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[54] **ENHANCING TISSUE PENETRATION OF PHYSIOLOGICALLY ACTIVE STEROIDAL AGENTS WITH DMSO**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 753,231, Aug. 16, 1968, Pat. No. 3,551,554, which is a continuation-in-part of Ser. No. 329,151, Dec. 9, 1963, abandoned.

[52] **U.S. Cl.** **424/243,** 424/337

[51] **Int. Cl.** **A61k 17/00**

[58] **Field of Search** 424/243, 337

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[57] **ABSTRACT**

A method of enhancing tissue penetration of physiologically active steroidal agents by conjointly applying them to the tissue with dimethyl sulfoxide. Penetration of the skin and the mucous membranes of the body cavities by these agents may be enhanced by cojoint application of such agents and dimethyl sulfoxide directly to such membranes. Preferably, for penetration of these agents through the skin compositions of DMSO at concentrations of 50 percent and above are employed and for penetration through mucous membranes, compositions including DMSO at concentrations of 10 percent and above are employed. Steroidal Agents may be advantageously administered by injection with DMSO in concentrations preferably up to 20 percent by weight to enhance penetration of internal tissue membranes barriers to achieve better distribution of these agents.

9 Claims, No Drawings

ENHANCING TISSUE PENETRATION OF PHYSIOLOGICALLY ACTIVE STEROIDAL AGENTS WITH DMSO

CROSS REFERENCES TO RELATED APPLICATION

This is a continuation-in-part of co-pending application Ser. No. 753,231, filed Aug. 16, 1968, now U.S. Pat. No. 3,551,554 dated Dec. 29, 1970 and which is, in turn, a continuation in part of application Ser. No. 329,151, filed Dec. 9, 1963, now abandoned.

BACKGROUND OF THE INVENTION

A predominant and limiting problem in the development and use of physiologically active agents is the inability to administer them as effectively as is desired. In particular, there is often a limitation as to the routes of administration because of the following factors:

1. Some agents are inactivated in the gastrointestinal tract or they are absorbed poorly into the body from the tract. Also, undesireable side effects may result which prevent effective oral administration.
2. In every case where injection must be resorted to, there is a risk of needle injury, infection and other trauma (including the emotional trauma inevitably associated with injections).
3. Few agents are absorbed through the skin or mucous membranes in effective quantities and the rate of absorption is less than would be desirable for those that do.
4. A local concentration for a local effect is often desired but a larger systemic dose must be given to achieve an effective concentration at the local area when the agent can only be injected or given orally (but not topically). This higher dose often causes undesirable side effects, since dosage-related side effects are very prevalent for many agents.

Animal tissues comprise various membranes which are selectively permeable and which allow some substances to pass freely, while rejecting others or permitting only slight passage. Such membranes comprise the body coverings and externally communicating cavities, including the skin and mucous membranes of the body cavities, e.g. alimentary tract, respiratory tract, genitourinary tract, oral cavity, eyes, etc. (collectively defined herein as external membranes). They also include internal membranes such as the linings of the various organs and other internal body structures, e.g. peritoneum and pleura, and the membranes surrounding cellular and intracellular structures. It is desirable in overcoming the aforementioned problems in drug administration to increase the passage or penetration of agents across such membranes and further to enhance their intercellular and intracellular diffusion in order for them to reach their situs of activity more rapidly to achieve the desired response more quickly and often more effectively. It is exceptionally desirable to do this in a reversible manner, by which is meant penetration of the agents in tissue without adversely affecting or impairing the function or structure of the tissue. It is known that certain substances will penetrate tissue only after the tissue has been irreversibly damaged, which is certainly undesirable. Certain agents, such as surfactants, have been known previously for increasing penetration of various agents. However, again such penetration was effected only through irreversible damage of the tissue.

It has been a major rule in medicine that the "-vehicles" or "carriers" have relatively little effect on the penetration rate for a given agent and this rule generally still holds true. Thus, with conventional carriers for medicines, such as alcohol, carbowax, water, etc., few agents will adequately penetrate such formidable external membrane barriers as the intact skin or mucous membrane. It is to be expected that this would be true of all potential vehicles or materials combined with physiologically active agents. However, surprisingly, it has been discovered that dimethyl sulfoxide (DMSO) has the unusual ability to greatly enhance the penetration of agents when they are applied to such membrane barriers along with dimethyl sulfoxide. The penetration of agents which previously have not penetrated these membranes to an effective degree may be enhanced sufficiently so that a useful result may be obtained. The penetration of agents which have been known to penetrate to a limited degree in conventional vehicles may be significantly enhanced. New and convenient routes of administration, often with a decrease in side effects of the agents, better localized concentration and a more sustained activity, may thereby be created for many agents.

In my co-pending application Ser. No. 615,377, filed Feb. 13, 1967, is disclosed my related discovery that DMSO enhances the penetration of plant-active agents (pesticides, dyes, nutrients, hormones, herbicides and the like) into plant tissue in a highly unusual manner.

Dimethyl sulfoxide is a water-white liquid at room temperature having a freezing point of approximately 18.5°C. and a specific gravity of approximately 1.1. Dimethyl sulfoxide is a well known industrial solvent and it has been available in commercial quantities for at least a decade (from Crown Zellerbach Corporation, San Francisco, Calif.). DMSO was originally synthesized in 1866 and since that time it has been extensively investigated for possible industrial and biological utility and a considerable amount of literature has developed on its properties and uses. Over the last 25 years it has found widespread use as a solvent in industry and in the laboratory.

DMSO has been investigated in the past for various biochemical uses, for example as a reaction solvent for preparing derivatives of various proteins and antibiotics, as an extraction solvent for various proteins, as an analytical solvent and as a solvent for various other laboratory uses. It has also been suggested as a solvent for certain pesticides (see, for example, U.S. Pat. No. 3,068,142).

DMSO has been investigated as a preservative agent for in vitro storage of chilled or frozen tissue and it has also been determined to have a protective effect in experimental animals subjected to X-irradiation following injection of DMSO into such animals.

In connection with topical application of the antifungal griseofulvin, DMSO has been listed along with various inert materials as "bland, high boiling fliuds" to be used as carriers for the griseofulvin in applying it to the skin to control fungus growth in the skin (see British Patent No. 810,377). DMSO has been employed as a solvent for preparation of certain injectable formulations, namely chloramphenicol and an anthelminic

preparation (see U.S. Pat. Nos. 3,044,936 and 3,067,096).

Despite the employment of DMSO as a solvent for these purposes and despite general experimentation with DMSO in the medical field, the unique ability of DMSO to alter membrane permeability and to thereby enhance penetration of physiologically active agents was neither suggested nor discovered. Although DMSO has been a well known and widely investigated solvent for many years, its unique ability to enhance penetration of external and internal membrane barriers as contemplated in the present invention has been totally unrecognized.

My co-pending application Ser. No. 753,231 is directed to utilizing DMSO to enhance penetration of various categories of physiologically active agents, including antineoplastic agents, antigens, antihistaminic agents, neuropharmacologic agents, diagnostic dyes and radiopaque agents and nutrients. Many of these categories are unrelated to steroids but some, such as antinoeplastic agents and antiinflammatory agents, comprehend the various steroids having the indicated physiological activity. The present application is directed specifically to physiologically active steroids inclusive of those steroids having activities falling within the categories of my co-pending application and those that do not.

SUMMARY OF THE INVENTION

By a mechanism or mechanisms not yet fully understood, DMSO, when applied to animal tissue, increases the permeability of the tissue in a reversible manner to cause a much greater penetration rate for conjointly applied physiologically active agents, and specifically steroids. Although the mode of activity is still unclear, it is definitely not that of the simple vehicle or carrier since the effect may be obtained to some extent even when the DMSO is applied to tissue separately and the enhanced penetrability of the tissue may last for as much as three hours after the DMSO treatment.

When applied to the intact skin along with dimethyl sulfoxide, particularly at a DMSO concentration of 50 percent by weight and above, or to skin pretreated with the dimethyl sulfoxide, a steroid may penetrate rapidly to and saturate the stratum corneum (the highly resistant "horny layer" of the skin which is the major barrier to penetration). The steroid continues to penetrate through the skin from this "reservoir" in the stratum corneum to the underlying tissue and into the circulatory system.

Similarly, penetration into underlying tissues and into the circulatory system may be obtained from topical application to the mucous membranes of the body cavities as in the case of intraoral, conjuctival sac, rectal, vaginal and bladder instillation administration, particularly where the DMSO is utilized at a concentration of 10 percent by weight and above. It is thus seen that a particularly important aspect of this invention is that penetration of agents, and specifically steroids, may be effectively enhanced following topical administration. As used in this connection herein, the term "topical" is intended to include application to all external membrane barriers, including the cutaneous or epidermis regions and the mucous membranes, including the gastrointetinal tract, the respiratory tract and the genitourinary tract.

Important advantages are also obtained through the injection routes for physiologically active steroidal agents. When these agents are injected into the tissues either in a composition including dimethyl sulfoxide (preferably at DMSO concentrations exceeding 1 percent and especially in the range of 10 – 20 percent by weight) or together with conjoint but separate application of DMSO to the tissues, the effect is an enhanced and more even distribution thereof into the tissues surrounding the injection site compared with conventional injection techniques. This more even distribution is of considerable advantage for both local and system effect for all of the usual injectable routes, e.g. subcutaneous, intramuscular, intraperitoneal, etc.

Where a local effect is desired, the intimate distribution of the steroidal agent in the tissue near the site of injection prolongs and enhances its physiologic activity at this local site. This may permit use of a lower dose to achieve the desired response with a smaller risk of side effects which may result from a higher dose.

For all routes of administration, conjoint application of DMSO along with physiologically active steroidal agents having an activity site in the individual cells of the host may additionally result in an enhanced effect of the agent through the ability of DMSO to increase the permeability of such individual cells to such agents.

As previously indicated, the mechanisms of penetration enhancement are as yet not fully elucidated. Accordingly, it is not believed that DMSO acts by several mechanisms in enhancing penetration. DMSO is believed to act directly on tissue to alter the general permeability of the tissue membrane. More specifically, DMSO when applied thereto is believed to decrease the natural resistance of tissue membranes to penetration by foreign agents. DMSO is also believed to promote penetration by a direct transport effect, perhaps by the mechanism of complexing with the agent. This mechanism is believed more applicable to cationic and anionic agents.

GENERAL DESCRIPTION OF THE INVENTION

This invention is applicable to the tissue or organisms of all animal phyla, DMSO having differing degrees of influence on penetration of various tissue types of a given animal. Animals of particular importance in the practice of the invention are the mammalians, especially man and veterinary animals. However, the invention may also be practiced with other vertebrates, as for example the amphibians, fishes, reptiles, etc., and with the lower species comprising the non-vertebrates.

As indicated previously, a measure of penetration enhancement may be obtained where the tissue is pretreated with DMSO prior to application thereto of the physiologically active steroidal agent. The tissue penetrability is thus altered by such pretreatment and this reversible effect gradually diminishes and the tissue returns to its normal permeability state. However, for convenience and optimal effect, it is frequently desirable to administer the DMSO and the agent simultaneously in the same composition.

Penetration enhancement is generally non-selective in terms of the type or physiological effect or effects of agents to be transported across membrane barriers.

The extent of penetration enhancement will depend upon many factors, the predominant factors being the relative natural permeability of the particular membrane, the concentration of DMSO applied, the extent of solubility of the agent in DMSO and the chemical and physical properties of the agent.

The size of the compound obviously may influence to some extent the relative ability of steroidal agents to penetrate tissue. However, effective membrane penetration utilizing DMSO has been demonstrated for extremely large compounds, for example compounds having molecular weights exceeding 40,000. Even for such a formidable membrance barrier as intact human skin, quite large compounds have been demonstrated to be effectively enhanced.

Standard occlusion techniques frequently may increase the percutaneous absorption of the larger molecules. In general, at least a limited degree of solubility of the agent in DMSO is desirable to achieve maximum benefit of the present invention. Naturally, the practitioner will select steroidal agents, routes of administration and composition forms guided by these well known principles.

Steroids are generally classed as organic molecules which have in common a perhydrocyclopentanophenanthrene nucleus and they are so named because they are related to and usually derived from sterols found abundantly in nature in animal and plant fats. Certain steroids are naturally produced in the body and they act as hormones to mediate and control many body functions. These hormones have been isolated or produced synthetically and used in replacement therapy for hormone deficiencies. Additionally and importantly, these steroids have been found to be highly useful drugs in the treatment of a wide range of disease states not primarily due to lack of hormones. In the recent past, extensive research effort has resulted in the synthesis of a vast number of new steroid hormone derivatives having biological activity (in excess of 1,500 compounds) and the list is growing rapidly. Such derivatives usually contain modifying groups linked to the steroid as by modifying, prolonging or increasing its activity, increasing stability and/or modifying its solubility characteristics. These modifying groups usually comprise addition salts to influence solubility of a side chain substitution on one or more reactive ring carbon atoms. The side chain may be a direct substitution for a ring hydrogen, an ester formed at a reactive hydroxyl group or an ether group. Many of these steroid derivatives have a higher potency than the naturally occurring steroid hormones, often with a decrease in the undesirable side effects which frequently result from administration of the natural steroids. As used herein, the term "steriods" and "steroidal agents" is intended to comprehend both the natural steroids and the biologically active modifications, derivatives and equivalents.

Steroid drugs may have one or more of many types of biological activity such as anabolic, androgenic, glucocorticoid, mineralocorticoid, estrogenic, progestogenic, lipoidiatic (removal of stored fat), circulatory system activity, central nervous system activity, anti-cancer and anti-osteroporic, Some steroid drugs have the ability to block the activity of other hormones, including the activity of other steroids. Their biological activity may be characterized as antiandrogenic, antiglucocorticoid, antimineralocorticoid (diuretic), antiestrogenic and antiprogestogenic. The term "physiologically active" in describing steroidal agents herein is intended to comprehend all of these and any other useful activities. Various activities will be considered hereinafter in connection with specific embodiments of this invention.

The concentration of the DMSO applied to enhance penetration may vary over wide limits. The concentration selected is desirably related to the route of administration to be employed. For cutaneous application, compositions including at least about 50 percent by weight DMSO are preferable in that they have been found to increase percutaneous penetration in a highly significant manner. Maximum cutaneous penetration is generally attained with DMSO concentrations closely approaching 100 percent (excluding the agent), but with concentrations much above 90 percent by weight the incremental increase in penetration rate over that achieved at 90 percent often is relatively small. On the other hand, above a 90 percent concentration of dimethyl sufoxide, the side effects of a burning sensation and erythema increase significantly. Accordingly, for topical use, it may be desirable, consistent with physical stability of the composition, to formulate the DMSO in compositions containing a DMSO concentration of between about 50 percent and 90 percent by weight and containing water, preferably 10 percent by weight or greater.

Application to mucous membranes follows generally the procedure for cutaneous administration. However, lower concentrations of DMSO, for example as low as 10 percent by weight, may be preferred since penetration of mucous membrane is more easily affected.

For most injection routes, preferably lower concentrations of DMSO of about 10 percent to about 20 percent by weight are utilized. For some injection routes, for example intra- and peri-articular routes, higher concentrations, say 30–40 percent, may be preferred.

The amount of the physiologically active steroidal agent to be administered will obviously be an effective amount for the desired result expected therefrom. This, of course, will be ascertained by the ordinary skill of the practitioner. Due to enhanced activity which may be achieved through better penetration, the dosage of agent may often be decreased from that generally applicable. In accordance with the usual prudent formulating practices, a dosage near the lower end of the useful range of the particular agent may be employed initially and the dosage increased as indicated from the observed response, as in the routine procedure of the physician.

As previously discussed, the DMSO may advantageously be compounded with the physiologically active steroidal agent for concurrent administration. The usual pharmaceutical compounding agents, diluents or carriers may be included in these compositions as desirable for the particular route of administration and dosage form. The amount and type of diluent or carrier used should, of course, be consistent with the compatability of the agent in DMSO and the diluent. A co-solvent, or other standard adjuvant such as a surfactant may be called for to maintain the agent in solution or suspension at the desired concentration. Where stability of the agent in the presence of DMSO at the

desired concentration is a problem, it may be desirable to prepare the formulation immediately before administration or to administer the DMSO and the agent separately to the tissue.

In selecting the route of administration for a given agent, obviously the known toxicity, side effects and effectiveness for a given route of administration should be taken into account. For example, due to skin irritation known to be caused by some agents or due to poor penetration characteristics, some other route than dermal application may be the route of choice for such agents.

Dosage forms for topical application may include solutions (paints), nasal sprays, lotions, ointments (including creams and gels), suppositories and the like. The solutions and nasal sprays may simply comprise the agent dissolved in DMSO, optionally with an amount of water, glycerine or other diluent. For nasal sprays and other mucous membrane applications, isotonic saline may be preferable as a diluent. The DMSO may be present in these forms in various concentration, say from about 10 percent to about 75 percent by weight or higher.

Lotions and gels, ointments or creams may contain the usual ingredients to provide a base, as for example cetyl alcohol, an emulsifier such as lauryl sulfate, and water. Another base may be formulated by combining equal weight amounts of stearic acid, cetyl alcohol, triethanolamine and glycerol monostearate with water. Still other bases may utilize polyethylene glycols of different viscosities, depending upon the desired consistency. DMSO may be added to the lotion or ointment base in varying amounts as desired, generally up to around 50 percent by weight.

A suppository form may be made from a high viscosity polyethylene glycol 4,000, water and DMSO, which may be present in an amount of about 20 percent by weight.

The concentration of physiologically active steroidal agent in the various dosage forms is, of course, commensurate with that normally utilized for the particular agent in conventional formulations for effective results for the intended route. Both the amount of physiologically active steroidal agent and the amount of DMSO will be influenced by the type of effect desired. If a more localized effect is required, as for example in treating a skin condition, lower amounts of physiologically active steroidal agent and lower concentrations of DMSO may be called for. Where deeper penetration is desired, a higher concentration of DMSO may be desirable to promote adequate penetration. Where general systemic concentration of an agent is desired for a topical preparation, generally higher concentrations of DMSO are desirable and the amount of steroidal agent may be included in the composition sufficient to provide the blood level desired.

The various pharmaceutical forms are desirably provided in determined amounts, as in containers of a given volume. These amounts may include 100 percent DMSO concentration containing the desired dose of the agent, or a lesser concentration of DMSO with a diluent and the physiologically active agent dose. Thus, for example, graduated ampules containing, say, 5 cc. of 100 percent DMSO with the agent dissolved therein may be provided. The practitioner need only open and dispense all or a determined part to a subject. Nasal spray bottles, aspirators, suppositories, cotton tipped stick applicators, squeeze tubes may all be utilized for topical application.

The following illustrates the practice of the present invention with various classes of steroidal agents.

DESCRIPTION OF PREFERRED EMBODIMENTS

GLUCOCORTICOIDS

Hormones produced naturally in the body by the adrenal cortex are called adrenal cortical steroids or corticoids. Some corticoids, predominantly cortisone and hydrocortisone, have the property of influencing the rate of metabolism of glucose. Hence they, along with their derivatives and modifications, are called glucocorticoids. Glucocorticoids have other predominant physiologic activity which makes them highly useful as drugs. One of the most important activities is the suppression of inflammation, particularly in the treatment of arthritis and rheumatic diseases. Glucocorticoids are also useful in the treatment of dermatoses, drug reactions, bronchial asthma, lupus erythematosus, angioneuroedema and many other disorders. Massive doses of corticosteroids have also been used to induce remissions in leukemia. Glucocorticoids are generally, 3-keto, Δ 4, 11-oxygen function (hydroxy or keto), 20-keto steroids of the pregnane series. Typically they also have a 21-hydrogen, halogen or hydroxy function. The 11-hydroxy glucocorticoids are of particular interest for local application with DMSO due to their ability to induce local effects. DMSO may be combined with glucocorticoids to enhance their penetration to the affected tissue for these various disorders. The following examples illustrate compositions and treatments for this purpose utilizing the most prominent and active natural and modified glucocorticoids.

EXAMPLE 1

Penetration of Injected Corticosteroids

A 32 year old white woman was seen with a 2 days' history of left subdeltoid bursitis. This gave her pain on minimal abduction particularly, but also was present in other movements of the shoulder joints. Physical examination revealed marked tenderness to pressure with obvious protective muscle spasm overlying the joint. Two ml of hydrocortisone was injected into the bursal area. This was associated with 3 hours' relief of pain. The patient was seen again 2 days later. At this examination her pain was just as marked as the first visit. Two ml. of hydrocortisone was injected and 5 cc. of 100 percent dimethyl sulfoxide was applied liberally to the entire left shoulder area. Within 15 minutes all pain disappeared and the patient reported no return of her symptoms when examined 1 week later.

Example 2

Penetration of Injected Corticosteroids

A 42 year old white male was examined with a 1 week history of acute subdeltoid bursitis of the right shoulder. Four mg. of Decadron was injected into the right subdeltoid bursa. The patient estimated that about a 20 percent relief of his discomfort was attained.

Full pain returned 1 day later. At this point he was reinjected with 4 mg. of Decadron and 4 cc. of 100 percent dimethyl sulfoxide was placed on the skin over the involved bursa. This time the pain disappeared completely and did not recur.

Both of the above examples show that cortisone injected for subdeltoid bursitis is obviously of benefit, but that its relief of symptomatology is enhanced with the simultaneous application of dimethyl sulfoxide to the skin.

Example 3

Penetration of Corticosteriods

A 24 year old medical student was seen with atopic dermatitis of the right antecubital fossa. Three cc. of 100 percent dimethyl sulfoxide was applied four times daily for 3 days. No benefit was noted. One mg. or one-fourth cc. of Decadron (dexamethasone 21-phosphate) was applied four times a day for 2 days without benefit. One mg. of dexamethasone 21-phosphate in 3 cc. of 100 percent dimethyl sulfoxide was painted onto the involved area four times daily for 3 days. At the end of this period all evidence of the inflammatory reaction had disappeared.

This example shows an improved action of dexamethasone 21-phosphate when used with dimethyl sulfoxide.

Example 4

The following lotion formulation may be prepared containing about 0.01 to 1.0 percent, and preferably 0.1 percent fluocinolone acetonide:

Fluocinolone acetonide	0.1–1.0 gm
Cetyl alcohol	200 gm
Propylene glycol	100 gm
Sodium lauryl sulfate	15 gm
DMSO	300 gm
Water	qs 1000 cc

The steroid is dissolved in the DMSO and added to a stirred, cooling melt of the other ingredients. The preparation is particularly useful for the treatment of inflamed dermatoses by topical application to the affected skin area. The amount and frequency of application is in accordance with standard practice for topical application of this steroid. Penetration of the steroid into the inflamed tissue in enhanced and a therapeutic level is achieved more rapidly than when the steroid is applied in conventional formulations.

Example 5

The following ointment (gel) formulation may be prepared containing about 0.2 percent to 1.0 percent, and preferably 0.6 percent triamcinalone acetonide:

Triamcinalone acetonide	0.2–10 gm
Polyethylene glycol 400	400 gm
Dimethyl sulfoxide	598 gm
Carboxy vinyl polymer powder	1 gm
Triethanolamine	0.4 gm

The corticosteroid is dissolved in a mixture of the first two ingredients and the carboxy vinyl polymer gelling agent is sprinkled on the surface of the combined liquids and stirred until all the particles have been wetted and dispersed. The triethanolamine is then added dropwise to the mixture until it has gelled, care being taken to minimize the air entrapment. This gel is particularly effective in the treatment of seborrhea and other scalp and hair inflammatory conditions and may be applied in amount and frequency conventionally used for topical application of this steroid. Better penetration and thereby an increased anti-inflammatory active is obtained for the amount of steroid applied than results from its application in conventional formulations.

Example 6

The following ointment formulation may be prepared containing about 0.1 percent to 1.0 percent prednisone and preferably 0.5 percent:

Prednisone	0.1–10 gm
Glyceryl monostearate, acid type	180 gm
Stearyl alcohol	50 gm
Polysorbate 80	20 cc
Water	450 cc
Dimethyl sulfoxide	300 cc

The product is prepared as described in Example 4. The ointment is a valuable base for application of the corticosteroid to inflammatory dermatological areas, particularly when they require inunction. Application is in accordance with that usual for topical application of this steroid in conventional bases.

Example 7

The following cream formulations may be prepared containing about 0.1 percent to 1 percent 16a-methyl prednisolone and preferably 0.5 percent:

16a-methyl prednisolone	0.1–10 gm
Stearic acid	200 gm
Glyceryl monostrearate, acid type	200 gm
Sodium lauryl sulfate	20 gm
Dimethyl sulfoxide	200 gm
Water	qs 1000 cc

As above, the product is prepared as directed in Example 4 and is useful in severe dermatoses requiring inunction.

What I claim is:

1. A method of enhancing the penetration into and across an external membrane barrier of a human or animal subject of a physiologically active glucocorticoid steroidal agent capable of eliciting a physiological effect upon topical application thereof, which comprises the concurrent topical administration to the external membrane of an amount of said steroidal agent effective to produce the desired physiological effect and an amount of DMSO sufficient to effectively enhance penetration of said steroidal agent to achieve the desired physiological effect.

2. A method as in claim 1 and wherein the said agent is applied to the intact skin in a composition which includes said DMSO and wherein the DMSO in said composition is at least about 50 percent by weight of the composition.

3. A method as in claim 1 and wherein said agent is applied to induce at least a physiological effect locally to the site of application.

4. A method as in claim 1 and wherein said glucocorticoid is a 3-keto, Δ 4, 11-oxygen function, 20-keto steroid of the pregnane series.

5. A method as in claim 4 and wherein said glucocorticoid is a 11-hydroxy steroid.

6. A method as in claim 1 and wherein said agent is applied to said membrane in a composition which includes said DMSO.

7. A method as in claim 6 and wherein said composition contains a pharmaceutically acceptable thickening agent in an amount sufficient to materially increase the viscosity thereof, whereby to facilitate topical application.

8. A method as in claim 7 wherein said composition is in the form of an ointment.

9. A method as in claim 7 and wherein said composition is in the form of a lotion.

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