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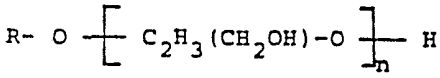
(54) **Composition for local corticotherapy containing hydrocortisone**

(57) Stable compositions for local corticotherapy contain, in the solubilised state, hydrocortisone in at least one solubilising agent which is: (i) caprolactam as an at least 30% by weight solution in an aliphatic alcohol having 2 to 12 carbon atoms, (ii) 2-isostearyl-1-hydroxyethyl-1-benzylimidazolinium chloride as an at least 25% by weight solution in water or (iii) an alkylphenol polyglycerol corresponding to the following formula:



in which R represents an octylphenyl or nonylphenyl radical and n is an integer from 4 to 10, preferably 6.

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SPECIFICATION

Composition for local corticotherapy containing hydrocortisone

The present invention relates to a composition for local corticotherapy which is capable of containing, in the solubilised state, a high percentage of hydrocortisone and which makes it possible to avoid the contraindications generally encountered on prolonged use of compositions based on hydrocortisone.

Improper and, in particular, prolonged use of lotions, pomades, creams or unguents based on hydrocortisone gives rise to certain secondary effects which, in time, are capable of causing real irreversible atrophy of the skin.

The current compositions usually contain a hydrocortisone dose in a percentage of less than about 2%, preferably of the order of 1%.

Compositions having a much lower concentration, of the order of 0.1%, can be used, in particular, in order to avoid the disadvantages of compositions having a higher concentration, but for these the treatment lasts longer and, as a result, requires close medical supervision.

Compositions in the form of dispersions have also been proposed, in order to reduce the duration of treatment and thus avoid the secondary effects. These compositions, although they lead to high concentrations of hydrocortisone, nevertheless are less effective because of a lack of penetration on the areas of skin to be treated.

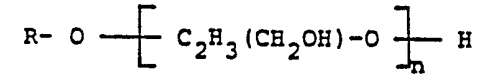
In addition, it has also been found that these compositions do not keep well when stored and the hydrocortisone degrades in the course of time, which similarly reduces their activity.

It has not yet been possible to develop stable compositions for local corticotherapy which are capable of containing a high concentration of hydrocortisone and which makes it possible to ensure good penetration and thus to reduce the treatment time and to avoid irreversible atrophy of the skin.

This problem has been solved, according to the invention, by using certain solubilising agents for hydrocortisone which are capable of solubilising an amount greater than or equal to 2%.

In addition, studies on the life of the compositions according to the invention have given excellent results, the degree of degradation, measured after a period of two months at room temperature, being less than 5%.

The present invention provides a stable composition for local corticotherapy which is based on hydrocortisone and contains, in the solubilised state, hydrocortisone in at least one solubilising agent which is: (i) caprolactam in at least 30% strength by weight solution in an aliphatic alcohol having 2 to 12 carbon atoms, (ii) 2-isostearyl-1-hydroxy-ethyle-1-benzyl-imidiazolinium chloride in at least 25% strength by weight solution in water and (iii) alkylphenol polyglycerols corresponding to the following formua:



in which R represents an octylphenyl or nonylphenyl radical and n is an integer from 4 to 10, preferably 6.

Examples which may be mentioned, in particular, of aliphatic alcohols which have 2 to 12 carbon atoms and are capable of giving solutions of caprolactam are ethanol, isopropanol, butanol, heptanol and dodecanol.

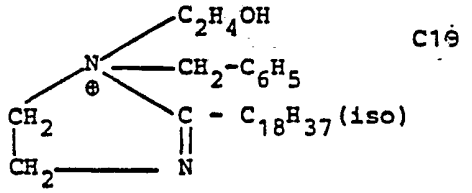
The solutions are preferably 40 to 70% strength by weight solutions of caprolactam, and the preferred alcohols are ethanol and dodecanol.

A 70% strength by weight solution of caprolactam in ethanol permits solubilisation of up to 12% by weight of hydrocortisone and ensures good storage, the degree of degradation, measured by HPLC after two months at room temperature, being only 2.3%.

A 40% strength by weight solution of caprolactam in dodecanol permits solubilisation of up to 5.5% by weight of hydrocortisone; the degree of degradation after two months at room temperature, measured under the same conditions as above, proved to be only of the order of 5%.

Experiments carried out using other lactams, such as caprylolactam or laurylolactam have given results which are clearly inferior to those observed with caprolactam, regardless of the nature of the solubilisation alcohol used, and as much from the point of view of the degree of solubilisation as of the storage life of the hydrocortisone.

2-Isostearyl-1-hydroxyethyl-1-benzylimidazolinium chloride is a yellow viscous liquid corresponding to the following formula:



and has the following characteristics: molecular weight: 478; specific gravity (25°C): 0.99; pH in 5% strength aqueous solution: 5—7.

Aqueous solutions of 2-isostearyl-1-hydroxyethyl-1-benzylimidazolinium chloride capable of being used according to the invention generally do not contain more than 90% by weight, and preferably contain 35 to 75% by weight, of the chloride.

Solutions containing 25% to 90% by weight permit solubilisation of 2% to 7% by weight of hydrocortisone, the degree of degradation of the hydrocortisone after two months at room temperature, measured by HPLC, being less than 5%.

Preferred alkylphenol polyglycerols which can be used according to the invention are octylphenyl polyglycerol ether containing 6 glycerol units (n=6) (viscous liquid, soluble in water and having a turbidity point as a 0.5%

solution in 5% brine of 63°C) and nonylphenyl polyglycerol ether containing 6 glycerol units (n=6) (viscous liquid, soluble in water and having a turbidity point as a 0.5% solution in water of 64°C).

These alkylphenol polyglycerols permit solubilisation of up to 2% by weight of hydrocortisone and ensure excellent storage life, the degree of degradation after two months at room temperature being less than 5%, measured by HPLC.

The concentration of hydrocortisone in the compositions according to the invention for local corticotherapy is generally not greater than 12%, depending on the solubilising agent used, and is preferably from 0.01 to 5% and especially from 0.5 to 4%, by weight, based on the total weight of the compostion.

According to the invention, the solubilising agent generally represents 8 to 98% by weight of the total weight of the composition.

The compositions according to the invention can be in various forms, in particular in the form of lotions, shampoos, pomades or gels, and are suitable for treatment of all diseases relevent to local corticotherapy.

The lotions essentially comprise the solubilising agent, and if desired, conventional additives for this type of preparation.

The gels can be obtained with the aid of gelling agents, such as silica, cellulose derivatives, carboxyvinyl polymers (Carbopols), and natural or synthetic gum, used at a concentration of, say, 0.5 to 15% based on the total weight of the composition.

Pomades are anhydrous compositions based, for example, on petroleum jelly, liquid paraffin and/or waxes.

The compositions according to the invention are especially indicated in the treatment of eczemas, eczematous or psoriatic erythrodermas, pruriginous lesions, chronic lupus erythematosis, psoriatic and parapsoriatic plaque, hyperthropic cicatrices and solar or radiotherapy erythemas.

These treatments require, on average, application twice daily, if necessary with massaging, in order to facilitate penetration.

The following Examples further illustrate the present invention.

Example A

Gel for local corticotherapy

Caprolactam, 50% strength solution in ethanol	95 g
Hydrocrotisone	3 g
Hydroxypropylcellulose acetate	2 g

Example B

Lotion for local corticotherapy

2-Isostearyl-1-hydroxyethyl-1-benzylimidazolinium chloride	45 g (active ingredient)
Hydrocortisone	3 g
Water q.s.p.	100 g

Example C

Pomade for local corticotherapy

Hydrocortisone	2.5 g
Caprolactam, 50% strength solution in ethanol	50.5 g
Polyoxyethylated C_{12}—C_{18} fatty acid glycerides	30 g
Miglyol	17 g

Example D

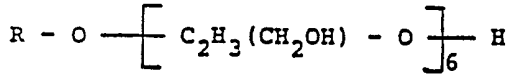
Lotion for local corticotherapy

Caprolactam, 50% strength solution in ethanol	92 g
Hydrocortisone	3.5 g
Glycerol	4.5 g

Example E

Shampoo for corticotherapy of the scalp

Alkylphenol polyglycerol of the formula:



R=nonylphenyl	50 g
Propylene glycol	20 g
Absolute ethanol	20 g
Hydrocortisone	1.5 g
Water q.s.p.	100 g

In this example, the alkylphenol polyglycerol can be replaced by the same compound in which R= octylphenyl.

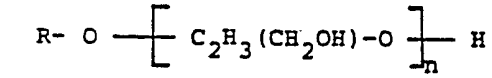
Compositions A to E above are stable on storage.

Good penetration is observed, as well as good tolerance.

In comparison with the conventional products based on hydrocortisone, it has been possible substantially to reduce the treatment times, thus avoiding prolonged use and the risks of cutaneous atrophy.

Claims

1. A composition suitable for local corticotherapy, which comprises hydrocortisone in at least one solubilising agent which is: (i) an aliphatic alcohol having 2 to 12 carbon atoms, containing, in solution, at least 30% by weight of caprolactam, (ii) an at least 25% by weight aqueous solution of 2-isostearyl-1-hydroxyethyl-1-benzylimidazolinium chloride or (iii) an alkylphenol polyglycerol corresponding to the following formula:



in which R represents an octylphenyl or nonylphenyl radical and n is an integer from 4 to 10.

2. A composition according to claim 1, which contains not more than 12% by weight of hydrocortisone, based on the total weight of the composition.

3. A composition according to claim 2, which contains 0.01 to 5% by weight of hydrocortisone.

4. A composition according to claim 3, which contains 0.5 to 4% by weight of hydrocortisone.

5. A composition according to any one of the preceding claims, in which the solubilising agent represents 8 to 98% by weight of the total weight of the composition.

6. A composition according to any one of claims 1 to 5, in which the caprolactam is in solution in ethanol, isopropanol, butanol, heptanol or dodecanol.

7. A composition according to any one of claims 1 to 6 in which the solution of caprolactam contains 40 to 70% by weight of caprolactam.

8. A composition according to any one of claims 1 to 5 in which the aqueous solution of 2-isostearyl-1-hydroxyethyl-1-benzylimidazolinium chloride contains 25 to 90% by weight of the chloride.

9. A composition according to any one of claims 1 to 5 in which n is 6.

10. A composition according to claim 9, in which the alkylphenol polyglycerol is an octylphenyl polyglycerol ether containing 6 glycerol units or a nonylphenyl polyglycerol ether containing 6 glycerol units.

11. A composition according to any one of the preceding claims, which is in the form of a lotion, a shampoo, a pomade or a gel.

12. A composition according to claim 1 substantially as described in any one of the Examples.

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