

# Dimethyl Sulfoxide

## History, Chemistry, and Clinical Utility in Dermatology

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### ABSTRACT

Dimethyl sulfoxide is a colorless liquid derived as a by-product from wood pulp in the production of paper. This colorless liquid found immediate application as a polar, aprotic solvent miscible with water and able to dissolve an enormous catalog of polar and nonpolar small molecules. It is presently scarcely used in dermatology, but given its useful properties as a penetration-enhancing solvent excipient and active anti-inflammatory pharmaceutical agent, dimethyl sulfoxide has the potential to be used in a much broader capacity. The authors review the history, chemistry, and clinical utility of dimethyl sulfoxide as it pertains to dermatology. (*J Clin Aesthet Dermatol.* 2012;5(9):24–26.)

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Topical agents have long been employed for surface therapies in dermatology. In addition to the diagnostic advantage afforded by visual signs present on readily accessible surfaces, in many cases, treatment can be directly applied to pathological lesions. The development of neat drug substances working only on the surface is trivial; no need to penetrate any physiological barriers, solubilize in carrier vehicles, or stabilize in specialized chemical mixtures. A step up from these most primitive therapies are the simple solutions, suspensions, and creams placed directly on affected areas that need only provide suitable surface delivery for the active agent. An armamentarium of novel formulation techniques has evolved for the treatment of deeper lesions or for the delivery of therapeutic agents that cannot be easily applied as rudimentary preparations. The authors discuss the history, chemistry, and clinical utility of one such agent—dimethyl sulfoxide (DMSO)—a common, controversial substance with a storied past. Its use in dermatology is now limited. It is most commonly used as a keratolytic agent in conjunction with potassium hydroxide (KOH) to enhance visualization of fungal hyphae when ascertaining the presence of dermatophyte infection. However, DMSO has the potential for much broader applications.

### HISTORY AND CHEMISTRY

Like so many modern medicinal products, DMSO traces its roots to the nascent German chemical industry of the

mid-to-late 19th century. In the search for cheaper, more efficient methods to produce paper from wood pulp, a process was developed in which its by-products included a variety of sulfide-containing compounds. These malodorous sulfides were converted to less-noxious sulfoxides, including DMSO. This colorless liquid found immediate application as a polar, aprotic solvent miscible with water and able to dissolve an enormous catalog of polar and nonpolar small molecules. Since the 1860s, DMSO has been extensively studied in the chemical literature. It is a preferred solvent for a host of named reactions and benefits from both hard and soft nucleophile properties. It is routinely used as a mild oxidant in a variety of synthetic schemes and has gained great utility for the study of carbanion chemistry. Aside from this novel reaction chemistry, DMSO was soon recognized to have the very unique ability to “carry” small molecules through a variety of barriers. It was noted that DMSO spilled onto the hands would quickly cause a distinctive garlic taste on the tongue, which led to the systematic investigation of DMSO as a transport agent that could be used to deliver small molecules through skin and mucosa.<sup>1</sup>

### EARLY CLINICAL USE OF DIMETHYL SULFOXIDE

The medical uses of DMSO have generally fallen in to three functional categories encompassing tissue/organ preservation, penetration-enhancing solvent excipients, and active pharmaceutical agents, primarily anti-inflammatory.

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Organ preservation studies by Dr. Stanley Jacob in the early 1960s led to subsequent pharmacotherapeutic investigations by his own lab and a host of other research groups.<sup>2</sup> The therapeutic history is controversial, to say the least, and has been extensively reviewed in both the scientific and popular literature. There are more than 1,200 publications on the merits of DMSO, but it fell out of favor in the 1960s after the United States Food and Drug Administration (FDA) became much more rigid following the discovery of limb defects in children born from mothers taking thalidomide. In 1978, the FDA finally approved a 50% DMSO solution for intravesicular administration under the brand name Rimso-50 (NDA#017788) for interstitial cystitis. Other than the generic version approved in 2002, this remains the only approved human indication. There are a variety of veterinary DMSO preparations, both alone and in combination with steroids, approved by the FDA originally in the 1970s and currently sold under a range of brands including Domoso, Domoso Gel, Synsac, and Synotoc Otic.

Jacob<sup>2</sup> discovered (in fact rediscovered, as it was already known in the German chemical literature as described above) that DMSO effectively penetrates the skin, an observation he first made in a series of nine patients treated for dermatitis using topical DMSO. This prompted a flurry of activity assessing effectiveness for different dermatological conditions with mixed results arising from incompletely understood mechanisms. The focus in most of these earlier studies was the demonstration of anti-inflammatory properties delivered locally rather than systemically. Cutaneous scleroderma showed potential promise, both subjectively and objectively. Dramatic healing of ischemic ulcers of fingertips was achieved with topical application several times daily over several weeks.<sup>3</sup> Increased skin flexibility and decreased pain resulting in greater range of motion were also noted in scleroderma patients. Keloids and hypertrophic scars showed flattening after several months of use, suggesting clinical utility in conditions and diseases affecting the dermis.<sup>4</sup> Systematic investigations of small molecule transport through the skin with DMSO as a carrier also began in the early 1960s as the potential for this novel effect began to emerge.<sup>5</sup>

## **CHEMISTRY AND MECHANISM OF PENETRATION AND TRANSPORT EFFECT**

The delivery of any active substance from the surface through to the deeper layers of the skin is governed by the barrier function of the stratum corneum. There are four principal variables that influence penetration of a solute through any given membrane: 1) the diffusion coefficient through the membrane, 2) the concentration of the agent in the vehicle, 3) the partition coefficient between the membrane and the vehicle, and 4) the thickness of the membrane barrier. Penetration agents are designed to affect one or more of these variables without causing permanent structural or chemical modification of the physiological barrier. Alteration of membrane thickness is less practical for drug delivery (it is difficult to conceive of

nontoxic agents that could reversibly decrease the thickness of the stratum corneum), so most penetration agents, including DMSO, attempt to reversibly alter principals 1 to 3. There is some evidence to suggest that DMSO can increase diffusion through the stratum corneum by disruption of the barrier function. This probably occurs through aprotic interactions with intercellular lipids and may also include reversible distortion of lipid head groups that produce a more permeable packing arrangement. DMSO may also play a role in partitioning as well by forming solvent microenvironments within the tissue that can effectively extract solute from vehicle. Finally, DMSO can have a profound solubilizing effect on less soluble agents in a variety of vehicles, increasing penetration simply by delivering a higher concentration to the membrane barrier.<sup>5</sup>

## **RECENT CLINICAL STUDIES WITH DIMETHYL SULFOXIDE**

Current use of DMSO in dermatology is quite limited. Enhanced penetration of known ingredients is the focus in which it is being used. Christensen et al<sup>6</sup> studied the effectiveness of photodynamic therapy with 5-aminolevulinic acid (5-ALA), dimethylsulfoxide, and curettage for 60 patients with basal cell carcinoma. At 72 months, 81 percent of patients remained disease free (confirmed by histopathology) with favorable cosmetic results.<sup>6</sup> An informative addition to this study would be a similar arm without the use of DMSO in order to assess clearance rates without a penetration enhancer. An additional similar study evaluated the long-term follow up for 19 cases of Bowen's disease and 15 cases of basal cell carcinoma using topical 5-ALA plus DMSO and ethylenediaminetetraacetic acid (EDTA) with a single exposure to 630nm diode laser at differing energy dosages. At 60 months, 57.7 percent of Bowen's disease and 63.3 percent of basal cell carcinomas remained histologically clear.<sup>7</sup> DMSO, with its unique solvent abilities, is being used to carry the 5-ALA further into the dermis in the hopes of being able to effectively treat nonmelanoma skin cancers with less invasive means.

Wound healing is another potential area of interest for use of DMSO. Applying DMSO cream during early stages of pressure ulcers leads to a decrease in pressure ulcer occurrence among high-risk patients.<sup>8</sup> A systematic review performed by Duimel-Peeters et al<sup>9</sup> looked at the efficacy of topical DMSO on wound healing of decubitus ulcers and its use as an anti-inflammatory drug. The effects reported were beneficial, both for wound healing and analgesia. The most frequent outcome measures were reduction of erythema and rapid healing of ulcers, along with decreased signs of inflammation, such as rubor, dolor, calor, and tumor.<sup>9</sup>

In the same vein, DMSO was found to be dramatically effective for healing severe skin necrosis caused by accidental extravasation of the anticancer drug mitomycin C during intravenous administration.<sup>10</sup> A combination of 10% alpha-tocopherole acetate and 90% DMSO applied topically

prophylactically, after extravasation into tissue of antineoplastic agents but before ulceration, has been found to universally prevent severe ulceration and tissue breakdown.<sup>11</sup>

Of interest, DMSO may have some antiviral effects as well. In a study looking at the effect of DMSO on several parameters of herpes simplex virus (HSV) replication, some surprising results were found. DMSO reduces virion infectivity, inhibits viral deoxyribonucleic acid (DNA) replication, and reduces the transcripts level of many HSV-1 genes. These findings suggest that the DMSO itself may have a role in antiherpetic activity, diverging from previous thought that it only functioned as a penetrant for antiviral medications.<sup>12</sup>

## SUMMARY

Dermatological studies with DMSO in humans have been scarce. The reason is not entirely clear because its application is not dangerous, rarely causing occasional side effects, such as itching, skin irritation, tingling or burning, and garlic odor from the breath. The most definitive role in dermatology for DMSO lies in its ability to act as an effective vehicle. It greatly enhances percutaneous penetration when used in combination with other substances. DMSO facilitates diffusion through the stratum corneum, triggers the formation of deposits in the dermis, and promotes transport into the local blood vessels, as demonstrated with increased penetration of 5-fluorouracil (5-FU) in the treatment of superficial malignancies and warts. Topical application of DMSO with 5-FU demonstrated superior absorption when compared to DMSO alone or 5-FU alone in cream bases.<sup>13</sup> This unique penetrating ability may lend itself to numerous applications for other future products in dermatology.

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