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(54) Benævnelse: **Farmaceutisk sammensætning til dermal anvendelse til behandling af psoriasis omfattende vitamin D og et corticosteroid**

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DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention concerns pharmaceutical compositions for dermal use which contain at least one vitamin D or vitamin D analogue and at least one corticosteroid. More specifically, the invention relates to pharmaceutical compositions containing two or more pharmacologically active compounds which have low compatibility with respect to the pH value of optimum stability, preferably, said pharmacologically active compounds are at least one vitamin D analogue and at least one corticosteroid.

BACKGROUND OF THE INVENTION

[0002] In the treatment of a number of conditions using dermal application, e.g. in the treatment of psoriasis, it is often indicated to employ a combination treatment incorporating two or even more different pharmacologically active compounds. Thus, in the treatment of e.g. psoriasis, it is common to use a combination treatment involving a steroid compound, such as a corticosteroid compound, and a vitamin D analogue such as calcipotriol, and where each of the active compounds are formulated in separate preparations.

[0003] Until now a topical pharmaceutical composition comprising a combination of a vitamin D analogue and a topical steroid has not been described. Moreover, these two types of compounds often have optimum stability values of pH that differ significantly from one another making it non-obvious to attempt to prepare a topical pharmaceutical preparation containing a steroid compound together with a vitamin D analogue. US patent No. 5,565,462 relates to topical pharmaceutical compositions containing certain xanthine compounds, and where said compositions may additionally contain active compounds, such as steroids and vitamin D and its derivatives. However, there is no disclosure of a topical composition containing both a steroid and a vitamin D or vitamin D analogue or derivative, nor is there any description of a method of preparing such a composition.

[0004] The following example describes the difficulties encountered when the skilled person wishes to prepare a combination composition for topical use comprising both a vitamin D or a vitamin D analogue or derivative and a topical steroid: The vitamin D analogue calcipotriol, as well as other examples of vitamin D analogues, requires a pH value above 8 for maximum stability, whereas corticosteroids such as Betamethasone (9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione) require pH values in the range of 4-6 for maximum stability. Since the base auxiliary materials and additives traditionally used in preparing topical formulations, such as creams and/or ointments, involve having some kind of acid or alkaline nature or reaction ability, it has therefore hitherto not been possible to combine the two active compounds in one single formulation while maintaining good stability of the active compounds.

[0005] Consequently, physicians have had to resort to letting patients under this type of two-component regimen perform sequential application of two creams/ointments, each containing one of the compounds formulated at its maximum stability pH. This may lead to incompatibility of the preparations so that patients must, e.g., apply one cream/ointment in the morning and the other in the evening. Needless to say, patient compliance as well as correct administration dosage is a problem under such circumstances. Richards, H.L. et al. report in J Am Acad Dermatol 1999 Oct; 41 (4):581-3 on a study of patients with psoriasis and their compliance with medication. They report that poor compliance with treatment advice in chronic conditions, such as psoriasis, represents a major challenge to health care professionals: Thirty-nine percent of participants reported that they did not comply with the treatment regimen recommended. The noncompliant group had a higher self-rated severity of psoriasis, was younger, and had a younger age at onset than those who were compliant. The noncompliant group reported that psoriasis had a greater impact on daily life.

[0006] B. Patel et al., J. Am. Acad. Dermatol. 38, 1998, pp. 1010-1011, disclose aqueous compositions comprising a mixture of calcipotriol ointment and hydrocortisone-17-valerate ointment or halobetasol propionate ointment or cream. The compositions do not include a polyoxypropylene alkyl ether as a solvent.

[0007] WO 94/14453 discloses aqueous compositions comprising a vitamin D analogue such as calcipotriol and optionally a corticosteroid such as betamethasone-17-valerate. The compositions do not include a polyoxypropylene alkyl ether as a solvent.

[0008] JP 7-196515 discloses non-aqueous compositions comprising the vitamin D compound 1α,24(R)-dihydroxycholecalciferol as the sole active ingredient. The compositions do not include a polyoxypropylene alkyl ether as a solvent.

[0009] US 4,083,974 discloses non-aqueous compositions comprising a corticosteroid and polyoxypropylene-15-stearyl ether. The compositions do not include a vitamin D analogue as a second active ingredient.

[0010] It is an object of the present invention to provide a pharmaceutical composition for dermal use where said composition alleviates the inconveniences of a two-component or multi-component regimen for the treatment of psoriasis and other inflammatory skin diseases including nail diseases. The provision of said composition will result in a substantial improvement in quality of life for a large population of psoriasis patients, especially the noncompliant group having a higher self-rated severity of psoriasis, being younger, and having a younger age at onset than those who are compliant.

SUMMARY OF THE INVENTION

[0011] In order to solve the above mentioned problems, the invention provides a non-aqueous

pharmaceutical composition for dermal use, said composition comprising a first pharmacologically active component A consisting of at least one vitamin D or vitamin D analogue and a second pharmacologically active component B consisting of at least one corticosteroid, characterised in that the difference between the optimum stability pH of said first component A and the optimum stability pH of said second component B is at least 1; and at least one solvent component C selected from the group consisting of:

1. (i) compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) wherein x is in the range of 2-60, R^1 in each of the x units is CH_3, and R^2 is straight chain or branched C_{1-20}alkyl or benzoyl.

DETAILED DESCRIPTION OF THE INVENTION

[0012] As a first pharmacologically active component A it is preferred to use a compound selected from the group consisting of seocalcitol; calcipotriol; calcitriol; tacalcitol, maxacalcitol; paricalcitol; falecalcitriol; 1α,24S-dihydroxy-vitamin D2; and 1 (S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene, as well as mixtures thereof.

[0013] More preferred are vitamin D analogues selected from the group consisting of calcipotriol, calcitriol, tacalcitol, maxacalcitol, and 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene as well as mixtures thereof. Synthetic vitamin D analogues are more preferred in the compositions according to the invention than naturally occurring vitamin D's or vitamin D derivatives, since the therapeutic effects of the latter may be less selective for the treatment of skin diseases, such as psoriasis.

[0014] Further non-limiting examples of vitamin D compounds constituting the first pharmacologically active component A are:

alphacalcidol;

1α-hydroxy-vitamin D2;

1α-hydroxy-vitamin D5;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6-hydroxy-6-methyl-1-heptyl)-9,10-secopregna-5(2),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6-hydroxy-6-methylhept-1(E)-ene-1-yl-9,10)-secopregna-

5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6-ethyl-6-hydroxy-1-octyl)-9,10)-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(7-hydroxy-7-methyl-1-octyl)-9,10)-secopregna-5(2),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(7-hydroxy-7-methyloct-1(E)-en-1-yl-9,10)-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6'-methyl-1'-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(5'-hydroxy-5'-methyl-1'-hexyloxy)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'ethyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6'-hydroxy-1'-hexyloxy-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5'-hydroxy-5'-ethyl-1'-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10,19-triene;

1(S),3(R)-Dihydroxy-20(R)-(5'-hydroxy-5'-methyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5'-methyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19-triene;

1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'-(1"-propyl)-1'-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'-methyl-1'-pentyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3'-hydroxy-3'-methyl-1'-butyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-(5Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-1-hept-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-hept-1(E)-en-1-yl),9,10-secopregna-5(2),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(2),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(5'-ethyl-5'hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(6'-hydroxy-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z)-7(E),10,19-triene (5'(R) and 5'(S) isomers);

1(S),3(R)-Dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3"(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-(2-hydroxy-2-pentyl)-phenylmethoxy)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-(3-hydroxy-3-propyl)-phenylmethoxy)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-methyl-1-pentyloxymethyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-methyl-1-pent-2-ynyloxymethyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-trifluoromethyl-5,5,5-trifluoro-1-pent-2-ynyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-[3-(2-hydroxy-2-propyl)-phenoxymethyl]-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-hydroxy-3-ethyl-1-pentylthiomethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-hydroxy-3-ethyl-1-pentylsulphonylmethyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-((1-hydroxy-1-methyl)ethyl)phenylthiomethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3,3-difluoro-4-hydroxy-4-methyl-1-pentyloxymethyl)-9,10-seco-pregna-5(Z)-7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6'-ethyl-6'-hydroxy-oct-1'-yn-1'-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(7'-ethyl-7'-hydroxy-non-1'-yn-1'-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-seco-pregna-

5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-methoxy-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-hydroxy-4-ethyl-2-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-ethyl-2-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20-(4-ethyl-4-hydroxy-1-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)17(20)(Z)-tetraene;

1(S),3(R)-Dihydroxy-20-(5-ethyl-5-hydroxy-1-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19),17(20)(Z)-tetraene;

1(S),3(R)-Dihydroxy-20-(6-ethyl-6-hydroxy-1-octyn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19),17(20)(Z)-tetraene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-4,4-difluoro-5-hydroxy-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4,4-dichloro-5-hydroxy-5-methyl-hexyloxy)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4,4-difluoro-5-hydroxy-5-methyl-hexyloxy)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-fluoro-4-methyl-pentyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-ethyl-4-fluoro-hexyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5-fluoro-5-methyl-hexyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R),20(S)-Trihydroxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-methoxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-ethoxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-[3-(2-hydroxy-2-methyl-1-propoxy)-prop-1E-en-1-yl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-ethyl-4-hydroxy-1-hexylthio)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-[5-methyl-5-hydroxy-1-hexylthio]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-[3-(1-methyl-1-hydroxyethyl)benzylthio]-9,10-seco-pregna-5(Z),7E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-methyl-3-hydroxy-1-butylthio)-9,10-seco-pregna-5(Z)-7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-hept-1(E)-en-3-yn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

24-oxo-1(S),3(R),25-Trihydroxy-20(S)-9,10-seco-cholesta-5(Z),7(E),10,19-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-oxo-4-hydroxy-4-ethyl-1-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(5-methyl-5-hydroxy-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-ethyl-4-hydroxy-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-ethyl-4-hydroxy-hex-2-ynyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-hydroxy-4-methylpentyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-hydroxy-4-methylpent)-2-yn-1-yloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(3,1-hydroxy-1-methylethyl)phenylmethyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-hydroxy-4-methyl-1-pentyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-methyl-1-pentyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A;

1(S),3(R),25-Trihydroxy-(20(S)-9,10-seco-cholesta-5(Z),7(E),10(19),23(E)-tetraene;

1(S),3(R)-Dihydroxy-(20(S)-(6'-hydroxy-6'-methyl-4'(E)-hepten-1'yl)-9,10-seco-pregna-

5(Z),7(E),10(19)-triene;

1(S),3(R),22(S),25-Tetrahydroxy-20(R),9,10-seco-cholesta-5(Z),7(E),10(19),23(E)-tetraene;

22(S)-Ethoxy-1(S)-3(R),25-trihydroxy-10(R)-,9,10-seco-cholesta-5(Z),7(E),10(1,23(E)-tetraene;

1(S),3(R)-Dihydroxy-20(S)-(3-(1-hydroxy-1-methylethyl)phenoxymethyl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(R) isomer;

1(S),3(R)-Dihydroxy-20(S)-(3-(1-hydroxy-1-methylethyl)phenylthiomethyl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(R) isomer;

1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-4-methylpent-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxyhept-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(S) isomer;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxyhepta-1(E),3(E)-dien-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(S) isomer;

1(S),3(R)-Dihydroxy-20(R)-(3-cyclopropyl-3-hydroxyprop-1(E)-en-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene (24(S) isomer) or the corresponding 24(R) isomer; and

1(S),3(R)-Dihydroxy-20(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, both 22-isomers.

[0015] As a second pharmacologically active component B it is preferred to use a group I, II or III topical steroid, more preferably a medium to weak acting steroid (groups I and II). Component B is preferably selected from the group consisting of Betamethasone (9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione) and esters thereof such as the 21-acetate, 17-adamantoate, 17-benzoate, 17-valerate, and 17,21-dipropionate; Alclomethasone and esters thereof such as the dipropionate; Clobetasole and esters thereof such as the propionate; Clobetasone and esters thereof such as the 17-butyrate; Desoximetasone; Diflucortolon and esters thereof, Diflorasone and esters thereof such as the diacetate; Fluocinonid; Flumetasone and esters thereof such as the pivalate; Fluocinolon and ethers and esters thereof such as the acetonide; Fluticasone and esters thereof such as the propionate; Fluprednidene and esters thereof such as the acetate; Halcinonide; Hydrocortisone and esters thereof such as the -17-butyrate; Mometasone and esters thereof such as the furoate; and Triamcinolon and ethers and esters thereof such as the acetonide; as well as mixtures thereof. More preferred examples of the corticosteroids are Betamethasone or esters thereof such as the 17-valerate or the 17,21-dipropionate, Clobetasole or esters thereof such as the propionate, Triamcinolon or ethers and/or thereof such as the acetonide or the acetonide-21-N-benzoyl-2-methyl-β-alaninate or the acetonide-21-(3,3-dimethylbutyrate), or Hydrocortisone

or esters thereof such as the 17-butyrate.

[0016] Moreover, the invention relates to non-aqueous pharmaceutical compositions for dermal use which contain at least one vitamin D or vitamin D analogue and at least one corticosteroid and which exhibits a higher efficacy in the treatment of psoriasis and other inflammatory skin diseases in humans and other mammals than any of the pharmacologically active components used alone. Said efficacy is preferably measured as percentage change in PASI score in psoriasis and related skin diseases, such as sebo-psoriasis and seborrhoic dermatitis.

[0017] PASI (Psoriasis Area and Severity Index) score assesses the extent and severity of the patient's psoriasis. The following formulae are used to calculate the PASI score:

Arms 0.2(R+T+S)E=X

Trunk 0.3(R+T+S)E=Y

Legs 0.4(R+T+S)E=Z

Where R=score for redness, T=score for thickness, S=score for scaliness, and E=score for extent where the score is assessed according to a scale from 0 to 4 as follows:

0=no involvement, 1=<10%, 2=10-29&, 3=30-49%, and 4=50-69%. The sum of X+Y+Z gives the total PASI score which can range from 0 to 64.8.

DESCRIPTION OF THE DRAWINGS

[0018]

Fig. 1 is a graphic illustration of the percentage change in PASI score obtained during 4 weeks of clinical trial where the efficacy of a preparation according to the invention ccontaining calcipotriol hydrate (52.2µg/g) and betamethasone dipropionate (0.643mg/g) is compared to that of a preparation in the same vehicle containing only calcipotriol hydrate (52.2µg/g) and a preparation in the same vehicle of betamethasone dipropionate (0.643mg/g). Fig. 1 shows an efficacy of the preparation of the invention which by far exceeds the efficacy obtainable by the two single component preparations. The change in PASI score reflects in the group of patients treated with the preparation of the invention a success of treatment of psoriasis hitherto unattainable by treatment with commercial preparations containing either calcipotriol or betamethasone, or by alternating treatment with such commercial preparations (cf.) thus proving the advantage of having the two active components present in the same preparation. (EOT=end of treatment).

Fig. 2 is a table showing the figures for percentage change in PASI score at each visit and end

of treatment for the same clinical trial as described for Fig. 1.

Fig. 3 is a bar diagram showing percentage of responders as a result of investigators' assessment of overall efficacy at each visit and end of treatment in the same clinical trial as for Fig. 1. Responders are defined as patients with marked improvement or clearance

Fig. 4 is a table showing the figures for percentage of responders as a result of investigators' assessment of overall efficacy at each visit and end of treatment, cf. Fig. 3, in the same clinical trial as for Fig. 1.

TOPICAL FORMULATIONS

[0019] In a preferred embodiment the invention provides a topical pharmaceutical composition in the form of an ointment, a cream, a lotion, preferably a scalp lotion, a liniment or other spreadable liquid or semi liquid preparation which isnon-aqueous . In one preferred embodiment, the composition of the invention is a mono-phase composition, i.e. a composition comprising a single solvent system, such as an ointment.

[0020] It has been found that in such combination compositions containing a solvent component C, the active components can co-exist without degradation, despite their different pH/stability profiles. The tendencies of the active compounds to affect one another with regard to pH is minimised or eliminated.

[0021] It is preferred that the maximum difference in optimum stability pH between the pharmacologically active compounds is at least 1.5, more preferred at least 2, in particular at least 2.5, more particularly at least 3, especially at least 4, such as at least 5.

[0022] In the general formula (II) defined above, it is preferred that the factor x (which designates the number of the units within the parentheses) is in the range 4-50, more preferably 4-40, in particular 4-30, especially 5-25, more especially 10-20, such as about 15.
As a non-limiting specific example of the solvent component C defined above may be mentioned the following, including the trade name:

Arlamol E (polyoxyethylene(15) stearyl ether).

[0023] The compositions of the present invention may be prepared in accordance with methods well known to the person skilled in the field of pharmacy. Thus, the non-aqueous compositions may be prepared by incorporating the components into a well known ointment or lotion base excipient such as white soft paraffin (also known as vaseline) or Plastibase™ (a base prepared from polyethylene (average MW about 21,000) and paraffin liquid) or ESMA-

P™ (a microcrystalline wax). As an example, preparation of a composition according to the invention is typically performed by melting white soft paraffin, adding a solution (typically at a concentration in the range of 0.0005-2.5% w/w) of the vitamin D analog in the required amount of solvent component C, e.g. Arlamol E, followed by addition of a dispersion of the corticosteroid component B in paraffin oil, typically with a particle size of from 0.1 to 20 µm, and then cooling the mixture. Typical content ranges of the various components in the finished composition according to the invention are 0.005 to 0.1 %w/w of the corticosteroid component B, from 0.0001 to 0.025 %w/w of the vitamin D analog component A, and from 1 to 20% w/w of the solvent component C, the remainder typically being primarily base excipient such as the above-mentioned white soft paraffin and/or paraffin oil. The composition may also contain other commonly used additives such as antioxidants (e.g. α-tocopherol).

[0024] The composition according to the invention provides the following therapeutic advantages in the treatment of skin diseases, such as psoriasis, sebo-psoriasis and related disorders, compared to the single compound therapy or combination therapy of the prior art:

- A clinical investigation has showed that treatment of psoriasis patients with a composition according to the invention comprising calcipotriol and betamethasone resulted in a faster onset of healing and a more effective healing of plaques than patients treated with only one of the active compounds.
- A composition combining a vitamin D analogue and a topical steroid provides synergy in the form of additional benefit to the patient apart from the direct therapeutic value of the active substances. It has been shown that the skin irritative side effects of a vitamin D analogue, such as calcipotriol, is alleviated by the simultaneous application of a steroid, such as betamethasone, onto psoriatic skin, an effect that is only attainable using a two-component or multi-component treatment regimen where a vitamin D analogue and a steroid cannot be applied simultaneously to affected skin due to incompatibility of the praparations. When both a vitamin D analogue and a topical steroid are used in a combination treatment of psoriasis it has hitherto been necessary to use separate applications, typically one in the morning and the other in the evening, making it impossible to obtain any synergistic effect of the two types of active compounds (cf. Ortonne, J.P., Nouv. Dermatol., 1994, 13(10), p. 746-751), or where a certain degree of synergistic effect, such as less skin irritation, has been reported for a two-component regiment (cf. Kragballe, K. et al. Br J Dermatol 1998 Oct;139(4):649-54, and Ruzicka, T. et Lorenz, B. Br J Dermatol 1998, 138(2), 254-58) a substantial proportion of psoriasis patients will not benefit due to non-compliance with the treatment regimen.
- Satisfactory medical treatment of skin disorders, such as psoriasis, can be attained in a shorter period of time using the composition according to the invention resulting in a reduction of steroid side effects, such as skin atrophy and rebound. Besides, it can be anticipated that even a milder acting steroid of group I, such as hydrocortisone which is presently not administered for psoriasis treatment, will be efficient in reducing or even eliminating the skin irritation which often follows calcipotriol treatment.
- Thus, the tolerance of the treatment will be considerably improved due to reduction of side effects of the active compounds.

- Instructions for treatment will be simpler when a single preparation is needed resulting in improved compliance for the patient and the possibility of efficient tretment of a much larger population of psoriasis patients.
- Instructions for treatment will be simpler when a single preparation is needed resulting in improved safety for the patient.

[0025] The invention also relates to a preferred pharmaceutical preparation according to the invention which is especially useful for the treatment of psoriatic skin diseases which are complicated by additional fungal infections, and which further contains an antifungal agent selected, e.g., from the group consisting of miconazol, clotrimazol, terbinafin, ciclopirox, bifonazol, nystatin, ketoconazol, econazol, and amorolfine.

[0026] Preferably, the compositions according to the invention do not contain other therapeutically effective compounds selected from the group consisting of the xanthine derivatives pentoxifylline, propentofyllin, and torbafylline, or any other xanthine or xanthine derivative.

[0027] The invention also relates to a method of treatment of psoriasis and related skin diseases comprising topically administering an effective amount of a composition according to the invention to a patient in need of such treatment. Said method preferably comprises topical administration once or twice daily of a medically sufficient dosage of said composition.

[0028] The composition according to the invention preferably contains 0.001-0.5mg/ g or ml or more preferably 0.001-0.25mg/g or ml of said component A and 0.05-0.1 mg/g or ml of said component B.

[0029] The invention is further illustrated by the following, non-limiting examples.

EXAMPLE 1

Ointment containing Calcipotriol and Betamethasone dipropionate

[0030] 919,3 g of White Soft Paraffin is melted at 80°C followed by cooling to 70°C and maintaining that temperature. Thereafter, 52.2 mg Calcipotriol hydrate (50 mg Calcipotriol) is dissolved in 50 g Arlamol E (polyoxypropylene-15-stearyl ether) to form a solution (Solution 1). Solution 1 is then added slowly into the molten paraffin while stirring.

[0031] Betamethasone (0,5 g, in the form of 0.643g of its dipropionate) in particulate form (99% <15µm) is dispersed in 30 g Paraffin Liquid to form Dispersion 1. Dispersion 1 as well as 20 mg α-tocopherol are added to the Calcipotriol-containing paraffin mixture of while stirring,

after which the mixture is cooled to below 30°C to give a composition according to the invention with the following composition:

1 g of ointment contains:	Betamethasone (as dipropionate 0.643 mg)	0.5mg
	Calcipotriol (as hydrate 52.2 µg)	50 µg
	Paraffin, Liquid	30 mg
	Polyoxypropylene-15-Stearyl Ether	50 mg
	α-Tocopherol	20 µg
	White Soft Paraffin	to make 1 g

EXAMPLE 2

Stability test

[0032] The chemical stability of the two active components was tested after storage for 1 month at 40°C and 3 months at 25°C and 40°C, respectively.The quantitative content of Calcipotriol was determined by HPLC.

[0033] The Calcipotriol was extracted from the preparation into a mixture of methanol and 0.01M diammonium hydrogenphosphate (70:30) and quantified under the following HPLC conditions: Column: about 125 mm Ø 4 mm (i.d.) stainless steel column with LiChrospher RP-18, 5 µm; mobile phase: acetonitrile-methanol-0.01 M aqueous ammonium phosphate pH 6 (20:50:30); flow: about 2 ml/min; detection: variable wavelength UV-detector set at 265 nm. Calcipotriol and the related substances were separated by the reverse phase HLPC-method described above; Column: Superspher RP-18, 4 µm; Flow: 1.2 ml/min. The quantitative content of Betamethasone Dipropionate was determined by HLPC.

[0034] The Betamethasone Dipropionate was extracted from the preparation into a mixture of acetonitrile:water (50 : 55) and quantified under the following HPLC conditions: Column: About 125 mm Ø 4 mm (i.d.) stainless steel column packed with LiChrospher RP-18, 5µm. Mobile phase: Acetonitrile: water (50 : 55). Flow: 2 ml/min. Detection: Variable wavelength UV-detector set at 240 nm. The related substances besides betamethasone were determined by a reverse phase HLPC-method analogous to the above. Betamethasone: Determined as above with the exception of the mobile phase: Acetonitrile/methanol/0.05M buffer pH7 (25:5:70).

[0035] The results are shown in the following Table 1.

Table 1

	Calcipotriol µg/g	Calcipotriol-related substances %	Betamethasone dipropionate mg/g	Betamethasone related substances %
Start	50.0	1.6	0.63	1.2
25°C				
3 months	50.5	1.4	0.64	0.2
40°C				
1 month	48.0	2.1	0.64	0.6
3 months	49.7	1.8	0.64	0.2

[0036] It will be seen from Table 1 that both Calcipotriol and Betamethasone ester are very stable under the test conditions.

[0037] The stability of Calcipotriol was compared to an similar ointment where propylene glycol was used as the solvent and lanolin used as an emulsifier. The composition of the comparison ointment was the same as the above with respect to Calcipotriol and Betamethasone dipropionate, as well as 10% w/w propylene glycol, 10% w/w anhydrous lanolin and 80% w/w White Soft Paraffin. The comparison ointment was stored for 2.5 months at 5°C and 40°C, respectively. Only the content of Calcipotriol-related substances was determined in the manner described above. The results are shown in Table 2.

Table 2

	Calcipotriol related substances %
5°C	20
40°C	96

[0038] As it will be seen from the results, Calcipotriol is degraded almost completely in the comparison composition under the test conditions as opposed to a composition of the invention, where the Calcipotriol is retained with essentially no degradation.

REFERENCES CITED IN THE DESCRIPTION

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compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US5565462A [0003]
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- **RICHARDS, H.L. et al.**J Am Acad Dermatol, 1999, vol. 41, 4581-3 [0005]
- **B. PATEL et al.**J. Am. Acad. Dermatol., 1998, vol. 38, 1010-1011 [0006]
- **ORTONNE, J.P.**Nouv. Dermatol., 1994, vol. 13, 10746-751 [0024]
- **KRAGBALLE, K. et al.**Br J Dermatol, 1998, vol. 139, 4649-54 [0024]
- **RUZICKA, T.LORENZ, B.**Br J Dermatol, 1998, vol. 138, 2254-58 [0024]

Patentkrav

1. Ikke-vandig farmaceutisk sammensætning til dermal anvendelse, hvilken sammensætning omfatter
en første farmakologisk komponent A bestående af mindst en vitamin D- eller vitamin D-analog og en anden farmakologisk aktiv komponent B bestående af mindst et corticosteroid, **kendetegnet ved at** forskellen mellem den optimale stabilitet pH af den første komponent A og den optimale stabilitet pH af den anden komponent B er mindst 1; og mindst en opløsningsmiddelkomponent C valgt fra gruppen bestående af:

(i) forbindelser med den almene formel $H(OCH_2C(R^1)H)_xOR^2$ (II) hvor x er i området på 2-60, R^1 i hver af x-enhederne er CH_3, og R^2 er ligekædet eller forgrenet C_{1-20}alkyl eller benzoyl.

2. Sammensætning ifølge krav 1, hvor komponent C er polyoxypropylen-15-stearylether.

3. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1 eller 2 hvor den anden komponent B er valgt fra gruppen bestående af Betamethason, Clobetasol, Clobetason, Desoximethason, Diflucortolon, Diflorason, Fluocinonid, Flumethason, Fluocinolon, Fluticason, Flupredniden, Halcinonid, Hydrocortison, Momethason, Triamcinolon, og farmaceutisk acceptable estere og acetonider såvel som blandinger deraf.

4. Farmaceutisk sammensætning ifølge krav 3, hvor esterne er valgt fra gruppen bestående af 17-valerat, 17-propionat, 17,21-dipropionat, acetonid, acetonid-21-N-benzoyl-2-methyl-β-alaninat, acetonid-21-(3,3-dimethylbutyrat), og 17-butyrat.

5. Sammensætning ifølge et hvilket som helst af kravene 1-4, hvor den første komponent A er valgt fra gruppen bestående af calcipotriol, calcitriol, tacalcitol, maxacalcitol, og 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-

methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-trien, såvel som blandinger deraf.

6. Sammensætning ifølge de foregående krav, hvor vitamin D-analogen er calcipotriol eller dets hydrat.

7. Sammensætning ifølge et hvilket som helst af de foregående krav indeholdende 0,001-0,25 mg/g eller ml af denne komponent A og 0,05-0,1 mg/g eller ml af denne komponent B.

8. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav til anvendelse i den topiske behandling af psoriasis hos mennesker og andre pattedyr.

DRAWINGS

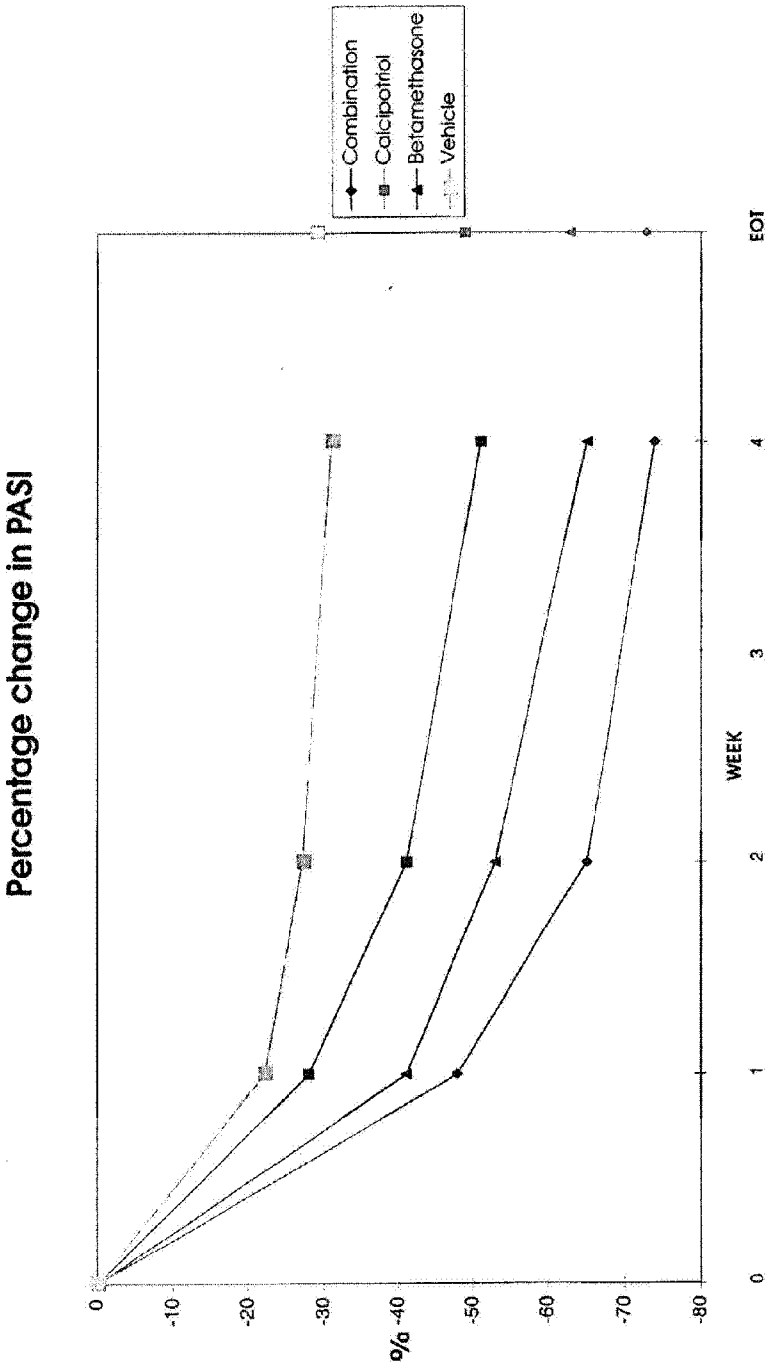

FIGURE 1

Percentage change in PASI score at each visit and end of treatment

Percentage change in PASI score	COMB (n=301)	CALC (n=308)	BETA (n=312)	VEHICLE (n=107)
Visit 1				
Mean	10.9	10.9	10.7	10.6
Percentage change				
To visit 2				
Mean	-48.1	-28.4	-41.4	-21.5
To visit 3				
Mean	-64.9	-40.8	-53.2	-27.4
To visit 4				
Mean	-73.9	-51.3	-64.5	-31.3
To end of treatment				
Mean	-73.2	-48.8	-63.1	-28.8

FIGURE 2

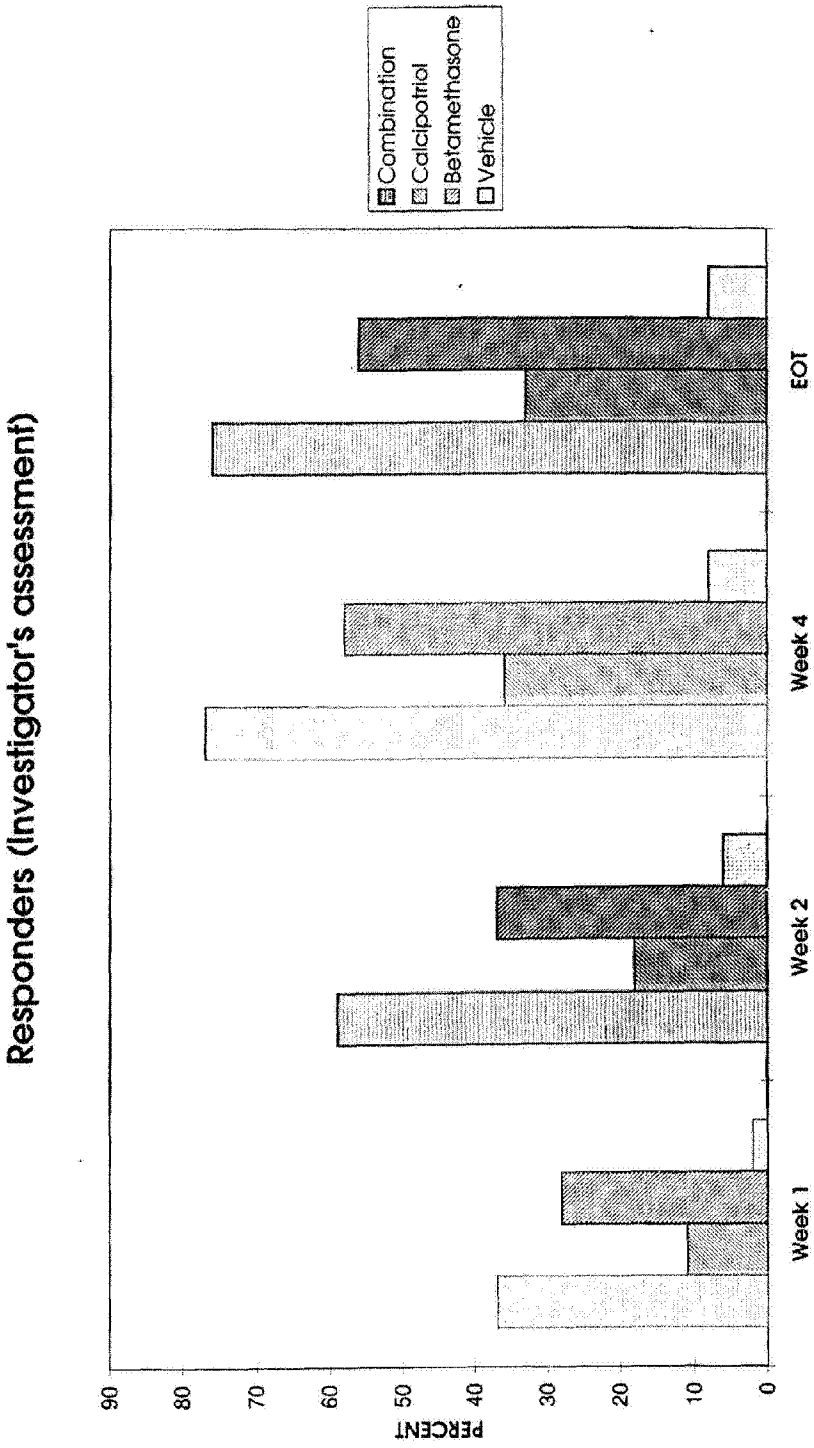
Responders (Investigator's assessment)
Combination
Calcipotriol
Betamethasone
Vehicle
PERCENT
0
10
20
30
40
50
60
70
80
90
Week 1
Week 2
Week 4
EOT

FIGURE 3

Investigator's assessment of overall Efficacy at each visit and end of treatment

Investigator's overall efficacy assessment	COMB (n=301) %	CALC (n=308) %	BETA (n=312) %	VEHICLE (n=107) %
Visit 2				
Non responder	63.5	89.5	72.5	98.1
Responder	36.5	10.5	27.5	1.9
Total	100.0	100.0	100.0	100.0
Visit 3				
Non responder	41.5	82.2	62.7	94.2
Responder	58.5	17.8	37.3	5.8
Total	100.0	100.0	100.0	100.0
Visit 4				
Non responder	23.1	64.4	42.4	91.9
Responder	76.9	35.6	57.6	8.1
Total	100.0	100.0	100.0	100.0
End of treatment				
Non responder	23.9	66.6	44.2	92.5
Responder	76.1	33.4	55.8	7.5
Total	100.0	100.0	100.0	100.0

FIGURE 4