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(54) ULTRAVIOLET SCREENING AGENTS

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with ultraviolet-screening agents, and with the use thereof.

The screening action of known light-screening agents is due to the fact that they keep the erythema-causing ultraviolet rays of the sun (between 290 and 320 nm) away from the living epidermal cells by specific absorption as in the case of UV B-filters proper or by dispersion or reflection as in the case of masking preparations such as zinc oxide.

It has now been surprisingly found in accordance with the present invention that cytosine, uracil, guanine and 5-chloro-uracil possess a marked ultraviolet-screening action, although they neither act by masking in the same manner as a powder nor does the absorption maximum thereof lie between 290 and 320 nm. Moreover, the light-screening action is more marked with a strong erythema than with a weak erythema or with no erythema. This is not found with conventional light-screening agents which act by absorption.

Accordingly, the ultaviolet-screening agents provided by the present invention contain as essential active ingredient cytosine, uracil, guanine and/or 5-chloro-uracil, and in accordance with the present invention a method for protecting the skin against harmful rays comprises applying to the skin such a screening agent.

The screening agent as produced and applied to the skin will also contain, an addition to the active ingredient, a compatible carrier material. The carrier material used in the light-screening agents of the present invention is preferably a solid or liquefied gaseous diluent or a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface active agent. Such carrier materials are used as the basis for cosmetic preparations; for example, a carrier material which is used in creams, ointments, gels, oils, solutions, sprays or the like. However, care should be exercised in choosing the carrier material since, as with carriers used for existing light-screening agents (e.g. those prepared with specifically absorbing filters), the light-screening action is dependent on the carrier material used. Further, it should be borne in mind that the concentration of the active ingredient has a bearing on the degree of activity of the agent. Suitable concentrations are, for example, between 1% and 30%, preferably between 2% and 5%, by weight based on the total weight of the screening agent.

The essential active ingredients aforesaid can be combined with other conventional light-screening substances, in which case a potentiation of the light-screen action (i.e. a synergistic effect) occurs. By conventional light-screening substances are meant organic compounds whose absorption maximum lies between about 290 and 329 nm. Since this filter property is characteristic of many organic compounds, compounds from diverse classes (of which only a few are named hereinafter) can be incorporated in the light-screen agents of this invention. Examples of such compounds are:

1) Derivatives of p-aminobenzoic acids such as for example, ethyl p-aminobenzoate and other esters such as propyl, butyl and isobutyl p-aminobenzoate, ethyl p-dimethylaminobenzoate, glyceryl p-aminobenzoate and amyl p-dimethylaminobenzoate.

2) Derivatives of cinnamic acid such as, for example, 2-ethoxyethyl p-methoxycinnamate, ethyl-hexyl p-methoxycinnamate, p-methoxycinnamic acid ester mixtures and cinnamic acid ester mixtures.

3) Dibenzalhydrazines.

4) Dervatives of 2-phenylbenzimidazole such as for example, 2-phenylbenzimidazole-5-sulphonic acid.

5) Derivatives of salicyclic acid such as, for example, salicyclic acid menthyl ester, sali-

cylic acid homomethyl ester and salicyclic acid phenyl ester.

6) Derivatives of benzophenone such as, for example, 4-phenylbenzophenone, 4-phenylbenzophenone-2-carboxylic acid isooctyl ester and 5-chloro-2-hydroxy-benzophenone.

7) Derivatives of coumarin such as, for example, 7-hydroxy-coumarin, β-umbelliferoneacetic acid and 6,7-dihydroxycoumarin.

8) Derivatives of gallic acid such as, for example, digalloyl trioleate.

9) Dehydroacetic acid (3-acetyl-6-methyl-1,2-pyran-2,4-dione).

10) Derivatives of quinoline such as, for example, the sodium salt of 8-ethoxyquinoline-5-sulphonic acid.

11) Derivatives of anthranilic acid such as, for example, anthranilic acid menthyl ester.

12) Hydroxyphenylbenztriazole.

The following Example illustrates the invention:

Example

(a) An agent in ointment form containing guanine as the active ingredient was manufactured as follows:

5.80 g (0.0385 mol) of guanine (2-amino-6-hydroxy-purine) were dissolved in a hot mixture of 56.7 g of distilled water, 11.5 g of propylene glycol and 1 ml of concentrated ammonia solution. At 75° C, the resulting solution was added with stirring to a hot (75° C) mixture of 15.0 g of stearyl alcohol, 5.0 g of white petroleum jelly and 5 g of a polyoxyethylene stearylether ("Brij J"—"Brij" is a trade mark). After cooling, the resulting cream was further rubbed down using a three-roller frame and filled into tubes.

In analogous manner, agents in ointment form respectively containing cytosine, 5-chlorouracil and uracil as active ingredients were obtained from 1) a solution of 4.27 g (0.0385 mol) of cytosine and 6.0 g of lactic acid in 53.23 g of distilled water and 11.5 g of propylene glycol, 2) a solution of 5.62 g (0.0385 mol) of 5-chloro-uracil and 1.53 g of sodium hydroxide in 56.35 g of distilled water and 11.5 g of propylene glycol, and 3) a solution of 4.51 g (0.0385 mol) of uracil and 3 g of lactic acid in 56.19 g of distilled water and 11.5 g of propylene glycol.

(b) An agent in ointment form containing guanine as the active ingredient as well as the conventional light-screening substance 2-ethoxyethyl p-methoxycinnamate, was manufactured as follows:

2.0 g (0.0133 mol) of guanine were dissolved in a hot mixture of 60.7 g of distilled water, 11.5 g of propylene glycol and 0.8 g of sodium hydroxide. At 75° C, the resulting solution was added with stirring to a hot (75° C) mixture of 13.0 g of steryl alcohol, 5.0 g of white petroleum jelly, 5.0 g of polyoxyethylene stearyl ether and 2.0 g of 2-ethoxy-ethyl p-methoxycinnamate. After cooling, the resulting cream was further rubbed down using a three-roller frame and filled into tubes.

(c) The agents manufactured as described earlier in this Example were tested for their light-screening action by determining the "mean screening factor" according to the method of SCHULZE (Parfümerie und Kosmetik, 1956, *37*, 310—365). An ointment base (consisting of 5.0 g of polyoxyethylene stearyl ether, 5.0 g of white petroleum jelly, 15.0 g of stearyl alcohol, 11.5 g of propylene glycol and 63.5 g of water) containing no active ingredient was also tested.

In carrying out the test, the dorsal skin of each experimental subject was divided into horizontal strips using adhesive plaster. An agent (or the ointment base) was applied to every second strip of skin on each subject (the sequence of application being changed with every second subject) and the other strips were left as untreated controls. The horizontal strips of skin were then each divided into eight fields each about 1 cm^2 in area by means of vertical strips of adhesive plaster and the remaining skin was covered with cloths. The test area was subsequently illuminated with a group of four Osram "Ultravitalux" ("Osram" and "Ultravitalux" are trade marks) lamps (which had already been operating for at least 5 minutes) from a distance of 40 cm and the vertical series of fields were successively covered up, from left to right, after increasing irradiation times selected from the geometric series 1, 1.4, 2, 2.8 etc minutes, the illumination being terminated after 11.2 or 16 minutes.

All the plasters were then removed, and evaluation of erythema swelling times (i.e. the irradiation time required to produce erythema) was made 24 hours later. The evaluation was carried out by two persons: the vertical rows were numbered, and the first person determined at what point of each horizontal row an erythema was just discernible then dictated the result for the second person to transcribe it into the test report.

The screening factor of a particular agent on a particular subject was then determined from the test report using the relationship

$$\text{screening factor} = \frac{\text{erythema swelling time of screened skin}}{\text{erythema swelling time of unscreened skin.}}$$

Each agent was tested on 20 adult persons of differing age, sex and skin type. The arithmetic mean of the resulting 20 individual values was then calculated to give the mean screening factor for the particular agent.

RESULTS

Active ingredient	Concentration (% by weight)	Mean screening factor (from 20 individual values)
Cytosine	4.27	2.85
Uracil	4.31	2.30
Guanine	5.8	2.91
5-Chloro-uracil	5.62	2.63
Guanine+2-ethoxy-ethyl p-methoxycinnamate	2.05	7.46
None (ointment base only)	—	1.41

We disclaim the use of the method claimed here in the prevention and/or treatment of disease in human beings. Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:—

1. A method for protecting the skin against harmful rays comprising applying to the skin a UV-screening agent which contains as essential active ingredient cytosine, uracil, guanine and/or 5-chloro-uracil.

2. A method according to claim 1, wherein cytosine or guanine is present as the essential active ingredient.

3. A method according to claim 1 or claim 2, wherein the essential active ingredient is present in a concentration of from 1% to 30% by weight, based on the weight of the screening agent.

4. A method according to claim 3 wherein the essential active ingredient is present in a concentration of from 2% to 5%, on the same basis.

5. A UV-screening agent suitable for topical application which contains as essential active ingredient cytosine, uracil, guanine and/or chloro-uracil and a solid or liquefied gaseous diluent or a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface active agent.

6. An agent according to claim 5 wherein cytosine or guanine is present as the essential active ingredient.

7. An agent according to claim 5 or claim 6, wherein the essential active ingredient is present in a concentration of from 1% to 30% by weight, based on the weight of the screening agent.

8. An agent according to claim 7, wherein the essential active ingredient is present in a concentration of from 2% to 5% by weight, on the same basis.

9. A UV-screening agent suitable for topical application which contains as essential active ingredient cytosine, uracil, guanine and/or chloro-uracil, in association with one or more conventional light-screening substances and a compatible carrier material.

10. An agent according to claim 9, wherein cytosine or guanine is present as the essential active ingredient.

11. An agent according to claim 9 or claim 10, wherein the essential active ingredient is present in a concentration of from 1% to 30% by weight, based on the weight of the screening agent.

12. An agent according to claim 11, wherein the essential active ingredient is present in a concentration of from 2% to 5%, on the same basis.

13. A UV-screening agent as claimed in claim 5 or claim 9, substantially as described herein.

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2. A method according to claim 1, wherein cytosine or guanine is present as the essential active ingredient.

3. A method according to claim 1 or claim 2, wherein the essential active ingredient is present in a concentration of from 1% to 30% by weight, based on the weight of the screening agent.

4. A method according to claim 3 wherein the essential active ingredient is present in a concentration of from 2% to 5%, on the same basis.

5. A UV-screening agent suitable for topical application which contains as essential active ingredient cytosine, uracil, guanine and/or chloro-uracil and a solid or liquefied gaseous diluent or a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface active agent.

6. An agent according to claim 5 wherein cytosine or guanine is present as the essential active ingredient.

7. An agent according to claim 5 or claim 6, wherein the essential active ingredient is present in a concentration of from 1% to 30% by weight, based on the weight of the screening agent.

8. An agent according to claim 7, wherein the essential active ingredient is present in a concentration of from 2% to 5% by weight, on the same basis.

9. A UV-screening agent suitable for topical application which contains as essential active ingredient cytosine, uracil, guanine and/or chloro-uracil, in association with one or more conventional light-screening substances and a compatible carrier material.

10. An agent according to claim 9, wherein cytosine or guanine is present as the essential active ingredient.

11. An agent according to claim 9 or claim 10, wherein the essential active ingredient is present in a concentration of from 1% to 30% by weight, based on the weight of the screening agent.

12. An agent according to claim 11, wherein the essential active ingredient is present in a concentration of from 2% to 5%, on the same basis.

13. A UV-screening agent as claimed in claim 5 or claim 9, substantially as described herein.

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