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TOPICAL ANTI-INFLAMMATORY PROCESS

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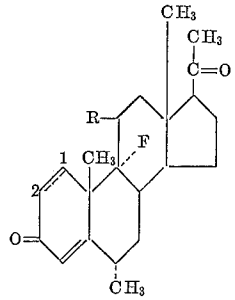
1 Claim. (Cl. 167—58)

This invention relates to pharmaceutical compositions for topical use and, more particularly, to such compositions in which the primary active ingredient is 6α-methyl-9α-fluoro-11β-hydroxyprogesterone, 6α-methyl-9α-fluoro-11-ketoprogesterone, 1-dehydro-6α-methyl-9α-fluoro-11β-hydroxyprogesterone and 1-dehydro-6α-methyl-9α-fluoro-11-ketoprogesterone.

The present application is a continuation-in-part of Patent No. 2,968,655 and Patent No. 3,045,031.

The primary active ingredients of these compositions can be represented by the following formula:



wherein R is β-hydroxy or keto and the dotted line at the 1-2 position indicates the optional double bond defining the 1-dehydro analogs.

The said active ingredients are highly potent, locally active anti-inflammatory agents. In tests on humans, for example, a representative composition hereof was found to exhibit approximately 120 times the topical anti-inflammatory activity of hydrocortisone, accompanied by no untoward side effects. These compositions are useful in the treatment of such inflammatory conditions as contact dermatitis, atopic dermatitis, neuro-dermatitis, anogenital pruritus, 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. In addition to the treatment of humans, 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, broadly described, is from about 0.001% to about 1%. Although higher concentrations can be employed in isolated instances, the exceptionally high anti-inflammatory activity characterizing these compounds when used topically generally obviates the necessity therefor. The preferred range for the majority of clinical indications is from about 0.01% to about 0.25%. 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 in this application 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, 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, 11th edition (1956), page 336, 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 for direct external application, such forms being sprays (e.g., for oral or nasal use), aerosols (e.g., for deeper penetration than is usually afforded by a spray), 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 (e.g., for intra-articular or intrabursal injection) and the like.

The primary active ingredients can be prepared as exemplified below:

PREPARATION 1

6α-Methyl-4,9(11)-Pregnadien-3,20-Dione

A solution of 5.0 grams of 6α-methyl-11β-hydroxyprogesterone in 58 milliliters of dry pyridine (distilled over barium oxide), was treated with 3.0 grams of N-bromoacetamide. The mixture was stirred for fifteen minutes and cooled to 0° C. Gaseous sulfur dioxide was slowly passed over the surface of the reaction mixture for a period of one-half hour at 12° C. until the reaction mixture gave a negative reaction with potassium iodide-starch paper. The reaction mixture was then poured into 150 milliliters of ice-water and stirred. A yellowish-white gummy material was collected on filter paper; the filtrate was extracted with three 50-milliliter portions of methylene chloride, and the gum was dissolved in the combined extracts of methylene chloride. The thus-obtained methylene chloride solution was washed several times with water, then dried over anhydrous sodium sulfate and evaporated to dryness at 60° C. in vacuo to yield a residue of 4.62 grams. This residue was chromatographed over 350 grams of Florisil (synthetic magnesium silicate). For the chromatography the 4.62 grams of residue was redissolved in 350 milliliters of methylene chloride and poured over the Florisil column. The first three fractions of 375 milliliters each of a solvent consisting of 5 percent acetone and 95 percent Skellysolve B (hexanes) were collected and discarded. Thereupon 15 fractions of 375 milliliters each, consisting of 8 percent acetone and 92 percent Skellysolve B, were collected, combined, dried and evaporated to give 3.27 grams of yellowish crystals. These crystals were recrystallized from methanol to give 2.18 grams of product melting between 115 to 118° C. (yield, 46.3 percent of theoretical). An analytical sample was prepared which melted at 117 to 119.5° C. and had rotation $[\alpha]_D$ at 22° C. of plus 114° in acetone.

Analysis.—Calcd. for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.80; H, 9.19.

PREPARATION 2

6α-Methyl-9α-Bromo-11β-Hydroxy-4-Pregnene-3,20-Dione

A solution of 3.68 grams of 6α-methyl-4,9(11)-pregnadien-3,20-dione in 68 milliliters of methylene chloride and 132 milliliters of tertiary-butanol was prepared. To this solution was added at room temperature (about 23° C.) a solution of 10.45 milliliters of 72 percent perchloric acid in 78.8 milliliters of water and a solution of 1.92 grams of N-bromoacetamide in 33.5 milliliters of tertiary-

butanol. The mixture was stirred for fifteen minutes and thereupon a solution of 1.92 grams of sodium sulfite in 104.5 milliliters of water was added. The mixture was then concentrated in vacuo until crystals appeared. The reaction mixture was thereupon cooled to 5° C. and diluted with 350 milliliters of ice-cold water while stirring. A solid of an off-white color was collected on filter paper, washed with water until neutral and dried in a vacuum dessicator at room temperature. The material obtained weighed 4.9 grams (yield, 102 percent of theoretical) and possessed a melting point of 144.5 to 145.5° C. This material was used in the next step without further purification.

PREPARATION 3

6α-Methyl-9β,11β-Oxido-4-Pregnene-3,20-Dione

A solution of 4.9 grams of crude 6α-methyl-9α-bromo-11β-hydroxy-4-pregnene-3,20-dione from Preparation 2 in 168 milliliters of acetone was stirred and refluxed with 5.8 grams of anhydrous potassium acetate for a period of 20½ hours. The yellow mixture was concentrated in vacuo to 75-milliliter volume and poured thereupon into one liter of water. After extracting the reaction mixture with three 250-milliliter portions of methylene chloride, drying the extracts over anhydrous sodium sulfate and evaporating to dryness in vacuo, 3.57 grams of an oil was obtained. The oil was dissolved in 300 milliliters of methylene dichloride and poured over a column of 300 grams of Florisil (magnesium silicate). The column was developed with 16 portions of 8 percent acetone–92 percent Skellysolve B (hexanes), and one portion of 10 percent acetone–90 percent Skellysolve B. Each solvent portion was 375 milliliters. Fractions 6 through 16 were combined, dried and evaporated to give 3.1 grams of semi-crystalline material which was recrystallized from methanol to give 2.35 grams of product as needles of melting point 119 to 122° C. (yield, 61 percent of theoretical). An analytical sample was prepared which melted at 120.5–122° C. and had a rotation of $[\alpha]_D$ of plus 69° acetone.

Analysis.—Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.84; H, 8.73.

PREPARATION 4

6α-Methyl-9α-Fluoro-11β-Hydroxy-4-Pregnene-3,20-Dione

A solution of 2.03 grams of 6α-methyl-9β,11β-oxido-4-pregnene-3,20-dione in 30 milliliters of methylene chloride and 16.8 grams of tetrahydrofuran was cooled in a Dry-Ice bath for ten minutes. This solution was added portionwise in a ten-minute period with agitation to 9.6 grams of hydrofluoric acid in a polyethylene bottle and cooled in a Dry-Ice bath. After standing in the bath for twenty minutes and thereafter in a refrigerator for 17 hours, the light amber-colored solution was poured into a solution of 46 grams of sodium bicarbonate in 920 milliliters of water and stirred until gas evolution ceased. The mixture was then separated and the aqueous layer extracted with methylene chloride. The combined extracts and organic layer were washed with water, dried over anhydrous sodium sulfate and evaporated to dryness in vacuo at 60° C. The thus-obtained oily residue of 3.15 grams weight was redissolved in 300 milliliters of methylene chloride and poured through a column, charged with 315 grams of Florisil (magnesium silicate). This column was developed as follows: Fractions 1 through 6 with solutions of 8 percent acetone and 92 percent Skellysolve B (hexanes); fractions 7 through 12, 12 percent acetone and 88 percent Skellysolve B. All fractions were 630-milliliter portions. Fractions 9 through 12 were combined and evaporated to give 1.46 grams of semi-crystalline material. This material was recrystallized from methanol to give 1.23 grams of product as white crystals of melting point 170 to 172.5° C. An analytical sample prepared by additional crystallization from methanol melted at 172 to 172.5° C. and had rotation of $[\alpha]_D$ plus 171° in acetone.

Analysis.—Calcd. for $C_{22}H_{31}O_3F$: C, 72.90; H, 8.62; F, 5.24. Found: C, 72.72; H, 8.98; F, 5.30.

Alternatively, 6α-methyl-9α-fluoro-11β-hydroxy-4-pregnene-3,20-dione can be conveniently prepared from 5α,11α-dihydroxy-6β-methylpregnane-3,20-dione [Spero et al., J. Am. Chem. Soc. 78, 6213 (1956)], by making the 11α-toluenesulfonate in known manner with toluenesulfonyl chloride, dehydrating the toluenesulfonate by heating in aqueous solution to obtain 5α-hydroxy-6β-methyl-9(11)-pregnene-3,20-dione, dehydrating thereafter with sodium hydroxide solution to obtain 6α-methyl-4,9(11)-pregnadiene-3,20-dione. This compound is then submitted to the steps shown in Examples 2 through 4, to give the desired 6α-methyl-9α-fluoro-11β-hydroxy-4-pregnene-3,20-dione.

PREPARATION 5

6α-Methyl-9α-Fluoro-11-Ketoprogesterone

To a solution of 0.5 gram of 6α-methyl-9α-fluoro-11β-hydroxyprogesterone in 10 milliliters of acetic acid was added 150 milligrams of chromic anhydride, dissolved in 3 milliliters of acetic acid and 0.2 milliliter of water. The mixture was allowed to stand at room temperature (24° C.) for a period of four hours, then poured into 50 milliliters of water, neutralized with sodium bicarbonate and extracted with three 25-milliliter portions of methylene chloride. The methylene chloride extracts were combined, washed twice with water, dried over anhydrous sodium sulfate, evaporated and the residue twice recrystallized from methanol to give 6α-methyl-9α-fluoro-4-pregnene-3,11,20-trione (6α-methyl-9α-fluoro- 11 -ketoprogesterone).

PREPARATION 6

1-Dehydro-6α-Methyl-9α-Fluoro-11β-Hydroxyprogesterone (6α-Methyl-9α-Fluoro-11β-Hydroxy - 1,4 - Pregnadiene-3,20-Dione)

0.7 gram of 6α-methyl-9α-fluoro-11β-hydroxyprogesterone was dissolved in 50 milliliters of tertiary butyl alcohol and thereto was added 5 milliliters of acetic acid and 250 milligrams of selenium dioxide. The mixture was heated to 75° C. and stirred for 24 hours. Thereafter another portion of 250 milligrams of selenium dioxide was added and heating at 75° C. and stirring continued. The mixture was then cooled, filtered to remove the excess selenium dioxide and evaporated. The thus-obtained residue was recrystallized four times from acetone-Skellysolve B (hexanes) to give pure 1-dehydro-6α-methyl-9α-fluoro-11β-hydroxyprogesterone.

PREPARATION 7

1-Dehydro-6α-Methyl-9α-Fluoro-11-Ketoprogesterone

In the same manner given in Preparation 5, oxidizing 1-dehydro-6α-methyl-9α-fluoro - 11β - hydroxyprogesterone with chromic anhydride in acetic acid and water, yielded 1 - dehydro-6α-methyl-9α-fluoro-11-ketoprogesterone (6α-methyl-9α-fluoro-1,4-pregnadiene-3,11,20-trione).

An alternate method to produce 1-dehydro-6α-methyl-9α-fluoro-11β-hydroxyprogesterone is as follows:

PREPARATION 8

1-Dehydro-6α-Methyl-9α-Fluoro-11β-Hydroxyprogesterone

Five 100-milliliter portions of a medium in 250-milliliter Erlenmeyer flasks containing one percent corn sugar, two percent corn steep liquor (60 percent solids) and tap water was adjusted to a pH of 4.95. This medium was sterilized for one hour at twenty pounds per square inch pressure and 120° C. and inoculated with a one to two day growth of *Septomyxa affinis* A.T.C.C. 6737. The flasks were shaken at room temperature (about 24° C.)

for three days. At the end of this period, this 500-milliliter volume was used as an inoculum for 10 liters of the same glucose-corn steep liquor medium which in addition contained 10 milliliters of an antifoam (a mixture of lard oil and octadecanol). The fermentor was placed in the water bath, adjusted to 28° C., and the contents stirred (300 r.p.m.) and aerated (0.5 liters air per 10 liters of beer per minute). After nineteen hours of incubation, when a good growth had developed, 2 grams of 6α-methyl-9α-fluoro-11β-hydroxyprogesterone, dissolved in 50 milliliters of acetone, and 1 gram of 11β,21-dihydroxy-4,17(20)-pregnadiene-3-one as promoter was added and the incubation (conversion) carried out at the same temperature and aeration for nineteen hours. The mycelium was filtered and the steroidal material was extracted with four 3-liter portions of methylene chloride. The mycelium was extracted with two 500-milliliter portions of acetone and two 500-milliliter portions of methylene chloride. The extracts were combined, evaporated and the residue chromatographed over Florisil (magnesium silicate). The fractions obtained with 5 to 15 percent acetone-Skellysolve B (hexanes) were combined, evaporated and the residue twice recrystallized from methanol to give white crystals of 1-dehydro-6α-methyl-9α-fluoro-11β-hydroxyprogesterone.

In the same manner given in Preparation 8 submitting 6α-methyl-9α-fluoro-4-pregnene-3,11,20-trione to fermentation by *Septomyxa affinis* A.T.C.C. 6737 results in the production of 1-dehydro-6α-methyl-9α-fluoro - 11 - ketoprogesterone. Alternatively 1-dehydro - 6α - methyl-9α-fluoro-11-ketoprogesterone is obtained by oxidizing 1-dehydro-6α-methyl-9α-fluoro - 11β - hydroxyprogesterone as shown in Preparation 5.

Instead of using *Septomyxa affinis* in the dehydrogenation of Preparation 8, 1-dehydro-6α-methyl-9α-fluoro-11β-hydroxyprogesterone and 1-dehydro-6α-methyl-9α-fluoro-11-ketoprogesterone can be prepared by dehydrogenating 6α-methyl-9α-fluoro-11β-hydroxyprogesterone or 6α-methyl-9α-fluoro-11-ketoprogesterone, respectively, with other species of the genus Septomyxa or species selected from the microorganisms of the genera Calonectria, Alternaria, Colletotrichum, Cylindrocarpon, Ophiobolus, Listeria, Corynebacterium, Erysipelothrix species of the family Tuberculariaceae, Nocardia, Cucurbitaria, Leptosphaeriae, Tricothecium, Mycobacterium, Fusarium, Didymella 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, various antibiotics such as neomycin, the tetracyclines, novobiocin, erythromycin, bacitracin, polymyxin, and penicillin alone or in combination; antifungal agents such as iodochlorohydroxyquin, filipin and nystatin; vasoconstrictors such as phenylephrine and isoproterenol, and local anesthetic agents such as procaine hydrochloride, ethylaminobenzoate, phenocaine hydrochloride, tetracaine hydrochloride, lidocaine hydrochloride, primoxine hydrochloride, and the like can be included in the formulation.

Broadly described, the method for the preparation of pharmaceutically acceptable formulations involves the incorporation of the primary active ingredients, 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 inventors for carrying out the invention but are not to be construed as limiting the scope thereof.

Example 1

Ointment

Five kilograms of an ointment containing 0.25% 6α-methyl-9α-fluoro - 11β - hydroxyprogesterone is prepared from the following types and amounts of materials, 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
0.25% 6α - methyl-9α-fluoro-11β-hydroxyprogesterone	12.5
White petrolatum, U.S.P., q.s.	5000

[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 6α-methyl-9α-fluoro-11β-hydroxyprogesterone 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 pruritus, seborrheic dermatitis and the like. The ointment is rubbed gently into the affected area three times daily.

Addition of 50 gm. of novobiocin acid calcium, 150 gm. of tetracycline hydrochloride, 50 gm. of bacitracin (50 units per mg.), 165 gm. of nystatin (3000 units per mg.), 50 gm. of filipin, 2.5 gm. of polymyxin B sulfate (10,000 units per mg.), 25 gm. of erythromycin, a combination of 37.5 gm. of neomycin sulfate and 50 gm. of filipin, a combination of 37.5 gm. of neomycin sulfate, 50 gm. of bacitracin (50 units per mg.) and 2.5 gm. of polymyxin B sulfate (10,000 units per mg.), a combination of 37.5 gm. of neomycin sulfate and 25 gm. of erythromycin, or a combination of 37.5 gm. of neomycin sulfate and 150 gm. of tetracycline hydrochloride is productive of an ointment having application as above in a variety of clinical conditions amenable to topical anti-inflammatory therapy.

Example 2

Ointment, Ophthalmic

Ten kilograms of an ophthalmic ointment containing 0.01% 6α-methyl-9α-fluoro-11β-hydroxyprogesterone 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
0.01% 6α - methyl - 9α - fluoro-11β-hydroxyprogesterone	1
White petrolatum, U.S.P., q.s.	10,000

The 6α-methyl-9α-fluoro-11β-hydroxyprogesterone 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 1% 6α-methyl-9α-fluoro-11β-hydroxyprogesterone and neomycin 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
0.5%	neomycin sulfate	5
1%	6α-methyl-9α-fluoro-11β-hydroxyprogesterone, micronized	10
	Deionized water, q.s.	1000

[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, 6α-methyl-9α-fluoro-11β-hydroxyprogesterone and neomycin sulfate 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 0.001% 6α-methyl-9α-fluoro-11β-hydroxyprogesterone is prepared from the following types and amounts of materials.

Per ml.:

50 mg.	propylene glycol, U.S.P.	gm..	500
2 mg.	methylparaben, U.S.P.	gm..	20
3 mg.	n-butyl-p-hydroxybenzoate	gm..	30
20 mg.	polysorbate 80, U.S.P.	gm..	200
80 mg.	glyceryl monostearate-diethylaminoethyl oleylamide phosphate (19:1)	gm..	800
35 mg.	spermaceti, U.S.P.	gm..	350
5.5 mg.	neomycin sulfate, U.S.P.	gm..	55
0.01 mg.	6α-methyl-9α-fluoro-11β-hydroxyprogesterone, micronized	gm..	0.1
	Perfume	gm..	25
	Deionized water, q.s.	liters..	10

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 neomycin sulfate is dissolved in 3 liters of deionized water and added to the prior mixture. The 6α-methyl-9α-fluoro-11β-hydroxyprogesterone 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 suspension containing 0.05% 6α-methyl-9α-fluoro-11β-hydroxyprogesterone with neomycin and phenylephrine hydrochloride is prepared in a volume of 15 liters from the following types and amounts of materials.

Per ml.:

5 mg.	polysorbate 80, U.S.P.	gm..	75
1 mg.	sodium chloride, U.S.P.	gm..	15
4.5 mg.	sodium citrate, U.S.P.	gm..	67.5
0.23 mg.	myristyl gamma picolinum chloride	gm..	3.5
14.3 mg.	glyceryl monostearate	gm..	214
0.73 mg.	diethylaminoethyl oleylamide phosphate	gm..	11
10 mg.	spermaceti, U.S.P.	gm..	150
10 mg.	propylene glycol, U.S.P.	gm..	150
6.4 mg.	neomycin sulfate powder	gm..	96
2.5 mg.	phenylephrine hydrochloride, U.S.P.	gm..	37.5
0.5 mg.	sorbic acid	gm..	7.5
0.5 mg.	6α-methyl-9α-fluoro-11β-hydroxyprogesterone, micronized	gm..	7.5
	Deionized water, q.s.	liters..	15

Twelve liters of deionized water are 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 6α-methyl-9α-fluoro-11β-hydroxyprogesterone 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 inflammation conditions such as allergic rhinitis.

EXAMPLE 6

Drops

A sterile suspension containing 0.02% 6α-methyl-9α-fluoro-11β-hydroxyprogesterone from the following types and amounts of materials.

Per ml.:

10 mg.	2-hydroxy-3-methylaminopropyl (propylamino)-benzoate hydrochloride	gm..	1
6 mg.	neomycin sulfate	gm..	0.6
4.5 mg.	sodium citrate, U.S.P.	gm..	0.45
150 mg.	polyethylene glycol	gm..	15
0.2 mg.	myristyl gamma picolinium chloride	gm..	0.02
1 mg.	polyvinylpyrrolidone	gm..	0.1
0.2 mg.	6α-methyl-9α-fluoro-11β-hydroxyprogesterone, sterile, micronized	gm..	20
	Deionized water, q.s.	ml..	100

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 0.05% 6α-methyl-9α-fluoro-11β-hydroxyprogesterone with neomycin, phenylephrine 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	900
Coloring powder	28
Starch, bolted	120
Phenylephrine hydrochloride	6
Ethylaminobenzoate	75
Neomycin sulfate	18
6α - methyl - 9α - fluoro - 11β - hydroxyprogesterone, micronized	1.5

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 0.1% 6α-methyl-9α-fluoro-11β-hydroxyprogesterone with phenylephrine hydrochloride is prepared from the following types and amounts of materials:

Absolute alcohol	gm.	4.37
Dichlorodifluoromethane	gm.	1.43
Dichlorotetrafluoroethane	gm.	5.70
Phenylephrine hydrochloride	mg.	45.29
6α - methyl - 9α - fluoro - 11β - hydroxyprogesterone	mg.	12.0

The 6α-methyl-9α-fluoro-11β-hydroxyprogesterone 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 0.08 mg. of 6α-methyl-9α-fluoro-11β-hydroxyprogesterone and 0.3 mg. of phenylephrine hydrochloride. The product is then ready for assay and clinical use.

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

EXAMPLE 9

Powder Inhaler

One kilogram of an aerosol inhalant powder for treating allergic or asthmatic conditions of the respiratory tract and containing 6α-methyl-9α-fluoro-11β-hydroxyprogesterone and isopropylarterenol hydrochloride is prepared from the following types and amounts of materials:

	Gm.
0.25% isopropylarterenol hydrochloride (crystalline), micronized	2.5
0.05% 6α-methyl-9α-fluoro-11β-hydroxyprogesterone (crystalline), micronized	0.5
0.50% sorbitan trioleate ("Span 85")	5.0
49.50% dichlorodifluoromethane ("Freon 12")	495.0
49.50% trichloromonofluoromethane ("Freon 11")	495.0

The finely divided isopropylarterenol and steroid are triturated well with the sorbitan trioleate and dispersed in the cooled liquid propellant mixture. This slurry is filled into a container fitted with a metering valve nozzle. On operating the valve, the powder will be dispersed in a stream of propellant which will vaporize, providing an aerosol of dry powder.

A single inhalation of the above powder three times daily is used in treatment of asthma.

EXAMPLE 10

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
55,00 units polymyxin B sulfate (10,000 units/mg.)	5.5
10 mg. 6α-methyl-9α-fluoro-11β-hydroxyprogesterone	10
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	4000
White petrolatum, q.s.	10,000

Suspend the neomycin sulfate, procaine penicillin, polymyxin B sulfate and 6α-methyl-9α-fluoro-11β-hydroxyprogesterone in 2000 gm. of white mineral oil and mix thoroughly. Mill through Fitzpatrick mill (80 mesh screen). Wash the mill with 1000 gm. of white mineral oil and add. Stir slowly for at least one hour to dissipate entrapped air. Add the chlorobutanol, polysorbate 80 and sorbitan monooleate 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, novobiocin sodium and dihydrostreptomycin sulfate, in amounts normally employed for such treatment, can be incorporated with the 6α - methyl-9α-fluoro-11β-hydroxyprogesterone. Alternatively, other antibacterials such as the sulfonamides, e.g., sulfisoxazole, and nitrofurazone and its derivatives can be used instead of the foregoing antibiotics.

EXAMPLE 11

Suspension

A lot of 10,000 ml. of a sterile aqueous suspension con-

taining 0.5 mg. of 6α-methyl-9α-fluoro-11β-hydroxyprogesterone per ml. (0.05%) is prepared from the following materials:

Polyethylene glycol 4000	gm.	300
Sodium chloride	gm.	90
Myristyl-gamma-picolinium chloride	gm.	2
6α - methyl - 9α - fluoro - 11β - hydroxyprogesterone	gm.	5
Water for injection, q.s	ml.	10,000

The vehicle is prepared by dissolving all the ingredients in the water except the steroid. The solution is sterilized by filtration. The steroid is micronized and sterilized by ethylene oxide vapors. The sterile, micronized steroid is then added aseptically to the sterile vehicle and dispersed therein by agitation. Complete dispersion of any remaining aggregates is accomplished by passing the suspension through a sterile colloid mill. The final suspension is filled into small, sterile containers which are then sealed.

The foregoing aqueous suspension of 6α-methyl-9α-fluoro-11β-hydroxyprogesterone 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.

For the 6α-methyl-9α-fluoro-11β-hydroxyprogesterone of each of the foregoing Examples 1 through 11 there can be substituted equal amounts of 6α-methyl-9α-fluoro-11-ketoprogesterone, 1-dehydro-6α-methyl-9α-fluoro-11β-hydroxyprogesterone and 1-dehydro-6α-methyl-9α-fluoro-11-ketoprogesterone to give compositions administrable for the same indications and in the same amounts as exemplified therein.

What is claimed is:

A method for treating inflammatory conditions amenable to topical therapy which comprises: topically applying about 1% of 6α-methyl-9α-fluoro-11β-hydroxyprogesterone, dispersed in a pharmaceutically acceptable topical carrier, at the site of the inflammation.

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