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[54] **FATTY ALCOHOL-PROPYLENE GLYCOL VEHICLE**

[75] Inventors: **Martin Katz**, Atherton, Calif.; **Herbert M. Neiman**, Philadelphia, Pa.

[73] Assignee: **Syntex Corporation**, Panama

[*] Notice: The portion of the term of this patent subsequent to July 13, 1988, has been disclaimed.

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Related U.S. Application Data

[62] Division of Ser. No. 745,989, July 19, 1968, Pat. No. 3,592,930.

[52] **U.S. Cl.** **424/358;** 424/243

[51] **Int. Cl.** **N61k 9/06**

[58] **Field of Search** 424/358

[56] **References Cited**

UNITED STATES PATENTS

2,165,857	7/1939	Jacobowitz	424/358 X
2,600,344	6/1952	Van Meter	424/240
2,779,707	1/1957	Jacobson et al.	424/240
2,841,527	7/1958	Freedman et al.	424/240
2,856,329	10/1958	Taylor et al.	424/240
3,071,511	1/1963	Sasaki et al.	424/243
3,210,248	10/1965	Feldmann et al.	424/239
3,342,676	9/1967	Szabo et al.	424/358 X
3,352,753	11/1967	Lerner	424/241
3,472,931	10/1969	Stoughton	424/240 X
3,482,018	12/1969	Szabo et al.	424/358 X
3,551,554	12/1970	Herschler	424/7
3,592,930	7/1971	Katz et al.	424/243

FOREIGN PATENTS OR APPLICATIONS

497,263	12/1938	United Kingdom
827,095	5/1958	France
696,429	8/1940	Germany
1,080,735	4/1960	Germany

Primary Examiner—Shep K. Rose

Attorney, Agent, or Firm—Joseph I. Hirsch; William B. Walker

[57] **ABSTRACT**

A substantially non-aqueous medicant vehicle containing from 15 to 45 parts saturated fatty alcohol having from 16 to 24 carbons, from 45 to 85 parts glycol solvent, from 0 to 15 parts plasticizer, from 0 to 15 parts coupling agent, 0 to 20 parts penetrant, and if desired, other pharmaceutical adjuvants. This base is a suitable vehicle for all types of therapeutic agents for topical application including antibiotics, steroids, antihistamines, antiseptics, anesthetics, antibacterials, fungicides, and the like. The vehicle has shown particular advantages with anti-inflammatory topical corticoids.

11 Claims, No Drawings

FATTY ALCOHOL-PROPYLENE GLYCOL VEHICLE

This application is a division of application Ser. No. 745,989, filed July 19, 1968, now U.S. Pat. No. 3,592,930 issued July 13, 1971.

This invention relates to vehicles for topical applications of medicants (i.e., active ingredients) and to mixtures of the vehicles and medicants. In particular, this invention relates to new, improved medicant vehicles having advantages over previously known vehicles.

One of the oldest types of medicant vehicles is the ointment, a preparation containing active medications that can be readily spread on and rubbed into the skin. It serves as a means for distributing the medication uniformly over the skin surface and maintaining it there until beneficial action can occur. The earliest preparations were based on fats, greases and petrolatum. These are, by nature, greasy, are not water-washable and have a limited ability to release medication to the skin. A non-aqueous ointment of more recent origin is Carbowax, a grease-like mixture of polyethylene glycols (molecular weight of 1000 to 20,000). This vehicle, although water-washable, has a greasy texture and does not provide an occlusive coating on a treated surface. Prior to this invention, these anhydrous ointment bases were the only vehicles available for medicants which deteriorate in the presence of moisture.

Emulsified creams, such as cold creams, were developed to reduce greasiness, while still maintaining the unctuousness and spreadability of the older grease-type ointments. The emulsified creams have an aqueous base, however, and are not suitable as vehicles for many drugs because their pH or water content may destroy the medicant. The medicant, in turn may destroy the emulsions, that is, break the emulsions and permit separation of the vehicle components. These emulsions also must contain surfactants as emulsifiers and wetting agents.

It is accordingly the purpose of this invention to provide an essentially anhydrous, water-washable base which is more effective than standard anhydrous ointment bases of the grease-type because it can preserve the activity of medicants which deteriorate in the presence of moisture; provide an occlusive film for longer and better therapeutic activity; release the medicants more quickly and effectively; bring dissolved antibacterial agents in known dilution in contact with the skin; spread evenly and adhere well even if the skin is moist; be easily removed with water from skin or fabrics; be soluble in water and thus permit the incorporation of aqueous ingredients; provide media to readily absorb discharges from wounds; serve as an excellent levigating material for many prescribed ingredients that usually require separate treatment before being incorporated into ointment bases; and because it does not hydrolyze, deteriorate, become rancid, or support mold growth.

The medicant vehicle or base according to this invention can have the composition shown in Table A.

Table A

Ingredient	Concentration [a]	
	Operable	Preferred
Fatty alcohol	15–45	20–35
Glycol solvent	45–85	55–80

Table A-Continued

Ingredient	Concentration [a]	
Compatible plasticizer	0–15	2–10
Compatible coupling agent	0–15	1–5
Penetrant	0–20	0–10

[a] Weight percent or parts by weight per 100 parts.

All concentrations are herein given as weight percents or parts by weight unless otherwise specified. It is also intended that the chemical compounds in each class of ingredients discussed hereinafter be limited to pharmaceutically acceptable compounds in the concentrations indicated.

The fatty alcohol ingredient in the vehicle composition of this invention can be any saturated fatty alcohol having from 16 to 24 carbons or mixtures thereof, and is preferably a monohydric primary alcohol. Suitable fatty alcohols include cetyl alcohol, stearyl alcohol, behenyl alcohol, and the like. Vehicles having excellent properties have been made using stearyl alcohol, or mixtures of cetyl, stearyl and behenyl alcohols as the fatty alcohol component. The fatty alcohol component must be substantially free from any significant amount of unsaturated alcohols or fatty alcohols having fewer than 16 carbons. The terms "substantially free from", as used herein, is defined as indicating the compositions of this invention contain less than irritating or otherwise medically undesirable amounts of the indicated substances. Since the C_{16} to C_{24} fatty alcohols available commercially contain impurities including some proportion of fatty alcohols having fewer than 16 carbons, total avoidance of alcohols having fewer than 16 carbons from the mixture is not practicable. Careful selection of raw materials is preferable, however, to maintain the percentage of irritating fatty alcohols to less than 10 percent of the total fatty alcohol concentration.

The glycol solvent component can be a propylene glycol such as 1,2-propylenediol, 1,3-propylenediol, polyethylene glycol having a molecular weight of from 100 to 800, dipropylene glycol, etc., and mixtures thereof.

The fatty alcohol and glycol solvent ingredients are the principle components and are satisfactory as the sole vehicle components in the composition of this invention. The glycol solvent can function either as a solvent for a glycol-soluble medicant or a carrier for a glycol-insoluble medicant. The fluidity of the composition increases with increased concentrations of the glycol solvent. In the combination with the glycol solvent, the fatty alcohol (a solid component which naturally thickens the composition) forms a unique protective, lubricant and occlusive film which is highly desirable in several types of dermatological preparations.

The composition can also contain a compatible plasticizer such as polyethylene glycol having a molecular weight of from above 800 to 20,000, 1,2,6-hexanetriol, sorbitol, glycerol, and the like. The plasticizer maintains homogeneity in the fatty alcohol-glycol solvent mixture at ambient temperatures, that is, temperatures at which the fatty alcohol is naturally a solid. This component also improves the plasticity and uniformity of medicant mixtures with the vehicle and provides to the vehicle smoothness and a more pleasing "feel"; hence the vehicle containing the plasticizer is more pharmacologically acceptable.

The term "compatible" is defined herein to indicate a component which will not cause separation (loss of homogeneity) of the other components, that is, the fatty alcohol and glycol solvent at temperatures up to 45°C.

The plasticizer concentration can be within the range of from 0 to 15 percent. Concentrations above 15 percent may provide a composition which has a consistency unsuitable for normal applications or cause instability of the vehicle mixture and some separation of the components. In general, the particular plasticizer concentration necessary to provide a desired consistency, degree of smoothness and plasticity will vary with the choice of the fatty alcohol component, the choice of glycol solvent, and the ratio of these components in the vehicle.

The particular concentration of plasticizer which will provide the most stable composition will depend upon the choice of plasticizer, and choice and concentration of the other ingredients. Preferably, the plasticizer concentration should be balanced so the vehicle has freeze-thaw stability, i.e., does not separate after repeated cycles of solidification (by cooling) and liquefaction (by heating).

The vehicle of this invention can also contain a compatible, pharmaceutically acceptable coupling agent, the term "compatible" having the above-defined meaning. Suitable coupling agents include saturated fatty acids having from 16 to 24 carbons such as stearic acid, palmitic acid, behenic acid; fatty amides such as oleamide, palmitamide, stearamide, behenamide; and esters of fatty acids having from 16 to 24 carbons such as sorbitan monostearate, polyethylene glycol monostearate, propylene glycol monostearate and the corresponding mono-esters of other fatty acids such as oleic acid and palmitic acid. Best coupling is achieved, particularly with the esters, if the fatty group of the coupling agent and fatty alcohol is the same or has approximately the same number of carbons. It is essential that the fatty acids be saturated and the fatty acids and amides be essentially free from irritating amounts of acids or amides having fewer than 16 carbons.

The coupling agent concentration can be within the range of from 0 to 10 percent. In general, the coupling agents maintain homogeneity of the vehicle and prevent exudation or "bleeding" of the more liquid components of the vehicle (glycol solvent) upon prolonged storage at elevated temperatures. The medicant vehicle preferably contains a quantity of the coupling agent sufficient to prevent visible exudation of the glycol solvent from the vehicle after storage at 45°C for 48 hours. No more of the coupling agent is required than is needed to prevent this exudation. Excess quantities are undesirable because other ingredients and their functions are needlessly diluted. If the coupling agent concentration is not carefully balanced with the other components, stability of the medicant vehicle after one or more repeated cycles of solidification (by cooling) and liquefaction (by heating), that is, the freeze-thaw stability is impaired.

The penetrants increase the penetration and therapeutic activity of the medicants and are usually solvents or co-solvents for the medicants. The penetrants can be used in concentrations which are pharmaceutically acceptable for the intended use not to exceed 20 percent of the weight of the vehicle. Representative examples of penetrants include dimethylsulfoxide, dimethylacetamide, dimethylformamide, and the like.

It should be understood that the medicant vehicles of this invention can also contain non-essential ingredients. The vehicle can contain up to 10 weight percent of conventional pharmaceutical adjuvants. These adjuvants or additives are conventionally used to improve consistency, homogeneity, spreadability, texture and appearance of the vehicle or its residual film. They can be used to give to a residual film, varying degrees of continuity, flexibility, adhesion, occlusion, water repellancy, washability, and the like. Examples of typical adjuvants include surfactants (cationic, anionic, or nonionic) such as Pluronics, polyoxyethylene-polyoxypropylene copolymers; gums such as natural gums including agar, acacia gum, guar gum, tragacanth, and the like; cellulose derivatives including cellulose ethers such as methyl cellulose, ethyl cellulose, carboxymethyl cellulose, and the like; starch and starch derivatives; and water-soluble vinyl polymers such as polyvinylpyrrolidone, polyvinyl alcohol, vinylpyrrolidone-vinyl alcohol copolymers, and the like.

The vehicle base of this invention does not contain any significant quantity of petrolatum or mineral oil. It is therefore not a classical "ointment" and is not water-insoluble.

The medicant vehicle of this invention is essentially a non-aqueous base, that is, it is not an emulsion and consequently is not a "cream" in the technical sense. It is preferably anhydrous, but can contain minor amounts of water such as up to 3 percent water. The water concentration should not be sufficient to cause separation of the other vehicle components or precipitant medicants dissolved in the vehicle.

The vehicle of this invention can be made from the above ingredients by throughly mixing them at ambient or elevated temperatures. Preferably the components are thoroughly mixed while each is in a liquid state, and the mixture is cooled with good agitation to room temperature. By way of referring to a preferred composition as an example, cetyl alcohol, stearyl alcohol, behenyl alcohol, stearic acid, polyethylene glycol and 1,2,6-hexanetriol can be mixed with stirring to about 80°–85°C; propylene glycol can be heated to 90°–95°C with stirring (a medicant stable at this temperature could be added to either phase during this step); and the two liquids can be mixed with stirring. Good agitation is provided until the mixture cools to room temperature.

If desired, additional mechanical agitation and/or shock cooling steps can be used as intermediate or final steps in the manufacturing process to impart more homogeneity or improve textuure. Processing equipment suitable for these steps is known and includes heat exchangers, propeller mixers, colloid mills, homogenizers, roller mills, and the like.

The base of this invention can be used successfully as a vehicle for most types of therapeutic agents for topical application including antibiotics such as oxytetracycline, chlortetracycline, streptomycin, bacitracin, chloramphenicol, tyrothricin and the like; steroids having anti-inflammatory or other beneficial activity; antihistamines such as prophenpyridamine maleate and diphenhydramine hydrochloride; anesthetics such as benzocaine and lidocaine; antibacterials including iodine, nitrofurazone, sulfanilamide and derivatives, and benzalkonium chloride; fungicides such as undecylenic

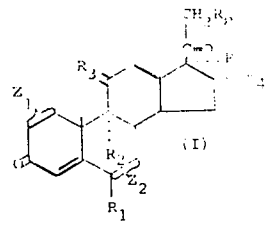
acid; and older therapeutic agents including coal tar, balsam Peru, ammoniated mercury, chrysarobin, ichthammol, sulfur, and the like.

In corporation of the medicament in this base requires no deviation from standard techniques such as those described in Remington's Practice of Pharmacy, 12th edition by Martin and Cook, Mack Publishing Company (1961). A bulky, insoluble powder should be mixed beforehand with a small proportion of the base mixture or propylene glycol and then blended with the remainder of the base. These products are usually improved by passing them through an ointment or roller mill. Many substances insoluble in conventional greasy bases will dissolve in the water-soluble propylene glycol ointment base to give completely homogeneous ointments. It may be desirable at times to add the medicinal as an alcoholic or aqueous solution, and these are readily miscible with the water-soluble bases. Coal tar, ichthammol, balsam Peru and others that require special processing in greasy bases can be readily incorporated in the base of this invention. The medicant can be incorporated into the final base or introduced into the base mixture with one of its components.

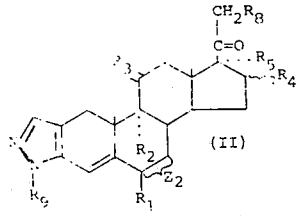
Medicants which are insoluble in propylene glycol can be dissolved or suspended in the melted fatty alcohol composition. Heat sensitive medicants (in particular some antibiotics) can be dissolved or suspended in a small amount of glycol solvent or other liquid, and then mixed with the vehicle during or after its preparation.

The amount of medicant to be incorporated into the base will, of course, depend upon the type of medicant and its intended use; the determination of suitable medicant concentrations is a routine matter fully within the conventional skills of the art. In general, therapeutically effective amounts of the medicant are incorporated into the vehicle.

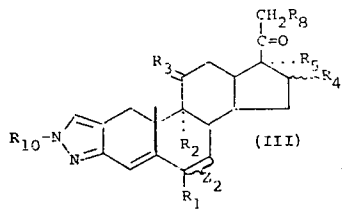
The vehicle of this invention is particularly suitable for use with anti-inflammatory topical steroids represented by Formulas I, II and III.



(I)



(II)



(III)

wherein

R_1 is hydrogen, methyl, fluoro, or chloro and when Z_2 is a single bond, R_1 can be either α or β oriented;

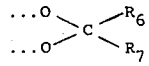
R_2 is hydrogen, chloro, or fluoro;

R_3 is keto or 

wherein R_3' is hydrogen, hydroxy, chloro, or fluoro;

R_4 is hydrogen, methyl, hydroxy, or conventional hydrolyzable esters thereof;

R_5 is hydrogen, hydroxy, conventional hydrolyzable esters thereof, or when taken together with R_4;



wherein

R_6 is hydrogen or alkyl of up to eight carbons, and

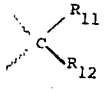
R_7 is hydrogen, or alkyl or an aryl group of up to eight carbons;

R_8 is hydroxy, conventional hydrolyzable esters thereof, tetrahydropyranyloxy, tetrahydrofuranyloxy, 4'-(lower)alkoxytetrahydropyran-4'-yloxy, lower alkoxy, lower cycloalkoxy, lower cycloalkenyloxy, chloro, or fluoro;

R_9 and R_{10} are hydrogen, methyl, phenyl, chlorophenyl, fluorophenyl, methylphenyl, or methoxyphenyl (the substituted phenyls preferably being substituted in the para position);

R_{11} and R_{12} each is hydrogen, chloro, or fluoro;

Z_1 and Z_2 each is a single bond, double bond, or



The terms "(lower)alkyl" and derivations thereof appearing in the above definitions and elsewhere in the instant specification denote alkyl groups having from one to six carbon atoms, inclusive, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, amyl, hexyl, and the like.

The term "conventional hydrolyzable ester" as used herein denotes those hydrolyzable ester groups conventionally employed in the steroid art, preferably those derived from hydrocarbon carboxylic acids or phosphoric acids and their salts. The term "hydrocarbon carboxylic acid" defines both substituted and unsubstituted hydrocarbon carboxylic acids. These acids can be completely saturated or possess varying degrees of unsaturation (including aromatic), can be of straight chain, branched chain, or cyclic structure, and preferably contain from one to 12 carbon atoms. In addition, they can be substituted by functional groups, for example, hydroxy, alkoxy containing up to six carbon atoms, acyloxy containing up to 12 carbon atoms, nitro, amino, halogeno, and the like, attached to the hydrocarbon backbone chain. Typical conventional hydrolyzable esters thus included within the scope of the term and the instant invention are acetate, propionate,

butyrate, valerate, caproate, enanthate, caprylate, pelargonate, acrylate, undecenoate, phenoxyacetate, benzoate, phenylacetate, diphenylacetate, diethylacetate, trimethylacetate, t-butylacetate, trimethylhexanoate, methylneopentylacetate, cyclohexylacetate, cyclopentylpropionate, adamantoate, glycolate, methoxyacetate, hemisuccinate, hemiadipate, hemi-β,β-dimethylglutarate, acetoxyacetate, 2-chloro-4-nitrobenzoate, aminoacetate, diethylaminoacetate, piperidinoacetate, β-chloropropionate, trichloroacetate, β-chlorobutyrate, dihydrogen phosphate, dibenzyl phosphate, benzyl hydrogen phosphate, sodium benzyl phosphate, cyclohexylammonium benzyl phosphate, sodium phenyl phosphate, sodium ethyl phosphate, di-p-nitrobenzyl phosphate, sodium o-methoxyphenyl phosphate, cyclohexylammonium p-cyanobenzyl phosphate, sodium phenacyl phosphate, benzyl o-carbomethoxyphenyl phosphate, and the like.

By the term "aryl" are included aryl, aralkyl, and alkaryl groups, such as phenyl, p-chlorophenyl, p-methoxyphenyl, benzyl, phenethyl, tolyl, ethylphenyl, and the like. The wavy line ({) designates and includes both the alpha and beta configurations.

The above anti-inflammatory steroids have been previously disclosed in U.S. Pats. Nos. 3,365,446, 3,067,194, 3,364,203 and 3,053,838 for example.

The 4′-(lower)alkoxytetrahydropyran-4′-yl are prepared from the corresponding hydroxy compounds by reacting the latter compounds under substantially anhydrous conditions with an excess of 4′-(lower)alkoxy-5′,6′-dihydro-2H-pyran. The reaction is conducted in the presence of a small amount of an acidic catalyst, such as hydrochloric acid, p-toluene-sulfonic acid, boron trifluoride etherate, and the like, either alone or together with an inert, organic solvent, such as benzene, diethyl ether, or the like, at a temperature ranging from abut 0°C to about 80°C for about five minutes to about 48 hours, thus giving the corresponding 21-(4′-loweralkoxytetrahydropyran-4′-yloxy) ethers as explained more fully in U.S. Pat. application Ser. No. 731,299 filed May 22, 1968.

Prior to the above reaction, protection should be provided for readily etherified hydroxyl groups other than the C-21 hydroxyl groups, e.g. 16α-hydroxy group. Such a group should be selectively acylated such as by reaction with acetic anhydride in pyridine, the quantity of acetic anhydride being sufficient to acylate both the C-16 and C-21 hydroxyl groups. Hydrolysis of the diacetate in methanol with less than one molar equivalent of sodium carbonate in water yields the 16-acetoxy-21-hydroxy product which can be separated by conventional chromatography on neutral alumina, for example. After the above etherification, the acetoxy protecting groups can be removed by treatment of the ester in a methanol solution of potassium hydroxide.

The above anti-inflammatory topical medicants are thoroughly mixed with the base in therapeutically effective amounts. The particular concentration of the medicant in the base will vary depending upon the particular activity of the steroid used considered in conjunction with the condition and subject to be treated. In general, therapeutically effective amounts of these compounds can be as low as 0.00001 weight percent or lower, for example. For some uses, as high as 5 weight percent steroid or higher may be desired.

The medicant base of this invention has been found to be unexpectedly superior to previously known vehicles for use with known topical corticoids, for example, fluocinolone acetonide (6α,9α-difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione) and the corresponding 21-acetate (6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-acetoxypregna-1,4-diene-3,20-dione). In preliminary tests, these medicants have been observed to have several times greater activity in comparision to their activity in previously known vehicles at the same concentration.

This invention is further illustrated by the following specific but non-limiting examples.

EXAMPLE 1

The following ingredients were mixed at 90°C and cooled to room temperature with good agitation.

Formula	Concentration, wt.% A	B	C
Ingredients			
Cetyl alcohol	7.35	9.50	12.60
Stearyl alcohol	6.30	8.00	9.45
Behenyl alcohol	11.55	12.00	13.65
Propylene glycol[1]	74.80	70.50	64.30

[1]1,2-propylene diol

These compositions were found to have the spreadability, penetrability and solvent powder required for use with medicants such as steroids, anesthetics, antiseptics, antibiotics, and the like.

EXAMPLE 2

The compositions of Example 1 were found to have greater plasticity and uniformity when mixed with polyethylene glycol and/or hexanetriol to provide the following formulas.

Formula D

Ingredients	Concentration, wt.%
Cetyl alcohol	1.75
Stearyl alcohol	7.00
Behenyl alcohol	12.25
Polyethylene glycol[1]	5.00
1,2,6-hexanetriol	6.00
Propylene glycol[2]	68.00

[1]molecular weight 6000.
[2]1,2-propylene diol

EXAMPLE 3

The addition of saturated fatty acids and/or fatty amides having at least 16 carbons to the ingredients of Formula D was found to provide a vehicle having improved storage characteristics at elevated temperatures. In preparing each of the following formulas, the ingredients with the exception of propylene glycol were mixed with stirring at 80°–85°C, and were then mixed with propylene glycol having a temperature of 90°–95°C. The mixture was permitted to cool to room temperature with good agitation.

Formula	Concentration, wt.% E	F
Ingredients		
Cetyl alcohol	1.75	1.75
Stearyl alcohol	3.50	7.00
Behenyl alcohol	12.25	9.75
Stearic acid	3.50	—
Stearamide	—	4.00
Polyethylene glycol[1]	5.00	5.00
1,2,6-hexanetriol	6.00	6.00
Propylene glycol[2]	68.00	66.50

[1]molecular weight 6000.
[2]1,2-propylene diol.

EXAMPLE 4

Following the general procedure of Example 3, a formula based entirely on stearly alcohol for the saturated monohydric alcohol was found to be suitable. The ingredients of this formula are shown below.

Formula G

Ingredients	Concentration, wt. %
Stearyl alcohol	30.0
Propylene glycol[1]	70.0

[1]1,2-propylene diol

EXAMPLE 5

Following the general procedure of Example 3, the following satisfactory formulations can be prepared.

Formula designation	Concentration, wt.% II	I	J	K	L
Ingredients					
Stearyl alcohol	25	25	28	25	25
Stearic acid	5	5	—	5	5
Polyethylene glycol[1]	—	5	5	—	5
Hexanetriol[2]	—	5	5	—	5
Sorbitan monostearate	—	—	2	—	—
Propylene glycol[3]	70	60	60	—	40
Polyethylene glycol[4]	—	—	—	70	20

[1]molecular weight, 6000
[2]1,2,6-hexanetriol
[3]1,2-propylenediol
[4]molecular weight, 400

EXAMPLE 6

In this example, 0.25 gm. of 6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-acetoxypregna-1,4-diene-3,20-dione, was mixed with 100 gm. of Formula A, Example 1 to form a highly effective anti-inflammatory mixture. The steroid was dissolved in 680 gm. of propylene glycol at 90°–95°C. The latter then was mixed with a mixture of the other ingredients at 80°–85°C. The mixture was cooled to room temperature with good agitation, mixed with the remainder of the propylene glycol heated to 45°C, allowed to settle and deaerate overnight, gently mixed and filled into containers.

The mixture was tested and found to be mold and bacteria resistant as follows. The test organisms used in the study were

Bacteria	ATCC No.
Pseudomonas aeruginosa	10145
Proteus vulgaris	881
Staphylococcus aureus	6538
Bacillus cereus	11778
Molds	
Aspergullus niger	9642
Penicillium luteum	9644
Candida albicans	10231
Tricophyton mentagrophytes	9533

The test procedure was as follows:

Twenty-four hour broth cultrues of the listed bacteria were prepared in Tryptose Phosphate Broth. The molds were grown in Sabouraud Liquid Medium. Just prior to the performance of the assay, all the test organisms were diluted 1:100 with the specific media as diluent. 0.01 ml. of each diluted organism was intimately mixed with a 15 ml. portion of the test material. Test samples inoculated with the mixture of bacteria were incubated at 37°C, and portions inoculated with the mixture of molds were incubated at room temperature. At the end of 48 hours contact and two weeks contact, samples were removed and plated out on appropriate media using the standard serial dilution technique.

The test compounds were found to be highly effective against both bacteria and mold pooled cultures after two days and two weeks exposure.

The procedure, repeated with 6α,9α-difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione, yielded the same results.

EXAMPLE 7

The steroids used in Example 6 (0.25 gm.) are mixed with 1000 gm. of each of Formulas B, C, D, E, F, G, H, I, J, K and L by the general procedure described in Example 6, the steroid being dissolved in glycol solvent before being mixed with the other components. The product compositions are mold and bacteria resistant when tested by the procedure described in Example 6.

EXAMPLE 8

Each of 0.25, 0.5 and 1.0 gm. quantities of the following anti-inflammatory steroids, when mixed with 1000 gm. of each of the vehicles described in Examples 1–5, inclusive, are effective for topical treatment of inflammation:

9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione,

9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-valeroxy-pregna-1,4-diene-3,20-dione,

17α,21-dihydroxypregn-4-ene-3,11,20-trione,

17α-hydroxy-21-acetoxypregn-4-ene-3,11,20-trione,

21-hydroxypregn-4-ene-3,20-dione,

21-acetoxypregn-4-ene-3,20-dione,

21-pivaloxypregn-4-ene-3,20-dione,

9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,

9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione-21-sodium phosphate,

6α,9α-difluoro-11β,21-dihydroxy-16α,17α-isopropylidene-dioxypregna-1,4-diene-3,20-dione,

6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-acetoxypregna-1,4-diene-3,20-dione,

6α-methyl-9α-fluoro-11β,17α-dihydroxypregna-1,4-diene-3,20-dione,

6α-fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione,

6α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione,

6α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione,

11β,17α-dihydroxy-21-acetoxypregn-4-ene-3,20-dione,

6αmethyl-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione,

6α-methyl-11β,17α-dihydroxy-21-acetoxypregna-1,4-diene-3,20-dione,

6α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,

6α-fluoro-11β,17α-dihydroxy-16α-methyl-21-acetoxypregna-1,4-diene-3,20-dione,

6α-fluoro-11β,17α-dihydroxy-16α-methyl-21-valeroxypregna-1,4-diene-3,20-dione,

11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione,

11β,17α-dihydroxy-21-acetoxypregna-1,4-diene-3,20-dione,

17α,21-dihydroxypregna-1,4-diene-3,11,20-trione,

17α-hydroxy-21-acetoxypregna-1,4-diene-3,11,20-trione,

9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione,

9α-fluoro-11β,16α,17α-trihydroxy-21-acetoxypregna-1,4-diene-3,20-dione,

9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione,

6α-fluoro-9α,11β-dichloro-16α,17α-isopropylidenedioxy-21-hydroxypregna-1,4-diene-3,20-dione,

6α9α-difluoro-11β,21-dihydroxy-16α-methyl-17α-valeroxypregna-1,4-diene-3,20-dione, 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,

6α,7α-difluoromethylene-11β,17α,21-trihydroxypregn-4-ene-3,20-dione,

6α-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione, and

6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-chloropregna-1,4-diene-3,20-dione.

The invention claimed is:

1. A substantially anhydrous pharmaceutical vehicle of cream-like consistency consisting essentially of

a. from 20 to 35 parts by weight saturated fatty alcohol having from 16 to 24 carbon atoms,

b. from 55 to 80 parts by weight of a glycol solvent selected from the group consisting of 1,2-propylenediol, 1,3-propylenediol, dipropylene glycol, and mixtures thereof,

c. from 0 to 15 parts by weight of compatible plasticizer,

d. from 0 to 15 parts by weight of compatible coupling agent,

e. from 0 to 20 parts by weight of penetrant, and

f. from 0 to 3 weight percent water, the composition being substantially free from petrolatum, mineral oil, monohydric fatty alcohols and fatty acids which are unsaturated, and monohydric alcohols, fatty acids and fatty amides which have less than 16 carbon atoms, said vehicle being particularly suitable for providing an occlusive film for releasing topically active cortico-steroids, and for distributing medication over the skin surface and maintaining it there until beneficial action occurs.

2. The vehicle of claim **1** wherein said vehicle includes

c. from 2 to 10 parts by weight of compatible plasticizer, and

d. a concentration of coupling agent sufficient to prevent visible exudation of the glycol solvent from the composition after storage for 48 hours at 45°C,

e. and from 0 to 10 parts by weight penetrant.

3. The composition of claim **1** wherein the compatible plasticizer is polyethylene glycol having a molecular weight of from above 800 up to 20,000, hexanetriol, sorbitol, glycerol or mixtures thereof.

4. The composition of claim **1** wherein the compatible coupling agent is fatty acid having from 16 to 24 carbons, fatty amide having from 16 to 24 carbons, fatty acid monoester with aliphatic alcohols or mixtures thereof.

5. The vehicle of claim **1** wherein said glycol solvent is propylene glycol, said propylene glycol being admixed with a polyethylene glycol which is liquid at room temperature.

6. A vehicle of claim **5** wherein said propylene glycol is 1,2-propylenediol.

7. A vehicle of claim **5** wherein said polyethylene glycol has an average molecular weight of about 400.

8. A vehicle of claim **5** wherein said propylene glycol is 1,2-propylenediol and said polyethylene glycol has an average molecular weight of about 400.

9. The vehicle of claim **1** wherein the glycol solvent is 1,2-propylenediol.

10. The vehicle of claim **1** wherein said vehicle contains about 30 parts by weight stearly alcohol.

11. The vehicle of claim **1** wherein said vehicle contains about 30 parts by weight stearly alcohol, 5 parts by weight polyethylene glycol 6000, 5 parts by weight 1,2,6-hexanetriol and about 60 parts by weight 1,2-propylenediol.

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 3,888,995

DATED : July 18, 1975

INVENTOR(S) : Martin Katz et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 9, line 39, in the heading of the Table on Example 5, change "II" to -- H --. Column 11, line 40, -- 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione, -- should be read as a separate listing. Column 12, line 26, change "composition" to -- vehicle --. Column 12, line 30, change "composition" to -- vehicle --. Column 12, line 50, change "stearly" to -- stearyl --.

Signed and Sealed this

ninth Day of *December 1975*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks