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Karrie Marren

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Dimethyl Sulfoxide: An Effective Penetration Enhancer for Topical Administration of NSAIDs

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Karrie Marren, PharmD[1]

[1]Covidien, Hazelwood, MO

Abstract: Dimethyl sulfoxide (DMSO) is a molecule with a long history in pharmaceutics and is now well established as a penetration enhancer in topical pharmaceutical formulations. It is currently used for this purpose in diclofenac sodium topical solution (approved in the United States to treat signs and symptoms of osteoarthritis) and idoxuridine topical solution (approved in Europe for the treatment of herpes zoster). This article reviews the mechanism of action of DMSO as a pharmaceutical penetration enhancer, the characteristics of the molecule that facilitate transdermal drug delivery, and studies of efficacy and safety. The clinical use of pharmaceutical-grade DMSO as a penetration enhancer is supported by the robust data that have accumulated over the past 3 decades demonstrating the favorable safety and tolerability profile. Dimethyl sulfoxide is a safe and effective mechanism for facilitating the transdermal delivery of both hydrophilic and lipophilic medications to provide localized drug delivery.

Keywords: NSAIDs; dimethyl sulfoxide; DMSO; topical diclofenac; osteoarthritis

Introduction

Dimethyl sulfoxide (DMSO) is a molecule with a long history in pharmaceutics. It was first identified in the 19th century as a byproduct of the paper and wood industries, and has been widely used as an industrial solvent.[1,2] Its biological properties were first recognized in the 1960s;[3] since then, it has been extensively investigated both as a vehicle for drug delivery and as an active therapeutic agent. It was approved by the US Food and Drug Administration (FDA) in 1978 for the treatment of interstitial cystitis[1,2] and has been subsequently evaluated in conditions as diverse as musculoskeletal disorders,[4] traumatic brain edema,[5] and chronic prostatitis.[6] Higher concentrations have been reported to have anti-inflammatory actions when applied topically.[3,7] Although many of these putative clinical uses have remained controversial, DMSO has attained an established place as a penetration enhancer for topical pharmaceuticals, a vehicle for parenteral drug administration, and a cryopreservative for human cells, tissues, and cell- and tissue-based products. As a therapeutic agent, it is approved in the United States for the treatment of interstitial cystitis in humans, and has also been approved for veterinary use in dogs and horses. Dimethyl sulfoxide-containing products currently licensed for these indications in the United States and the European Union are listed in Table 1.[8]

Dimethyl sulfoxide is one of the earliest and most widely studied compounds to be used as a penetration enhancer in pharmaceuticals.[9] It serves as a mechanism for facilitating the transdermal delivery of medications to provide localized drug delivery. It is currently used for this purpose in diclofenac sodium topical solution (Pennsaid®; Mallinckrodt, Inc., Hazelwood, MO), a topical preparation approved in the United

Correspondence: Karrie Marren, PharmD,
Covidien,
675 McDonnell Blvd.,
Hazelwood, MO 63042.
Tel: 760-494-4748
E-mail: karrie.liuchan@covidien.com

States for treatment of signs and symptoms of osteoarthritis of the knee. Dimethyl sulfoxide is also used as a penetration enhancer in 5% idoxuridine topical solution (Herpid®; Astellas Pharma, Staines, United Kingdom), a preparation approved in Europe for the treatment of herpes zoster (Table 1).

Methods

This article reviews the use of DMSO as a pharmaceutical penetration enhancer. Cited papers were identified from MEDLINE (PubMed) searches covering the period 1975 to 2011 with keywords such as "dimethyl sulfoxide," "penetration enhancer," "efficacy," and "safety," obtained from the references of retrieved articles, and identified through the author's own knowledge. The final selection of material judged to be relevant to this article was the responsibility of the author.

Transdermal Drug Delivery

Advantages and Obstacles

Transdermal drug delivery offers a number of potential advantages over oral delivery, particularly for conditions such as osteoarthritis, in which the desired site of action is readily accessible through the skin.[10,11] In contrast to oral administration, the absorption of topical formulations is not affected by factors such as food intake or gastrointestinal pH and motility. Transdermal delivery also avoids first-pass metabolism in the intestinal mucosa and liver, which can significantly reduce the bioavailability of some drugs after oral administration. Topical formulations also offer the potential for more prolonged and controllable drug delivery than can be achieved with oral administration because transdermal delivery can be sustained for longer than the usual gastrointestinal transit time. For patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs), a further advantage of topical formulations is that effective drug concentrations can be delivered to the site of inflammation while systemic concentrations remain low. As a result, some of the well-documented adverse effects of NSAIDs, particularly gastrointestinal and cardiovascular adverse effects, may be reduced by topical therapy.[11–13] This in turn may decrease the need for concomitant medication, such as proton pump inhibitors. The potentially superior safety profile of topical NSAIDs compared with oral therapy is an important consideration because patients receiving NSAIDs are often elderly and may be at increased risk for gastrointestinal or cardiovascular adverse events. Transdermal delivery may also increase patients' adherence to therapy by avoiding the need for regular oral treatment and potentially improving tolerability.

However, a major obstacle to transdermal drug delivery is the highly efficient barrier function of human skin.[10,14] The outermost layer of the skin, the stratum corneum (Fig-

Table 1. Approved DMSO Products

Use	Brand Name	Formulation	Indication
Products Approved in the United States			
Parenteral products	RIMSO-50®	50% w/w DMSO	Symptomatic relief of interstitial cystitis
	Viadur®	104 mg DMSO, 72 mg leuprolide acetate solution	Treatment of prostate cancer
Drug devices	Onyx®	DMSO used as solubilizing excipient to deliver ethyl vinyl alcohol copolymer	Treatment of brain arteriovenous malformations
	Tegress™	DMSO used as solubilizing excipient to deliver ethyl vinyl alcohol copolymer	Urethral bulking agent
Penetration enhancer for topical preparations	Pennsaid®	Topical diclofenac preparation containing 45.5% w/w DMSO	Treatment of signs and symptoms of osteoarthritis of the knee
Cryopreservation	–	–	Cryoprotectant for human cells, tissues, and cellular and tissue-based products
	NucliSens® HIV-IQT		HIV test kit
Veterinary products	Domoso®	90% DMSO	Treatment of acute swelling in horses
	Synotic®	60% DMSO, 0.01% fluocinolide acetonide	Treatment of inflammatory conditions of the ear in dogs
Products Approved in the European Union			
Penetration enhancer for topical preparations	Herpid®	Idoxuridine 5% topical solution[a]	Treatment of herpes zoster
Parenteral products	Dolicur®[b]	50% w/w DMSO	Symptomatic relief of interstitial cystitis

[a]Also approved in Canada.
[b]Other proprietary brands approved for the treatment of interstitial cystitis include: Decap®, Deltan®, Demasorb®, Demavet®, Dimexide®, Dipirartril-tropico®, Doligur®, Dromisol®, Durasorb®, Gamasol 90®, Hyadur®, Infiltrina®, Kemsol®, Sclerosol®, Syntexan®, and Topsym®.
Data from *Pharm Tech*.[8]
Abbreviations: DMSO, dimethyl sulfoxide; HIV, human immunodeficiency virus.

ure 1A), is the principal barrier to penetration of exogenous materials such as drugs across the skin; by contrast, the viable epidermis and dermis offer little or no impediment to penetration.[10,14–16] The stratum corneum has an average thickness of approximately 10 μm, although it is much thicker (400–600 μm) on the palms of the hands and soles of the feet.[10] It consists of about 10 to 25 parallel layers of dead, keratinized cells known as corneocytes, which are embedded in an intercellular lipid matrix in a "bricks-and-mortar" arrangement.[10,14] This matrix consists predominantly of ceramides and cholesterol, which account for approximately 50% and 25%, respectively, of the total lipids, with smaller amounts of fatty acids (10%–15%), cholesterol sulfate (~5%), and cholesterol esters.[14] These lipids are arranged in lamellar structures, either as bilayers or as 3-layer structures consisting of a fluid inner layer surrounded by condensed outer layers.[14]

Because the stratum corneum comprises dead cells with no active transport capability, transport of substances across it is solely due to passive diffusion.[15] Drugs can penetrate the stratum corneum via 3 routes (Figure 1B).[10,15] The principal routes involve delivery through the interstitial spaces (intercellular penetration) or through the corneocytes themselves (transcellular penetration). Transappendageal transport, in which substances are transported along hair follicles, sebaceous glands, and sweat glands, is of minor importance for pharmaceutical delivery because these structures account for only 0.1% of the total skin area.[10,15]

Overcoming the Skin Barrier

Various techniques have been used in attempts to overcome the efficient barrier function of the skin to facilitate drug delivery through the stratum corneum. The most important of these has been the use of penetration enhancers such as DMSO, terpenes, fatty acids, alcohols, and water in attempt to increase the fluidity of stratum corneum lipids.[9,15] Ideally, such penetration enhancers should show a number of characteristics (Table 2).[9,15] They should be chemically stable and pharmacologically inert, nontoxic, nonirritant, nonsensitizing, and potent at low concentrations. Their action should be unidirectional (increasing the permeation of drugs across the skin without increasing loss of endogenous substances from the body), and barrier function should be readily restored following removal of the enhancer. Penetration enhancers should also be compatible with diverse topical formulations and cosmetically acceptable to the user. Although no single compound has been shown to display all of these characteristics, several (including DMSO) do show many of them.

Figure 1. A) Diagrammatic representation of the structure of human skin. The outer stratum corneum is the principal barrier to transdermal drug delivery. **B)** Routes of drug penetration through the stratum corneum. Pharmaceuticals are principally delivered via the transcellular and intercellular routes.

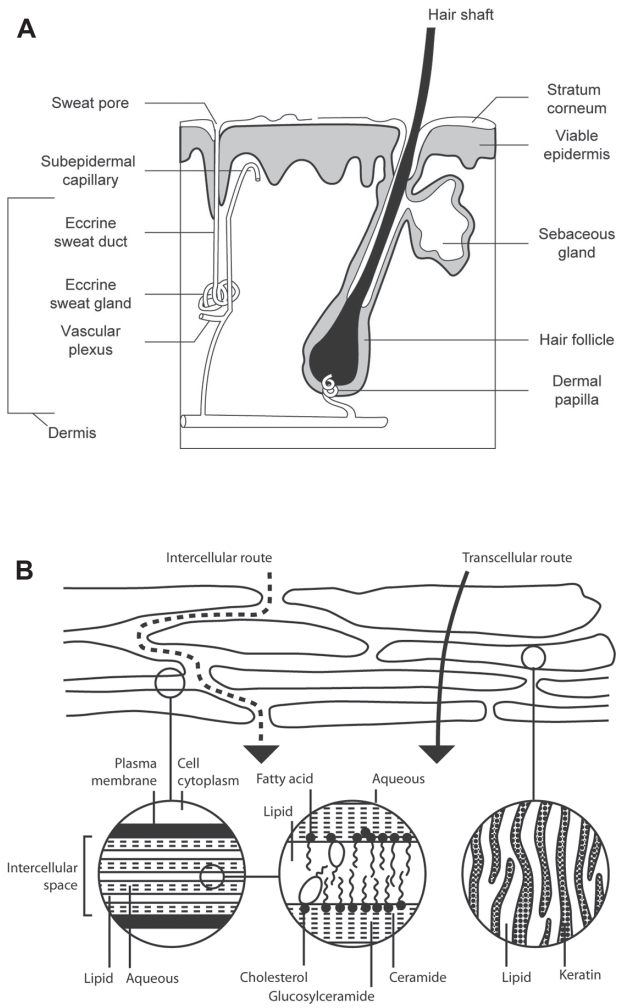


Figure 1A reproduced with permission from *Expert Opin Drug Deliv.*[15]
Figure 1B reproduced with permission from *Pharm Weekbl Sci.*[10]

DMSO as a Penetration Enhancer

Mechanism of Action

Penetration enhancement is a characteristic property of dipolar aprotic solvents (ie, solvents that cannot donate a hydrogen ion to substances dissolved in them), such as DMSO.[8] Dimethyl sulfoxide is a small amphiphilic molecule consisting of a hydrophilic sulfoxide group and 2 hydrophobic groups (Figure 2). This amphiphilic nature is central to the interactions between DMSO and cell membranes, and hence to DMSO's efficacy as a penetration enhancer.[17] Dimethyl sulfoxide is capable of enhancing the permeation of both hydrophobic and hydrophilic molecules across cell membranes.[9,18] This allows DMSO to facilitate the transdermal delivery of any medication that would not normally be able to cross the skin to provide localized drug delivery.

Table 2. Characteristics of an "Ideal" Penetration Enhancer

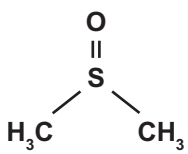
- Pharmacologically inert, chemically stable
- Potent at low concentrations
- Compatible with all formulation components, excipients, and drugs
- Nontoxic, nonsensitizing, nonirritant
- Unidirectional action (ie, enhancing drug penetration without causing loss of material from inside the body)
- Barrier function readily restored on removal of the enhancer
- Cosmetically acceptable, with good aesthetic appeal

Data from *Adv Drug Deliv Rev*[9] and *Pain*.[13]

Early pharmacokinetic studies showed that DMSO is readily absorbed after topical application, with peak serum concentrations attained within 4 to 8 hours.[19] Results of an in vitro study in living human skin showed that the permeability rate of DMSO was 176 g/m^2 per hour compared with 14.8 g/m^2 per hour for water.[20] The ability of compounds to permeate through the skin in this model was dependent on their molecular weight; butyl acetate (molecular weight, 116.16 d) was able to permeate through the skin, whereas no permeation was seen with octyl acetate (molecular weight, 172.27 d). Hence, small amphiphilic molecules such as DMSO would be expected to readily permeate through the skin.

Studies of the mechanism of action of DMSO have cast light on the interactions between DMSO and cell membranes. In an early study, phospholipid liposomes containing a fluorescent marker were incubated with various concentrations of DMSO at different temperatures, and leakage of the marker was monitored over time.[21] Leakage increased with both DMSO concentration and temperature; infrared spectroscopic analyses suggested that the increased leakage was due to a hydrophobic association between DMSO and the lipid bilayer of the liposomes, resulting in destabilization of the membrane.[21] Further evidence for an interaction between DMSO and cell membranes came from a radiograph diffraction study, which suggested that DMSO penetrates between the polar head groups of phospholipid molecules in liquid-crystal phosphatidylcholine bilayers, resulting in a progressive decrease in the thickness of the bilayer and an increase in the area occupied by phospholipids at the bilayer surface.[22] Another radiograph diffraction study suggested that DMSO displaces water from the surface of the lipid bilayer, thereby modifying the structure of the bilayer.[23] Penetration of DMSO molecules into the lipid/water interface of the membrane is accompanied by the loss of lateral interactions between the lipid head groups of bilayer. Effects such as thermal fluctuations cause the lipid/water interface of the bilayer to become prone to structural defects, resulting in pore formation (within a certain DMSO concentration range).[18]

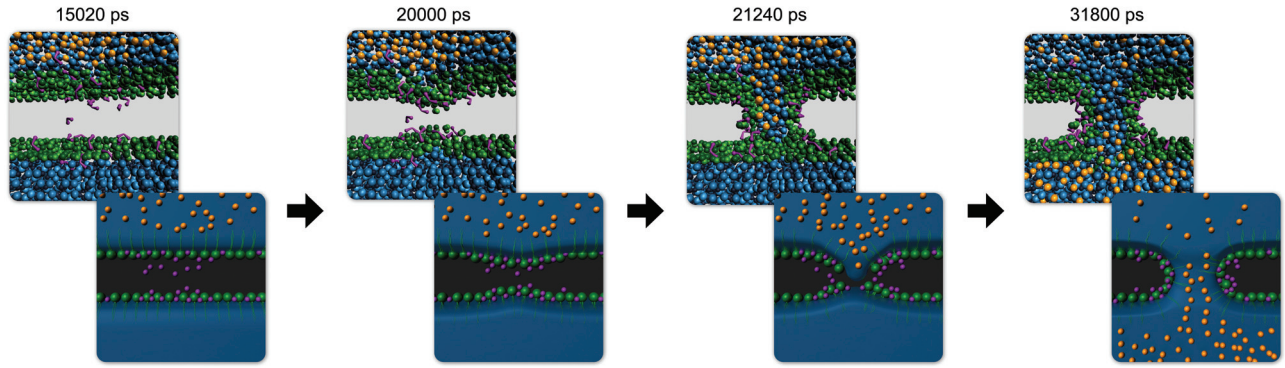
Figure 2. Chemical structure of dimethyl sulfoxide.



Further insights into the mechanism of action of DMSO as a penetration enhancer have come from molecular simulation studies of water/lipid/DMSO mixtures. One study, modeling the behavior of dipalmitoylphosphatidylcholine lipid bilayer/water systems in the presence of DMSO concentrations between 2 and 100 molar percentage,[24] showed that DMSO penetrates deeply into the lipid bilayer without interacting with the polar regions of the lipid head groups. Increasing concentrations of DMSO were associated with an increase in the area per head group, a finding consistent with the radiograph diffraction results described above.[22] This finding was attributed to DMSO penetrating the bilayer and remaining preferentially in the spaces immediately beneath the head groups.[24] Additional studies using "coarse-grained" simulations, in which a number of atoms are represented by a single particle, suggested that high concentrations of DMSO enhance permeability by increasing the fluidity of the lipids of the stratum corneum.[14,25] These studies showed that DMSO accumulates in the head group region and weakens the lateral forces between ceramide molecules (the largest fraction of stratum corneum lipids). At DMSO of $\geq$ 40 mol %, this results in a shift to a more fluid configuration of the lipid phase.[14] Together, these modeling studies suggest that DMSO enters the area just below the lipid head groups, pushing the head groups apart and thereby increasing the average area per head group. This causes the tail region of the membrane to become less dense so that the tails of neighboring lipids can expand into a larger volume.[25] The net result of these changes is an increase in the fluidity of cell membrane lipids.

Atomic-level simulations have shown that DMSO has 3 distinct effects on cell membranes, depending on its concentration.[17,18] At low concentrations (2.5–7.5 mol %), it induces expansion and thinning of the lipid bilayer, as described above, thereby increasing the fluidity of the hydrophobic region of the membrane. These concentrations are comparable with the 45.5% w/w (approximately 5.8 M) solution used in diclofenac topical solution and the 50% solution used in the treatment of interstitial cystitis. At higher concentrations (10–25 mol %), DMSO induces the formation of transient "water pores" in the cell membrane (Figure 3).[17,25] This appears to be a consequence of water entering the membrane as a result of the DMSO-

Figure 3. Pore formation in the lipid bilayer membranes of the skin after application of 10 mol % DMSO. Water is shown in blue, DMSO in purple, lipid head groups in green, and drug in yellow.



Adapted with permission from *J Phys Chem B*.[17]
Abbreviations: DMSO, dimethyl sulfoxide; ps, picoseconds.

induced increase in the fluidity of the bilayer. When sufficient water molecules enter the membrane, significant reorientation of the lipid head groups is necessary to minimize the free-energy of the system, which results in pore formation.[18] At the highest concentrations of DMSO (25–100 mol %), individual lipid molecules are extracted from the membrane, ultimately resulting in disintegration of the bilayer structure.[17]

Efficacy

The efficacy of DMSO as a penetration enhancer can be illustrated by the experience with diclofenac sodium topical solution (TDiclo), which contains a 45.5% w/w solution of purified DMSO (Procipient®; Gaylord Chemicals, Tuscaloosa, AL) (Table 1). An in vitro study in viable human skin compared the absorption of diclofenac from TDiclo with that of an aqueous topical solution.[26] After repeated dosing, TDiclo produced significantly higher absorption of diclofenac compared with the aqueous solution. Mean (SD) absorption was 10.2 (6.7) µg versus 8.3 (1.5) µg, respectively, at a dose of 2 µL/cm^2, and 26.2 (17.6) µg versus 12.5 (5.7) µg, respectively, at a dose of 5 µL/cm^2 (Figure 4). Absorption of diclofenac from TDiclo continued for ≥ 48 hours.

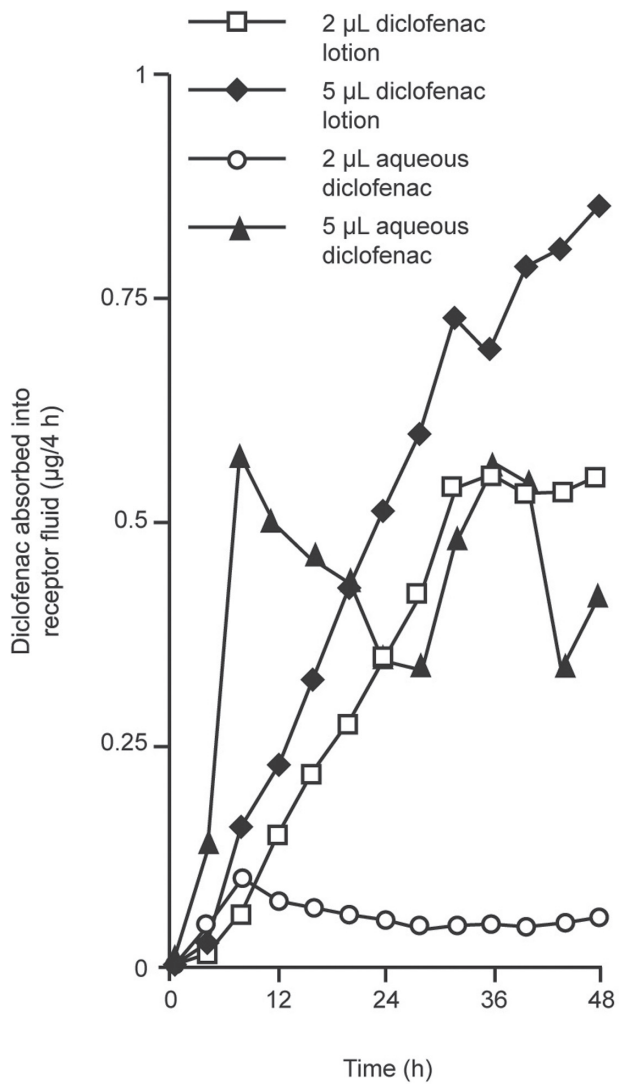
The effective transdermal delivery of diclofenac shown with TDiclo in vitro was also shown in a pharmacokinetic study in healthy volunteers who received a single application of TDiclo containing [^{14}C]-diclofenac on the knee for 24 hours.[27] Radioactivity was detectable in the blood within 1 hour after dosing, and peak concentrations of diclofenac were achieved after a mean (SD) of 30 (12) hours. Measurements of radioactivity in the urine suggested that absorption of diclofenac ceased only when the preparation was washed from the skin. Topical absorption was 6.6% of the applied dose; 26% of the dose was recovered from the skin surface after 24 hours, suggesting that the drug remained in contact with the skin throughout the dosing period. Randomized controlled clinical trials have shown that administration of diclofenac in DMSO results in effective symptom relief in patients with osteoarthritis of the knee.[12,13,28–30] In a comparative study with TDiclo and oral diclofenac, for example, there was no significant difference in efficacy between treatments with the 2 preparations, as measured by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function scores and patients' overall health assessments.[13]

Safety of DMSO

Although DMSO was first identified in the 19th century and has been widely available as an industrial solvent since the 1940s, the first trials of DMSO as a therapeutic agent were approved by the FDA in 1963.[1–3] However, investigation was subsequently suspended because of reports of changes in the refractive index of the eye in animals receiving high doses of industrial- or laboratory-grade DMSO (Table 3).[31] As data showing the favorable safety profile of DMSO accumulated over the next 2 decades, these restrictions were progressively relaxed, and clinical investigation of DMSO has not been specifically regulated by the FDA since 1980 (Table 3).[1,2]

A robust summary of DMSO toxicity data have been filed as part of the US Environmental Protection Agency's High Production Volume Challenge Program.[32] Dimethyl sulfoxide has shown low acute or chronic toxicity to animal, plant, or aquatic life.[32,33] Oral LD50 values (ie, doses resulting in 50% mortality rates) of between 4 and 29 g/kg after acute dosing have been reported in a variety of laboratory animals, including rodents, dogs, and primates.[33,34] Dimethyl sulfoxide is not listed as a carcinogen by regulatory agencies[8,33] and is neither mutagenic nor clastogenic in standard tests. Due to

Figure 4. Absorption of diclofenac through human skin in vitro after multiple dosing with a DMSO-containing lotion or an aqueous solution.



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its lack of mutagenic activity, it is widely used as a solvent in mutagenicity tests.[35] No genetic adverse events have been reported following medicinal use of DMSO,[33,36] and no such effects have been documented during > 40 years of industrial exposure.[33] Dimethyl sulfoxide is not considered to be directly toxic to embryos and has been used as a cryopreservative for mammalian semen and embryos.[32,33,36] Due to this low toxicity, it has been suggested that DMSO might be an appropriate vehicle to deliver medications that are poorly soluble in other solvents transdermally directly to their site of action.[8]

Toxicity of Topical DMSO

Concerns have been expressed that DMSO could enhance general permeation through the skin, thereby increasing the risk of increased absorption of any unwanted substances.[8] However, this is unlikely for a number of reasons.[8,20] Although all dipolar aprotic solvents such as DMSO can enhance skin penetration to some extent, no compound has the universal ability to fully overcome the barrier properties of human skin.[8] Furthermore, the penetration-enhancing capabilities of DMSO are diminished when water is included in the formulation.[8] In addition, as noted previously, the ability of molecules to permeate through the skin is dependent on their molecular weight,[20] and so it is unlikely that DMSO would enhance the permeation of large molecules such as proteins or polymers.[8]

Although DMSO is rapidly absorbed through the skin, it shows little toxicity when administered transdermally.[32,33] Reported LD50 values following topical application were 40 to 50 g/kg in rodents, and >11 g/kg in dogs and primates.[8,33] Additionally, it is unlikely that such high concentrations would be attained during clinical use of topical formulations. It has long been recognized that topical administration of DMSO can result in local skin reactions, such as reddening, itching, or burning, at the application site.[37] Such reactions are usually mild and self-limiting, and seldom necessitate discontinuation of treatment.[12,13,28–30,38]

Dimethyl sulfoxide is metabolized in humans to dimethyl sulfone and dimethyl sulfide. The latter is excreted via the lungs.[39] The adverse effect, imparting a garlic-like odor to the breath, is almost nonexistent when DMSO is used topically in the highly purified form of a pharmaceutical penetration enhancer.[12,13,28–30]

Table 3. The Regulatory History of DMSO

19th century	DMSO identified as by-product of wood and paper industries
Pre-1963	DMSO used as an industrial solvent and for cryopreservation of tissues
1963	FDA approves first human study of DMSO
1965	FDA bans human investigation of DMSO because of appearance of changes in the refractive index of the eye in experimental animals
1966	FDA allows study of DMSO in serious conditions such as scleroderma, persistent herpes zoster, and severe rheumatoid arthritis
1972	FDA commissions a review of all available data on DMSO by the National Academy of Sciences
1978	FDA grants marketing approval for Rimso, the first commercial DMSO preparation
1980	FDA no longer specifically regulates investigations of DMSO
2009	FDA approves the first topical NSAID formulation with DMSO

Adapted with permission from *US Pharmacist.*[1] Additional data from Pennsaid [package insert].[35]

Abbreviations: DMSO, dimethyl sulfoxide; FDA, Food and Drug Administration; NSAID, nonsteroidal anti-inflammatory drug.

As described previously, clinical investigation of DMSO was suspended following reports of ocular lens abnormalities in nonprimates that were receiving high doses of industrial-grade or laboratory-grade DMSO.[31] These changes were subsequently shown to be distinct from age-related cataracts in humans,[31] and no such effects were observed in young monkeys exposed to lower doses.[40] Further studies in humans showed no evidence of ocular toxicity following topical application of high doses of DMSO, even when DMSO was applied directly to the eye.[41–43] This is consistent with the experience in clinical trials of TDiclo in patients with osteoarthritis, which have shown no increase in ocular abnormalities compared with placebo in patients receiving TDiclo or DMSO vehicle.[30]

The favorable safety profile of topical DMSO is illustrated by a 12-week, double-blind, randomized controlled study of the safety of TDiclo, oral diclofenac, DMSO, and placebo in patients with osteoarthritis of the knee.[13] In this study, the most common adverse events associated with the DMSO treatment group were dry skin (11.2%) and contact dermatitis without vesicles (3.1%).[13] There was no evidence of any ocular adverse events associated with DMSO, and only 1 patient (0.6%) reported an abnormal taste. This safety profile is consistent with other trials that evaluated DMSO as a treatment group.[12,28–30]

Conclusion

Dimethyl sulfoxide is a molecule with a long and diverse history, including clinical evaluation in a variety of indications, use as an excipient in pharmaceuticals and as a cryopreservative, and applications in veterinary medicine.[1–3] It currently has an important role in the topical treatment of interstitial cystitis and as a penetration enhancer in pharmaceutical formulations. Dimethyl sulfoxide has been shown to fulfill many of the criteria for an ideal penetration enhancer (Table 2), reflecting its amphiphilic and aprotic nature, and recent studies at the molecular level have cast light on the mechanisms underlying this effect. The clinical use of DMSO as a penetration enhancer is further supported by the robust data that have accumulated over the past 3 decades demonstrating the favorable safety and toxicity profile.

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Conflict of Interest Statement

Karrie Marren, PharmD discloses that she is an employee of Covidien (Hazelwood, MO).

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