56). Grepioni *et al.* indicated that using DEGME for the crystallization of rifaximin would lead to higher solubility and storage stability (31). Furthermore, Makoni *et al.* evaluated the miscibility of clarithromycin, efavirenz, minocycline hydrochloride, mometasone furoate, and didanosine with solid (Compritol®, Precirol®, Gelucire®, cetyl palmitate, stearic acid, Geleol™) and liquid (Labrafac® PG, DEGME (as Transcutol® HP), Capryol™ 90, Lauroglycol® FCC) lipid excipients for the production of solid lipid nanoparticles and nanostructured lipid carriers. They denoted that the Hansen solubility parameters approach is valid for lipid screening (57).

MECHANISMS OF DEGME AS EXCIPIENTS

Osborne *et al.* reviewed various articles to investigate the mechanism of DEGME in skin penetration and permeation. They revealed that the efficiency of DEGME as a solubilizer /penetration enhancer depends on its performed concentration alone or in combination with other excipients (58). DEGME can easily penetrate the stratum corneum and interact strongly with water through the intercellular route. This DEGME /water interaction may alter the stratum corneum barrier in a number of ways. As DEGME penetrates the stratum corneum, it changes the molecular mobility of proteins and lipids in the stratum corneum and decreases the skin's barrier function. Furthermore, transdermal penetration of DEGME increases drug solubility in the stratum corneum and reduces the skin barrier for active ingredients. Additionally, it increases the retention of the stratum corneum for non-permeable active ingredients (58).

PHARMACOKINETIC PROPERTIES AND TOXICITY

The US-FDA's Inactive Ingredients Database dated January 2022 (61), states that DEGME should be used less than 50% topically and up to 5% transdermal. Moreover, Gattefossé Corporation, as a manufacturer, advocates a limit of 20 mg/kg for

Table 2. Drugs with reported solubility data in DEGME as a solvent at various temperatures

Drug	Temperature (K)	Solvents	Ref.
Trans-resveratrol	288.2 – 313.2	DEGME (as Transcutol® HP) + water mixtures	(30)
Rifaximin	–	Solid-state solvation with DEGME	(31)
Candesartan cilexetil	–	Neusilin US2, Aerosil 200 and DEGME (as Transcutol® HP)	(32)
6-Phenyl-pyridazin-3(2H)-one	298.2 – 318.2	Dimethy sulfoxide, polyethylene glycol-400, DEGME, ethyl acetate, 2-butanol, 1-butanol, propylene glycol, isopropyl alcohol, ethylene glycol, ethanol, methanol, and water	(33)
Gemfibrozil	298.2 – 318.2	Water, methanol, ethanol, isopropanol, 1-butanol, 2-butanol, ethylene glycol, propylene glycol, polyethylene glycol-400, ethyl acetate, dimethyl sulfoxide, and DEGME	(34)
Osimertinib	298.2 – 318.2	Water, ethanol, propylene glycol, ethyl acetate, isopropyl myristate, dichloromethane, DEGME (as Transcutol® HP), and polyethylene glycol-400	(35)
Sunitinib malate	298.2 – 318.2	Ethanol, isopropanol, ethylene glycol, propylene glycol, polyethylene glycol-400, DEGME (as Transcutol® HP), water, and various DEGME (as Transcutol® HP) + water mixtures	(36)
Apremilast	298.2	DEGME + water mixtures	(37)
Delafloxacin	298.2 – 318.2	Water, ethanol, DEGME (as Transcutol® HP), and three different alkyl imidazolium-based ionic liquids	(38)
Piperine	298.2 – 318.2	DEGME + water mixtures	(39)
Gefitinib	298.2 – 318.2	Methanol, ethanol, isopropanol, 1-butanol, 2-butanol, ethylene glycol, propylene glycol, polyethylene glycol-400, dimethyl sulfoxide, and DEGME (as Transcutol® HP)	(40)
Ketoconazole	293.2 – 313.2	Carbitol® + water mixtures	(41)
c-Met Inhibitor (ABN401)	298.2 – 318.2	Mono solvents (Transcutol HP®, acetone, 1-butanol, 1-propanol, 2-butanol, ethyl acetate, acetonitrile, 2-propanol, ethanol, methanol, water) and DEGME (as Transcutol® HP) water mixture	(42)
Rifampicin	298.2 – 318.2	Permeation enhancers such as surfactants [Span 80, DEGME (as Transcutol® HP), and triacetin], lipids [limonene, isopropyl myristate, and eugenol], and organic solvents [ethanol, 2-butanol, isopropyl alcohol, and ethyl acetate	(43)
6-Phenyl-4,5-dihydropyridazin-3(2H)-one	293.2 – 313.2	Aqueous mixtures of DEGME and PEG 400	(44)
Gliclazide	–	DEGME + water mixtures	(45)
Delafloxacin	298.2 – 318.2	DEGME (as Transcutol® HP) and 1-butyl-3-methyl imidazolium hexafluorophosphate ionic liquid mixtures	(46)
Cinnarizine	293.2 – 313.2	DEGME (as Transcutol® P) + water mixtures	(47)
Sulphadiazine	278.2 – 313.2	DEGME (as Carbitol®) + water mixtures	(48)
6-Phenyl-pyridazin-3(2H)-one	298.2 – 318.2	Dimethyl sulfoxide, polyethylene glycol-400, DEGME, ethyl acetate, 2-butanol, 1-butanol, propylene glycol, isopropyl alcohol, ethylene glycol, ethanol, methanol, and water	(49)
Tadalafil	298.2 – 313.2	Aqueous mixtures of DEGME and PEG 400	(50)
Vinpocetine	298.2 – 323.2	Water, 1-butanol, dimethyl sulfoxide, ethyl acetate, ethylene glycol, ethanol, isopropyl alcohol, polyethylene glycol-400, polyethylene glycol, and DEGME	(51)
Temozolomide	323.2	Dimethyl sulfoxide, polyethylene glycol-400, DEGME, ethylene glycol, propylene glycol, water, ethyl acetate, ethanol, isopropyl alcohol, 1-butanol	(52)
Glibenclamide	293.2 – 323.2	Dimethyl sulfoxide, N-Methyl-2-pyrrolidone, 1,4-dioxane, polyethylene glycol-400, DEGME (as Transcutol® HP), water, and aqueous mixtures	(53)

dermal and 10 mg/kg for oral administration (12). In Europe, the Middle East, the USA, and Africa, there are no limits set for DEGME in over-the-counter pharmaceutical products. However, in Japan, DEGME is endorsed for use in quasi-drug components. DEGME (as Transcutol® CG) has been accepted at a maximum concentration of 2.6% in cosmetic products such as spray products, fine fragrances, hair sprays, and antiperspirants/deodorants. The other application and its restricted levels are reported to be: 10% in rinse-off products, 7.0% in oxidative, and 5% in non-oxidative hair dye formulations (3, 11).In Australia, DEGME is approved as an active ingredient for prescription medicines, as an excipient in devices, and may be used in listed medications (OTC and prescription) for export purposes (11).

Furthermore, in rats and mice, the LD_{50} for intraperitoneal DEGME (as Carbitol®) was 5.39 mL/kg. For *Saccharomyces cerevisiae* and *Salmonella typhimurium*, the Ames test proved only very slightly mutagenic. According to reports,

DEGME (as Carbitol®) causes congenital disabilities in mice and rats. DEGME (as Carbitol®) can also cause dermatitis with both immediate and delayed hypersensitivity when applied topically (59).

The Consumer Safety Science Commission noticed that to avoid consumer exposure to high doses of EG, it is necessary to lower the level of this toxic contaminant up to ≤ 0.1%. Utilizing DEGME in oral hygiene and eye care products has not been given in depth evaluation (3).

The uptake, distribution, and excretion of DEGME has been examined in two strains of rats after single oral or intravenous doses of 20 mg/kgof labelled compound. Over 90% of the radioactivity is shown to be rapidly excreted in the urine in 24 h. As expected, the maximum systemic concentration, is found after intravenous injection. The half-life of DEGME in plasma is about 37-84 hours (12). Several toxicological reports have inferred the safe use and low irritation by DEGME in approved pharmaceutical and veterinary products (11, 12). The toxicity of DEGME is evaluated from 1974 through 2007 (11). Toxicokinetics, local tissue tolerance (skin, eye, intravenous, and mucosal irritation), sensitization, hemocompatibility, parenteral irritation, acute toxicity studies, repeat-dose toxicity studies, genotoxicity studies, reproductive, developmental toxicity, and carcinogenicity of DEGME has been assessed (12).

Panchal *et al.* determined the *in-vitro*, *ex-vivo*, and *in-vivo* evaluations for their engineered DEGME (as Transcutol® P) free aqueous intramuscular injectable formulation of diclofenac. They reported improved properties of diclofenac sodium when administered in vitamin E TPGS. (60).

CONCLUSIONS

DEGME is one of the predominant solvents, especially in cosmetic products. In addition, it is recognized as a penetration and permeation enhancer with favorable safety profile and versatility. Even though DEGME is considered non-genotoxic/mutagenic in humans by the Scientific Europan Committee, the data on the pharmacokinetics, teratogenicity, mutagenicity, and toxicity of this solvent in human subjects are scarce.

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CONFLICT OF INTEREST. The authors report there are no competing interests to declare.

REFERENCES

1. Osborne DW. Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products. Journal of Cosmetic Dermatology. 2011; 10 (4): 324-329. DOI:10.1111/j.1473-2165.2011.00590.x
2. Javadzadeh Y, Adibkia K, Hamishekar H. Transcutol® (diethylene glycol monoethyl ether): A potential penetration enhancer. Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement. 2015: 195-205. DOI:10.1007/978-3-662-47039-8_12
3. Ether DGM. Opinion on diethylene glycol monoethyl ether (degee). European Commission. 2013; DOI:10.2772/36098
4. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharmaceutical Research. 2004; 21 (2): 201-230. DOI:10.1023/b:pham.0000016235.32639.23
5. Ha E-S, Lee S-K, Choi DH, Jeong SH, Hwang S-J, Kim M-S. Application of diethylene glycol monoethyl ether in solubilization of poorly water-soluble drugs. Journal of Pharmaceutical Investigation. 2020; 50 (3): 231-250. DOI:10.1007/s40005-019-00454-y
6. National-Toxicology-Program. Institute of Environmental Health Sciences, National Institutes of Health (NTP). Chemical Repository Database 1992.
7. Guard UC. Chemical hazard response information system (CHRIS)-hazardous chemical data, Commandant Instruction 16465.12 C. Washington, DC: US government printing office, 1999.
8. Hansch C, Leo A, Hoekman D. Exploring QSAR.: Fundamentals and applications in chemistry and biology. Journal of the American Chemical Society. 1996; 56 (1): 78.
9. Pearce EM. Kirk-Othmer encyclopedia of chemical technology. Journal of Polymer Science: Polymer Letters Edition. 1978; 16 (5): 248. DOI:10.1002/pol.1978.130160508
10. Lifi M, Bazile JP, Muñoz-Rujas N, Galliero G, Aguilar F, Daridon JL. Density, viscosity, and derivative properties of diethylene glycol monoethyl ether under high pressure and temperature. Journal of Chemical Engineering Data 2021; 66 (3): 1457-1465. DOI:10.1021/acs.jced.0c01055
11. Sullivan Jr DW, Gad SC, Julien M. A review of the nonclinical safety of Transcutol®, a highly

purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient. Food and Chemical Toxicology. 2014; 72: 40-50. DOI:10.1016/j.fct.2014.06.028

12. Web site: https://www.gattefosse.com/pharmaceuticals-products/transcutol: Gattefossé Corporation 2022.
13. Seshadri V, Manohari P, Kunchithapatham J, Kulathingal J. Formulation and evaluation of dapsone topical gel, 7.5% w/w. World Journal of Pharmaceutical Research. 2018; 7(5): 1281-1299.
14. Mangla B, Neupane YR, Singh A, Kumar P, Shafi S, Kohli K. Lipid-nanopotentiated combinatorial delivery of tamoxifen and sulforaphane: ex vivo, in vivo and toxicity studies. Nanomedicine. 2020; 15 (26): 2563-2583. DOI:10.2217/nnm-2020-0277
15. Špaglová M, Čuchorová M, Šimunková V, Matúšová D, Čierna M, Starýchová L, et al. Possibilities of the microemulsion use as indomethacin solubilizer and its effect on in vitro and ex vivo drug permeation from dermal gels in comparison with Transcutol®. Drug Development and Industrial Pharmacy. 2020; 46 (9): 1468-1476. DOI:10.1080/03639045.2020.1802483
16. Lopez RR, de Rubinat PGF, Sánchez L-M, Tsering T, Alazzam A, Bergeron K-F, et al. The effect of different organic solvents in liposome properties produced in a periodic disturbance mixer: Transcutol®, a potential organic solvent replacement. Colloids and Surfaces B: Biointerfaces. 2021; 198: 111447. DOI:0.1016/j.colsurfb.2020.111447
17. Sahu P, Kashaw SK, Sau S, Kushwah V, Jain S, Agrawal RK, et al. pH triggered and charge attracted nanogel for simultaneous evaluation of penetration and toxicity against skin cancer: in-vitro and ex-vivo study. International Journal of Biological Macromolecules. 2019; 128: 740-751. DOI:10.1016/j.ijbiomac.2019.01.147
18. Abdel-Hafez SM, Hathout RM, Sammour OA. Curcumin-loaded ultradeformable nanovesicles as a potential delivery system for breast cancer therapy. Colloids and Surfaces B Biointerfaces. 2018; 167: 63-72. DOI:10.1016/j.colsurfb.2018.03.051
19. Hernandez C, Jain P, Sharma H, Lam S, Sonti S. Investigating the effect of Transcutol® on the physical properties of an O/W cream. Journal of Dispersion Science and Technology. 2020; 41 (4): 600-606. DOI:10.1080/01932691.2019.1609362
20. Hosny KM, Alhakamy NA, Al Nahyah KS. The relevance of nanotechnology, hepato-protective agents in reducing the toxicity and augmenting the bioavailability of isotretinoin. Drug Delivery. 2021; 28 (1): 123-133. DOI:10.1080/10717544.2020.1862365
21. Pitzanti G, Rosa A, Nieddu M, Valenti D, Pireddu R, Lai F, et al. Transcutol® P containing SLNs for improving 8-methoxypsoralen skin delivery. Pharmaceutics. 2020; 12 (10): 973. DOI:10.3390/pharmaceutics12100973
22. Zhang Y, Zhang K, Wang Z, Hu H, Jing Q, Li Y, et al. Transcutol® P/Cremophor® EL/ethyl oleate–formulated microemulsion loaded into hyaluronic acid–based hydrogel for improved transdermal delivery and biosafety of ibuprofen. American Association of Pharmaceutical Scientists. 2020; 21 (1): 1-10. DOI:10.1208/s12249-019-1584-8
23. Loo YS, Madheswaran T, Rajendran R, Bose R. Encapsulation of berberine into liquid crystalline nanoparticles to enhance its solubility and anticancer activity in MCF7 human breast cancer cells. Journal of Drug Delivery Science and Technology. 2020; 57: 101756. DOI:10.1016/j.jddst.2020.101756
24. Singh D, Tiwary AK, Bedi N. Canagliflozin loaded SMEDDS: formulation optimization for improved solubility, permeability and pharmacokinetic performance. Journal of Pharmaceutical Investigation. 2019; 49 (1): 67-85. DOI:10.1007/s40005-018-0385-5
25. Venkatesan K, Haider N, Yusuf M, Hussain A, Afzal O, Yasmin S, et al. Water/ Transcutol®/lecithin/M-812 green cationic nanoemulsion to treat oxytetracycline contaminated aqueous bulk solution. Journal of Molecular Liquids. 2022: 119154. DOI:10.1016/j.molliq.2022.119154
26. Alghananim A, Ozalp Y, Mesut B, Serakinci N, Ozsoy Y, Gungor S. A solid ultra fine self-nanoemulsifying drug delivery system (S-SNEDDS) of deferasirox for improved solubility: optimization, characterization, and in vitro cytotoxicity studies. Pharmaceuticals. 2020; 13 (8): 162. DOI:10.3390/ph13080162
27. Shradha T, Shailesh W, Surendra G. Nateglinide silica lipidhybrid particles for improved solubility. Indian Drugs. 2020; 57 (6): 73-78. DOI:10.53879/id.57.06.12348
28. Hussien AA, Al-Tamimi DJ. Formulation and characterization of self-microemulsifying drug delivery system of tacrolimus. Iraqi Journal of Pharmaceutical Sciences. 2021; 30 (1): 91-100. DOI:10.31351/vol30iss1pp91-100

29. Raghuveer P, Rani AP. Self nano-emulsifying drug delivery system to enhance solubility and dissolution of candesartan cilexetil. International journal of Pharmaceutical Investigation. 2020; 10 (4): 506-511. DOI:10.5530/ijpi.2020.4.88
30. Ha E-S, Kuk D-H, Kim J-S, Kim M-S. Solubility of trans-resveratrol in Transcutol® HP+ water mixtures at different temperatures and its application to fabrication of nanosuspensions. Journal of Molecular Liquids. 2019; 281: 344-351. DOI:10.1016/j.molliq.2019.02.104
31. Grepioni F, Braga D, Chelazzi L, Shemchuk O, Maffei P, Sforzini A, et al. Improving solubility and storage stability of rifaximin via solid-state solvation with Transcutol®. CrystEngComm. 2019; 21 (35): 5278-5283. DOI:10.1039/c9ce00567f
32. Argade P, Patole VC, Pandit AP. Liquisolid compact tablet of candesartan cilexetil with enhanced solubility using Neusilin US2, Aerosil 200 and Transcutol HP. Indian Journal of Pharmaceutical Education and Research. 2019; 53 (3): 457-467. DOI:10.5530/ijper.53.3.78
33. Shakeel F, Imran M, Haq N, Alshehri S, Anwer MK. Synthesis, characterization and solubility determination of 6-Phenyl-pyridazin-3(2H)-one in different pharmaceutical solvents. Molecules. 2019; 24 (18): 3404. DOI:10.3390/molecules24183404
34. Kalam MA, Alshehri S, Alshamsan A, Alkholief M, Ali R, Shakeel F, et al. Solubility measurement, Hansen solubility parameters and solution thermodynamics of gemfibrozil in different pharmaceutically used solvents. Drug Development and Industrial Pharmacy. 2019; 45 (8): 1258-1264. DOI:10.1080/03639045.2019.1594884
35. Anwer MK, Mohammad M, Fatima F, Alshahrani SM, Aldawsari MF, Alalaiwe A, Al-Shdefat R, Shakeel F. Solubility, solution thermodynamics and molecular interactions of osimertinib in some pharmaceutically useful solvents. Journal of Molecular Liquids. 2019; 284: 53-58. DOI: 10.1016/j.molliq.2019.03.128
36. Alshehri S, Shakeel F. Solubility determination, various solubility parameters and solution thermodynamics of sunitinib malate in some cosolvents, water and various (Transcutol + water) mixtures. Journal of Molecular Liquids. 2020; 307: 112970. DOI:10.1016/j.molliq.2020.112970
37. Jouyban A, Acree Jr WE, Martínez F. Preferential solvation of apremilast in some (Transcutol®+ water) mixtures. Journal of Molecular Liquids. 2020; 316: 113905. DOI:10.1016/j.molliq.2020.113905
38. Anwer MK, Mohammad M, Khalil NY, Imam F, Ansari MJ, Aldawsari MF, et al. Solubility, thermodynamics and molecular interaction studies of delafloxacin in environmental friendly ionic liquids. Journal of Molecular Liquids. 2020; 305: 112854. DOI:10.1016/j.molliq.2020.112854
39. Shakeel F, Haq N, Alshehri S. Solubility data of the bioactive compound piperine in (Transcutol + water) mixtures: computational modeling, Hansen solubility parameters and mixing thermodynamic parameters. Molecules. 2020; 25 (12): 2743. DOI:10.3390/molecules25122743
40. Alanazi A, Alshehri S, Altamimi M, Shakeel F. Solubility determination and three dimensional Hansen solubility parameters of gefitinib in different organic solvents: Experimental and computational approaches. Journal of Molecular Liquids. 2020; 299: 112211. DOI:10.1016/j.molliq.2019.112211
41. Barzegar-Jalali M, Mazaher Haji Agha E, Adibkia K, Martinez F, Jouyban A. The solubility of ketoconazole in binary Carbitol + water mixtures at T = (293.2–313.2) K. Journal of Molecular Liquids. 2020; 297: 111756. DOI:10.1016/j.molliq.2019.111756
42. Ravi M, Julu T, Kim NA, Park KE, Jeong SH. Solubility determination of c-Met inhibitor in solvent mixtures and mathematical modeling to develop nanosuspension formulation. Molecules. 2021; 26 (2): 390. DOI:10.3390/molecules26020390
43. Hussain A, Altamimi MA, Alshehri S, Imam SS. Assessment of solubility and Hansen solubility parameters of rifampicin in various permeation enhancers: experimental and computational approach. Journal of Molecular Liquids. 2021; 328: 115432. DOI:10.1016/j.molliq.2021.115432
44. Alshehri S, Shakeel F, Alam P, Jouyban A, Martinez F. Solubility of 6-phenyl-4,5-dihydropyridazin-3(2H)-one in aqueous mixtures of Transcutol and PEG 400 revisited: Correlation and preferential solvation. Journal of Molecular Liquids. 2021; 344: 117728. DOI:10.1016/j.molliq.2021.117728
45. Jouyban A, Acree Jr WE, Martínez F. Dissolution thermodynamics and preferential solvation of gliclazide in (Transcutol®+ water) mixtures. Physics and Chemistry of Liquids. 2021; 59 (4): 607-621. DOI:10.1080/00319104.2020.1793336

46. Shakeel F, Anwer MK, Youssof AME, Haq N, Alanazi FK, Alsarra IA. Solubilization, Hansen solubility parameters, and thermodynamic studies of delafloxacin in (transcutol + 1-butyl-3-methyl imidazolium hexafluorophosphate) mixtures. Drug Development and Industrial Pharmacy. 2021; 47 (4): 654-662. DOI:10.1080/03639045.2021.1908338
47. Shakeel F, Kazi M, Alanazi FK, Alam P. Solubility of cinnarizine in (Transcutol + water) mixtures: determination, Hansen solubility parameters, correlation, and thermodynamics. Molecules. 2021; 26 (22): 7052. DOI:10.3390/molecules26227052
48. Osorio IP, Martínez F, Peña MÁ, Jouyban A, Acree Jr WE, Liquids Co. Solubility of sulphadiazine in some {Carbitol®(1)+ water (2)} mixtures: Determination, correlation, and preferential solvation. Physics and Chemistry of Liquids. 2021; 59 (6): 890-906. DOI:10.1080/00319104.2020.1858420
49. Shakeel F, Imran M, Haq N. Detailed study on synthesis, characterization and solubility determination of 6-phenyl-pyridazin-3 (2H)-one in different pharmaceutical solvents. Current Advances in Chemistry and Biochemistry. 2021; 2: 83-100. DOI:10.9734/bpi/cacb/v2/7337D
50. Shakeel F, Alshehri S, Ghoneim MM, Martinez F, Peña M, Jouyban A, et al. Solubility of tadalafil in aqueous mixtures of Transcutol® and PEG 400 revisited: correlation, thermodynamics and preferential solvation. Physics and Chemistry of Liquids. 2022: 1-17. DOI:10.1080/00319104.2022.2048385
51. Ahad A, Shakeel F, Raish M, Ahmad A, Bin Jardan YA, Al-Jenoobi FI, et al. Solubility and thermodynamic analysis of vinpocetine in various mono solvents at different temperatures. Journal of Thermal Analysis and Calorimetry. 2021; 147 (4): 3117-3126. DOI:10.1007/s10973-021-10757-8
52. Ahad A, Shakeel F, Raish M, Ahmad A, Bin Jardan YA, Al-Jenoobi FI, et al. Thermodynamic solubility profile of temozolomide in different commonly used pharmaceutical solvents. Molecules. 2022; 27 (4): 1437. DOI:10.3390/molecules27041437
53. Maharjan R, Jeong J, Bhujel R, Kim MS, Han HK, Kim NA, et al. Correlation of solubility thermodynamics of glibenclamide with recrystallization and in vitro release profile. Molecules. 2022; 27 (4): 1392. DOI:10.3390/molecules27041392
54. Khoubnasabjafari M, Shayanfar A, Martinez F, Acree Jr WE, Jouyban A. Generally trained models to predict solubility of drugs in Carbitol+ water mixtures at various temperatures. Journal of Molecular Liquids. 2016; 219: 435-438. DOI:10.1016/j.molliq.2016.03.043
55. Romdhani A, Osorio IP, Martínez F, Jouyban A, Acree Jr WE. Further calculations on the solubility of trans-resveratrol in (Transcutol®+ water) mixtures. Journal of Molecular Liquids. 2021; 330: 115645. DOI:10.1016/j.molliq.2021.115645
56. Delongeas JL, de Conchard GV, Beamonte A, Bertheux H, Spire C, Maisonneuve C, et al. Assessment of Labrasol/Labrafil/Transcutol (4/4/2, v/v/v) as a non-clinical vehicle for poorly water-soluble compounds after 4-week oral toxicity study in Wistar rats. Regulatory Toxicology and Pharmacology. 2010; 57 (2-3): 284-490. DOI:10.1016/j.yrtph.2010.03.008
57. Makoni PA, Ranchhod J, WaKasongo K, Khamanga SM, Walker RB. The use of quantitative analysis and Hansen solubility parameter predictions for the selection of excipients for lipid nanocarriers to be loaded with water soluble and insoluble compounds. Saudi Pharmaceutical Journal. 2020; 28 (3): 308-315. DOI:10.1016/j.jsps.2020.01.010
58. Osborne DW, Musakhanian J. Skin penetration and permeation properties of Transcutol®—neat or diluted mixtures. American Association of Pharmaceutical Scientists 2018; 19 (8): 3512-3533. DOI:10.1208/s12249-018-1196-8
59. Goldman MP, Guex J. Mechanism of action of sclerotherapy. Sclerotherapy, treatment of varicose vein and telangiectatic leg veins. 2017; 173-199. DOI:10.1016/B978-0-323-37726-3.00007-1
60. Panchal N, Kaur M, Tharmatt A, Thakur S, Jain SK. Development, characterization and evaluation of parenteral formulation of diclofenac sodium. American Association of Pharmaceutical Scientists. 2020; 21 (6): 219. DOI:10.1208/s12249-020-01729-6
61. https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download

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