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DERMATOLOGICAL PREPARATIONS COMPRISING A CORTICOSTEROID AND CROTONIC ACID-N-ETHYL-O-TOLUIDIDE

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The present invention concerns new preparations for use in dermatology as well as the production of these preparations.

The use of corticosteroids as active ingredients for anti-inflammatory skin ointments is known; for example, for the treatment of eczema of various origin. Some ointments, for example, contain 1% of hydrocortisone. It has now been found that the content of corticosteroids such as e.g. hydrocortisone, hydrocortisone acetate or prednisolone, can be considerably reduced or, with the same concentration, more active preparations can be obtained, if crotonic acid-N-ethyl-o-toluidide is added to such preparations. Preparations according to the invention contain corticosteroids and crotonic acid-N-ethyl-o-toluidide in a ratio of about 1 part of the corticosteroid to about 10–100 parts of crotonic acid-N-ethyl-o-toluidide.

The corticosteroid and crotonic acid-N-ethyl-o-toluidide are employed in conjunction with a pharmaceutically acceptable carrier. Preparations according to the invention contain about 0.1–1% by weight of the corticosteroid and about 2–10% by weight of the crotonic acid-N-ethyl-o-toluidide.

Solids, liquids or semi-liquids may be employed as carriers. The preparations according to the invention can be in the form of emulsions of oil-in-water or emulsions of water-in-oil or in the form of anhydrous mixtures or organic solutions. In consistency they can be ointment-like or liquid. Examples of suitable carriers include monohydric alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert. butyl alcohols etc. (isopropyl alcohol being especially suitable), polyhydric alcohols, e.g. glycerin, propylene glycol etc., polyalkylene glycols, e.g. polyethylene glycol 400, polyethylene glycol 4000, polyethylene glycol 6000, polypropylene glycols etc., fatty acid hydrocarbon esters, e.g. ethyl acetate, propyl stearate, oleyl oleate, ethyl oleate etc., partial fatty acid esters of polyvalent alcohols, e.g. glycerin monostearate, glycerin distearate, glycol distearate etc., mineral or vegetable fats and oils, e.g. paraffine oil, flash point (Cleveland open cup) 148–232° C., Vaseline (a mixture of hydrocarbons of the paraffin series obtained from the residues of petroleum), kerosene (a mixture of hydrocarbons, B.P. 150–280° C.), petrolatum (B.P. 330–390° C.), olive oil etc., waxes e.g. beeswax etc., spermaceti, emulsions of oil-in-water or water-in-oil wherein any of the foregoing can be used as the oily phase. Mixtures of the foregoing carriers can be employed, e.g. a mixture of Vaseline and paraffine oil or a mixture of glycerin monostearate and paraffine oil. Gaseous propellants, e.g. any of the Freons, can be admixed with the carriers.

It is generally advantageous when preparing the emulsions that the organic compounds be dispersed in water with the aid of conventional emulsifying agents or, vice versa, water is added to the mixture or solution of the other components, i.e. to the organic phase. Suitable emulsifying agents are: anion active substances such as soaps, e.g. triethanolamine stearate, sodium stearate etc., salts of sulphuric acid esters of higher alcohols, e.g. sodium lauryl sulphate, which salts if desired may be combined with higher alcohols, e.g. cetyl alcohol, stearyl alcohol, and/or combined with glycol monofatty acid esters, e.g. glycol monostearate, also salts of acid sterols

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such as the sodium salts of bile acids, and also salts of acid carbohydrates as gum arabic; cation active substances such as quaternary ammonium salts, e.g. cetylpyridinium chloride; non-ionogenic emulsifying agents such as condensation products of ethylene glycol and/or propylene glycol with fatty alcohols, fatty acids or/and with partial fatty acid esters of glycerin or sorbitan, e.g. polyethylene glycol monostearate, polyethylene glycol dipalmitate, polyethylene glycol monolaurate, the condensation product of polyethylene glycol monostearate with glycerin distearate. Also natural and synthetic amphoteric emulsifying agents such as lecithins, proteins etc., are suitable emulsifying agents. Corticosteroids such as e.g. hydrocortisone or its acetate can either be added as such to an emulsion which already contains crotonic acid-N-ethyl-o-toluidide and the additives or first the corticosteroids can be dissolved in the crotonic acid-N-ethyl-o-toluidide and the solution obtained can be emulsified in water either by itself or together with the additives.

To produce anhydrous mixtures according to the invention, or of solutions of liquid or ointment-like consistency according to the invention, corticosteroid and crotonic acid-N-ethyl-o-toluidide are either mixed with the carrier or dissolved therein or the corticosteroid is first dissolved in the amide mentioned. Liquid or semi-solid hydrocarbons such as paraffine oil or Vaseline (petroleum jelly) for example can be used as organic carriers.

In addition, the preparations according to the invention contain conserving agents such as e.g. low p-hydroxybenzoic acid alkyl esters, 8-hydroxyquinoline sulphate or sorbic acid and, if desired, perfume or other dermatologically active substances, in particular bactericides and antimycotics such as e.g. 5,7-dichloro-8-hydroxyquinoline.

Because of the anti-pruritic and synergistic action of crotonic acid-N-ethyl-o-toluidide, the dermatological preparations according to the invention, e.g. skin ointments or lotions, have both an objectively and subjectively very favourable effect on skin diseases such as contact dermatitis, acute and chronic, particularly dry or only slightly weeping eczemas. In the form of ointments, lotions or sprays they can be pleasantly and unnoticeably applied and they do not dirty the clothes.

The following examples illustrate the production of the emulsions according to the invention without limiting it in any way. Parts are given as parts by weight and their relationship to parts by volume is as that of grams to cubic centimetres. The temperatures are in degrees centigrade.

EXAMPLE 1*Ointment-Like Oil-in-Water Emulsion*

To prepare the fat phase of this ointment, 12.650 parts of glycerin monostearate, 1.850 parts of potassium stearate, 3.500 parts of stearic acid, 2.500 parts of polyethylene glycol 1500, 6.000 parts of white wax, 2.500 parts of wool fat and 2.500 parts of viscous paraffine oil are melted together and 0.072 part of p-hydroxybenzoic acid-n-propyl ester are dissolved therein. 0.200 part of hydrocortisone are dissolved in 5.000 parts of crotonic acid-N-ethyl-o-toluidide and the solution is mixed into the above melt. The whole is kept at 70° to emulsify.

The aqueous phase is prepared by dissolving 2.500 parts of polyoxyethylene sorbitan mono-oleate, 0.168 part of p-hydroxybenzoic acid methyl ester, 0.050 part of 8-hydroxyquinoline sulphate and 3.000 parts of glycerin in 57.380 parts of distilled water and, after warming to 70°, this is poured while stirring vigorously into the fat phase in a thin stream. The whole is allowed to cool while still stirring and, at 40°, 0.130 part of perfume are added.

Instead of dissolving the hydrocortisone in the crotonic acid-N-ethyl-o-toluidide, this can be suspended as

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the last ingredient in the ointment prepared from the other components.

EXAMPLE 2

Ointment-Like Water-in-Oil Emulsion

73.000 parts of white Vaseline, 8.000 parts of viscous paraffine oil and 2.000 parts of sorbitan mono-oleate are melted together and 0.10 part of p-hydroxybenzoic acid-n-propyl ester are dissolved in the melt. 0.200 part of hydrocortisone are dissolved separately in 5.000 part of crotonic acid-N-ethyl-o-toluidide and this solution is mixed with the above melt at 70° and the whole is kept at 70° to emulsify.

To prepare the aqueous phase, 0.100 part of p-hydroxybenzoic acid methyl ester and 0.005 part of citric acid are dissolved in 10.595 parts of hot distilled water and 1.000 part of polyoxyethylene sorbitan mono-oleate are mixed therein. The aqueous phase, heated to 70°, is then poured in a thin stream while stirring vigorously into the fat phase and the whole is allowed to cool while stirring.

In this case too, if desired, the hydrocortisone can be suspended as last component in the ointment prepared from the other components.

EXAMPLE 3

Lotion

7.695 parts of glycerin monostearate, 1.125 parts of potassium stearate, 4.800 parts of stearic acid and 1.500 parts of mobile paraffine oil are melted together and 0.072 part of p-hydroxybenzoic acid-n-propyl ester are dissolved in the melt. 0.200 part of hydrocortisone are dissolved in 10.000 parts of crotonic acid-N-ethyl-o-toluidide, the solution is mixed with the above melt and the whole is kept at about 70° to emulsify.

2.500 parts of polyoxyethylene sorbitan mono-oleate, 0.168 part of p-hydroxybenzoic acid methyl ester, 0.050 part of 8-hydroxyquinoline sulphate, 1.500 parts of polyethylene glycol 1500 and, finally, 3.000 parts of glycerin are dissolved in 67.290 parts of distilled water. The aqueous phase, heated to 70°, is then added while stirring vigorously to the above fat phase and the whole is left to cool, while still stirring, 0.100 parts of perfume being added at 40°.

As a modification of the above process, the hydrocortisone can also be suspended in the lotion as final ingredient,

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EXAMPLE 4

Anhydrous Ointments

80.000 parts of anhydrous Vaseline and 14.800 parts of viscous paraffine oil are melted together. 0.200 part of hydrocortisone are dissolved in 5.000 parts of crotonic acid-N-ethyl-o-toluidide. This solution is mixed into the above melt at about 60° while stirring and the whole is left to cool while stirring.

In an analogous manner, the hydrocortisone can be suspended, only after the cooling, in the ointment prepared from the other components.

EXAMPLE 5

Solution

10.000 parts of crotonic acid-N-ethyl-o-toluidide and 0.250 part of hydrocortisone are dissolved in 49.750 parts of isopropanol. This solution is mixed with 40 parts of Freon 12 (dichloromethane) and placed in an aerosol flask for direct use.

What I claim is:

1. A dermatological preparation comprising a corticosteroid, crotonic acid-N-ethyl-o-toluidide and a pharmaceutically acceptable carrier.
2. A dermatological preparation comprising a corticosteroid and crotonic acid-N-ethyl-o-toluidide in a weight ratio from about 1:10 to 1:100, and a pharmaceutically acceptable carrier.
3. A dermatological preparation according to claim 2 wherein the corticosteroid is a member selected from the group consisting of hydrocortisone, hydrocortisone acetate and prednisolone.
4. A dermatological preparation according to claim 2 wherein the carrier is isopropyl alcohol.
5. A dermatological preparation according to claim 2 wherein the carrier is an oil-in-water emulsion.
6. A dermatological preparation according to claim 2 wherein the carrier is a water-in-oil emulsion.
7. A dermatological preparation according to claim 2 wherein the carrier is a mixture of petroleum jelly and paraffine oil.
8. A dermatological composition according to claim 5, said composition also containing a conserving agent.

References Cited in the file of this patent

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