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

<table>
<thead>
<tr>
<th>MP¹</th>
<th>BP²</th>
<th>FP³</th>
<th>Solubility (g/L)</th>
<th>Density (g/cm³)</th>
<th>log P</th>
<th>ST⁴ (dyn/cm)</th>
<th>Viscosity (cPs)</th>
<th>VP⁵ (mm Hg)</th>
<th>MW (g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-108</td>
<td>396</td>
<td>205</td>
<td>≥100 (at 20 °C) (6)</td>
<td>0.99 (at 20 °C) (7)</td>
<td>-0.54 (at 25 °C) (9)</td>
<td>31.8 (at 25 °C) (6)</td>
<td>3.85 (at 25 °C) (6)</td>
<td>0.13 (at 25 °C) (10)</td>
<td>134.17 (at 25 °C) (10)</td>
</tr>
</tbody>
</table>

¹Melting Point, ²Boiling Point, ³Flash Point, ⁴Surface Tension, and ⁵Vapor 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 Gatéfossé 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, Piloseryl, 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 capcitabine 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, Pecpel, 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-solvent 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-Acrease
model for predicting drug solubility in DEGME and water combinations at different temperatures:

\[
\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + \left( \frac{f_1 f_2}{T} \right) \left[ 92.4 - 1510.6(f_1 - f_2) + 1395(f_1 - f_2)^2 \right]
\]

(1)

where \(X_{m,T} \), \(X_{1,T} \), and \(X_{2,T} \) denote 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:

\[
\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + \left( \frac{f_1 f_2}{T} \right) + \left( \frac{f_1 f_2 (f_1 - f_2)}{T} \right) - \left( 2789 - 2846E + 2275 + 4033A + 6963B + 376W - 4146A \cdot B \right) + \left( f_1 f_2 (f_1 - f_2) \right) \left( 5691 - 5369E - 9105s - 8789A + 15519B + 9140A \cdot B \right) + \left( f_1 f_2 (f_1 - f_2) \right) \left( 3444 - 5096E - 1880S + 5505A + 15745B - 8095A \cdot B \right)
\]

(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 by using 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

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

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 LD₅₀ 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/kg of labelled compound. Over 90% of the radioactivity 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.

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