A formulation for topical use comprising a lipophilic phase which includes vitamin E or a pharmaceutically acceptable ester thereof, preferably vitamin E acetate, amongst its components, generally in an amount of from 20 to 100%, preferably from 51 to 100%, based on the weight of the lipophilic phase; the latter phase may also contain animal, vegetable or synthetic fats and oils or mineral oils. The ointment may be in the form of an oil, ointment, cream, hydrophobic gel, or paste. The vitamin E acetate is used as an excipient or as a component of excipients for pharmaceutical formulations for topical use.
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"Formulations for topical use"

DESCRIPTION

The present invention relates to the field of pharmaceutical technology.

In particular, the invention relates to novel formulations for topical use, having a liquid or semisolid consistency, that are to be applied to the skin.

Depending on the physical system by which they are constituted, such formulations are subdivided into grease, ointments, creams, gels and pastes.

Greases, in their turn, are subdivided into oils and ointments and the latter, in their turn, are subdivided into hydrophobic ointments, water-absorbing ointments and hydrophilic ointments.

Among creams, a distinction is made between hydrophobic creams, hydrophilic creams and amphiphilic creams, and among gels a distinction is made between hydrophobic gels and hydrophilic gels.

The above-mentioned topical formulations constitute the basis of officinal galenica, that is to say, formulations of constant composition ready for use as such in pharmacy, of magistral galenica and of many medical specialities for topical use.

With the exception of hydrophilic ointments and hydrophilic gels, all the formulations mentioned
above contain a lipophilic phase, generally composed of petroleum jelly, paraffin and mineral oils, to which emulsifiers are optionally added to permit the incorporation of active ingredients dissolved in aqueous phases.

However, the above-mentioned substances are hydrocarbons derived from petroleum, which, even if subjected to purification processes, still contain contaminating substances, and especially polycyclic aromatic hydrocarbons which are regarded as being responsible for some forms of contact dermatitis and as having a carcinogenic action.

Furthermore, the topical formulations based on the above-mentioned lipophilic substances, and especially creams and hydrophobic ointments, have the major disadvantage of leaving the skin greasy and of imparting to the user a feeling of having foreign matter on his or her skin, giving rise to a need for cleansing.

The aim of the present invention is to provide a topical formulation which overcomes the disadvantages discussed above with reference to the products of the prior art.

This aim has been achieved by means of a formulation for topical use comprising a lipophilic phase, characterised in that it includes vitamin E (dl-alpha-tocopherol) or a pharmaceutically acceptable ester thereof amongst the components of
the lipophilic phase.

Preferably, the topical formulation according to the invention includes vitamin E acetate (dl-alpha-tocopherol) amongst the components of the lipophilic phase.

Naturally, it is also possible to use l-alpha-tocopherol acetate and d-alpha-tocopherol acetate instead of dl-alpha-tocopherol acetate.

The lipophilic phase of the formulation generally comprises from 20 to 100% by weight of vitamin E acetate, preferably from 30 to 100%, most preferably from 51 to 100% by weight, optionally in admixture with animal, vegetable or synthetic fats and oils, mineral oils and silicone oils.

Among the animal and vegetable fats and oils with which the vitamin E acetate can be mixed, there may be mentioned beeswax, lanolin and its derivatives, olive oil, almond oil, sesame oil, coconut oil, groundnut oil, jojoba oil, avocado oil, karite butter and, as mineral oils, liquid paraffin, petroleum jelly, silicone oil, volatile silicones.

If it is desired to modify the consistency or the viscosity of the topical formulations prepared using vitamin E acetate, it is possible to add to the vitamin E acetate one or more vegetable or mineral oils or waxes and long-chained aliphatic alcohols, such as, for example, stearyl alcohol and cetostearyl alcohol, or, in the case of hydrophobic
gels, polyethylene, colloidal silicon dioxide, Zn or Al soaps and hydrogenated castor oil.

In order to permit the preparation of galenic formulations containing hydrophilic active substances, it is possible to add to the vitamin E acetate or to a mixture thereof with other oils or fats, a surfactant, such as, for example, sodium lauryl sulphate, cetomacrogol, monoglycerides or other, similar, substances customarily used in the basic ointments of the various pharmacopoeias.

If it is desired to minimise the risk of allergic reaction as far as possible, it is advisable to use the vitamin E acetate as the only component of the lipophilic phase of the formulations according to the invention.

The possibility of using vitamin E acetate as the principal component of the lipophilic phase of topical formulations is somewhat surprising because such a use has never even been suggested in the prior art.

Vitamin E and its derivatives are substances widely used in the pharmaceutical and cosmetic industry, owing to their alleged anti-oxidant properties and properties of removing free radicals, in the preparation of formulations for healing skin disorders or for combating or preventing unsightly skin imperfections.

For those reasons, vitamin E and its derivatives
are often present in cosmetic formulations as "active" components in concentrations varying from 1 to 25%, although, in fact, the anti-oxidant and anti-ageing action of vitamin E on the skin has never been demonstrated scientifically.

However, it has now been found experimentally that vitamin E acetate has chemico-physical properties rendering it suitable for use as the principal component of the lipophilic phase of topical formulations.

Vitamin E acetate can be spread reasonably easily, is absorbed with surprising rapidity, does not give rise to unpleasant sensations of heat, leaves the skin shiny only for a few minutes and then soft, elastic and non-sticky and is resistant to cleansing with water or detergents.

In addition, owing to the fact that vitamin E acetate is not a molecule foreign to the human organism, it can readily be integrated in the lipids present in the stratum corneum and can facilitate absorption of substances dispersed therein through the skin.

In order to evaluate the absorption of vitamin E acetate, subjective tests were carried out on 20 individuals aged from 25 to 60.

The application of vitamin E acetate was pleasant owing to the absence of any odour, owing to the feel of skin softness, the absence of greasiness, the
absence of any sensation of applied foreign matter and, consequently, the absence of a need for cleansing, the lack of side effects during absorption (no stinging of the skin, no sensation of the stabbing type, even where the skin was irritated).

Two minutes after the application of vitamin E acetate, the skin did not exhibit any residual greasiness.

Using vitamin E acetate as the principal component of the lipophilic phase of topical formulations, various formulations exhibiting optimum application, absorption and thermal stability characteristics were prepared for topical use.

The following formulations, in which the percentages of the individual components are by weight based on the total weight of the formulation, are given by way of example:

**Ointment containing cetomacrogol**

dl-alpha-tocopherol acetate  70%
cetostearyl alcohol  24%
cetomacrogol  6%

The ointment is prepared by heating the components together until they melt and agitating until cooling has occurred.
**Sodium lauryl sulphate ointment base**

dl-alpha-tocopherol acetate 70%
cetostearyl alcohol 27%
sodium lauryl sulphate 3%

The ointment is prepared by heating the components together until they melt and agitating until cooling has occurred.

**Cream base containing cetomacrogol (O/W)**

dl-alpha-tocopherol acetate 21%
cetostearyl alcohol 7.2%
cetomacrogol (1000) 1.8%
purified water 70%

The cream is prepared by melting the solid components in the dl-alpha-tocopherol acetate and adding freshly boiled water at the same temperature, agitating slowly until cooling has occurred.

**Fatty cream base containing cetomacrogol (W/O)**

dl-alpha-tocopherol acetate 39%
cetostearyl alcohol 18%
cetomacrogol (1000) 4.5%
purified water 25%

The cream is prepared by melting the solid components in the dl-alpha-tocopherol acetate and
adding freshly boiled water at the same temperature, agitating slowly until cooling has occurred and reintegrating any evaporated water.

**Oily cream**

dl-alpha-tocopherol acetate 60%
cetyl palmitate 7%
white wax 6%
glyceryl monostearate 2%
purified water 25%

The above composition is a lipophilic cream base W/O and corresponds to the "oily fatty cream base" of the Codex of conventional galenic preparations of magistral derivation, from which it differs by the substitution of groundnut oil by dl-alpha-tocopherol acetate.

The cream is prepared by heating the dl-alpha-tocopherol acetate, the cetyl palmitate, the glyceryl monostearate and the white wax to approximately 60°C and adding to the molten mass so obtained, at the same temperature, freshly boiled water, agitating slowly until cooling has occurred.

**Amphiphilic cream base**
dl-alpha-tocopherol acetate 20%
white petroleum jelly 9%
liquid semisynthetic triglycerides 4%
cetostearyl alcohol 6%
glycerol monostearate 4%
polyethylene glycol stearate 7%
propylene glycol 10%
purified water 40%

The cream is prepared by heating the dl-alpha-tocopherol acetate, the petroleum jelly, the triglycerides, the cetostearyl alcohol and the glycerol monostearate to approximately 60°C until melting takes place. The other components are dissolved in freshly boiled water and the solution obtained, heated to approximately 60°C, is combined with the molten mass, agitating until cooling has occurred and optionally integrating any evaporated water.

Hydrophobic gels
a)
dl-alpha-tocopherol acetate 20%
cyclomethicone 64%
dimethiconol 16%

The gel is prepared by dispersing the dl-alpha-tocopherol acetate in a preformed mixture of cyclomethicone:dimethiconol 8:2 w/w.

b)
dl-alpha-tocopherol acetate 30%
cyclomethicone 52%
dimethiconol 13%
hydrogenated castor oil 5%

The gel is prepared by adding dl-alpha-tocopherol acetate to a previously prepared mixture of dimethiconol and cyclomethicone and then dispersing the hydrogenated castor oil in the mixture thus obtained.

Below are two examples of officinal galenic formulations in which vitamin E acetate is used instead of the mineral oils provided for in the corresponding formulations of the pharmacopoeias.

**Paste containing zinc oxide**

dl-alpha-tocopherol acetate 70%
zinc oxide 30%

The consistency of this formulation can be varied by altering the percentages of the components within a range of from 50 to 85% in the case of dl-alpha-tocopherol acetate and from 15 to 50% in the case of zinc oxide, bearing in mind that an increase in the content of zinc oxide involves an increase in the consistency of the paste.

Compared with the zinc oxide pastes of the official pharmacopoeias, which contain mineral oils, the paste prepared using vitamin E acetate as excipient has a lesser greasiness and is safer to use owing to the absence of mineral oils.
Ointment containing salicylic acid:

- dl-alpha-tocopherol acetate: 95.0-99.9%
- salicylic acid: 0.1-5.0%

In this case too, the ointment so prepared exhibits a lesser greasiness and a lower risk of toxicity or allergenicity than do conventional salicylic acid ointments containing mineral oils.

In addition, the keratolytic action of the ointment is accompanied by a lesser irritating effect on the skin than that observed with the conventional salicylic acid ointments.

Ointment containing clotrimazole

- dl-alpha-tocopherol acetate: 99.0%
- clotrimazole: 1.0%

The ointment so prepared exhibited a very good absorption rate and the antifungal effect of clotrimazole resulted to be enhanced and accelerated with respect to the topical formulations so far available on the market.

Among the active ingredients for which the suitability of the topical formulations according to the invention as excipients was checked experimentally, there may be mentioned, purely by way of example, antibiotics, such as gentamicin, neomycin, clindamycin and tetracyclines,
disinfectants, such as chlorhexidine, corticosteroids, such as hydrocortisone acetate or butyrate, diflucortolone valerate, methylprednisolone aceponate, mometasone furoate, and esters of betametasone, antimycotic agents, such as e.g. clotrimazole, miconazole, ketoconazole, econazole, tolnaftate, topical anti-inflammatory agents, such as nimesulide, ibuprofen, benzydamine and bendazac, trans-retinoic acid, calcipotriol, vitamins such as retinol and its derivatives (retinol acetate and palmitate), lipophilic derivatives of ascorbic acid, such as palmitoylascorbic acid, vitamin K, vitamin D, escin and capillary protectants, such as quercetin, rutin and flavonoids.

Pharmaceutical formulations for topical use based on vitamin E acetate and containing up to 3% of the above-mentioned antibiotics, other formulations containing up to 0.1% of trans-retinoic acid, formulations containing up to 0.005% of calcipotriol, formulations containing up to 70000 IU% of retinol, formulations containing up to 2% clotrimazole and finally formulations containing up to 1% of hydrocortisone acetate or butyrate or of diflucortolone valerate were prepared.

All of the formulations mentioned above were found to exhibit optimum stability in respect of heat and time and rapid absorption both of the
excipient and of the active ingredient dispersed therein.

A pharmaceutical formulation in cream for topical use containing, as active ingredients, diflucortolone valerate and chlorquinaldol is given hereinafter purely by way of example.

diflucortolone valerate 0.1%
chlorquinaldol 1%
dl-alpha-tocopherol acetate 20%
stearyl alcohol 8%
PEG monostearate 3%
disodium EDTA 0.1%
carboxypolymethylene 0.3%
NaOH 0.07%
purified water 67.43%

The cream is prepared by moistening the carboxypolymethylene with 10 parts of water and then by adding the rest of the water, agitating until a dispersion free from lumps is obtained. The disodium EDTA and the PEG stearate are then added, with agitation, to the dispersion, while heating at approximately 70°C.

The dispersion so obtained is combined, by mixing, with a mixture of dl-alpha-tocopherol acetate and stearyl alcohol previously heated to approximately 60°C.

The sodium hydroxide is added in the form of a 10% p/v solution, with agitation, to the emulsion
obtained, re-integrating any water that has evaporated and continuing to agitate until cooling has occurred.

Finally, dl-alpha-tocopherol acetate may be used as a component of sunscreen products instead of most or all the animal, vegetable or mineral oils therein contained. An example of a sunscreen product containing vitamin E acetate as the main lipophilic component is the following:

dl-alpha-tocopherol acetate  20%
p-aminobenzoic acid  5%
stearic acid  3%
propylene glycol  2.9%
cetyl alcohol  0.5%
triethanolamine  0.5%
methyl and propyl paraben 5:1  0.25%
perfume  0.25%
water  67.6%

In addition to p-aminobenzoic acid, all the other usual sunscreens can be used in the sunscreen formulations containing vitamin E acetate as the main lipophilic component: for instance chemical sunscreens such as p-aminobenzoic acid esters, benzophenone derivatives, cinnamic acid derivatives, benzyldene camphor derivatives, salicylate derivatives, and physical sunscreens such as titanium dioxide and zinc oxide.

Vitamin E acetate can suitably be used for
sunscreens formulation of any nature: lotions, creams, sprays etc..
1. A formulation for topical use, comprising a lipophilic phase, characterised in that it includes vitamin E or a pharmaceutically acceptable ester thereof among the components of the lipophilic phase.

2. A formulation according to claim 1, wherein said vitamin E or a pharmaceutical ester thereof is vitamin E acetate.

3. A formulation according to claim 2, wherein the lipophilic phase comprises from 20 to 100% by weight of vitamin E acetate.

4. A formulation according to claim 3, wherein the lipophilic phase comprises from 51 to 100% by weight of vitamin E acetate.

5. A formulation according to claim 4, wherein the lipophilic phase is constituted by vitamin E acetate.

6. A formulation according to any one of claims 1 to 4, wherein the lipophilic phase contains vitamin E acetate in admixture with animal, vegetable or synthetic fats and oils or mineral oils.

7. A formulation according to any one of the preceding claims, characterised in that it is in the form of an oil.

8. A formulation according to any one of claims
1 to 6, characterised in that it is in the form of
an ointment.

9. A formulation according to any one of claims
1 to 6, characterised in that it is in the form of
a cream.

10. A formulation according to any one of claims
1 to 6, characterised in that it is in the form of
a hydrophobic gel.

11. A formulation according to claim 10,
characterized in that said lipophilic phase
comprises vitamin E acetate and a mixture of
cyclomethicone and dimethiconol.

12. A formulation according to claim 11,
characterized in that cyclomethicone and
dimethiconol are contained in said mixture in a
weight ratio of 8:2.

13. A formulation according to any one of claims
1 to 6, characterised in that it is in the form of
a paste.

14. Use of vitamin E acetate as excipient for
pharmaceutical formulations for topical use.

15. A pharmaceutical formulation for topical use
constituted by at least one active substance and by
an excipient comprising a lipophilic phase of which
the principal component is vitamin E or a
pharmaceutically acceptable ester thereof.

16. A pharmaceutical formulation according to
claim 15, characterized in that said principal
component is vitamin E acetate.

17. A pharmaceutical formulation for topical use according to claim 16, wherein the lipophilic phase includes from 51 to 100% by weight of vitamin E acetate.

18. A pharmaceutical formulation according to claim 16, wherein the at least one active substance is zinc oxide and the excipient is constituted by vitamin E acetate.

19. A pharmaceutical formulation according to claim 18, constituted by from 51 to 85% by weight of vitamin E acetate and from 15 to 49% by weight of zinc oxide.

20. A pharmaceutical formulation according to claim 16, wherein the at least one active substance is salicylic acid and the excipient is constituted by vitamin E acetate.

21. A pharmaceutical formulation according to claim 20, constituted by from 0.1 to 5% by weight of salicylic acid and from 95 to 99.9% by weight of vitamin E acetate.

22. A sunscreen product containing a lipophilic phase, characterized in that the main component of said lipophilic phase is vitamin E acetate.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K47/22 A61K47/44

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X Further documents are listed in the continuation of box C.  

X Patent family members are listed in annex.

* Special categories of cited documents:

"A" - document defining the general state of the art which is not considered to be of particular relevance
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T later document published after the international filing data or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"S" document member of the same patent family

Date of the actual completion of the international search

9 January 1998

Date of mailing of the international search report

21/01/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx: 3 1651 epo nl, Fax: (+31-70) 340-3016

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