Description

Background of the Invention

This invention relates to a synergistic skin depigmentation composition comprising 4-hydroxyanisole and a retinoid such as all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate.

4-Hydroxyanisole is present as the active ingredient in products used topically for depigmenting or lightening of skin. These products are used in the treatment of hyperpigmentation of skin associated with various skin disorders or diseases. The hyperpigmentation is generally the result of increased melanin deposition in epidermal cells. Hyperpigmentation of skin is associated with freckles, senile lentigo, lentigines, melasma, post-inflammatory hyperpigmentation, sunburn, phototoxic reactions and other conditions. In general, these cases of hyperpigmentation are not life-threatening, but are viewed as cosmetically undesirable and psychologically debilitating.

Local side effects are often associated with the existing products containing greater than 2% hydroquinone or 4-hydroxyanisole. These side effects include localized irritation and irreversible depigmentation. Products containing 2% or less of hydroquinone or 4-hydroxyanisole are generally regarded as ineffective in the treatment of lentigo or melasma.

All-trans retinoic acid (vitamin A acid) applied topically has been reported to lighten the color of lentigo in humans. All-trans retinoic acid is known to increase epidermal cell turnover in normal skin and suppress epidermal cell turnover under stimulated or hyperproliferative conditions. It causes epidermal keratinization and decreases the number of normal cell layers of the stratum corneum. This decrease in thickness of the barrier may potentiate the penetration of other topical agents.

U.S. Patent No. 3,856,934 and Canadian Patent No. 982,945 disclose a synergistic composition for depigmentation of skin comprising a mixture of hydroquinone, retinoic acid, and a corticosteroid. The U.S. patent also discloses that the double combination of hydroquinone and retinoic acid was not synergistic. Therefore, all three components were needed for the synergistic activity. The Canadian patent discloses that hydroquinone monomethyl ether (4-hydroxyanisole) may be used in the composition instead of hydroquinone. In these patents the corticosteroid is regarded as necessary to bring irritation down to acceptable levels. However, the use of a corticosteroid possesses some disadvantages, i.e., it can be dangerous to use in intertriginous regions, and it may cause skin atrophy, rebound phenomenon and telangiectasia.

Brief Description of the Invention

It has now been discovered that the combination of 4-hydroxyanisole and a retinoid, such as all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate, without the presence of a corticosteroid, results in synergistic depigmentation with diminished irritation of the skin when applied topically in a pharmaceutically acceptable topical vehicle. For example, the combination of 1% by weight of 4-hydroxyanisole and 0.01% by weight of all-trans retinoic acid produced depigmentation of skin that was equivalent to the effect produced by 5% by weight of 4-hydroxyanisole. Individually, 4-hydroxyanisole (1% by weight) and all-trans retinoic acid (0.01% by weight) are without any significant activity. 4-Hydroxyanisole alone at 5% by weight caused depigmentation that was slower to reverse in Yucatan minipigs. The depigmentation produced by the combination of 1% by weight of 4-hydroxyanisole with 0.01% by weight of all-trans retinoic acid showed little or no local irritation, and the depigmentation was reversible in 6-7 weeks after stopping the treatment.

Brief Description of the Drawings

Figs. 1 and 8 show the synergistic interaction of all-trans retinoic acid and 4-hydroxyanisole.

Fig. 2 shows the synergistic interaction of all-trans retinoic acid and 4-hydroxyanisole over a 12 week period.

Fig. 3 shows the lack of synergism of a composition containing all-trans retinoic acid and hydroquinone.

Figs. 4 and 5 show the results of various combinations of ingredients.

Fig. 6 shows the reversibility of depigmentation of various compositions.

Fig. 7 shows the irritation effects of various combinations.

Fig. 9 shows the interaction of (N-acetyl-4-aminophenyl) retinoate and 4-hydroxyanisole.

Fig. 10 shows the interaction of all-trans 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone and 4-hydroxy anisole.

Detailed Description of the Invention

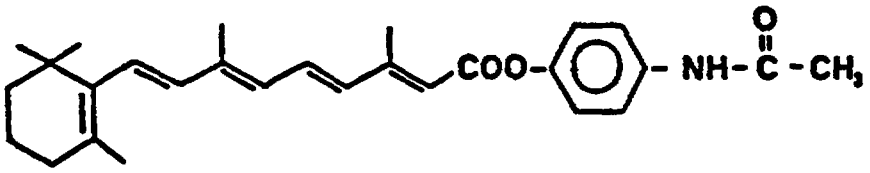
In one aspect of the present invention, there is provided a synergistic composition for skin depigmentation, which does not contain a corticosteroid, comprising 4-hydroxyanisole and a retinoid, such as all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate, in a pharmaceutically acceptable topical vehicle.

In another aspect, the present invention relates to a method for skin depigmentation comprising topically applying to the skin a combination of 4-hydroxyanisole and a retinoid, such as all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate, in a pharmaceutically acceptable topical vehicle.

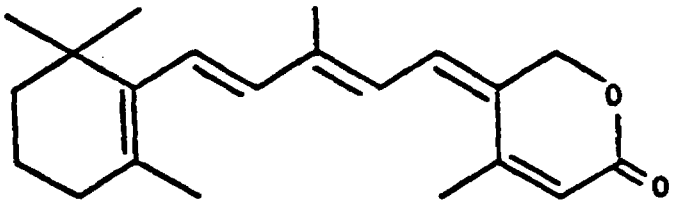
A pharmaceutically acceptable topical vehicle into which the 4-hydroxyanisole and retinoid are incorporated may be a cream, gel, ointment, powder, aerosol, emulsion or solution suitable for topical administration. Such topical vehicles are well-known in the art as exemplified by U.S. patent 4,185,100.

Preferably, the composition of this invention will contain from 0.1% by weight to 5% by weight of 4-hydroxyanisole and from 0.001% by weight to 1% by weight of all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate. A particularly preferred composition comprises from 1% by weight to 2% by weight of 4-hydroxyanisole and from 0.01% by weight to 0.1% by weight of all-trans retinoic acid 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate.

The compound (N-acetyl-4-aminophenyl) retinoate has the formula:



and the compound 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone has the formula:



IN VIVO EXPERIMENTS

A. Normal Depigmenting Activity

Healthy, female Yucatan minipigs weighing from 25-40 kgms were used in these studies. The animals were selected for even tan to brown skin color. These animals were housed individually in standard stainless steel pens in temperature and humidity controlled rooms with 12-hour cycled lighting. Food was provided at specified times and water was available ad libitum.

Test materials were prepared as solutions in a PEG8/ethanol vehicle comprising 5 parts by weight of PEG8 (polyethylene glycol 400, a polymer of ethylene oxide that conforms generally to the formula H-$(OCH_2CH_2)_nOH$, wherein n has an average value of 8) and 95 parts by weight of ethanol. Test solutions (25 µl) were applied twice daily to a 12.5 cm^2 area of the flank skin five days a week for 8-12 weeks. Test sites were graded at weekly intervals for signs of local irritation and changes in depigmentation using the

following grading system:

1 = Complete depigmentation
2 = Definite uniform depigmentation of test site
3 = Small spots of depigmentation
4 = Same color as the normal skin

At the end of 8-12 weeks of treatment, selected test sites were biopsied and skin specimens were processed for microscopic examination. The remaining sites were observed for the next 7 weeks for repigmentation or reversibility of depigmentation.

The results of 1% by weight of 4-hydroxyanisole (4HA) combined with 0.01% of all-trans retinoic acid (TRA) are shown in Fig. 1. 4-Hydroxyanisole combined with all-trans retinoic acid showed moderate depigmentation during 6-12 weeks of treatment. Under the same conditions, 4-hydroxyanisole or all-trans retinoic acid alone produced slight to no effect.

Fig. 2 shows that 2% by weight of 4-hydroxyanisole combined with 0.01% by weight of all-trans retinoic acid showed an earlier onset of depigmentation than 4-hydroxyanisole or all-trans retinoic acid alone.

In contrast to the combination of 4-hydroxyanisole and all-trans retinoic acid, 2% by weight of hydroquinone (HQ) combined with 0.01% all-trans retinoic acid was only slightly active and more irritating after eight weeks of treatment, whereas hydroquinone alone was moderately active and all-trans retinoic acid alone was inactive, see Fig. 3. The lower activity with the hydroquinone and all-trans retinoic acid combination is reflective of an increase in pigmentation noted on sites exposed to all-trans retinoic acid. This may be caused by the increased irritation caused by all-trans retinoic acid and hydroquinone.

Fig. 4 shows that 2% by weight of hydroquinone combined with 0.01% by weight of all-trans retinoic acid and 2% by weight of hydrocortisone was comparatively more active than 2% by weight of hydroquinone or 0.01% by weight of all-trans retinoic acid each alone, or a combination of 2% by weight of hydroquinone and 0.01% by weight of all-trans retinoic acid. Hydroquinone combined with all-trans retinoic acid was, in general, less effective than the combination of 4-hydroxyanisole and all-trans retinoic acid.

Fig. 5 shows that 2% by weight of hydroquinone combined with 0.1% by weight of all-trans retinoic acid and 2% by weight of hydrocortisone was less effective than the combination of 2% by weight of 4-hydroxyanisole with 0.1% by weight of all-trans retinoic acid.

The results shown in Fig. 6 again show that the combinations of 1% by weight of 4-hydroxyanisole with 0.01% all-trans retinoic acid applied for eight weeks is active, whereas 1% by weight of 4-hydroxyanisole or 0.01% all-trans retinoic acid alone have little or no activity. These results also show that the moderate depigmentation produced by the combination of 2% by weight or 1% by weight of 4-hydroxyanisole with 0.01% by weight of all-trans retinoic acid is reversible and returns to near normal color within seven weeks after discontinuing the treatment. On the other hand, 2% by weight of hydroquinone plus 0.01% by weight of all-trans retinoic acid, which showed moderate activity after eight weeks of application, failed to show any significant degree of reversibility of the depigmentation during the same time period. It is desirable to have reversible rather than permanent depigmentation since permanent depigmentation results in an unsightly area of light skin which does not recover its normal pigmentation.

B. Local Irritation

Local irritation was assessed on pig skin during the course of daily topical application of the respective agents. Comparison of the local skin irritation potential of 4-hydroxyanisole and hydroquinone with and without all-trans retinoic acid is based on the summation of Draize scores for erythema, edema and scaling. 1 = minimum effect, 2 = slight effect, 3 = moderate to severe effect, and 4 = severe effect. The maximum attainable score = 12. Results are given in Table 1 and Fig. 7.

Table 1

Comparison of Local Skin Irritation Potential of 4-Hydroxyanisole and Hydroquinone Based on the Summation of Draize Scores for Erythema, Edema and Scaling of Skin			
Treatment	Skin Irritation		
	WK 1	WK 3	WK 6
2% by weight 4-hydroxyanisole	3	0	0
2% by weight hydroquinone	3	6	4
0.01% by weight all-trans retinoic acid	3	0	2
2% by weight 4-hydroxyanisole + 0.01% by weight all-trans retinoic acid	3	0	1
2% by weight hydroquinone + 0.01% by weight all-trans retinoic acid	3	6	3

It will be seen from Table 1 that 4-hydroxyanisole with and without all-trans retinoic acid elicited less irritation than hydroquinone with and without all-trans retinoic acid. Hydroquinone combined with all-trans retinoic acid and hydrocortisone was generally more irritating than hydroquinone combined with all-trans retinoic acid. It is speculated that the vasoconstrictor action of hydrocortisone causes the longer retention of hydroquinone and all-trans retinoic acid locally, leading to greater irritation.

Hence, 4-hydroxyanisole combined with all-trans retinoic acid showed less irritation and a synergistic depigmenting activity, whereas hydroquinone combined with all-trans retinoic acid was more irritating and showed similar or lower activity than hydroquinone alone. These results show that the combination of low concentrations of 4-hydroxyanisole and all-trans retinoic acid without hydrocortisone unexpectedly produce effective depigmentation with lower irritation and improved potential for inducing reversible skin depigmentation.

Fig. 7 shows that the greater depigmentation noted with 2% by weight of 4-hydroxyanisole combined with the low dose of 0.01% by weight of all-trans retinoic acid was associated with less local irritation compared to the combination of 2% by weight of hydroquinone and 0.01% by weight of all-trans retinoic acid.

In general, hydroquinone alone or combined with all-trans retinoic acid and/or hydrocortisone was more locally irritating than similar concentrations of 4-hydroxyanisole alone or combined with all-trans retinoic acid.

C. Depigmentation Activity on UVR-Induced Hyperpigmentation

Exposure of human skin to ultraviolet radiation (UVR) leads to the appearance of erythema and hyperpigmentation (tanning). In a similar manner, exposure of Yucatan minipig skin to UVR also elicits erythema followed by hyperpigmentation. The Yucatan pig skin shares many physiologic and morphologic characteristics with human skin. The thickness and general morphology of epidermis and dermis, tritiated thymidine labeling pattern and index of epidermal cells, epidermal cell turnover time and size, orientation, and distribution of vessels in skin are similar to that in humans. In view of the similarity of the pig skin to human skin, the Yucatan pig was used as a model for screening depigmenting activity on UVR induced hyperpigmentation of various compounds.

Lentigo is localized skin hyperpigmentation which is characterized by a basal melanin synthesis rate and an increased number of melanocytes at the basal level. In the treatment of solar lentigo, it is desirable to only depigment the elevated or locally stimulated hyperpigmentation and not affect normally pigmented skin around the lesion.

In the following studies, Yucatan pigs were exposed to UVR to induce hyperpigmentation. The test materials were prepared as solutions in a PEG8/ethanol vehicle comprising five parts by weight of PEG8

and 95 parts by weight of ethanol. Test solutions were applied twice daily at a dose of 2 $\mu l/cm^2$ of the flank skin. Test sites were graded on a scale of 0-4, with 4 being the maximum degree of induced hyperpigmentation and 0 representing complete depigmentation of the induced hyperpigmentation, i.e., back to the color of the normal skin.

As shown in Fig. 8, 2% by weight of 4HA combined with 0.01% by weight of TRA is significantly more active than 2% by weight of 4HA by itself and produced complete depigmentation of the UVR-induced hyperpigmented spot within eight weeks of treatment. Additionally, the depigmentation of the induced pigmentation by the combination of 4HA and TRA was apparent after the first week of treatment.

Fig. 9 shows that 2% by weight of 4HA combined with 0.01% by weight of the retinoid (N-acetyl-4-aminophenyl) retinoate is more active than 2% by weight of 4HA by itself.

Fig. 10 shows that 2% by weight of 4HA combined with 0.1 % by weight of the retinoid 11-cis-13-cis-12-hydroxymethyl retinoic acid δ-lactone is more active than 2% by weight of 4HA by itself.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A synergistic composition for skin depigmentation which does not contain a corticosteroid comprising 4-hydroxyanisole and a retinoid in a pharmaceutically acceptable topical vehicle.

2. A composition as defined in claim 1 wherein said retinoid is all-trans retinoic acid.

3. A composition as defined in claim 2 containing from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of all-trans retinoic acid.

4. A composition as defined in claim 3 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01 to 0.1% by weight of all-trans retinoic acid.

5. A composition as defined in claim 1 wherein said retinoid is (N-acetyl-4-aminophenyl) retinoate.

6. A composition as defined in claim 5 containing from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of (N-acetyl-4-aminophenyl) retinoate.

7. A composition as defined in claim 6 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01 to 0.1% by weight of (N-acetyl-4-aminophenyl) retinoate.

8. A composition as defined in claim 1 wherein said retinoid is 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

9. A composition as defined in claim 8 containing from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

10. A composition as defined in claim 9 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01 to 0.1% by weight of 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

11. A method for cosmetic skin depigmentation which comprises topically applying to the skin a synergistic composition according to any one of claims 1 to 10.

12. A process for preparing a composition according to Claim 1 which comprises incorporating 4-hydroxyanisole and a retinoid into a pharmaceutically acceptable topical vehicle.

Claims for the following Contracting States : ES, GR

1. A process for preparing a synergistic composition for skin depigmentation which does not contain a corticosteroid comprising incorporating 4-hydroxyanisole and a retinoid into a pharmaceutically acceptable topical vehicle.

2. A process as claimed in claim 1 wherein said retinoid is all-trans retinoic acid.

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and 95 parts by weight of ethanol. Test solutions were applied twice daily at a dose of 2 µl/cm² of the flank skin. Test sites were graded on a scale of 0-4, with 4 being the maximum degree of induced hyperpigmentation and 0 representing complete depigmentation of the induced hyperpigmentation, i.e., back to the color of the normal skin.

As shown in Fig. 8, 2% by weight of 4HA combined with 0.01% by weight of TRA is significantly more active than 2% by weight of 4HA by itself and produced complete depigmentation of the UVR-induced hyperpigmented spot within eight weeks of treatment. Additionally, the depigmentation of the induced pigmentation by the combination of 4HA and TRA was apparent after the first week of treatment.

Fig. 9 shows that 2% by weight of 4HA combined with 0.01% by weight of the retinoid (N-acetyl-4-aminophenyl) retinoate is more active than 2% by weight of 4HA by itself.

Fig. 10 shows that 2% by weight of 4HA combined with 0.1 % by weight of the retinoid 11-cis-13-cis-12-hydroxymethyl retinoic acid δ-lactone is more active than 2% by weight of 4HA by itself.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A synergistic composition for skin depigmentation which does not contain a corticosteroid comprising 4-hydroxyanisole and a retinoid in a pharmaceutically acceptable topical vehicle.

2. A composition as defined in claim 1 wherein said retinoid is all-trans retinoic acid.

3. A composition as defined in claim 2 containing from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of all-trans retinoic acid.

4. A composition as defined in claim 3 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01 to 0.1% by weight of all-trans retinoic acid.

5. A composition as defined in claim 1 wherein said retinoid is (N-acetyl-4-aminophenyl) retinoate.

6. A composition as defined in claim 5 containing from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of (N-acetyl-4-aminophenyl) retinoate.

7. A composition as defined in claim 6 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01 to 0.1% by weight of (N-acetyl-4-aminophenyl) retinoate.

8. A composition as defined in claim 1 wherein said retinoid is 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

9. A composition as defined in claim 8 containing from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

10. A composition as defined in claim 9 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01 to 0.1% by weight of 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

11. A method for cosmetic skin depigmentation which comprises topically applying to the skin a synergistic composition according to any one of claims 1 to 10.

12. A process for preparing a composition according to Claim 1 which comprises incorporating 4-hydroxyanisole and a retinoid into a pharmaceutically acceptable topical vehicle.

Claims for the following Contracting States : ES, GR

1. A process for preparing a synergistic composition for skin depigmentation which does not contain a corticosteroid comprising incorporating 4-hydroxyanisole and a retinoid into a pharmaceutically acceptable topical vehicle.

2. A process as claimed in claim 1 wherein said retinoid is all-trans retinoic acid.

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3. A process as claimed in claim 2 wherein said composition contains from 0.1 % to 5 % by weight of 4-hydroxyanisole and from 0.001 % to 1 % by weight of all-trans retinoic acid.

4. A process as claimed in claim 3 wherein said composition contains from 1 to 2 % by weight of 4-hydroxyanisole and from 0.01 to 0.1 % by weight of all-trans retinoic acid.

5. A process as claimed in claim 1 wherein said retinoid is (N-acetyl-4-aminophenyl) retinoate.

6. A process as claimed in claim 5 wherein said composition contains from 0.1 % to 5 % by weight of 4-hydroxyanisole and from 0.001 % to 1 % by weight of (N-acetyl-4-aminophenyl) retinoate.

7. A process as claimed in claim 6 wherein said composition contains from 1 to 2 % by weight of 4-hydroxyanisole and from 0.01 to 0.1 % by weight of (N-acetyl-4-aminophenyl) retinoate.

8. A process as claimed in claim 1 wherein said retinoid is 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

9. A process as claimed in claim 8 wherein said composition contains from 0.1 % to 5 % by weight of 4-hydroxyanisole and from 0.001 % to 1 % by weight of 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

10. A process as claimed in claim 9 wherein said composition contains from 1 to 2 % by weight of 4-hydroxyanisole and from 0.01 to 0.1 % by weight of 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

11. A method for cosmetic skin depigmentation which comprises topically applying to the skin a synergistic composition prepared according to any one of claims 1 to 10.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Synergistisches Mittel zur Hautdepigmentierung, das kein Corticosteroid enthält, umfassend 4-Hydroxyanisol und ein Retinoid in einem pharmazeutisch verträglichen, topischen Vehikel.

2. Mittel gemäß Anspruch 1, worin das Retinoid all-trans Retinoesäure ist.

3. Mittel gemäß Anspruch 2, enthaltend 0,1 Gew.-% bis 5 Gew.-% 4-Hydroxyanisol und 0,001 Gew.-% bis 1 Gew.-% all-trans Retinoesäure.

4. Mittel gemäß Anspruch 3, enthaltend 1 Gew.-% bis 2 Gew.-% 4-Hydroxyanisol und 0,01 Gew.-% bis 0,1 Gew.-% all-trans Retinoesäure.

5. Mittel gemäß Anspruch 1, worin das Retinoid (N-Acetyl-4-aminophenyl)-retinoat ist.

6. Mittel gemäß Anspruch 5, enthaltend 0,1 Gew.-% bis 5 Gew.-% 4-Hydroxyanisol und 0,001 Gew.-% bis 1 Gew.-% (N-Acetyl-4-aminophenyl)-retinoat.

7. Mittel gemäß Anspruch 6, enthaltend 1 Gew.-% bis 2 Gew.-% 4-Hydroxyanisol und 0,01 Gew.-% bis 0,1 Gew.-% (N-Acetyl-4-aminophenyl)-retinoat.

8. Mittel gemäß Anspruch 1, worin das Retinoid 11-cis,13-cis-12-Hydroxymethyl-retinoesäure-δ-lacton ist.

9. Mittel gemäß Anspruch 8, enthaltend 0,1 Gew.-% bis 5 Gew.-% 4-Hydroxyanisol und 0,001 Gew.-% bis 1 Gew.-% 11-cis,13-cis-12-Hydroxymethyl-retinoesäure-δ-lacton.

10. Mittel gemäß Anspruch 9, enthaltend 1 Gew.-% bis 2 Gew.-% 4-Hydroxyanisol und 0,01 Gew.-% bis 0,1 Gew.-% 11-cis,13-cis-12-Hydroxymethyl-retinoesäure-δ-lacton.

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11. Verfahren zur kosmetischen Hautdepigmentierung, wobei man ein synergistisches Mittel gemäß einem der Ansprüche 1 bis 10 topisch auf die Haut aufbringt.

12. Verfahren zur Herstellung eines Mittels gemäß Anspruch 1, wobei man 4-Hydroxyanisol und ein Retinoid in ein pharmazeutisch verträgliches, topisches Vehikel aufnimmt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung eines synergistischen Mittels zur Hautdepigmentierung, das kein Corticosteroid enthält, wobei man 4-Hydroxyanisol und ein Retinoid in ein pharmazeutisch verträgliches, topisches Vehikel aufnimmt.

2. Verfahren gemäß Anspruch 1, wobei das Retinoid all-trans Retinoesäure ist.

3. Verfahren gemäß Anspruch 2, wobei das Mittel 0,1 Gew.-% bis 5 Gew.-% 4-Hydroxyanisol und 0,001 Gew.-% bis 1 Gew.-% all-trans Retinoesäure enthält.

4. Verfahren gemäß Anspruch 3, wobei das Mittel 1 Gew.-% bis 2 Gew.-% 4-Hydroxyanisol und 0,01 Gew.-% bis 0,1 Gew.-% all-trans Retinoesäure enthält.

5. Verfahren gemäß Anspruch 1, wobei das Retinoid (N-Acetyl-4-aminophenyl)-retinoat ist.

6. Verfahren gemäß Anspruch 5, wobei das Mittel 0,1 Gew.-% bis 5 Gew.-% 4-Hydroxyanisol und 0,001 Gew.-% bis 1 Gew.-% (N-Acetyl-4-aminophenyl)-retinoat enthält.

7. Verfahren gemäß Anspruch 6, wobei das Mittel 1 Gew.-% bis 2 Gew.-% 4-Hydroxyanisol und 0,01 Gew.-% bis 0,1 Gew.-% (N-Acetyl-4-aminophenyl)-retinoat enthält.

8. Verfahren gemäß Anspruch 1, wobei das Retinoid 11-cis,13-cis-12-Hydroxymethyl-retinoesäure-δ-lacton ist.

9. Verfahren gemäß Anspruch 8, wobei das Mittel 0,1 Gew.-% bis 5 Gew.-% 4-Hydroxyanisol und 0,001 Gew.-% bis 1 Gew.-% 11-cis,13-cis-12-Hydroxymethyl-retinoesäure-δ-lacton enthält.

10. Verfahren gemäß Anspruch 9, wobei das Mittel 1 Gew.-% bis 2 Gew.-% 4-Hydroxyanisol und 0,01 Gew.-% bis 0,1 Gew.-% 11-cis,13-cis-12-Hydroxymethyl-retinoesäure-δ-lacton enthält.

11. Verfahren zur kosmetischen Hautdepigmentierung, wobei man ein gemäß einem der Ansprüche 1 bis 10 hergestelltes synergistisches Mittel topisch auf die Haut aufträgt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Une composition synergique de dépigmentation de la peau, exempte de corticostéroïde comprenant 4-hydroxyanisole et un rétinoïde dans un véhicule topique pharmaceutiquement acceptable.

2. Une composition telle que définie dans la revendication 1, dans laquelle ledit rétinoïde est un acide rétinoïque en configuration totalement trans.

3. Une composition telle que définie dans la revendication 2, contenant de 0,1% à 5% en poids de 4-hydroxyanisole et de 0,001% à 1% en poids d'acide rétinoïque en configuration totalement trans.

4. Une composition telle que définie dans la revendication 3, contenant de 1 à 2% en poids de 4-hydroxyanisole et de 0,01 à 0,1% en poids d'acide rétinoïque en configuration totalement trans.

5. Une composition telle que définie dans la revendication 1, dans laquelle ledit rétinoïde est le (N-acétyl-4-aminophényl)-rétinoate.

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6. Une composition telle que définie dans la revendication 5 contenant de 0,1% à 5% en poids de 4-hydroxyanisole et de 0,001% à 1% en poids de (N-acétyl-4-aminophényl)-rétinoate.

7. Une composition telle que définie dans la revendication 6, contenant de 1 à 2% en poids de 4-hydroxyanisole et de 0,01 à 0,1% en poids de (N-acétyl-4-aminophényl)-rétinoate.

8. Une composition telle que définie dans la revendication 1, dans laquelle ledit rétinoïde est le δ-lactone de l'acide 11-cis,13-cis-12-hydroxyméthylrétinoïque.

9. Une composition telle que définie dans la revendication 8, contenant de 0,1 à 5% en poids de 4-hydroxyanisole et de 0,001% à 1% en poids de δ-lactone de l'acide 11-cis,-13-cis-12-hydroxyméthylrétinoïque.

10. Une composition telle que définie dans la revendication 9, contenant de 1 à 2% en poids de 4-hydroxyanisole et de 0,01 à 0,1% en poids de δ-lactone de l'acide 11-cis,13-cis-12-hydroxyméthylrétinoïque.

11. Un procédé pour la dépigmentation cosmétique de la peau consistant en l'application topique sur la peau d'une composition synergique selon l'une quelconque des revendications 1 à 10.

12. Un procédé de préparation d'une composition selon la revendication 1, comprenant l'incorporation de 4-hydroxyanisole et d'un rétinoïde dans un véhicule topique pharmaceutiquement acceptable.

Revendications pour les Etats contractants suivants : ES, GR

1. Un procédé de préparation d'une composition synergique pour la dépigmentation de la peau, exempte de corticostéroïde et qui comprend l'incorporation de 4-hydroxyanisole et de rétinoïde dans un véhicule topique pharmaceutiquement acceptable.

2. Un procédé tel que revendiqué dans la revendication 1, dans lequel ledit rétinoïde est un acide rétinoïque en configuration totalement trans.

3. Un procédé tel que revendiqué dans la revendication 2, dans lequel ladite composition contient de 0,1 à 5% en poids de 4-hydroxyanisole et de 0,001% à 1% en poids d'acide rétinoïque en configuration totalement trans.

4. Un procédé tel que revendiqué dans la revendication 3, dans lequel ladite composition contient de 1% à 2% en poids de 4-hydroxyanisole et de 0,01% à 0.1% en poids d'acide rétinoïque en configuration totalement trans.

5. Un procédé tel que revendiqué dans la revendication 1, dans lequel ledit rétinoïde est le (N-acétyl-4-aminophényl)-rétinoate.

6. Un procédé tel que revendiqué dans la revendication 5, dans lequel ladite composition contient de 0,1 à 5% en poids de 4-hydroxyanisole et 0,001% à 1% en poids de (N-acétyl-4-aminophényl)-rétinoate.

7. Un procédé tel que revendiqué dans la revendication 6, dans lequel ladite composition contient de 1 à 2% en poids de 4-hydroxyanisole et de 0,01 à 0,1% en poids de (N-acétyl-4-aminophényl)-rétinoate.

8. Un procédé tel que revendiqué dans la revendication 1 dans lequel ledit rétinoïde est un δ-lactone de l'acide 11-cis,13-cis-12-hydroxyméthylrétinoïque.

9. Un procédé tel que revendiqué dans la revendication 8, dans lequel ladite composition contient de 0,1 à 5% en poids de 4-hydroxyanisole et de 0,001% à 1% en poids de δ-lactone de l'acide 11-cis,13-cis-12-hydroxyméthylrétinoïque.

10. Un procédé tel que revendiqué dans la revendication 9, dans lequel ladite composition contient de 1 à 2% en poids de 4-hydroxyanisole et de 0,01 à 0,1% en poids de δ-lactone de l'acide 11-cis,13-cis-12-

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hydroxyméthylrétinoïque.

11. Un procédé de dépigmentation cosmétique de la peau qui comprend l'application topique sur la peau d'une composition synergique préparée selon l'une quelconque des revendications 1 à 10.