Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products

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Summary

Background The solvent diethylene glycol monoethyl ether (DEGEE) is currently used in over 500 cosmetic products and has enabled the formulation of a topical 5% dapsone gel for the treatment of acne. It is anticipated that this common cosmetic ingredient will be a component in numerous future prescription topical products approved for the US market. Dermatologists are already treating patients that apply products containing 5–40% of this solvent multiple times each day.

Aims To provide dermatologists a review of this solvent's safety and tolerance in addition to describing how it interacts with the stratum corneum, sebum, and resident microflora.

Methods To critically review technical and patent literature that provides insight into this novel solvent.

Results Diethylene glycol monoethyl ether when used in a 99.9+% pure pharmaceutical grade is safe and well tolerated. Up to half of the applied solvent crosses the skin's barrier and becomes systemic. For certain drug actives, this solvent provides for an intracutaneous depot. This solvent has not demonstrated any inherent antimicrobial properties but was found to be mildly inhibitory toward *Propionibacterium acnes*.

Conclusions This safe, well-tolerated solvent is already used in many cosmetics and will become an ingredient in an increasing number of prescription products. Its ability to modify the skin delivery of actives it is formulated with (or formulation components that are applied just shortly before or after) make it important for dermatologists to have an understanding of this emerging solvent.

Keywords: acne, barrier function, topical administration, drug delivery formulation

Introduction

Diethylene glycol monoethyl ether (DEGEE) is a liquid with a long history of use in cosmetic and over-the-counter topically applied products. DEGEE is the official United State Pharmacopeia name for this solvent, although cosmetic products list this ingredient on their labels as ethoxydiglycol in accordance with the International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Both official names refer to the pharmaceutical/cosmetic solvent having the trade name TRANSCUTOL. The first FDA-approved prescription drug product to contain DEGEE was 5% dapsone topical gel. Other prescription topical products that contain DEGEE either have been approved or are currently under development. It is anticipated that this excipient will be a component of a significant number of dermatology products approved in coming years. It is the goal of this review to: (i) summarize the established safety and

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tolerance data for DEGEE; (ii) introduce dermatologists to the properties of this solvent that makes it a preferred choice for dermatology products; and (iii) review what is known about how DEGEE interacts with the stratum corneum, sebum, and resident microflora.

Chemistry, nomenclature, and purity

With the molecular formula of $CH_3CH_2OCH_2CH_2OCH_2CH_2OH$ and a molar mass of 134.17, DEGEE is a solvent with many commercial applications that only relatively recently include use in topical products. The IUPAC name is 2-(2-ethoxyethoxy) ethanol [CAS Number 111-90-0] and has been used as an industrial solvent for many years under the trade names Carbitol, Dioxitol, Poly-solve DE, and Dowanal DE. DEGEE is compatible with alcohol, propylene glycol, and oleic acid, but is not mutually soluble with vegetable oils or mineral oil according to the TRANSCUTOL Technical Bruochure.[1] Atenolol, griseofulvin, clebopride, dexamethasone, and ivermectin are pharmaceutical actives listed as being successfully formulated using TRANSCUTOL.[1] It is important to note that the industrial grades of this solvent are contaminated with relatively high levels of ethylene glycol and diethylene glycol. Toxicology studies completed on DEGEE prior to the 1990s used material that was at best 98% pure, with many of the observed adverse effects being attributed to the toxicity of the ethylene glycol impurity. USP-NF grades of DEGEE for use in pharmaceutical products contain not more than 50 μg/g 2-methoxyethanol, not more than 160 μg/g 2-ethoxyethanol, not more than 620 μg/g ethylene glycol, and not more than 150 μg/g diethylene glycol.[2] To put these numbers in perspective 500 μg/g is the same as 500 ppm or 0.05 weight percent. Thus, pharmaceutical DEGEE has >99.9% purity. The primary supplier in the US for pharmaceutical grade DEGEE is Gattefosse using the trade name TRANSCUTOL-P.

Use of DEGEE in topically applied products

Diethylene glycol monoethyl ether is commonly used as a solvent for topical products, with pharmaceutical formulators taking advantage of its ability to modify skin penetration and the cosmetic industry using it to alter product rub-in and feel. The Environmental Working Group's ''Skin Deep'' cosmetic safety database (cosmeticsdatabase.com) listed 509 products that contain DEGEE when accessed during the summer 2011.[3] DEGEE has been a favorite excipient for formulators of sunless tanning products because it spreads easily without streaking. These products often contain high concentrations of DEGEE (20–40%) and can be applied frequently to large skin surface areas. DEGEE is also contained in a wide range of hair coloring products that are rinse-off applications. Although some of these products are known to be irritating, DEGEE itself is not considered the source of irritation. However, DEGEE by virtue of its solvent properties may promote the delivery of other excipients that are contained in the product that are irritating to the skin.

The Scientific Committee on Consumer Products (SCCP) issued an opinion on DEGEE in December 2006.[4] This opinion provides an excellent toxicological evaluation summary of DEGEE. Animal testing shows that DEGEE produces little repro- or hematotoxicity. Two negative *in vivo* mutagenicity studies and the structure of the substance caused the SCCP to not expect that DEGEE will have relevant mutagenic potential. A series of Gatteffosse reports cited in the SCCP review indicate that: (i) neat DEGEE dosed at 0.020 mL per about 50 mm^2 of human volunteer skin (occluded for 48 h) was well tolerated (n = 10); and (ii) use of Marzulli and Maibach's method with 24 adult volunteers concluded that no pathological irritation or sensitization reaction significant to a cutaneous intolerance was noted.

Although an adequate carcinogenicity study has not been published, a 40% DEGEE in water solution was orally administered to female rats for 92 weeks and male rats for 100 weeks as one of the control arms for the development of 5% dapsone topical gel.[5] DEGEE used at this concentration was found to not be carcinogenic. The 5% dapsone topical gel vehicle, which contained 25% DEGEE, was used as a control in a hairless mouse photocarcinogenicity study.[6] In this 52-week study, male and female albino hairless Crl:SKH1-hrBR mice were dosed topically with product or vehicle and then given a cumulative UV dose of 600 Robertson–Berger units (RBU) per week. A total of 400 RBU approximate one minimum erythema dose in previously untanned human skin. In this study, the 5% dapsone topical gel vehicle containing 25% DEGEE demonstrated tumor growth essentially identical to untreated control animals when both groups received 600 RBU/week. As all animals in this carcinogenicity model develop tumors from the UV exposure, the study showed that DEGEE does not cause an increase in the number of tumors, nor does it cause the tumors to develop sooner. The 5% dapsone topical gel vehicle also contains water, <1% carbopol 980 gelling agent, and 0.2% methyl paraben that is pH adjusted with NaOH.

The Scientific Committee on Consumer Products issued opinion on DEGEE[4] provided a detailed synopsis of three well-conducted *in vitro* studies on percutaneous

DEGEE absorption through excised human skin. Carbon-14 radiolabeled DEGEE was formulated at 5% and 10% DEGEE concentrations in a shampoo formulation, at 15% DEGEE in a hydro-alcoholic gel formulation, and at 2%, 5%, and 10% DEGEE in a Oil-in-Water (O/W) emulsion formulation. The shampoo formulation was applied to the skin for 30 min and then ''rinsed-off''. Twenty-four hours after initial application 21.6% of the applied dose had been absorbed (epidermis + dermis + receptor fluid) for the 5% DEGEE shampoo compared with 17.5% of the applied dose for the 10% DEGEE shampoo. The hydro-alcoholic gel was studied with and without occlusion. In two studies without occlusion 51.0% and 44.9% of the applied dose of DEGEE was absorbed, but only about 50% of the radioactivity was recovered. This was attributed to evaporation of radiolabeled DEGEE. When the hydroalcoholic gel was applied under occlusion, average recovery was 92% with 51.5% of the applied dose of DEGEE being absorbed. For the O/W emulsion, the studies completed without occlusion had about 50% total radioactivity recovery compared with about 90% recovery for the occluded samples. For the 2% emulsion, the percent of applied dose absorbed was 43.2% and 45.6% for the two experiments nonoccluded and 55.9% for the occluded study. For the 5% emulsion, results were 56.1% and 44.4% nonoccluded and 63.8% occluded compared with the 10% emulsion having percent of applied dose absorbed values of 50.4% and 51.6% nonoccluded and 56.4% occluded. As seen, a significant amount of the DEGEE applied to the skin becomes systemic. Fortunately, DEGEE's low systemic toxicity results in a margin of safety (MOS) score of 102 as calculated by the SCCP, where the MOS is the no-observed-adverse-effect level (NOAEL) divided by the systemic exposure dose (SED) following topical application. This MOS score means that dosing of the 2% DEGEE emulsified formulation will result in blood levels about 100 times lower than the blood level at which DEGEE first causes observable adverse effects. Although hair dyes and sunscreens may have MOS scores above 500,[7] the primary requirement for drugs is that the MOS be above one.[8]

Advantages of DEGEE as a solvent: the dapsone example

Although DEGEE was used in cosmetic and hair care products for a number of years, the first use of this solvent in a pharmaceutical product was 5% dapsone topical gel. A quick review of the history of 5% topical dapsone development demonstrates the advantages of DEGEE as a solvent for topical dermatological products. Dapsone has negligible water solubility and is generally poorly soluble in the oils and solvents that are established inactive ingredients in FDA-approved topical products. Dapsone does have reasonable alcohol and glycol solubility, but the addition of even small amounts of water results in the rapid and dramatic precipitation of the dissolved dapsone. Building upon recent formulation success,[9] the solubility of dapsone was tested in DEGEE and found to be remarkably high. More importantly, blends of water and DEGEE produced a solubility profile (Fig. 1) that could be exploited for the treatment of acne when formulating an active having both antimicrobial and anti-inflammatory properties.

The formulation strategy for how DEGEE might be an advantage in a formulation for the topical treatment of acne is described in US patents 5,863,560[10] and 6,060,085,[11] Ideally, a topical antimicrobial would be primarily delivered into the pilosebaceous unit, with only minimal active crossing of the skin barrier. Intact stratum corneum lines the upper third of the pilosebaceous unit, and it is into this upper third of the hair follicle that the sebaceous duct secretes sebum. Thus, a need exists for an acne treatment that maximizes antimicrobial drug levels in the upper third of the pilosebaceous unit. Additionally, when an anti-inflammatory agent is used to treat acne, it is important to increase the level of drug that will cross the intact stratum corneum lining the upper third of the pilosebaceous unit. By definition, inflammation is the response of the viable epidermis to irritants and sensitizers. To reduce the amount of inflammation, the active pharmaceutical must penetrate past the stratum corneum and

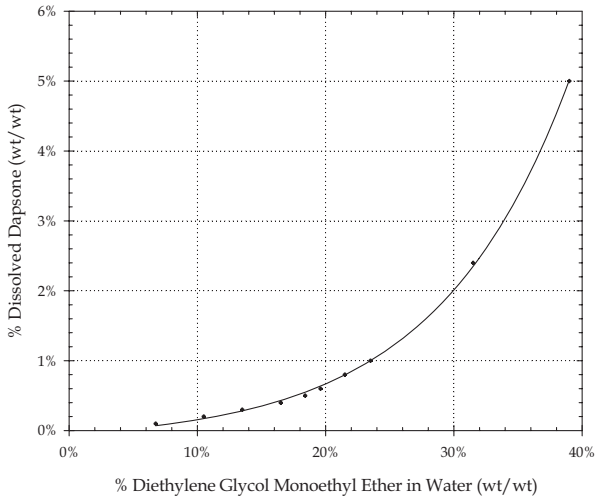

Figure 1 Dapsone solubility as a function of increasing percentage of diethylene glycol monoethyl ether (DEGEE) blended with water.

interfere with the cascade of inflammatory events. Ideally, delivery of an anti-inflammatory for acne requires that steady-state levels be sustained. By adjusting the ratio of dissolved dapsone to particulate dapsone, the amount of active crossing the epithelium (dissolved dapsone) to treat inflammation was optimized with regard to the amount of active agent targeted to remain within the follicle (particulate dapsone) to reduce the levels of *Propionibacterium acnes*. Although rigorous scientific proof of this optimization was not available in the mid-1990s, it is now well established that particles >10 nm in diameter will accumulate in the hair follicle openings, especially after rub-in.[12]

Thus, the use of a novel excipient, DEGEE, allowed optimization of the ratio of dissolved to particulate dapsone by carefully selecting the ratio of DEGEE and water. For the 5% dapsone gel, approximately one-third of the dapsone is dissolved and two-thirds of the dapsone is suspended as uniformly dispersed drug particulates. Despite a relatively high amount of dispersed dapsone, the product does not feel gritty during rub-in. This is partly because of the dapsone crystalline particulates inherently forming flat plates that tend to break apart during the shear of rubbing-in the product. The particle size is controlled and monitored throughout the shelf-life of the product. In addition, a third factor was found to significantly impact the feel of the product. Water is more volatile than DEGEE; thus, as the 5% dapsone topical gel is being applied, evaporation of water effectively increases the ratio of DEGEE to water. Increased DEGEE improves the solubility of dapsone, further reducing particle size as the product is being rubbed-in. Having the better solvent being less volatile avoids having the drug active precipitate on the surface of the skin, even at a 5% level of drug loading. For this reason, properly formulated aqueous DEGEE gels will not leave a visible drug residue on patients.

DEGEE as a skin penetration modifier

Many studies evaluating DEGEE as a skin penetration modifier have shown that DEGEE enhances a permeant's solubility in the skin without significantly influencing the diffusivity of the permeant in the skin, that is, stratum corneum.[13–16] For the permeants dexamethasone and hydrocortisone, the presence of DEGEE resulted in enhanced skin retention although the permeability and therefore the systemic uptake were significantly decreased.[17] This effect has been called the intracutaneous depot and can be conceptualized as DEGEE increasing the reservoir capacity of the stratum corneum. Thus, although DEGEE is a skin penetration modifier, it is not accurate to describe DEGEE as a skin penetration enhancer. Solvents such as ethanol and propylene glycol are penetration enhancers[18] that when used at sufficient concentrations increase the penetration of dissolved drugs. Although enhancement ranges from minimal to dramatic, use of these solvents universally enhances skin penetration. In contrast, DEGEE may increase penetration or it may significantly decrease systemic uptake of a dissolved drug. When formulating with DEGEE, it is difficult to predict how this solvent will modify skin penetration of drugs contained in the formulation.

A review of the literature on the effect of DEGEE on skin permeation[19,20] provides a number of *in-vitro* studies using excised animal skins and infinite dose applications (>5–8 $\mu L/cm^2$ of skin surface area) showing that DEGEE increases the amount of permeant that crosses the skin. These penetration enhancement factors often do not translate into meaningful increases in delivery when the product progresses into the clinic. *In vitro* infinite dose animal skin studies tend to bias high the enhancement factors for any solvent that can extract the lipids from the stratum corneum. As excess product resides for hours on the skin surface, skin lipids are extracted and the barrier properties of the skin are reduced by a mechanism that cannot occur when a clinically relevant dose of product is rubbed into the skin.

Does DEGEE have activity in the treatment of acne?

When the topical dapsone clinical trial results were first published,[21] the 40–42% reduction for inflammatory lesions for the vehicle seemed high, especially when compared to adapalene 0.1% cream in which one of the pivotal clinical trials reported only a 6% reduction in inflammatory lesions for the vehicle control group (17% reduction in inflammatory lesions for the active group).[22] The vehicle for topical dapsone is <1% carbomer, water, 25% DEGEE, and a standard amount of methyl paraben. Carbomer gels containing methyl paraben have been used for over 40 years in pharmaceutical and OTC products without any mention of activity in the treatment of acne. If the dapsone vehicle has activity in acne, it is likely that this activity will be linked to the 25% DEGEE in the formulation. To determine whether DEGEE has activity in acne, it is necessary to first compare the topical dapsone vehicle effect with other recently approved acne products. Is a 40–42% reduction in inflammatory lesions for a topical vehicle unexpectedly high? Next, data on the microbial

properties of DEGEE will be summarized, and finally the unique interaction between DEGEE and skin lipids will be discussed.

Does the ACZONE vehicle have activity in the treatment of acne? Based on package insert information for four recently approved acne products,[23–26] each of these product vehicles had percent reduction in inflammatory lesions at 40% or higher. The vehicle effect seen for ACZONE is not sufficiently different from other topical acne product vehicles to conclude that the ACZONE vehicle has activity in the treatment of acne.

Does DEGEE have antimicrobial activity against *P. acnes* and therefore have activity in the treatment of acne? Some of the solvents used to dissolve pharmaceutical actives have well-established antimicrobial activity, and formulators use this information to develop self-preserving products or products that have minimum levels of a single preservative. Most notable is benzoyl alcohol, which has been used as an inactive ingredient at concentrations as high as 50% in an FDA-approved topical gel.[27] Benzyl alcohol levels of 1–3% are adequate to fully preserve a topical product. Likewise, propylene glycol when used at concentrations around 20% is fully effective as a preservative for molds and yeast. When DEGEE was first selected as the solvent system for a topical dapsone gel, the potential preservative properties were thoroughly evaluated using the USP preservative efficacy test[28] in which gram-positive, gram-negative, molds, and yeasts are inoculated into the product to assure that bacterial colony-forming units are quickly reduced, while molds and yeasts are not allowed to propagate. DEGEE repeatedly showed inertness with regard to microbial growth. DEGEE did not provide any bacterialcidal, bacterialstatic, or microbial inhibition with regard to the USP test organisms. Likewise, using a time-kill assay against *P. acnes*, a 10% aqueous solution of DEGEE showed only a slight inhibitory effect at 48 and 72 h.[29] In summary, *in-vitro* microbiology testing does not indicate that DEGEE has significant antimicrobial activity.

Does the unique interaction between DEGEE and skin lipids lead to activity in the treatment of acne? Experimentally, this question is very difficult to answer. As described in the skin penetration modifier section aforementioned, DEGEE blends very well with lipids of the skin. Although the epidermal lipids filling the intercellular spaces of the stratum corneum are different from lipids of sebaceous origin;[30] from a penetration and blending with DEGEE perspective, skin surface lipids and epidermal lipids will both be very compatible with DEGEE. This ability of DEGEE to partition into and blend with skin lipids to change the physical properties of the lipids could impact the formation of acne lesions. DEGEE may fluidize the lipids and thus retard the formation of microcomedones. If DEGEE keeps the lipids from ''gluing together'' the desquamated keratinocytes, then the number of plugged follicles and subsequently the number of inflammatory lesions would be reduced. This would explain how a solvent known to partition into skin lipids could have activity in the treatment of acne. Although this mechanistic description is in agreement with the physical chemical properties of DEGEE, it is only speculation at this point.

Conclusion

Diethylene glycol monoethyl ether is a safe and well-tolerated solvent that has been an ingredient in cosmetic products for many years and in the last 5 years has become an FDA-approved inactive ingredient in prescription topical dermatology products. This molecule tends to penetrate the skin well with up to half of the applied concentration becoming systemic after topical application. The ability of DEGEE to dissolve active pharmaceutical ingredients not soluble in propylene glycol or alcohol make it a highly useful pharmaceutical excipient. DEGEE does not appear to possess significant antimicrobial properties, but may blend with skin lipids in a way that reduces microcomedone formation. Dermatologists will find that in the near future, this solvent will be a key component to many of the cosmetic and prescription products that their patients use on a daily basis.

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