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# GLYCERALDEHYDE AS A TOPICAL ANTI-INFLAMMATORY AGENT

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This invention relates to pharmaceutical compositions for topical use and, more particularly, to such compositions in which the primary active ingredient is a glyceraldehyde.

Specifically included within the term "glyceraldehyde" are the individual d- and l-isomers and mixtures of such isomers, including racemic mixtures thereof.

The primary active ingredients of these compositions have unexpectedly been found to demonstrate high local anti-inflammatory activity. An important aspect of the usefulness of these compositions is the virtual freedom from undesirable systemic effects, a factor probably attributable to the conversion of glyceraldehyde to glucose in the body. These compositions are useful in the treatment of such inflammatory conditions as contact dermatitis, atopic dermatitis, neurodermatitis, anogenital pruritis, seborrheic dermatitis, and the like. The said compositions can also be advantageously employed in the suppression of inflammation associated with rheumatoid and osteoarthritis, bursitis and ganglia of the wrist, knee joints and tendon sheaths. The novel compositions hereof find application in the topical treatment of inflammatory conditions in animals, especially animal mastitis, a disease of the mammary glands which can be of particular concern in milk producing animals such as cows.

The concentration of primary active ingredient in these compositions in the treatment of mammals and birds for dermatological applications can range from about 1 to about 50%, from about 5 to about 25% being preferred. For intra-articular use, from about 50 to about 300 mg. per joint, depending on the size of the joint and severity of the condition, is injected. In use, these compositions are employed in a manner appropriate to the specific pharmaceutical form indicated for the condition and locale being treated. Application one to three times daily is usually sufficient, with frequency being reduced as improvement is noted.

The term "topical" as employed herein relates to the introduction of the medication, incorporated in a suitable base or vehicle, at the site of the inflammation for exertion of local action. Accordingly, such topical compositions include those pharmaceutical forms in which the medication is applied externally by direct contact with the surface to be treated. Conventional pharmaceutical forms for this purpose include ointments, lotions, pastes, jellies, powders, solutions for wet dressings and paints, and the like. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases as described in Remington's Practice of Pharmacy, 12th Edition (1961), page 410, Mack Publishing Company. Topical compositions as herein defined include also those pharmaceutical forms which afford local as opposed to systemic release into the immediate affected areas where such areas are not accessible by direct external application, such forms including sprays (e.g., for oral or nasal use), aerosols (e.g., for deeper penetration than is usually afforded by sprays), drops (e.g., for use in the eyes and ears), suppositories (e.g., for rectal or vaginal use), powders (e.g., for insufflation), sterile aqueous suspensions or solutions (e.g., for intra-articular or intra-bursal injection), and the like.



Various other active ingredients can be included in the formulations of the present invention to provide a desirable supplementary effect which, when employed in the treatment of particular conditions, enhances the usefulness of the said primary active ingredients. Thus, combinations of glyceraldehyde with antibiotics and/or steroids, such as glyceraldehyde with neomycin and/or 6α-fluoroprednisolone or 6α-methylprednisolone, provides useful combined therapy. Glyceraldehyde with vasoconstrictors such as epinephrine or phenylephrine or glyceraldehyde with, for example, pyribenzamine, 6α-methylprednisolone and a suitable analgesic is likewise useful.

Broadly described, the method for the preparation of pharmaceutically acceptable formulations involves the incorporation of the primary active ingredient, together with any supplementary active ingredients to be included, into the selected pharmaceutical carrier, utilizing techniques well known in the art. By "pharmaceutically acceptable carrier" or "base" as used herein is meant the vehicle into which the active ingredients are incorporated, the said vehicle comprising various pharmaceutically and physiologically suitable additives for the purpose of facilitating the formulation of the said active ingredients into the desired pharmaceutical form.

The following examples illustrate the best mode contemplated by the inventor for carrying out the invention, but these are not to be construed as limiting the scope thereof.

*Example 1.—Ointment*

Five kilograms of an ointment containing 50% dl-glyceraldehyde is prepared from the following types and amounts of materias, the percentages being by weight:

| | Gm. |
|---|---|
| 4% Multiwax No. W-445 [1] | 200 |
| 20% white mineral oil, U.S.P., viscosity 180 | 1000 |
| 0.5% cholesterol, U.S.P. | 25 |
| 0.02% methylparaben, U.S.P. | 1 |
| 0.18% n-butyl-p-hydroxybenzoate | 9 |
| 50% dl-glyceraldehyde | 2500 |
| White petrolatum, U.S.P., q.s. 5000 gm. | |

[1] High melting point wax from L. Sonneborn and Sons, Inc., New York City, N.Y.

The petrolatum and Multiwax are melted together and the mineral oil added. The mixture is heated to 190° F. and the cholesterol added. After cooling to 170° F., the paraben and hydroxybenzoate are introduced. The resulting mixture is strained and cooled to between 130 and 135° F. The dl-glyceraldehyde is added and mixed in thoroughly with a high-speed mixer. The whole is then passed through a mill and mixed in a high-speed mixer until the product is congealed. The product is then ready for potency assay and packaging.

The foregoing ointment can be employed in the treatment of allergic dermatoses and other inflammatory skin conditions, such as contact dermatitis, atopic dermatitis, neurodermatitis, anogenital pruritis, seborrheic dermatitis and the like. The ointment is rubbed gently into the affected area three times daily.

*Example 2.—Ointment, Ophthalmic*

Ten kilograms of an ophthalmic ointment containing

1% dl-glyceraldehyde is prepared from the following types and amounts of materials:

| | Gm. |
|---|---|
| 25% light mineral oil, U.S.P. | 2500 |
| 20% wool fat, U.S.P. | 2000 |
| 1% dl-glyceraldehyde | 100 |

White petrolatum, U.S.P., q.s. 10,000 gm.

The dl-glyceraldehyde is ground with the mineral oil in a colloid mill. The wool fat and petrolatum are melted, strained, and the temperature adjusted to 45 to 50° C. The mineral oil slurry is added with thorough stirring which is continued until the temperature drops to about 35° C. The product is then ready for potency assay and filling into ophthalmic tubes.

The ointment is placed in the conjunctival sac three times daily for treatment of inflammatory conditions of the eye, such as allergic conjunctivitis.

Following exactly the procedure above but including in the formulation 66.7 gm. of neomycin sulfate is productive of an ophthalmic ointment having wide application in treatment of inflammatory conditions of the eye originating with or complicated by bacterial infections.

Similarly, substitution of 30 gm. of tetracycline hydrochloride for the neomycin is productive of an ophthalmic ointment advantageously used where the bacterial infection is believed susceptible to tetracycline hydrochloride.

*Example 3.—Cream*

A cream containing 25% dl-glyceraldehyde is prepared in a 1000-gm. lot from the following types and amounts of materials:

| | Gm. |
|---|---|
| 15% Tegacid Regular [1] | 150 |
| 10% spermaceti, U.S.P. | 100 |
| 5% propylene glycol, U.S.P. | 50 |
| 0.5% polysorbate 80, U.S.P. | 5 |
| 0.1% methylparaben, U.S.P. | 1 |
| 25% dl-glyceraldehyde | 250 |

Deionized water, q.s. 1000 gm.

[1] Self-emulsifying glyceryl monostearate from Goldschmidt Chemical Corporation, New York N.Y.

The Tegacid and spermaceti are melted together at a temperature of 70 to 80° C. The methylparaben is dissolved in about 500 gm. of water, and the propylene glycol, polysorbate 80, and dl-glyceraldehyde are added in turn, maintaining a temperature of 75 to 80° C. The methylparaben mixture is added slowly to the Tegacid and spermaceti melt, with constant stirring. The addition is continued for at least 30 minutes with additional stirring until the temperature has dropped to 40 to 45° C. The pH of the final cream is adjusted to 3.5 by incorporating, with stirring, 2.5 gm. of citric acid, U.S.P. and 0.2 gm. of dibasic sodium phosphate heptahydrate dissolved in about 50 ml. of water. Finally, sufficient water is added to bring the final weight to 1000 gm. and the preparation is stirred until homogeneous. The resulting product is then assayed and packaged for clinical use.

The above cream is applied once daily to the inflamed area.

*Example 4.—Lotion*

Ten liters of a viscous lotion containing 5% dl-glyceraldehyde is prepared from the following types and amounts of materials.

| Per ml.: | Gm. |
|---|---|
| 50 mg. propylene glycol, U.S.P. | 500 |
| 2 mg. methylparaben, U.S.P. | 20 |
| 3 mg. n-butyl-p-hydroxybenzoate | 30 |
| 20 mg. polysorbate 80, U.S.P. | 200 |
| 80 mg. glyceryl monostearate-diethylaminoethyl oleylamide phosphate (19:1) | 800 |
| 35 mg. spermaceti, U.S.P. | 350 |
| 50 mg. dl-glyceraldehyde | 500 |
| Perfume | 25 |

Deionized water, q.s. 10 liters.



The methylparaben and n-butyl-p-hydroxybenzoate are dissolved in 4.5 liters of deionized water and the solution heated to 70 to 80° C. To this solution are added the propylene glycol, polysorbate 80, glyceryl monostearate-diethylaminoethyl oleylamide phosphate and spermaceti. The temperature of the mixture is maintained at 70 to 80° C. for 30 minutes and then allowed to cool to 35 to 45° C. The dl-glyceraldehyde is then introduced with vigorous mixing, water added to make 10 liters, and the resulting product strained and put through a homogenizer. This product is then ready for assay and packaging for clinical use.

The above lotion is applied twice daily to the inflamed area.

*Example 5.—Nasal Spray*

A preparation containing 5% dl-glyceraldehyde with neomycin and phenylephrine hydrochloride is prepared in a volume of 15 liters from the following types and amounts of materials.

| Per ml.: | Gm. |
|---|---|
| 5 mg. polysorbate 80, U.S.P. | 75 |
| 1 mg. sodium chloride, U.S.P. | 15 |
| 4.5 mg. sodium citrate, U.S.P. | 67.5 |
| 0.23 mg. myristyl gamma picolinium cholride | 3.5 |
| 14.3 mg. glyceryl monostearate | 214 |
| 0.73 mg. diethylaminoethyl oleylamide phosphate | 11 |
| 10 mg. spermaceti, U.S.P. | 150 |
| 10 mg. propylene glycol, U.S.P. | 150 |
| 6.4 mg. neomycin sulfate powder | 96 |
| 2.5 mg. phenylephrine hydrochloride, U.S.P. | 37.5 |
| 0.5 mg. sorbic acid | 7.5 |
| 50 mg. dl-glyceraldehyde | 750 |

Deionized water, q.s. 15 liters.

Twelve liters of deionized water is heated in a suitable container to 70 to 75° C. Sodium chloride, sodium citrate, myristyl gamma picolinium chloride and sorbic acid are dissolved therein. Polysorbate 80 and propylene glycol are added and the dl-glyceraldehyde thoroughly dispersed in the resulting mixture.

Glyceryl monostearate, diethylaminoethyl oleylamide phosphate and spermaceti are then introduced. While stirring constantly, the temperature is maintained at 75° C. for about 30 minutes and then cooled to room temperature. The neomycin sulfate and phenylephrine are then dissolved in the cooled mixture. Deionized water is added to bring the volume to 15 liters, and the resulting product is thoroughly stirred. The product is then ready for assay and packaging for clinical use as a nasal spray.

The foregoing spray is administered three times daily for treatment of nasal inflammatory conditions such as allergic rhinitis.

*Example 6.—Drops*

A sterile suspension containing 5% dl-glyceraldehyde is prepared from the following types and amounts of materials.

| Per ml: | Gm. |
|---|---|
| 10 mg. 2-hydroxy-3-methylaminopropyl (propylamino)-benzoate hydrochloride | 1 |
| 6 mg. neomycin sulfate | 0.6 |
| 4.5 mg. sodium citrate, U.S.P. | 0.45 |
| 150 mg. polyethylene glycol | 15 |
| 0.2 mg. myristyl gamma picolinium chloride | 0.02 |
| 1 mg. polyvinylpyrrolidone | 0.1 |
| 50.0 mg. dl-glyceraldehyde | 5 |

Deionized water, q.s. 100 ml.

The foregoing formulation produces a suspension which is stable, readily resuspendable and does not cake. On

mixing, sterilizing and suspending, the product is ready for assay and sterile packaging.

The suspension is useful for treatment of eye and ear infections characterized by inflammation. One drop is administered three times daily to the eye or external ear canal.

*Example 7.—Suppository*

A suppository containing 5% dl-glyceraldehyde with neomycin, phenylphrine hydrochloride and ethylaminobenzoate is prepared from the following types and proportions of materials:

| | Parts |
|---|---|
| Polyethylene glycol 6000 | 750 |
| Polyoxyethylene sorbitan monostearate | 300 |
| Spermaceti | 330 |
| Polyethylene glycol 400 | 321 |
| Polyoxyethylene palmitate | 150 |
| Sodium sulfate | 750 |
| Coloring powder | 30 |
| Starch, bolted | 120 |
| Phenylephrine hydrochloride | 6 |
| Ethylaminobenzoate | 75 |
| Neomycin sulfate | 18 |
| dl-Glyceraldehyde | 150 |

The polyethylene glycol 6000, polyoxyethylene sorbitan monostearate and spermaceti are melted together at 180 to 190° F. The coloring powder, starch, about 15% of the sodium sulfate and the four active ingredients are dispersed in the polyethylene glycol 400. The dispersion is added to the melted mixture. The balance of the sodium sulfate is added. The whole is stirred at 180 to 190° F. to insure smoothness. The completed mass is allowed to cool and is then poured into chilled containers which are stored approximately 24 hours under refrigeration prior to extrusion to form shaped suppositories weighing 3 gm. each. The product is then ready for assay and packaging.

The foregoing suppositories are given rectally twice daily in the treatment of rectal conditions involving inflammation and/or infection, such as localized proctitis.

*Example 8.—Aerosol*

An aerosol containing approximately 2.5% dl-glyceraldehyde with phenylephrine hydrochloride is prepared from the following types and amounts of materials:

| | | |
|---|---|---|
| Absolute alcohol | gm. | 4.37 |
| Dichlorodifluorotetrafluoroethane | gm. | 1.43 |
| Dichlorotetrafluoroethane | gm. | 5.70 |
| Phenylephrine hydrochloride | mg. | 45.29 |
| dl-Glyceraldehyde | mg. | 300 |

The dl-glyceraldehyde and phenylephrine hydrochloride are dissolved in the absolute alcohol and the resulting solution filtered to remove particles and lint. This solution is chilled to about minus 30° C. To this is added the chilled mixture of dichlorodifluoromethane and dichlorotetrafluoroethane. Thirteen ml. plastic-coated amber bottles are cold filled with 11.5 gm. each of the resulting solution and capped with a metering valve. The resulting package, when inverted into an oral inhalation adapter and the valve opened, will deliver a metered dose containing 2 mg. of dl-glyceraldehyde and 0.3 mg. of phenylephrine hydrochloride. The product is then ready for assay and clinical use.

The aerososl is administered three times daily in treating allergic or asthmatic conditions of the respiratory tract system which are characterized by local inflammation.

*Example 9.—Mastitis Preparation*

A lot of 10,000 gm. of a veterinary preparation is made with the following ingredients.

| Each 10 gm. contains: | Gm. |
|---|---|
| 275 mg. neomycin sulfate, micronized | 275 |
| 110,000 units procaine penicillin G, sterile | 110 |
| 55,000 units polymyxin B sulfate (10,000 units/mg.) | 5.5 |
| 1000 mg. d-glyceraldehyde | 1000 |
| 30% white mineral oil | 3000 |
| 0.525% chlorobutanol anhydrous | 52.5 |
| 0.5% polysorbate 80 | 50 |
| 0.5% sorbitan monooleate | 50 |
| 40% 2% aluminum monostearate-sesame oil gel | |
| White petrolatum, q.s. 10,000 gm. | |

Suspend the neomycin sulfate, procaine penicillin, polymyxin B sulfate and d-glyceraldehyde in all of the white mineral oil and mix thoroughly. Mill through Fitzpatrick Mill (80 mesh screen). Stir slowly for at least one hour to dissipate entrapped air. Add the chlorobutanol, polysorbate 80 and sorbitan monoleate to 1400 gm. of the 2% aluminum monostearate-sesame oil gel and mix thoroughly with an air mixer until completely dissolved. Strain into the remainder of the 2% aluminum monostearate-sesame oil gel and mix. Melt the petrolatum and strain into the gel, with thorough mixing. Add the mineral oil-powder mixture and adjust the temperature to 120° F., while stirring. Continue stirring only until the temperature is reduced to 100° F. Allow to cool to room temperature before filling into 100-cc. vials or 10-cc. disposable syringes.

Administration by udder instillation in 10-gm. doses once daily affords effective therapy in the treatment of bovine mastitis.

Other antibiotics conventionally employed in the management of veterinary mastitis can be substituted for the neomycin, penicillin and polymyxin above. For example, such antibiotics as erythromycin, tetracycline, novobiocin sodium and dihydrostreptomycin sulfate, in amounts normally employed for such treatment, can be incorporated with the d-glyceraldehyde. Alternatively, other antibacterials such as the sulfonamides, e.g., sulfisoxazole, and nitrofurazone and its derivatives can be used instead of the foregoing antibiotics.

*Example 10.—Sterile Aqueous Preparation*

A lot of 10,000 ml. of a sterile aqueous preparation containing 100 mg. l-glyceraldehyde per ml. (10%) is prepared from the following materials:

| | Gm. |
|---|---|
| Sodium chloride | 90 |
| Myristyl-gamma-picolinium chloride | 2 |
| l-Glyceraldehyde | 1000 |

Water for injection, q.s. 10,000 ml.

The vehicle is prepared by dissolving all the ingredients in the water except the l-glyceraldehyde. The solution is sterilized by filtration. The l-glyceraldehyde is micronized and sterilized by ethylene oxide vapors. The sterile, micronized l-glyceraldehyde is then dispersed aseptically in the sterile vehicle. The final aqueous preparation is filled into small, sterile containers which are then sealed.

The foregoing aqueous preparation of l-glyceraldehyde is used clinically in 1-ml. doses by intra-articular injection into the synovial sac of a joint affected with rheumatoid arthritis to suppress inflammation. If required, additional 1-ml. doses can be given at weekly intervals.

In a similar manner, a 25% preparation is prepared by replacing the 1000 gm. of l-glyceraldehyde by 2500 gm. of drug. It is used clinically in 0.5 to 1 ml. doses as indicated above.

For the dl-glyceraldehyde of each of the foregoing Examples 1 through 8 there can be substituted equal amounts of either the individual d- or l-isomer or mixtures thereof in other than equal amounts to give compositions administrable for the same indications and in the same quantities as exemplified therein.

What is claimed is:

1. A method of local anti-inflammatory thereapy which comprises: topically applying glyceraldehyde at the side of the inflammation.

2. A method of local anti-inflammatory therapy which comprises: topically applying a lotion containing from about 5 to about 25% dl-glyceraldehyde at the site of the inflammation.



3. A method of local anti-inflammatory therapy which comprises: topically applying from about 1 to about 50% glyceraldehyde, dispersed in a topical pharmaceutical carrier.

**References Cited** in the file of this patent

Manly: Drug and Cosmetic Industry, vol. 76, pages 326–7 and 422–5, 1955.