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| EXAMINER |
|---|
| HARTSFIELD, KATHRIEN ANN |

| ART UNIT | PAPER NUMBER |
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| 1627 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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PTOL-90A (Rev. 04/07)



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IPR Petition - USP 11,311,482

| *Office Action Summary* | Application No. 16/179,576 | Applicant(s) Angel et al. | |
|---|---|---|---|
| | Examiner KATHRIEN A HARTSFIELD | Art Unit 1627 | AIA (FITF) Status Yes |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 12/8/2022.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 1,6-10,12 and 27 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,6-10,12 and 27 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 12/8/2022.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

***Notice of Pre-AIA or AIA Status***

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

**DETAILED ACTION**

Claims 1, 6-10, 12 and 27 is pending.

Applicants response filed 12/8/2022 has been received and entered in the application.

**Action Summary**

Claims 1, 6-10, 12 and 27 are rejected under 35 U.S.C. 103 as being unpatentable over Tazaorac (Highlights of Prescribing Information, LABEL (fda.gov), 12/2013) and Angel et al (WO2012/087443 published 06/28/2012) both are of record is maintained.

Claims 1, 6-10, 12 and 27-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787 is maintained.

Claims 1, 6-10, 12 and 27-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895 is maintained.

Claims 1, 6-10, 12 and 27-28 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561 is maintained.



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***Response to Arguments***

Applicants again argue on page 5 of the response that Dr. Dow explains that he would not expect to achieve effective delivery of tazarotene from a composition formulated for delivery of halobetasol propionate. This argument has been fully considered but has not been found persuasive the formulation for delivery as applicants assert is the very same formulation as instant claimed. Therefore, it would have been obvious to substitute tazarotene in same formulation. Additionally, Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate. it would have been obvious to substitute tazarotene instead of halobetasol propionate because both agents are known in the art to treat skin disorder and the composition for delivery (as applicants assert) is the same, thus taken the cited art, it would have been obvious to administer tazarotene with diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary



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Applicants assert on page 8 bridging page 9 unexpected results (e.g. surprising properties) in which Dr. Dow that a skilled artisan would not expect the surprising advantages of the claimed lotion composition. This argument has been fully considered but has not been found persuasive. This has been previously been addressed in the non-final rejection dated 6/8/2022. And applicant response to that response to the argument is that applicants has compared Tazorac® 0.1% to composition A of 0.045%. However, Tazorac also discloses 0.05% (emphasis added), which was not compared and is the closest concentration of claimed concentration. An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness (emphasis added). In re Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). "A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." In re Merchant, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). Where the comparison is not identical with the reference disclosure, deviations therefrom should be explained, In re Finley, 174 F.2d 130, 81 USPQ 383 (CCPA 1949), and if not explained should be noted and evaluated, and if significant, explanation should be required. In re Armstrong, 280 F.2d 132, 126 USPQ 281 (CCPA 1960) (deviations from example were inconsequential) (MPEP 716.02(e). In this case, applicant compared 0.1% tazarotene to composition A; however, Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active



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ingredient, tazarotene. Nothing has been compared to the concentration closest the claimed concentration which would be 0.05%.

Applicants argue on page 11 that there is has not been a prima case of obviousness established by the Office. This argument has been fully considered but has not been found persuasive. Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of water within each, both are oil-in-water compositions). Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 % ( example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%,



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mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0. It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben to the oil-in-water cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary. Additionally, applicants only compared 0.1%, but Tazorac also teaches 0.05%, in which applicants has not made any comparison. In which this argument has been addressed above.

## Previous Rejection

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.



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Claims 1, 6-10, 12 and 27 are rejected under 35 U.S.C. 103 as being unpatentable over Tazaorac (Highlights of Prescribing Information, LABEL (fda.gov), 12/2013) and Angel et al (WO2012/087443 published 06/28/2012) both are of record.

Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of water within each, both are oil-in-water compositions). (11, under Description).

Tazaorac does not disclose diethyl sebacate, sorbitol solution, methyl and propyl paraben nor the concentrations of the inactive agents. Tazaorac does not disclose the pH.

Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the agent in a formulation containing a liquid oil component that includes a dicarboxylic acid ester and/or a monocarboxylic acid ester (page 6). Angel teaches the components of the aqueous



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phase and of the oil phase may be separately combined and mixed until homogenous solutions are obtained and then the aqueous solution and the oil solution may be combined and mixed, such as by shear mixing, to form the formulation. The oil phase may be added to the water phase, or the water phase may be added to the oil phase. The phases may be combined and mixed, such as at elevated temperatures of 50-90°C or at room temperature, that is between 20-30°C, or at a temperature between room temperature and the elevated temperatures (page 12). Angel teaches that with high speed rotor-stator mixing, the oil phase containing the drug is added to the aqueous phase. Mixing is continued until a homogeneous emulsion is obtained. Anger teaches that the thickening agent is miscible or soluble in an aqueous fluid. Examples of suitable thickening agents include acacia, alginic acid, bentonite, carbomers, also known as carboxy vinyl polymers, such as sold under the tradename Carbopol® (page 10 bridging page 11). Angel further teaches that in a manufacturing vessel, purified water and disodium edetate dihydrate are combined a d the mixture is agitated until a clear solution is achieved. Sorbitol, methylparaben, and propylparaben are then added to the mixture. The mixture is continuously mixed and is heated to approximately 75°C. The mixture is agitated until a solution is obtained. The mixture is then removed from the heat source and allowed to cool to below 40°C with continued mixing. With continuous propeller agitation Carbopol 981 at a concentration of 0.6% and Pemulen™ (polymeric emulsifier) at a concentration of 0.4% are added to the mixture and fully dispersed. (page 20). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 %



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(example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0 (table 4). Angel exemplify a 0.01 %wt. a formulation comprising the dermatological carrier of light mineral oil and diethyl sebecate and purified water, q.s ad (page 20). Regarding the limitation of claims 1, 8, 31-32, Angel teaches the claimed amounts of diethyl sebecate (2.97% wt.), the claimed amount of light mineral oil (8.03% wt.), the claimed amount of carbomer copolymer type B (Pemulen TR-1 0.40% wt.; see Table 3, page 20 of instant specification defines Pemulen TR-1 as a carbomer copolymer type B) and claimed amount of carbomer homopolymer type A found within the instant claims (carbopol 981, 0.6% wt., see Table 3, page 20 of instant specification defines carbomer 981 as a carbomer homopolymer type A).

It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl, propyl paraben, water, carbopol® and Pemulen ™ to the oil-in-water with an oil phase and aqueous phase in a cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben and purified water q.s. ad because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl, propyl paraben, water and Pemulen ™ are useful in topical administration for enhancing the solubility, chemical stability and



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penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.

One of ordinary skill in the art of preparing a topical lotion and cream emulsions consisting of tazarotene would have found it prima facie obvious to administer the concentration of tazarotene in the emulsion of Tazaorac in order to arrive at the instantly claimed emulsion. Tazaorac teaches the concentration of tazaotene of 0.05% and 0.1% contains 0.5 and 1 mg respectively. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Lab. Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997); Smith v. Nichols, 88 U.S. 112, 118-19 (1874) (a change in form, proportions, or degree "will not sustain a patent"); In re Williams, 36 F.2d 436, 438 (CCPA 1929) ("It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions."). See also KSR Int' l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007) (identifying "the need for caution in granting a patent based on the combination of elements found in the prior art."). Therefore, the ordinary artisan would have been motivated to optimize the



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workable ranges disclosed by Tazaorac, with the reasonable expectation of making formulations which possess improved solubility and pharmaceutical properties such as high bioavailability and prolonged effect. Furthermore, it is obvious to vary and/or optimize the amount of tazarotene provided in the composition, according to the guidance provided by Tazaorac, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regards to the of concentrations of sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, is diethyl sebacate in a concentration of 2.10 % ( the combination of mineral oil and diethyl sebacate is 11.8%), sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60%, Carbopol® at a concentration of 0.6% and Pemulen™ (polymeric emulsifier) at a concentration of 0.4% as disclosed by Angel. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Lab. Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d



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1362 (Fed. Cir. 1997); Smith v. Nichols, 88 U.S. 112, 118-19 (1874) (a change in form, proportions, or degree "will not sustain a patent"); In re Williams, 36 F.2d 436, 438 (CCPA 1929) ("It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions."). See also KSR Int' l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007) (identifying "the need for caution in granting a patent based on the combination of elements found in the prior art."). Therefore, the ordinary artisan would have been motivated to optimize the workable ranges disclosed by Tazaorac and Angel, with the reasonable expectation of making formulations which possess improved solubility and pharmaceutical properties such as high bioavailability and prolonged effect. Furthermore, it is obvious to vary and/or optimize the amount of sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60%, Pemulen™ (polymeric emulsifier) at a concentration of 0.4% provided in the composition, according to the guidance provided by Tazaorac and Angel, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges



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by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With respect to the art rejection above, it is noted that the reference does not teach that the composition can be used in the manner instantly claimed, treating acne. However, the intended use of the claimed composition does not patentably distinguish the composition, per se, because such undisclosed use is inherent in the reference composition. In order to be limiting, the intended use must create a structural difference between the claimed composition and the prior art composition. If the prior art structure is capable of performing the intended use, then it meets the claim. The logic flows from MPEP 2115:

- "A claim is only limited by positively recited elements. Thus, "[i]nclusion of the material or article worked upon by a structure being claimed does not impart patentability to the claims." *In re Otto*, 312 F.2d 937, 136 USPQ 458, 459 (CCPA 1963); see also *In re Young*, 75 F.2d 996, 25 USPQ 69 (CCPA 1935);
- "the manner or method in which such machine is to be utilized is not germane to the issue of patentability of the machine itself." See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

An intended use will not limit the scope of the claim because it merely defines a context in which the invention operates. (*Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003)). Moreover "the patentability of apparatus or composition claims depends on the claimed structure, not



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on the use or purpose of that structure." (*Catalina Mktg. Int'l, v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002). Additionally, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. (See MPEP 707.07(f) and 2141.02 I; *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and MPEP 2111.02 II; *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951)).

In the instant case, the intended use does not create a structural difference and the body of the claim does not depend on the intended use for completeness but rather can stand alone. Consequently, the intended use is not limiting.

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.



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Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file



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provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1, 6-10, 12 and 27 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '787 patent is that the '787 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '787 patent possess significant overlapping scopes of invention.

Claims 1, 6-10, 12 and 27 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895. Although the claims at issue are not identical, they are not patentably distinct from each



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other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '895 patent is that the '895 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '895 patent possess significant overlapping scopes of invention.

Claims with modification due to applicants amendment of claims. is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561. Although the claims at issue are not identical, they are not patentably distinct from each other because both the instant claims and the '561 application recite a composition (tazarotene) for the treatment of acne. Taken that both applications disclose the same compound (tazarotene) to treat acne, one of ordinary skills in the art would recognize that both application possess significant overlapping scopes of invention with a reasonable expectation of success.

Claims 1, 6-10, 12 and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-13 of copending Application No. 17/719278 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both applications are drawn to a topical pharmaceutical composition comprising tazarotenic in a concentration of 0.045. This difference is that in the '278 application the inactive ingredients are in dependent claims rather in one claim as in the present application. However, both application have overlapping scopes of inventions.



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This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

## Conclusion

Claims 1, 6-10, 12 and 27 is rejected.

No claims are allowed.

## Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHRIEN A. HARTSFIELD whose telephone number is (571)270-5238. The examiner can normally be reached on Monday - Thursday 8-6pm.



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Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney L. Klinkel can be reached on (571) 270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN A HARTSFIELD/
Primary Examiner, Art Unit 1627



Padagis Ex. 1029
IPR Petition - USP 11,311,482

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/179,576 | Angel et al. |
| | Examiner | Art Unit |
| | KATHRIEN A HARTSFIELD | 1627 |

| CPC - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10 | 08/05/2020 | kc |
| A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10 | 02/23/2021 | kc |
| A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10 | 06/07/2021 | kc |
| A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10 | 06/03/2022 | kc |
| A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10 | 01/12/2023 | kh |

| US Classification - Searched* | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

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|---|---|
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| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/179,576 | Angel et al. |
| | Examiner | Art Unit |
| | KATHRIEN A HARTSFIELD | 1627 |

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
| EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB) | 03/15/2019 | KC |
| EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB) | 10/23/2019 | kc |
| EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB) | 02/24/2020 | kc |
| EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB) | 08/05/2020 | kc |
| P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT) | 02/23/2021 | kc |
| INVENTOR | 02/23/2021 | kc |
| P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT) | 06/07/2021 | kc |
| INVENTOR | 06/07/2021 | kc |
| P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT) | 06/03/2022 | kc |
| INVENTOR | 06/03/2022 | kc |
| P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT) | 01/12/2023 | kh |
| INVENTOR | 01/12/2023 | kh |

| Interference Search | | | |
|---|---|---|---|
| **US Class/CPC Symbol** | **US Subclass/CPC Group** | **Date** | **Examiner** |
| | | | |

## PE2E SEARCH - Search History (Prior Art)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| L1 | 0 | "il in water" SAME lotion | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/22 04:51 PM |
| L2 | 2 | "20140336161" | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/22 06:07 PM |
| L3 | 3 | "20190133943".pn. | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/23 03:23 PM |
| L4 | 567473 | L3 OR ( (A61K31/4436 OR A61K47/14 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61K47/06 OR A61K47/32 OR A61P17/00 OR A61P17/10).cpc.) | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/23 03:27 PM |
| L5 | 5309 | L4 AND tazarotene | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/23 03:28 PM |
| L6 | 279 | L5 AND "diethyl sebacate" | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/23 03:28 PM |
| L7 | 189 | L6 AND "mineral oil" | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/23 03:29 PM |
| L8 | 119 | L7 AND "sorbitan monooleate" | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/23 03:29 PM |
| L9 | 40 | L8 AND @py<2015 | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; | OR | ON | ON | 2021/02/23 03:29 PM |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | IBM_TDB) | | | | |
| L10 | 190 | L3 OR ( ("ARTURO A".ine. OR "ARTURO; ANGEL".ine. OR "CHOI YOON E".ine. OR "JEON MIN SEO".ine. OR "KIM SOK".ine. OR "PARK YUN HWAN".ine. OR "PILLAI R".ine. OR "PILLAI; RADHAKRISHNAN".ine .)) | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/23 03:30 PM |
| L11 | 24 | L10 AND tazarotene | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2021/02/23 03:30 PM |
| L12 | 30 | L11 | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2022/06/03 01:18 PM |
| L13 | 41 | L9 | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2022/06/03 01:18 PM |
| L14 | 127 | ("11311482"\|"20040081668"\|"20070196459"\|"20080044444"\|"20090012051"\|"20090176750"\|"20130310355"\|"20180177803"\|"20180360752"\|"20190133942"\|"20190231797"\|"20210145847"\|"20210330681"\|"4048310"\|"4083974"\|"4233295"\|"4244942"\|"4299828"\|"4370322"\|"4619921"\|"4767751"\|"4918065"\|"5256691"\|"5326566"\|"5422361"\|"5472982"\|"6479058"\|"6517847"\|"6656928"\|"6765001"\|"6974807"\|"7300669"\|"7820145"\|"8071578"\|"8962028"\|"9782341").PN. | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2023/01/12 01:55 PM |
| L15 | 41 | L13 | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2023/01/12 01:56 PM |
| L16 | 36 | L11 | (US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; | OR | ON | ON | 2023/01/12 01:58 PM |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | JPO; DERWENT; IBM_TDB) | | | | |

**PE2E SEARCH - Search History (Interference)**

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|---|
| There are no Interference searches to show. |

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | **Application Number** | 16/179,576 |
| | **Filing Date** | November 2, 2018 |
| | **First Named Inventor** | Arturo Angel |
| | **Art Unit** | 1627 |
| | **Examiner Name** | Kathrien Ann Hartsfield |
| | **Attorney Docket Number** | 095920-004120US-1240999 |

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| Examiner Initial* | Cite No | Patent Number | Kind Code [1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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| | **Application Number** | 16/179,576 |
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| | **First Named Inventor** | Arturo Angel |
| | **Art Unit** | 1627 |
| | **Examiner Name** | Kathrien Ann Hartsfield |
| | **Attorney Docket Number** | 095920-004120US-1240999 |

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| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
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IPR Petition - USP 11,311,482

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| | **Art Unit** | 1627 |
| | **Examiner Name** | Kathrien Ann Hartsfield |
| | **Attorney Docket Number** | 095920-004120US-1240999 |

| NON-PATENT LITERATURE DOCUMENTS | | | |
|---|---|---|---|
| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
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| | **Application Number** | 16/179,576 |
| | **Filing Date** | November 2, 2018 |
| | **First Named Inventor** | Arturo Angel |
| | **Art Unit** | 1627 |
| | **Examiner Name** | Kathrien Ann Hartsfield |
| | **Attorney Docket Number** | 095920-004120US-1240999 |

| NON-PATENT LITERATURE DOCUMENTS | | | |
|---|---|---|---|
| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
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|---|---|---|
| | **Application Number** | 16/179,576 |
| | **Filing Date** | November 2, 2018 |
| | **First Named Inventor** | Arturo Angel |
| | **Art Unit** | 1627 |
| | **Examiner Name** | Kathrien Ann Hartsfield |
| | **Attorney Docket Number** | 095920-004120US-1240999 |

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| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
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Padagis Ex. 1029
IPR Petition - USP 11,311,482

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| | **Art Unit** | 1627 |
| | **Examiner Name** | Kathrien Ann Hartsfield |
| | **Attorney Docket Number** | 095920-004120US-1240999 |

| EXAMINER SIGNATURE | | | |
|---|---|---|---|
| Examiner Signature | /KATHRIEN A HARTSFIELD/ | Date Considered | 01/12/2023 |

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.



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I hereby certify that this correspondence is being filed with the United States Patent and Trademark Office via the Office electronic filing system on December 8, 2022.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Sharleen Lane/
Sharleen Lane

PATENT
Attorney Docket No.: 095920-004120US-1240999
Client Ref. No.: DOW-P05877-2-C1

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Arturo Angel *et al.*

Application No.: 16/179,576

Filed: November 2, 2018

For: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

Customer No.: 112120

Confirmation No.: 1093

Examiner: Kathrien Ann Hartsfield

Art Unit: 1627

**AMENDMENT / RESPONSE TO OFFICE ACTION**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Office Action mailed June 8, 2022, please enter the following amendments and consider the following remarks:

**Amendments to the Claims** are reflected in the listing of claims, which begins on page 2 of this paper.

**Remarks/Arguments** begin on page 4 of this paper.

## AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in the application.

**Listing of Claims:**

1. (Previously presented) A topical pharmaceutical composition for treating acne, comprising:

a sole active pharmaceutical ingredient consisting of tazarotene at a concentration of 0.045 percent by weight of the composition;

wherein said composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase,

wherein the oil phase comprises a dicarboxylic acid ester and a mineral oil,

wherein the aqueous phase comprises water and a carbomer homopolymer,

wherein the composition further comprises a polymeric emulsifier, and

wherein the tazarotene is in solution in the oil phase.

2-5. (Canceled)

6. (Previously presented) The topical pharmaceutical composition of claim 1, wherein:

the dicarboxylic acid ester and the mineral oil are present in a total amount of 10-12 percent by weight of the composition,

the carbomer homopolymer is present in an amount of 0.5-0.7 percent by weight of the composition, and

the polymeric emulsifier is present in an amount of 0.3-0.5 percent by weight of the composition.

7. (Previously presented) The topical pharmaceutical composition of claim 1, wherein the dicarboxylic acid ester in the oil phase of the emulsion is diethyl sebacate.

8. (Previously presented) The topical pharmaceutical composition of claim 1, wherein the composition further comprises sorbitol solution, 70%.

9. (Previously presented) The topical pharmaceutical composition of claim 8, wherein the sorbitol solution, 70%, is present in an amount of 10-11 percent by weight of the composition.

10. (Previously presented) The topical pharmaceutical composition of claim 1, wherein the oil phase comprises diethyl sebacate and light mineral oil.

11. (Canceled)

12. (Original) The topical pharmaceutical composition of claim 1, having a pH of about 4 to about 6.

13-26. (Canceled)

27. (Previously presented) The topical composition of claim 1 consisting essentially of:

0.045 weight % tazarotene;
2.5 -3.5 weight % diethyl sebacate;
7.5-8.5 weight % light mineral oil;
0.05-0.2 weight % sorbitan monooleate;
10-11 weight % sorbitol solution, 70%;
0.1-0.2 weight % methylparaben;
0.02-0.04 weight % propylparaben;
0.03-0.06 weight % edetate disodium dihydrate;
0.3-0.05 weight % carbomer polymer type B;
0.5-0.7 weight % carbomer homopolymer type A;
sodium hydroxide, q.s. to pH 5.5 ±0.5; and
purified water, q.s. to 100 weight %.

28. (Canceled)

## REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1, 6-10, 12, and 27 will be pending in this application. No claims are amended, canceled, or newly added. No new matter is introduced by this Amendment. Based on the following remarks, Applicant respectfully requests reconsideration and allowance of the pending claims.

### I. Rejection of Claims under 35 U.S.C. § 103

Claims 1, 6-10, 12, and 27-28 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Tazorac ("Highlights of Prescribing Information, LABEL (fda.gov), December 2013) in view of Angel *et al.* (WO 2012/087443; "Angel"). In response, Applicant respectfully traverses the rejection.

In the Office Action, it is stated that Tazorac discloses tazarotene cream, 0.05% and 0.1%, for topical use, containing benzyl alcohol, carbomer 1342, carbomer homopolymer type B; edetate disodium; medium chain triglycerides, mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monoleate.[1]

It is acknowledged that Tazorac fails to disclose the amount of tazarotene as presently claimed, the pH of the formulation as presently claimed, and diethyl sebacate, sorbitol solution, methyl paraben, and propyl paraben as presently claimed.[2] However, the Examiner asserts that it would be obvious to combine the disclosure of Tazorac with the disclosure of Angel so as to arrived at the presently claimed lotion composition, stating:

> It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl, propyl paraben water, carbopol® and Pemulen™ to the oil-in-water with an oil phase an aqueous phase in a cream of tazarotene of Tazorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben and purified water q.s. ad because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl, propyl paraben, water and Pemulen™ are useful in topical administration for enhancing the solubility, chemical stability and

[1] Office Action at page 4.
[2] Office Action at page 7.

> penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.[3]

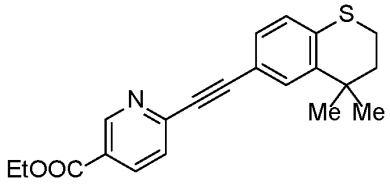
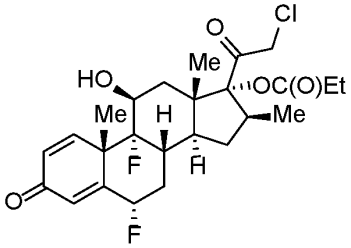
Applicant respectfully disagrees with the Examiner assertions. One of skill in the art would *not* be motivated to combine the references as suggested in the Office Action and one of skill in the art would *not* have expected the surprising combination of efficacy and tolerability provided by the claimed composition. In support of this position, the Examiner is referred to the Declaration of Dr. Gordon Dow, which was filed pursuant to 37 C.F.R. § 1.132 on May 27, 2021.

**A. ONE OF SKILL IN THE ART WOULD NOT BE MOTIVATED TO COMBINE THE CITED REFERENCES.**

As noted above, it is alleged that the skilled artisan would be motivated to modify the cream of Tazorac by using diethyl sebacate, sorbitol, and parabens, because Angel discloses that such excipients are useful for enhancing solubility, chemical stability, and penetration properties. Applicant respectfully submits that the skilled artisan would *not* be motivated to combine the references as proposed in the Office Action, because the Tazorac reference and Angel reference are directed to two very **different** active agents that are known in the art to be interchangeable from a formulation perspective.

As stated by Dr. Dow, who is named as a co-inventor on the Angel reference and an expert in the field of topical formulation development, the skilled artisan would *not* be motivated by the disclosure of Angel to modify Tazorac to arrive at the claimed lotion composition. Dr. Dow explained that halobetasol propionate, a steroid disclosed by Angel for the treatment of psoriasis, has a *vastly different* chemical structure and physicochemical properties as compared to tazarotene, a retinoid, disclosed by Tazorac. Some of these differences are tabulated below. As shown below, the logP values for tazarotene, a retinoid, and halobetasol propionate, a steroid, indicate that ***tazarotene is almost 1000 times less lipophilic than halobetasol propionate***.

[3] Office Action at pages 10-11.

| | Tazarotene | Halobetasol propionate |
|---|---|---|
| |  |  |
| Mol. Wt. | 351.46 | 484.96 |
| logP [a] | 5.987+/-0.448 | 2.947+/-0.630 |

[a] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 at 25 °C.

Dr. Dow explained that he would not expect to achieve effective delivery of tazarotene from a composition formulated for delivery of halobetasol propionate. This is because the physicochemical properties of halobetasol propionate, a steroid, are entirely different from the physicochemical properties of tazarotene, a retinoid. Dr. Dow explained that the skilled artisan would ***not*** expect Angel's results for halobetasol propionate to extend to a tazarotene formulation given the considerable differences between the active agents. Rather, the skilled formulator would understand that the stability and delivery considerations for halobetasol propionate could ***not*** be translated to tazarotene, and the skilled formulator would ***not*** look to the disclosure of Angel when formulating tazarotene.

Applicant respectfully submits that the physical differences between the two active agents, as explained in the Declaration, are indeed the "evidence to the contrary" that the Examiner repeatedly calls for.

In the Office Action, the Examiner dismisses this evidence and asserts:

> One of ordinary skill in the art of preparing a topical lotion and cream emulsions consisting of tazarotene would have found it prima facie obvious to administer the concentration of tazarotene in the emulsion of [Tazorac] in order to arrive at the instantly claimed emulsion.[4]

However, contrary to the Examiner's assertion, the claimed formulation is **not** the emulsion of Tazorac with a lower concentration of tazarotene; it is a formulation that is **different**

[4] Office Action at page 10.

from the Tazorac formulation and that has a lower concentration of tazarotene. As the Examiner points out in the Office Action, "Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1 %; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate."[5] As acknowledged in the Office Action, [Composition] A has ingredients not disclosed in Tazaorac."[6] As recited in the claims, the claimed topical pharmaceutical composition, which is exemplified by Composition A in Table 6, is an oil-in-water emulsion that is a lotion and that comprises an oil phase and an aqueous phase, wherein the oil phase comprises a dicarboxylic acid ester and a mineral oil. As taught by Tazorac, the Tazorac cream formulation does not have an oil phase comprising a dicarboxylic acid ester and a mineral oil.

It is important for the Examiner to appreciate that not every emulsion is the same, not every cream is the same, and not every lotion is the same. Moreover, it is important for the Examiner to appreciate that because one active agent can be formulated in a particular emulsion, cream, or lotion does **not** necessarily mean that a different active agent can successfully be formulated in that same emulsion, cream, or lotion. The Examiner seems to have lost sight of the many challenges faced by drug formulators, and the Examiner seems to be asserting that **every** formulation, regardless of the active formulated, the dosage form, mode of administration, or the formulation components employed, **is obvious**, when the Examiner repeatedly states:

> The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant ***are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration***.[7]

This position is inconsistent with the reality faced by those of skill in the art of formulation development, and it is clearly not supported by the case law. As the Examiner is aware, the United States Patent & Trademark Office has over the years issued numerous patents directed to different formulations of a given active agent, to different dosages of a given active agent, to

[5] Office Action at page 4.
[6] *Id.*
[7] Office Action at both page 10 and page 11 (emphasis added).

different modes of administration of a given active agent, *etc.* As explained by Dr. Dow in his Declaration, one of ordinary skill in the art would ***not*** expect Angel's results for halobetasol propionate to extend to a tazarotene formulation given the considerable differences between the two active agents. Rather, the skilled formulator would understand that the stability and delivery considerations for halobetasol propionate could ***not*** be translated to tazarotene, and the skilled formulator would ***not*** look to the disclosure of Angel when formulating tazarotene. For at least these reasons, Applicant respectfully maintains that one of skill in the art would not be motivated to combine the references as suggested by the Examiner.

**B. THE SURPRISING PROPERTIES OF THE CLAIMED COMPOSITION ARE EVIDENCE OF NON-OBVIOUSNESS.**

It is made clear in the MPEP that "A chemical composition and its properties are inseparable."[8] The improved efficacy and tolerability of the claimed lotion composition, as compared to TAZORAC cream, result from the components of the lotion as presently claimed. Dr. Dow previously explained that he and other skilled artisans would not have expected these improved properties based on the teachings of Tazorac and Angel.

The increased efficacy provided by the claimed 0.045% tazarotene lotion, as compared to TAZORAC cream, is set forth in Table 6. Regarding this data, the Examiner alleged the following:

> (I)n looking at table 6 in which applicants assert unexpected results; applicants compare 0.1% to composition A, which is 0.45%. The difference appears to approximately 1.3% favoring the 0.45% which is additive effect rather than synergism or unexpected results.[9]

Applicant respectfully disagrees. Table 6 is reproduced below, and shows that the improvement over placebo observed for 0.045% tazarotene lotion ("Composition A") was substantially higher than the improvement over placebo observed for 0.1% TAZORAC cream.

Table 6
Treatment % Success (Intention-To-Treat) at 12 Weeks

[8] MPEP § 2112.01(II)
[9] Office Action at page 4.

| | Combined Placebo N=69 | Composition A N=69 | Tazorac® 0.1% Cream N=72 |
|---|---|---|---|
| EGSS – Clear or Almost Clear | 10.1% | 18.8% | 16.7% |
| Inflammatory Lesions | | | |
| Absolute Change | -14.0 | -18.1 | -16.8 |
| % Change | -51.41% | -63.75% | -59.99% |
| Non-inflammatory Lesions | | | |
| Absolute Change | -13.1 | -21.6 | -20.3 |
| % Change | -35.18% | -56.86% | -54.09% |

Applicant notes that 18.8% of acne patients receiving Composition A reached an Evaluator's Global Severity Score (EGSS) equating to "clear" or "almost clear," whereas only 16.7% of patients receiving TAZORAC cream achieved this score. Applicant notes that this difference amounts to a **31.8% improvement** for Composition A, as compared to TAZORAC, over the combined placebo population in the study as outlined below.

Improvement over placebo: $\frac{(Composition\ A\ result - placebo\ result) - (TAZORAC\ result - placebo\ result)}{(TAZORAC\ result - placebo\ result)} \times 100\%$

$\frac{(18.8\% - 10.1\%) - (16.7\% - 10.1\%)}{(16.7\% - 10.1\%)} \times 100\%$

$= 31.8\%$

The *greater* efficacy over placebo provided by Composition A in the claimed method is particularly surprising when considering that the method employed *less than half* the tazarotene dose of TAZORAC. Applicant submits that the skilled artisan would *not* expect to increase the efficacy when decreasing the amount the active agent by over half. On the contrary, one of skill in the art would expect that decreasing the amount of tazarotene would decrease the efficacy of the method. Nothing in the cited references suggests otherwise. Indeed, nothing in the cited references suggests the superior results provided by administering the claimed amount of tazarotene using the claimed vehicle in the claimed method.

In response to these unexpected results, the Examiner asserts:

> Applicants assert unexpected results (e.g. surprising properties) in which Dr. Dow that a skilled artisan would not expect the surprising advantages of the claimed lotion composition. This argument has been fully considered but has not been found persuasive. Additionally, in looking at table 6 in which applicants assert unexpected results; applicants compare Tazorac® to composition A.

> First, the specification does not disclose all of the ingredients disclosed in Tazorac®. Second, Compound A has ingredients not disclosed in Tazaorac. Inactive ingredients may play part in the bioavailability and results of compartment of compound A and Tazorac®. Therefore, this is not a true comparison. In order to properly compare, all of ingredients with the same concentration and the only difference is the concentration of tazarotene (0.045) versus 0.1 %). Therefore, applicants [have] not established unexpected results.

In response to the Examiner's first assertion, it is pointed out that the specification states that a "commercially available 0.1 % tazarotene cream (Tazorac® 0.1 % cream) was employed in this clinical study for comparison purposes." Tazorac 0.1% cream was available prior to the priority date of the present application, and the prescribing information for the Tazorac 0.1% cream discloses all the ingredients in the Tazorac 0.1% cream. In fact, in the Office Action, the Examiner provides a listing of all ingredients in the Tazorac 0.1% cream and these ingredients are consistent with the ingredients disclosed in the prescribing information, which was available at the time of filing. As explained above, the ***greater*** efficacy over placebo provided by Composition A in a method for treating acne is particularly surprising when considering that the method employed ***less than half*** the tazarotene dose of TAZORAC.

In response to the Examiner's second allegation, it is point out that the comparison carried out in Example 6 of the specification is, in fact, a true comparison. The Examiner suggests that "in order to properly compare, all of ingredients with the same concentration and the only difference is the concentration of tazarotene (0.045) versus 0.1 %)." Again, as explained above, Applicant is not claiming the Tazorac formulation with the only difference being a lower concentration of tazarotene; Applicant is claiming a different formulation with a lower concentration of tazarotene that provides greater efficacy over placebo in a method for treating acne, which is particularly surprising when considering that the method employed ***less than half*** the tazarotene dose of TAZORAC.

The Examiner is reminded that although evidence of unexpected results must compare the claimed invention with the closest prior art, Applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art. *In re Geiger*, 815 F.2d 686, 689, 2 USPQ2d 1276, 1279 (Fed. Cir. 1987) (Newman, J., concurring) (Evidence rebutted prima facie

case by comparing claimed invention with the most relevant prior art. Note that the majority held the Office failed to establish a prima facie case of obviousness.); *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966) (Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 "would be requiring comparison of the results of the invention with the results of the invention." 357 F.2d at 422, 148 USPQ at 714.). In the specification, Composition A was compared to Tazorac, which Applicant believed is the closest prior art and the most reasonable comparator to the claimed invention. In doing so, Applicant again unexpectedly discovered that Composition A provides greater efficacy over placebo in a method for treating acne, which is particularly surprising when considering that the method employed ***less than half*** the tazarotene dose of TAZORAC.

Applicant respectfully submits that one of skill in the art would *not* be motivated to combine the references as suggested in the Office Action due to the vast differences in the chemical structures and physicochemical properties of the active agents. Even if the combination were made in the absence of such motivation, one of skill in the art would *not* have expected the surprising combination of efficacy and tolerability provided by the claimed lotion. For at least these reasons, Applicant submits that the claims are *not* obvious over the cited references and respectfully requests that the rejection be withdrawn.

## II. Double Patenting Rejections

The claims are rejected on the grounds of non-statutory obviousness-type double patenting over claims in U.S. Patent Nos. 10,426,787 and 10,251,895. In addition, the claims are provisionally rejected on the grounds of non-statutory obviousness-type double patenting over claims in Pat. Appl. No. 16/179,561 (now issued as U.S. Pat. No. 11,311,482) and in Pat. Appl. No. 17/719,278.

The Examiner has not yet indicated that the pending claims are in condition for allowance. As such, the filing of a terminal disclaimer is premature. Applicant therefore respectfully requests, without acquiescing to the validity of these rejections, that the rejections be

held in abeyance until the pending claims are in condition for allowance. At that time, Applicants will address the non-statutory double patenting rejections as necessary.

## CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Director is authorized to charge any additional fees during pendency of this application, including any required extension of time fees, or credit any overpayment to Deposit Account Number 20-1430. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. § 1.136(a)(3).

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at (925) 472-5000 or egwackowski@kilpatricktownsend.com.

Respectfully submitted,

/Eugenia Garrett-Wackowski/
Eugenia Garrett-Wackowski
Registration No. 37,330

KILPATRICK TOWNSEND & STOCKTON LLP

| Electronic Patent Application Fee Transmittal | |
|---|---|
| **Application Number:** | 16179576 |
| **Filing Date:** | 02-Nov-2018 |
| **Title of Invention:** | TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES |
| **First Named Inventor/Applicant Name:** | Arturo Angel |
| **Filer:** | Eugenia Garrett-Wackowski/Sharleen Lane |
| **Attorney Docket Number:** | 095920-004120US-1240999 |

Filed as Large Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 3 months with $0 paid | 1253 | 1 | 1480 | 1480 |
| **Miscellaneous:** | | | | |
| SUBMISSION- INFORMATION DISCLOSURE STMT | 1806 | 1 | 260 | 260 |
| | | **Total in USD ($)** | | **1740** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 47174146 |
| **Application Number:** | 16179576 |
| **International Application Number:** | |
| **Confirmation Number:** | 1093 |
| **Title of Invention:** | TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES |
| **First Named Inventor/Applicant Name:** | Arturo Angel |
| **Customer Number:** | 112120 |
| **Filer:** | Eugenia Garrett-Wackowski/Sharleen Lane |
| **Filer Authorized By:** | Eugenia Garrett-Wackowski |
| **Attorney Docket Number:** | 095920-004120US-1240999 |
| **Receipt Date:** | 08-DEC-2022 |
| **Filing Date:** | 02-NOV-2018 |
| **Time Stamp:** | 23:44:29 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $1740 |
| RAM confirmation Number | E2022B8N45141394 |
| Deposit Account | |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Extension of Time | 095920-004120US_EOT.pdf | 180048<br>443273804068e4fc2cf8b8c9ca6711c1f0bef097 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | | 095920-004120US_AMD.pdf | 338043<br>6ad7bb694ec518e13ab86ff3f5e238740212 79f4 | yes | 12 |
| | **Multipart Description/PDF files in .zip description** | | | | |
| | **Document Description** | | **Start** | **End** | |
| | Amendment/Request for Reconsideration-After Non-Final Rejection | | 1 | 1 | |
| | Claims | | 2 | 3 | |
| | Applicant Arguments/Remarks Made in an Amendment | | 4 | 12 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Fee Worksheet (SB06) | fee-info.pdf | 40881<br>9fe82bcfd3e309de1856edaacea0d936ce28eab4 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 558972 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/AIA/22 (10-20)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)** | Docket Number (Optional) 095920-004120US-1240999 |
|---|---|
| Application Number 16/179,576 | Filed November 2, 2018 |
| For TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES | |
| Art Unit 1627 | Examiner Kathrien Ann Hartsfield |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|
| ☐ One month (37 CFR 1.17(a)(1)) | $220 | $110 | $55 | $_____ |
| ☐ Two months (37 CFR 1.17(a)(2)) | $640 | $320 | $160 | $_____ |
| ☒ Three months (37 CFR 1.17(a)(3)) | $1,480 | $740 | $370 | $1,480 |
| ☐ Four months (37 CFR 1.17(a)(4)) | $2,320 | $1,160 | $580 | $_____ |
| ☐ Five months (37 CFR 1.17(a)(5)) | $3,160 | $1,580 | $790 | $_____ |

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430.

☒ Payment made via EFS-Web.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71 Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 37,330

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____

| /Eugenia Garrett-Wackowski/ | December 8, 2022 |
|---|---|
| Signature | Date |
| Eugenia Garrett-Wackowski | (925) 472-5000 |
| Typed or printed name | Telephone Number |

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 47174133 |
| **Application Number:** | 16179576 |
| **International Application Number:** | |
| **Confirmation Number:** | 1093 |
| **Title of Invention:** | TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES |
| **First Named Inventor/Applicant Name:** | Arturo Angel |
| **Customer Number:** | 112120 |
| **Filer:** | Eugenia Garrett-Wackowski/Sharleen Lane |
| **Filer Authorized By:** | Eugenia Garrett-Wackowski |
| **Attorney Docket Number:** | 095920-004120US-1240999 |
| **Receipt Date:** | 08-DEC-2022 |
| **Filing Date:** | 02-NOV-2018 |
| **Time Stamp:** | 20:34:16 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| Submitted with Payment | no |
|---|---|

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Non Patent Literature | Lebwohl_Tazarotene01GelPlus Corticosteroid.pdf | 1053496<br>3d4371e86782e2735051f8348725b6379160259c | no | 7 |
| **Warnings:** | | | | | |



Padagis Ex. 1029
IPR Petition - USP 11,311,482

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| **Information:** | | | | | |
| 2 | Non Patent Literature | Lebwohl_TazaroteneInCombination.pdf | 720336<br>82c6f1897996fce1f7d000276a938be98393927d | no | 5 |
| **Warnings:** | | | | | |
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| 3 | Non Patent Literature | Lebwohl_TopicalApplications.pdf | 1121818<br>ee7baf98cbc1281322e941d3b9400decefb06465 | no | 4 |
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| 4 | Non Patent Literature | Leyden_October2004_Cutis.pdf | 18205816<br>40194cbe8b0833b605a6d58d86c6c1c401e0a7ce | no | 7 |
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| 5 | Non Patent Literature | Loder.pdf | 2689541<br>b908f7bc16b1b147c8917cc2f162d594f1008316 | no | 20 |
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| 6 | Non Patent Literature | Lubrizol_EmulsificationProperties.pdf | 4964005<br>a3d7e65bab70f0d230624437b186eaa02cc2ef71 | no | 8 |
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| 7 | Non Patent Literature | Lubrizol_IntroducingPemulen.pdf | 4821893<br>80af7b4dec35f57432612e798e266999972b4e4f | no | 7 |
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| 8 | Non Patent Literature | Lubrizol_ProductGuideAndRegulatoryOverview.pdf | 816527<br>07c09fc83decb8ee7a11e1fc44efbf375526fb5b | no | 2 |
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| 9 | Non Patent Literature | Medicis_Vanos_Label.pdf | 1707427<br>056e67bf5a79cbfc810fd129e111df30889f339f | no | 9 |
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| 10 | Non Patent Literature | Okuyama_WithCertifiedEnglish Translation.pdf | 3269208<br>d18fb9b5dcc5b0a4c3ecc3377b255d4fd58c06fc | no | 15 |
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| 11 | Non Patent Literature | Oneil_MerckIndex_13thEd.pdf | 5152535<br>ccac8e44dd0cd9b255e5ec9f16aabba4949d138c | no | 6 |
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| 12 | Non Patent Literature | Ostrenga.pdf | 7406591<br>54a1374b67f77116ec1613447876c7e170d4bf1d | no | 8 |
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| **Information:** | | | | | |
| 14 | Non Patent Literature | Ranbaxy_Label_Ultravate_2012 .pdf | 4398546<br>78c01a9d3a0e48c25b72180c756c68e5f709680d | no | 6 |
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| 15 | Non Patent Literature | Rowe_Handbook_110-114_445 -449_675-678.pdf | 4957050<br>6f5dcdb999c3b0a8ae1cfdfb225c06a416612263 | no | 17 |
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| 16 | Non Patent Literature | Ryatt.pdf | 555307<br>7439ebe38a356ae0f77a41f3e2498206a85faeda | no | 7 |
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| 17 | Non Patent Literature | Schering-Plough_Diprosone_OV_Label.pdf | 1301763<br>9574b8cafd40e472df98541839008a6507c12dd3 | no | 5 |
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| 18 | Non Patent Literature | Shah.pdf | 6373533<br>00caf1cc4ebebf360112a49d3fe9693ada7bcce0 | no | 36 |
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| 19 | Non Patent Literature | Surber.pdf | 18962152<br>8e6a161dcab9aab33160cd45eb7d7f1fb1f67e76 | no | 100 |
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| 20 | Non Patent Literature | Tanghetti_May2010_JDrugsDermatol.pdf | 4186294<br>e6c75a896340820f6e17936557f1dc12d0fdca7e | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 21 | Non Patent Literature | Taropharma_Product_Monograph_Lyderm_2003.pdf | 2897745<br>e4460e9157991b22c14a77239cb8301125d95941 | no | 17 |
| **Warnings:** | | | | | |
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| 22 | Non Patent Literature | ThomsonPDR_PhysiciansDeskReference_58thEd_2004.pdf | 6074409<br>ce62edfdb976bd46efac6b24d7e2a73c9a8e7ebe | no | 5 |
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| 23 | Non Patent Literature | Weinberg.pdf | 13243700<br>72210bbfc4dfd9b110956b798162afa442370d54 | no | 75 |
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| 24 | Non Patent Literature | Zografi_Remingtons_18thEd.pdf | 24621933<br>4f39c563e986b779f781f5f93a3df60b3645e12c | no | 68 |
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**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

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| | **Art Unit** | 1627 |
| | **Examiner Name** | Kathrien Ann Hartsfield |
| | **Attorney Docket Number** | 095920-004120US-1240999 |

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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(19)(CA) **CANADIAN PATENT** (12)

# (54) Composition and Method for Delivering a Steroid Active Ingredient

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# COMPOSITION AND METHOD FOR DELIVERING A STEROID ACTIVE INGREDIENT

## BACKGROUND OF THE INVENTION

The field of the present invention relates generally to time release delivery of a steroid active ingredient, and in particular a corticosteroid active ingredient useful as, for example, an anti-inflammatory agent.

In order to maximize the benefit of such application, the vehicle should allow delivery to and absorption through the skin surface to which it is applied. Additionally, it would be preferable to provide a time release mechanism for absorption of the active ingredient.

There are a wide variety of controlled release products presently being utilized in numerous applications, including pharmaceutical, agricultural and veterinary applications. Generally speaking, an active ingredient is released over time. The active ingredient may be contained in a variety of media, such as coated particles (e.g. sphere, aggregate, multiple coating or pill), solid solutions (e.g. beadlet, film, bandage or cube), compositions (e.g. sphere, tablet, pills or strip), containers (e.g. capsule, breakable ampule or capillary), and combinations (e.g. in a liquid, in a capsule or in a pill).

Microencapsulation is the most common process for preparing a time release delivery vehicle. Generally speaking, microencapsulation utilizes a coating to contain the active ingredient which is then released by rupture or dissolution of the coating. Alternatively,



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the coating or membrane may be semi-permeable or porous to allow the active ingredient to diffuse out of the microencapsule.

United States Patent No. 4,322,311 describes an encapsulation technique for producing semi-permeable or controlled porosity microcapsules. An active ingredient and a monomer in a first solution are emulsified in a hydrophobic solvent. A monomer complementary to the first monomer which is soluble in the hydrophobic solvent is added to the emulsion to initiate interfacial polymerization about the aqueous droplets. During the course of reaction, the affinity of the continuous phase for the first monomer is varied by adding a solvent to the continuous phase to vary its polarity. This promotes diffusion into the continuous phase resulting in a porous membrane. Since the patent describes the use of an amine monomer, some amine monomer may remain encapsulated within the microcapsule.

Another encapsulation technique is described in United States Patent No. 4,444,699 wherein minute capsules are manufactured en masse. The process utilizes polycondensation of melamine with formaldehyde or in situ polymerization of methylol melamine or esterified methylol melamine, or a low molecular weight polymer thereof, in an aqueous vehicle and the reaction is conducted in the presence of polyelectrolyte material and certain salts. However, this process will typically leave some residue of formaldehyde which may pose a health problem.

Other examples of encapsulation techniques include, by way of example only, United States Patent Numbers: 4,324,683, 4,353,809, 4,353,888, 4,353,962, 4,391,909, 4,396,670, 4,407,957, 4,439,488, and 4,464,271. The microcapsules produced by these types of processes will typically possess limited mechanical strength and will release all of the active ingredients at once if the membrane is ruptured. The limited



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mechanical stability can create problems with incorporating the microcapsules into a medium and will also limit the shelf life of these delivery vehicles. In addition, the microcapsules will typically contain reactive groups which may create problems of chemical stability.

Another delivery vehicle for an active ingredient is described in United States Patent No. 3,985,298 which utilizes a process to impregnate an active ingredient into and within a cellulosic polymer-liquid composite material as a part of or all of the liquid phase. The active ingredient is released from the gel matrix which shrinks or collapses as the active ingredient is removed. The gel structure is not mechanically strong and therefore it suffers some of the mechanical problems associated with microspheres.

A number of problems have been encountered in the formulation of corticosteroid medicinal agents using delivery vehicles in the prior art. For example, in order to maximize topical corticosteroid penetration of, e.g., fluocinolone acetonide, the corticosteroid is initially dissolved in a co-solvent such as propylene glycol. This solution is then dispersed in, for example, a primarily aqueous vehicle such as oil-in-water emulsion creams or lotions. Unfortunately, the initial solution of steroid in propylene glycol becomes diluted into the aqueous base, in which it miscible, and the steroid precipitates, resulting in a suspension of corticosteroid which is less favorable for percutaneous absorption than a solution of corticosteroid. It would therefore be desirable to dissolve the steroid in a water immiscible solvent/penetrant, such as Azone™. Unfortunately, Azone may accentuate skin reactions associated with some formulation excipients, as for example the skin irritation associated with propylene glycol and certain preservatives. In addition, this approach would require emulsification of the Azone solution

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using other lipophilic materials and emulsifiers. However, these are contraindicated since it has been observed that large amounts of lipophilic agents such as petrolatum, mineral oil, high molecular weight polyethylene glycols, or esters of mono- and dicarboxylic acids, e.g., isopropyl myristrate, diethyl sebacate and diisopropyl adipate, should be avoided since they appear to dissolve Azone and suppress its penetration-enhancing activity.

In addition, when petrolatum or other lipophilic vehicles are used as topical corticosteroid delivery vehicles, other problems exist. A typical corticosteroid ointment consists of a solution of steroid in propylene glycol and/or propylene carbonate which is dispersed in immiscible petrolatum with the aid of emulsifying agents such as Amerchol™ CAB (a mixture of sterols and higher alcohols). In this case, the steroid solution is only quasi-emulsified and separates out on standing, resulting in a non-homogenous product. This separation drastically interferes with the uniformity of the medication. Furthermore, the use of Azone as a penetration enhancer is precluded from use as a solvent for steroids and other functional drugs for forming ointments in lipophilic vehicles because, as noted above, such vehicles may suppress the penetration-enhancing activity of Azone.

The use of encapsulation in connection with corticosteroid agents requires a shell which must be dissolved or ruptured to release the contained corticosteroid. The use of such an encapsulated form of medication may present the problems of poor mechanical stability or reduced shelf life. Furthermore, time-release control of the contained corticosteroid may be difficult to obtain because full release occurs upon rupture or dissolution of the encapsulant.

Accordingly, there exists a need for an economical time-release delivery vehicle with high mechanical

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strength useful in a controlled-release application for delivering steroid active agents, as for example corticosteroids.

## SUMMARY OF THE INVENTION

The invention relates to a method for delivering a steroid active ingredient, and in particular a corticosteroid active ingredient, to a skin surface by controlled time-release. In another aspect of the present invention, a composition of matter useful in the method of the instant invention is disclosed.

In the instant invention, a delivery vehicle comprised of a preformed polymeric bead having a network of pores with a solution of the active ingredient held within the network is utilized to provide a controlled time release of the active ingredient. A percutaneous absorption enhancer, which provides increased thermodynamic activity and penetrability of the active ingredient through the skin surface, may be used to form the active ingredient solution. The delivery vehicle may be incorporated in a medium, such as a gel, a cream, a lotion, an ointment, a liquid or the like, which may then be applied to a skin surface. The solution is released from the network of pores over time.

A delivery vehicle according to the present invention has continued mechanical stability during use as compared to a microencapsulated or gel delivery vehicle. The network of pores of a bead according to the present invention will not be subject to osmotic shock which might occur in prior art delivery vehicles. In addition, the increased mechanical stability allows a delivery vehicle to be manufactured, processed and handled under more severe conditions, such as mechanical stirring, which might otherwise rupture or damage some prior art gel or microencapsulated delivery vehicles. Thus, a delivery vehicle according to the pres-



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ent invention can easily be incorporated in certain media in which it would prove difficult or more expensive to incorporate delivery vehicles of the prior art.

The use of the delivery vehicle of the present invention allows the entrapment of a solution of steroid in a solvent such as, for example, Azone which can then readily be dispersed in typical aqueous gel, lotion and cream formulations, as well as in lipophilic delivery vehicles. The entrapment of Azone in the polymer beads substantially prevents any dilution of the contained solution by contraindicated lipophilic materials. Upon evaporation or dissipation of the aqueous or lipophilic medium, the beads remain intact and the contained solution of active agent and, for example, Azone is released in a highly concentrated manner to the skin through contact pressure, exudation and capillary action.

In contrast to quasi-emulsified steroid solutions formed in petrolatum and other lipophilic media, the suspension of the polymer beads of the present invention is highly stable and does not tend to separate from the delivery medium over time. This results in a product which remains uniformly dispersed throughout the delivery medium and does not tend to agglomerate or pool.

Furthermore, as discussed above, Azone may accentuate skin reactions typically seen with some formulation excipients. By formulating products with Azone entrapped in the bead, problems such as irritation enhancement may be reduced.

When a delivery vehicle according to the present invention is polymerized from styrene and divinylbenzene, the delivery vehicle will possess greater chemical stability over previous delivery vehicles because the styrene divinylbenzene polymeric bead will not contain reactive groups and will consist essentially of of hydrocarbon backbone with benzene rings. Because the



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styrene divinylbenzene polymeric bead does not contain reactive groups, the bead will not readily undergo unwanted reactions, it will be stable over a very wide pH range, it will resist moderate oxidation and reduction, it will be stable to higher temperatures, it will not be subject to attack by moisture, and it will have a longer shelf life. In addition, in contrast to some prior art delivery vehicles, a styrene divinylbenzene polymeric bead of the present invention does not contain any reactive groups or polymeric structure which may cause a problem of toxicity, irritation or the like when applied topically to skin.

Another advantage of a delivery vehicle prepared in accordance with the present invention is the substantial absence of unreacted monomer. Thus, in a micoencapsulation delivery vehicle it may be difficult to remove unreacted monomer because it might become encapsulated along with the active ingredient inside of the membrane. This problem is especially acute in some prior art delivery vehicles which utilize urea-formaldehyde microcapsules which can create potential health problems.

Accordingly, it is a primary object of the present invention to provide a delivery vehicle for delivering an active ingredient by controlled time release over a period of time to a skin surface. This and further objects and advantages of the present invention will become apparent to one of ordinary skill in the art in connection with the detailed description of the preferred embodiments set forth below.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

In accordance with the present invention, an active ingredient solution is suspended in a network of pores of a porous polymeric bead which is dispersed in a vehicle substantially immiscible with the solution.



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A percutaneous absorption enhancer will typically be used as a solvent for the active ingredient.

A porous polymeric bead according to the present invention can be prepared by polymerizing one or more monomers by a free radical suspension polymerization process. A monomer or pair of comonomers is dissolved in an inert porogen to form a solution which is suspended in a phase or solvent imcompatible with the solution.

An example of such a phase or solvent might be water with stabilizing additives. After the solution is suspended in the phase, the solution and phase are agitated to form a plurality of droplets of solution suspended in the phase. After the formation of the plurality of droplets, the monomer or monomers in the plurality of droplets are activated to initiate a polymerization reaction in which one or more monomers are polymerized to form porous beads having a network of pores with the porogen held within the network of pores. The activation may be triggered by an initiator which is soluble in the monomer solution. Alternatively, activation may be triggered by an energy source such as radiation. The inert porogen will serve as an internal diluent during polymerization to introduce the desired sponge-like macroporous structure or network of pores into the finished polymeric bead. The inert porogen should not react with the monomer present during polymerization or inhibit the polymerization. The polymeric bead may or may not swell in the inert porogen. After the formation of the porous polymeric beads, the polymeric beads are separated from the phase and subjected to one or more purification steps, such as washing, to remove any unreacted monomer or impurity from the beads.

Porous polymeric beads useful in the present invention can be prepared utilizing the general description and procedures set forth in United States Patent



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4,690,825, issued in September 1987. However, unless the active ingredient solution can serve as a porogen during the polymerization of the polymeric beads, then the porogen must be removed and replaced by said solution. Although these extra steps are not as desirable as using the solution as the porgen, satisfactory porous polymeric beads can still be obtained if the network of pores of said beads is substantially non-collapsible after removal of the porogen and remains substantially non-collapsible upon removal of the active ingredient.

The polymeric beads used in the present invention can be designed so as to control porosity and the particle diameter of the beads, which may be considered substantially spherical. Under identical polymerization conditions, the porosity can be increased by increasing the calculated or theoretical cross-linking density or by increasing the porogen concentration in the solution. An increase in porosity will increase the surface area of the bead and hence the weight percent of the porgen which can be held within the bead. To decrease the particle diamete under identical polymerization conditions, the agitation or the concentration of dispersion agents in the phase should be increased. By controlling the porosity and the particle diameter of the bead, a delivery vehicle suitable for use in the method of the present invention can be obtained. Generally speaking, it has been found that it is preferable for the bead to have a diameter from about 10 microns to about 100 microns, and have a calculated cross-linking in excess of about 10%. A cross-linking of approximately 20% to 50% is preferred, with the range of approximately 25% to 30% being especially preferred. The pores in the beads of the present invention will typically range in diameter from approximately 10 angstroms to approximately 500 ang-

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stroms. The solution of the active ingredient should comprise between approximately 5% to approximately 80% of the total weight of the composition or delivery vehicle comprising the polymeric bead and said solution.

To distinguish whether a porous polymeric bead possesses sufficient mechanical strength to be used as a delivery vehicle for providing controlled time-release of the solution containing the active ingredient, the composition can be subjected to a wetting test. If the composition has a calculated cross-linking density and a solution concentration such that substantially all of the solution will be released from the network of pores when the bead is placed in a solvent, in which the solution is soluble, for a sufficient length of time to wet the bead, then the composition can be used in the method of the present invention.

A wetting test can be performed by weighing a dry sample of material to be tested containing an original amount of solution containing the active ingredient. The dry sample is then mixed with a solvent in which the solution is soluble to form a wet sample. The wet sample is then agitated for a sufficient length of time to wet the bead if the dry sample is comprised of a delivery vehicle according to the present invention. The amount of solution released into the solvent is then determined. The amount of solution released into the solvent will be substantially the same as the original amount of solution if the dry sample consisted essentially of the delivery vehicle whereas the released amount will be substantially less than the original amount if the dry sample contained a substantial amount of a gel product or a microencapsulated product. If the solution containing the active ingredient is not the porogen, then a wetting test can be used to confirm that the porogen has not been encapsu-



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lated. The concentration of the active ingredient in such a delivery vehicle can be determined by a solvent wetting test followed by an assay, such as a gravimetric or UV assay.

To utilize a delivery vehicle in accordance with the method of the present invention, the delivery vehicle may be mixed with a delivery medium to form a mixture which is applied to a skin surface. The solution of the active ingredient is then released from the network of pores by a force or energy. Thus, by way of example only, the controlled time release might occur through diffusion. Because the solution is held (primarily by absorption) within the network of pores of the polymeric beads, the concentration of the solution in the medium will tend to be fairly uniform and will not be as likely to agglomerate or pool as if the solution had simply been dispersed within the medium. As the solution is delivered to the skin surface, the percutaneous absorption enhancer solvent will promote maximum thermodynamic activity and penetrability of the active ingredient. Examples of possible percutaneous absorption enhancers include propylene glycol and propylene carbonate which are useful with corticosteroids. Numerous other possible percutaneous absorption enhancers are well-known to one skilled in the art and might include, by way of example only, dialkysulfoxides having up to 22 carbons in each alkyl group, e.g., dimethylsulfoxide, dimethylformamide, dimethylacetamide, diisopropyl adipate, isopropyl myristate, tetrahydrofuran, tetrahydrofurfuryl alcohol, glycerol, N-methyl-2-pyrrolidone and a product available under the trademark AZONE (1-dodecylhexahydro-2H-azepin-2-one).

A number of delivery media may be used in conjunction with the polymer bead delivery vehicle of the present invention, and may be formulated using materials and techniques well-known in the art. A



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petrolatum/polysiloxane-based delivery medium appropriate for use herein is described in U.S. Patent No. 4,017,615. The delivery medium should be substantially immiscible with the solution containing the active ingredient. Petrolatum compounds ranging in viscosity from mineral oil to paraffin waxes are suitable media, with a paraffin compound having approximately the consistency of petrolatum NF (petroleum jelly) being especially preferred as an ointment base. Polysiloxane compounds (also known as silicones) having appropriate viscosity characteristics (approximately 0.5 to $10^6$ centistokes) are also suitable for use as delivery media components. Other materials known to the art, including without exclusion adjuvants (such as beeswax, spermaceti, paraffin waxes, and fatty acids, alcohols and amides having 10 to 22 carbon atoms), surfactants, thickeners, preservatives, inhibitors and emulsifiers may be included within the delivery medium used herein.

The polymer bead delivery vehicle of the present invention is mechanically strong because of the polymeric structure of the bead and the degree of cross-linking or copolymerization. It is believed that the bead can be conceptualized as a rigid sponge, i.e., a structural network formed by three dimensional cross-linking or copolymerization which leaves random spaces or holes which collectively form the network of pores. The polymer structure or bead physically holds the solution and is then held or trapped until an external force or energy releases the solution from the network of pores in the polymerized bead. However, unlike a gel in which the polymeric structural network collapses when the material held within said network is removed or released, a delivery vehicle according to the present invention must possess a certain minimum degree of calculated cross-linking density for a given solution so as to give the entire structure or bead sufficient strength to prevent substantial shrinking or



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collapse of the bead when the solution is removed from the network of pores.

The pore surface area, pore diameter and active ingredient release characteristics of the beads of the present invention may be adjusted through proper selection of a porogen. In general, pore surface area, pore diameter and active ingredient release rate may be increased by using a non-solvent type porogen such as mineral oil or an aliphatic hydrocarbon such as heptane. Conversely, those characteristics may be reduced by using a solvent-type porogen such as toluene.

The invention will be further illustrated in the example that follows wherein the delivery vehicle is copolymerized from styrene and divinylbenzene which is an especially preferred comonomer pair because of the chemical stability of styrene divinylbenzene. As would be apparent to one skilled in the art, the term "divinylbenzene" as used in this description, as well as in the appended claims, is meant to include pure divinylbenzene as well as commercial divinylbenzene which is really a mixture of divinylbenzene and ethylvinylbenzene. Other preferred comonomer pairs are vinyl stearate and divinylbenzene, and methyl methacrylate and ethylene glycol diamethacrylate. In the following example the active ingedient is fluocinonide, although other steroids such as fluocinolone acetonide, triamcinolone acetonide, betamethasone valerate, timobesone acetate, hydrocortisone, hydrocortisone acetate, triamcinolone, prednisolone, prednisolone acetate, dexamethasone, beclomethasone dipropionate, betamethasone dipropionate, betamethasone benzoate, clocortolone pivalate, halcinonide, flumethasone pivalate and desonide may also be used. A number of anti-inflammatory steroids suitable for use in the present invention have been disclosed in U.S. Patent



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Nos. 4,017,615, 3,365,446, 3,067,194, 3,364,203, 3,053,833, and 3,513,162, for example.

A 2000 ml four-necked reaction flask equipped with a stirrer, condenser, thermometer, and nitrogen inlet was evacuated and charged with nitrogen. 800 ml deionized water, 6.4 grams of gum arabic and 6.4 grams of a lignosulfonate available from the American Can Co. under the trademark Marasperse N-22, were charged into the reaction flask. The mixture was stirred for about 30 minutes. To this mixture was added a freshly prepared solution of 85.6 grams of styrene (99.8% purity), 102.3 grams commercial divinylbenzene (55% divinylbenzene), 5.33 grams benzoyl peroxide (70% active ingredient and 30% water), and 187.9 grams of toluene to serve as a porogen. The phase and solution were agitated by a mechanical stirrer whose stirring rate of about 900-1200 rpm was adjusted to obtain a plurality of droplets having a droplet diameter smaller than about 50 microns. The gum arabic and lignosulfonate serve to stabilize the plurality of droplets. The reaction mixture was heated to about 78 degrees Celsius while maintaining a constant rate of stirring and passing a slow stream of nitrogen through the reaction vessel. After about 2 hours cross-linking became noticeable. The mixture was stirred another 22 hours at 78°C and was then allowed to cool to room temperature. The porous polymeric beads were removed from the reaction flask by filtration and washed several times with water to remove gum arabic and lignosulfonate, followed by several washes of isopropanol/acetone mixed solvent (7:3 by volume) and were finally stirred in 400 ml of isopropanol/acetone mixed solvent (7:3) for 20 hours. The polymer was filtered and dried overnight at 65°C in vacuo. The yield was practically quantitative. The residual monomers such as styrene, DVB and naphthalene were smaller than about 0.01%.



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The calculated or theoretical cross-linking density of the purified beads is 30%. This density is calculated by multiplying the weight of divinylbenzene (102.3 g) by the purity of the divinylbenzene (.55) to get the actual weight of pure divinylbenzene which is then divided by the total weight of monomer (102.3 g + 85.6 g).

The surface area of a sample of the purified beads was determined by the B.E.T. method to be 1.8 meters$^2$/gram. The B.E.T. method is described in detail in Brunauer, S. Emmet, P.H., and Teller, E., J.Am.Chem.Soc., 60, 309-16 (1938). The surface area of the polymer can be modified by using different porogens such as stable oil compounds which might include, by way of example only, mineral oil, vegetable oils or silicon oils.

The particle size of the beads was determined by an optical microscope to be 60 microns or less with an average approximate particle size diameter of about 10 microns.

The active ingredient fluocinonide (Syntex) is entrapped in the beads described above by exposing the beads to a 1% solution of fluocinonide in propylene carbonate : propylene glycol (7:3) for a period of time sufficient to allow the beads to absorb the active ingredient solution. The amount of active ingredient solution used relative to the amount of polymer beads is adjusted according to the desired final concentration of active ingredisnt to be contained within the beads. Where a low final concentration is desired, the active ingredient solution may be further diluted with a solvent such as acetone, methanol or ethanol prior to combining the solution with the beads in order to achieve a sufficient amount of starting solution to form a slurry with the beads. The diluent solvent is later removed by heating under a vacuum.



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For example, to obtain beads with a final active ingredient concentration of 0.05%, 7.6 g of the polymer beads described above is combined with 0.4 g of a 1% solution of fluocinonide in propylene carbonate : propylene glycol (7:3) and 14.8 g acetone. The initial slurry is stirred approximately every five minutes over a period of approximately thirty minutes, during which period the mixture becomes cake-like and, finally, powder-like in consistency. The resulting powder is then oven-dried for approximately three hours at 40 - 60°C and 25 mmHg, at which point the powder has reached a constant weight and the acetone has been removed. Similarly, a 0.25% formulation may be achieved by mixing 4.8 g polymer beads, 3.2 g steroid solution and 6.4 g acetone as described above.

The beads containing active ingredient as described above may be utilized as prepared in a powder-form topical formulation, or the beads may be combined with other delivery media in order to achieve, e.g., an ointment, cream, gel or other dosage form. In general, the amount of polymer beads containing active ingredient that must be combined with other delivery media in order to achieve a therapeutic result will depend on the nature of the delivery media and the particular active ingredient. It has been found that the therapeutic anti-inflammatory activity of fluocinonide-containing beads in a petrolatum-based delivery medium is comparable, based on final weight concentration of the fluocinonide, to that of commercially-available fluocinonide ointments such as Lidex® (Syntex). Thus, ointments formed using the delivery vehicles of the present invention may employ active ingredient concentration parallel to those of typical ointments, i.e., 0.01% to 1% by weight. It should be noted, however, that therapeutically effective anti-inflammatory compositions may include as little as 0.00001% by weight steroid active ingredient and as much as 5% by weight



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steroid or higher. A range of 0.01% to 0.2% is particularly useful, with 0.01% to 0.05% being preferred for the more active corticosteroids such as the fluocinonides, and 0.01% to 0.1% being preferred for less active corticosteroids such as the betnovates and the triamcinolones. When polymer beads containing active ingredient are used topically in powder form, therapeutic anti-inflammatory activity may be lower than that of commercial ointments, although activity is increased and/or provided over longer time periods if the polymer beads are rubbed occasionally to promote release of the active ingredient.

Suitable ointments containing polymer beads with active ingredient may be prepared by combining an appropriate amount of the polymer beads with petrolatum and an emulsifier such as Amerchol CAB. To achieve a 0.05% fluocinonide ointment, for example, 4.6 parts by weight (pbw) Amerchol CAB, 32.2 pbw white petrolatum USP (Ultima) and 50.7 pbw white petrolatum USP were first combined and melted, and 12.5 pbw 0.4% fluocinonide polymer beads was then mixed with the melted mixture and cooled. Similarly, a 0.1% ointment was obtained by combining 4.0 pbw Amerchol CAB, 28.4 pbw white petrolatum USP (Ultima) and 42.6 pbw white petrolatum (USP) with 25.0 pbw 0.4% fluocinonide beads. A 0.2% ointment was formulated by combining 2.6 pbw Amerchol CAB, 19.0 pbw white petrolatum (USP) and 28.4 pbw white petrolatum USP with 50.0 pbw 0.4% fluocinonide beads. By starting with polymer beads containing different amounts of active ingredient, the relative weight proportion of polymer bead delivery vehicle can be modulated.

The efficacy of the polymer bead delivery vehicle of the present invention has been demonstrated for both the powder and ointment forms of the beads using a vasoconstriction assay. This method is based on the Stoughton-McKenzie vasocontriction assay for cortico-



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steroid formulations (McKenzie, A.W., and Stoughton, R.B., "Method for Comparing Percutaneous Absorption of Steroids," Arch. Dermatol., 86, 608-10 (1962)). All test preparations are placed in identical containers, coded and assigned by random tables to individual test sites. The test subjects are normal adult male and female volunteers not receiving any steroids and who have not participated in any studies using steroids for at least four weeks prior to testing. The forearms of the subjects are prepared by gentle washing and drying. Strips of double-adhesive coated Blenderm® tape with 7 x 7 mm prepunched squares (3M) are applied to each forearm to isolate the application sites. An appropriate dose of the test formulation (either 2 mg or 3 mg) is then applied to the skin in each square and is spread and rubbed with consistent pressure using a clean HPLC vial at each application site. In cases where powder-form polymer beads containing fluocinonide is used, the forearm is inverted after application and each individual site is gently brushed with a clean square of gauze to remove excess polymer beads. A protective cage is applied over the sites on the forearm designated for "open" application. On the other arm ("occluded") the sites are covered with Saran Wrap®, the margins sealed with tape and a protective cage placed over the sites. After six hours of exposure of the skin to the corticosteroid preparations, all the tapes are removed and the forearms are washed.

Scoring in the assay is preformed by two experienced observers who independently score the presence or absence of vasoconstriction and the degree and blanching at 8, 24 and 32 hours after the time of application of the formulations to the sites.

As evidenced in Table 1, the powder form polymer bead formulations of the present invention achieves significant vasoconstriction as compared to commercially-supplied Lidex® fluocinonide ointment (Syntex) not



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using a polymer bead delivery vehicle. Although vasoconstriction due to the powder form polymer beads is somewhat less than that observed with the Lidex® ointment, this difference may be due to the fact that excess powder formulation is brushed off after application to the forearms. Table 2 demonstrates that intermittent rubbing of the powder-form formulations acts to promote and prolong vasoconstriction activity. Table 3 demonstrates that the polymer bead delivery vehicle of the present invention, when applied in an ointment form comparable to that of commercially-supplied fluocinonide ointment, achieves a level of vasoconstriction approximately equal to that of the commercially-supplied product. This effect is achieved independent of any rubbing of the polymer bead ointment subsequent to application. It may be expected that such rubbing will further enhance vasoconstriction activity attributable to the delivery vehicle of the present invention.



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TABLE 1

Vasoconstriction Assay Readings--
Polymer Powder Formulations

| | Hours After Application 8 | 24 | 32 | Total % |
|---|---|---|---|---|
| FLUOCINONIDE FORMULATION | | | | |
| Polymer Beads (0.4%) | | | | |
| Occluded Application: | | | | |
| Sites Responding (%): | 50.0 | 62.5 | 50.0 | 162.5 |
| Intensity of Response (%): | 22.9 | 22.9 | 16.7 | 62.5 |
| Polymer Beads (0.4%) | | | | |
| Open Application: | | | | |
| Sites Responding (%): | 62.5 | 56.3 | 25.0 | 143.8 |
| Intensity of Response (%): | 25.0 | 18.8 | 8.3 | 52.1 |
| Ointment (0.05%) | | | | |
| Occluded Application: | | | | |
| Sites Responding (%): | 100.0 | 87.5 | 75.0 | 262.5 |
| Intensity of Response (%): | 72.9 | 33.3 | 27.1 | 133.3 |
| Ointment (0.05%) | | | | |
| Open Application: | | | | |
| Sites Responding (%): | 93.8 | 100.0 | 93.8 | 287.6 |
| Intensity of Response (%): | 68.8 | 39.6 | 31.3 | 139.7 |

NOTE: Dosage was 2 mg of polymer powder, with entrapped fluocinonide (0.4%), or 2 mg Lidex® 0.05% fluocinonide ointment. Test sites were rubbed at time zero, washed at time 6 hours, and read at the times indicated.



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TABLE 2

Effect of Re-Rubbing on Vasoconstriction
Effect of Polymer Powder Formulations

| | Hours After Application | | | |
|---|---|---|---|---|
| | 8 | 24 | 32 | Total % |
| FLUOCINONIDE FORMULATION | | | | |
| Polymer Beads (0.5%) | | | | |
| Sites Responding (Increase %) | 25.0 | 12.5 | 31.3 | 62.8 |
| Intensity of Response (Increase %) | 8.3 | 4.1 | 10.4 | 22.8 |
| Polymer Beads (0.25%) | | | | |
| Sites Responding (Increase %) | 0 | 31.3 | 31.3 | 62.6 |
| Intensity of Response (Increase %) | 0 | 10.4 | 12.5 | 22.9 |
| Polymer Beads (0.4%) | | | | |
| Sites Responding (Increase %) | -18.7 | 12.5 | 25.0 | 18.8 |
| Intensity of Response (Increase %) | -10.4 | 4.1 | 10.4 | 4.1 |

NOTE: Dosage was 2 mg of polymer powder, with entrapped fluocinonide at indicated proportion. All test sites were left open (unoccluded) and were rubbed and brushed off at time zero. Control powder sites were washed at time 6 hours; re-rubbed powder sites were re-rubbed at 6, 8, and 24 hours. Readings were made at times indicated. Data represents percent readings taken at re-rubbed sites minus percent readings taken at corresponding control sites.



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TABLE 3

Vasoconstriction Assay Readings--
Polymer-in-Ointment Formulations

| | Hours After Application | | | |
|---|---|---|---|---|
| | 8 | 24 | 32 | Total % |
| FLUOCINONIDE FORMULATION | | | | |
| Polymer Beads (0.05% in Ointment-- Occluded) | | | | |
| Sites Responding (%) | 87.5 | 68.8 | 81.3 | 237.6 |
| Intensity of Response (%) | 75.0 | 29.2 | 29.2 | 133.4 |
| Polymer Beads (0.05% in Ointment--Open) | | | | |
| Sites Responding (%) | 87.5 | 62.5 | 68.8 | 218.8 |
| Intensity of Response (%) | 72.9 | 20.8 | 25.0 | 118.7 |
| Polymer Beads (0.1% in Ointment--Occluded) | | | | |
| Sites Responding (%) | 87.5 | 62.5 | 68.8 | 218.8 |
| Intensity of Response (%) | 66.7 | 25.0 | 22.9 | 114.6 |
| Polymer Beads (0.1% in Ointment--Open) | | | | |
| Sites Responding (%) | 93.8 | 75.0 | 81.3 | 250.1 |
| Intensity of Response (%) | 72.9 | 27.1 | 29.2 | 129.2 |
| Polymer Beads (0.2% in Ointment--Occluded) | | | | |
| Sites Responding (%) | 75.0 | 81.3 | 81.3 | 237.6 |
| Intensity of Response (%) | 58.3 | 29.2 | 29.2 | 116.7 |
| Polymer Beads (0.2% in Ointment--Open) | | | | |
| Sites Responding (%) | 93.8 | 62.5 | 37.5 | 193.8 |
| Intensity of Response (%) | 68.8 | 25.0 | 12.5 | 106.3 |
| Commercial Ointment (0.05%--Occluded) | | | | |
| Sites Responding (%) | 93.8 | 68.8 | 68.8 | 231.4 |
| Intensity of Response (%) | 79.2 | 27.1 | 22.9 | 129.2 |
| Commercial Ointment (0.05%--Open) | | | | |
| Sites Responding (%) | 87.5 | 75.0 | 87.5 | 250.0 |
| Intensity of Response (%) | 77.1 | 27.1 | 33.3 | 137.5 |

NOTE: Dosage was 3 mg of petrolatum-based ointment containing polymer powder, with entrapped fluocinonide at indicated proportion, or 3 mg Lidex® 0.05% fluocinonide ointment. Test sites were rubbed at time zero, washed at time 6 hours, and read at the times indicated.



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In an additional study, fluocinonide was dissolved in a 30/70 propylene glycol/propylene carbonate system and entrapped in the microsponge sponge entrapment system in accordance with the present invention. The degree of vasoconstriction produced served as an indicator of the release of the corticosteroid solution from the microsponge entrapment system. Equal amounts of the microscopic sponge particles were directly applied to human forearms, rubbed gently, and the excess powder brushed off. On one arm, no further application or manipulation was made. On the other arm, the site of initial application was gently rubbed at 7, 23, and 31 hours, but no additional product was added.

Vasoconstriction responses were measured and recorded at 8, 24, and 32 hours and the results are presented in Table 4. The increased and continued vasoconstriction produced in the arm that was rubbed several times is definitive evidence of the demand and sustained release of the corticosteroid solution from the microsponge entrapment system.



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TABLE 4

Demand and Sustained Release of Corticosteroid Solution from Microsponges Measured by Vasoconstrictor Response

| CORTICOSTEROID* CONCENTRATION | 0.05% | | 0.25% | |
|---|---|---|---|---|
| APPLICATION | Initial Application Only | Reactivate at 6, 8, 24 Hours | Initial Application Only | Reactivate at 6, 8, 24 Hours |
| TIME (HOURS) AFTER APPLICATION | RESPONSE PERCENT | | | |
| 8 | 12.5 | 37.5 | 0 | 0 |
| 24 | 12.5 | 25 | 0 | 31.3 |
| 32 | 0 | 31.3 | 12.5 | 43.8 |

- Corticosteroid Solution bearing microsponges applied to both arms and excess removed.
- Application sites reactivated again on one arm at 6, 8, and 24 hours.
- Corticosteroid Solution release and effect measured by vasoconstrictor response at 8, 24, and 32 hours.

*Fluocinonide.



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Having fully described the present invention, it will be apparent from the above description that various modifications in the specific compositions, procedures, methods and processes may be made within the scope of the invention. Therefore, the invention is not intended to be limited to the particular compositions, processes or methods except as may be required by the lawful scope of the following claims.



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WE CLAIM:

1. A composition of matter comprising a steroid active ingredient solution absorbed within a network of pores of a preformed porous polymer bead, said network of pores being substantially noncollapsible upon removal of the solution.

2. A composition of matter comprising a steriod active ingredient solution absorbed within a network of pores of a preformed porous polymeric bead, said bead being dispersed in a medium substantially immiscible with the solution, and said network of pores being substantially non-collapsible upon removal of the solution.

3. A composition of matter comprising a steroid anti-inflammatory active ingredient solution absorbed within a network of pores of a preformed porous polymeric bead, said bead being dispersed in a medium substantially immiscible with the solution, and said network of pores being substantially non-collapsible upon removal of the solution.

4. A composition as recited in Claim 3 wherein the steroid anti-inflammatory active ingredient is selected from the group consisting of fluocinonide, fluocinolone acetonide, triamcinolone, betamethasone valerate, timobesone acetate, hydrocortisone, hydrocortisone acetate, triamcinolone, prednisolone, prednisolone acetate, dexamethasone, beclomethasone dipropionate, betamethasone dipropionate, betamethasone benzoate, clocortolone pivalate, halcinonide, flumethasone pivalate and desonide.

5. A composition as recited in Claim 3 wherein the steroid anti-inflammatory active ingredient is fluocinonide.



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6. A composition as recited in Claim 3 wherein the steroid anti-inflammatory active ingredient solution comprises a steroid anti-inflammatory active ingredient and percutaneous absorption enhancer selected from the group consisting of propylene glycol, propylene carbonate, a mixture of propylene glycol and propylene carbonate, Azone, dimethylsulfoxide, dimethylformamide, dimethylacetamide, diisopropyl adipate, isopropyl myristate, tetrahydrofuran, tetrahydrofurfuryl alcohol, glycerol and N-methyl-2-pyrrolidone.

7. A composition as recited in Claim 1 wherein the polymeric bead has a diameter from about 10 microns to about 100 microns and a calculated cross-linking density in excess of about 10%.

8. A composition as recited in Claim 7 wherein said calculated cross-linking density is between about 20% and about 50%.

9. A composition as recited in Claim 1 wherein the polymeric bead is copolymerized from a comonomer pair selected from the group consisting of styrene and divinylbenzene, vinyl stearate and divinylbenzene, and methyl methacrylate and ethylene glycol dimethacrylate.

10. A composition as recited in Claim 2 wherein the medium includes a component selected from the group consisting of petrolatum, polysiloxane, paraffin wax, mineral oil, beeswax, spermaceti, and fatty acids, alcohols and amides having from 10 to 22 carbon atoms, and mixtures of the foregoing components.

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PATENT
11692-4-1

# COMPOSITION AND METHOD FOR DELIVERING A STEROID ACTIVE INGREDIENT

## ABSTRACT OF THE DISCLOSURE

Delivery vehicle comprising a polymeric bead having a network of pores with a solution of an active ingredient absorbed within the network is provided for use with or without a medium in a method to provide controlled release of the active ingredient useful for topical therapeutic use. The network of pores is substantially noncollapsible upon removal of the solution.

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## (54) Use of retinoids for reversing glucocorticoid-induced skin atrophy

Verwendung von Retinoiden zur Umkehr glucocorticoid-induzierter Hautatrophie

Utilisation des rétinoides pour contrer l'atrophie cutanée induite par les glucocorticoides

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## Description

### BACKGROUND OF THE INVENTION

#### Field of the Invention

The present invention relates to a method for reversing the effects of glucocorticoid-induced skin atrophy by the topical administration of retinoids.

#### Description of the Prior Art

The most widely prescribed drugs to treat dermatologic disease are glucocorticosteroids. Approximately 50% of prescriptions written by dermatologists are for topical glucocorticosteroids. Since the introduction of these substances in the early 1950's for dermatologic disease, topical corticosteroid therapy continues to be the mainstay for the management of a broad spectrum of inflammatory dermatoses. Although systemic corticosteroids are often required in some dermatologic diseases, topical treatment is preferred in most responsive cases because it causes fewer systemic adverse effects.

Topical corticosteroids are generally most effective in the treatment of acute and chronic dermatoses such as seborrheic or atopic dermatitis, contact dermatitis of the irritant or allergic type, localized neurodermatitis, anogenital pruritus and psoriasis.

Individual topical corticosteroid preparations vary in anti-inflammatory potency and clinical efficacy. Therapeutic efficacy of a particular steroid can often be enhanced by increasing the concentration or by using occulsive dressings. Topical corticosteroids may be grouped according to relative anti-inflammatory potency. Still activity may vary considerably depending upon the vehicle, the site of application, disease, the individual patient, and whether or not an occlusive dressing is used.

Although some dermatoses may require therapy with a potent corticosteroid initially, treatment with hydrocortisone, betamethasone, dexamethasone, methylprednisolone, or prednisolone, is often sufficient and is less likely to cause adverse reactions. Although fluorinated corticosteroids are generally potent and efficacious, fluorination is not essential for increased anti-inflammatory potency (e.g., hydrocortisone valerate has greater anti-inflammatory activity than does betamethasone or dexamethasone). Potent corticosteroids are customarily used for severe or resistant dermatoses such as psoriasis and chronic neurodermatitis. Dermatoses such as discoid lupus erythematosus, lichen planus, granuloma annulare, and psoriasis of palms, soles, elbows and knees or psoriatic plaques usually require potent corticosteroids.

In general, topical application of corticosteroids does not produce systemic side reactions, although abnormal laboratory tests may occur, viz., decreased adrenal production of cortisol. However, systemic corticosteroid side effects may occur when the drugs are used on large areas of the body, for prolonged periods of time, with an occlusive dressing, and/or in infants and children. These include Cushing's disease, acne, osteoporosis, etc.

Potent topical corticosteroids often cause dermatologic side effects. These are most likely to occur in intertriginous and facial areas and are most severe with fluorinated corticosteroids, especially on the face where steroids are rapidly absorbed. Local corticosteroid side effects occur most frequently with occlusive dressings, especially with prolonged therapy.

Local side effects have become more frequent with the clinical use of newer and more potent glucocorticosteroidal analogs. The most common adverse reaction is skin atrophy, i.e., a thinning of the epidermis and dermis accompanied by telangiectasia and striae. Minimal trauma to atrophic skin may also produce purpuric lesions. Other dermatologic side effects include acneiform eruption, pruritus, hypertrichosis, rosacea-like eruptions on the face, perioral dermatitis, burning or stinging sensation, folliculitis, and hypopigmentation. Skin ulceration has occurred in patients with impaired circulation. Because of the high prevalence and seriousness of skin atrophy, it would be very valuable to have available a preparation which was anti-inflammatory but did not cause skin thinning or striae; the latter is a permanent scar or one which would reverse the effects of skin atrophy after they appear.

Topical retinoids such as tretinoin (all-trans-retinoic acid) have been used by dermatologists for almost twenty years. For example, tretinoin is used topically in the treatment of acne vulgaris, primarily grades I-III, in which comedones, papules, and pustules predominate.

In concentrations of 0.1% to 0.3%, tretinoin has been used successfully in the reatment of other skin conditions such as psoriasis, ichthyosis congenita, Darier's disease, epidermolytic hyperkeratosis, senile comedones, senile keratosis, trichostasis, flat warts and basal cell carcinomas.

### SUMMARY OF THE INVENTION

The present invention is directed to a method for reversing the effects of glucocorticoid-induced skin atrophy. The



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method comprises the topical administration of retinoids. The retinoids may be any natural and/or synthetic analog which possess the biological activity of vitamin A.

In co-pending EP-A-026692 a method for preventing glucocorticoid-induced skin atrophy by the topical administration of retinoids such as tretinoin is described. We have now found that in addition to preventing glucocorticoid-induced skin atrophy, topical administration of retinoids will reverse the effects of glucocorticoid-induced skin atrophy.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to the use of retinoids for reversing the effects of glucocorticoid-induced skin atrophy, a side effect of prolonged topical glucocorticoid therapy for dermatological diseases.

Retinoids have been defined narrowly as comprising simply vitamin A (retinol) and its derivatives, such as vitamin A aldehyde (retinal) and vitamin A acid (retinoic acid), which comprise so-called natural retinoids. However, subsequent research has resulted in a much larger class of chemical compounds that are deemed retinoids due to their biological similarity to vitamin A and its derivatives. Compounds useful in the present invention include all natural and/or synthetic analogs of vitamin A or retinol-like compounds which possess the biological activity of vitamin A in the skin. These include: regulation of epithelial cell differentiation in the epidermis, for example, keratinocytes; stimulation of new collagen synthesis in the dermis, and production of new blood vessels (angiogenesis). Accordingly, as used herein for purposes of the present invention, the term "retinoid" will be understood to include any of the foregoing compounds. Examples of suitable retinoids in the present invention are set forth in Table I, although it will be understood that the invention is not limited thereto.

TABLE I

all-trans-retinoic acid

13-cis-retinoic acid

(all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester

(all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid

N-ethyl-9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7,-dimethyl-2,4,6,8-nonatetraenamide

(E,E)-9-(2,6-dichloro-4-methoxy-3-methylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester

7,8-didehydroretinoic acid

(E,E)-4-[2-methhy-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadienyl]benzoic acid



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(E)-4-[4-methyl-6-(2,6,6-triemthyl-1-cyclohexen-1-yl)-1,3,5-hexatreinyl]benzoic acid

(all-E)-3,7-dimethyl-(3-thienyl)-2,4,6,8-nonatetraenoic acid

(E,E,E)-3-methyl-7-(5,6,7,8-tetrahydro-5,5,8,8.-tetramethyl-2-naphthalenyl)-2,4,6-octatrienoic acid

(E)-6-[2-(2,6,6-trimethyl-1-cyclohexen-1-yl)ethenyl]-2-naphthalenecarboxylic acid

(E,E,E)-7-(2,3-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-3-methyl-2,4,6-octatrienoic acid

(E)-4-[2-(2,3,-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-1-propenyl]benzoic acid

(E)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl-1-propenyl]benzoic acid

(E)-4-[2-(5,6,7,8-tetrahydro-3-methyl-5,5,8,8,-tetramethyl-2-naphthalenyl-1-propenyl]benzoic acid

(E)-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-(1-methyl-2-phenylethenyl)naphthalene

6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl-2-naphthalenecarboxylic acid



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(E)-6-[2-(4-(ethylsulfonyl)phenyl]-1-methylethenyl]-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)ethynyl]benzoic acid

(E)-2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl)-1-[4-tetrazol-5-yl)phenyl]-1-propene

(E)-4-[2-(5,6,7,8-tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzyl alcohol

retinoyl palmitate, retinyl palmitate
retinyl propionate
(6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoic acid)

Also encompassed within the term "retinoid" are geometric and stereoisomers of the retinoids.

A pharmaceutical composition containing a retinoid as the active ingredient in intimate admixture with a pharmaceutical carrier can be prepared according to conventional pharmaceutical compounding techniques, such as those known for topical application of all-trans-retinoic acid. The carrier may take a wide variety of physical forms such as creams, dressings, gels, lotions, ointments or liquids. The retinoid will be present in an amount from about 0.00001% by weight to about 3.0% by weight, depending on the potency of the retinoid. A suitable topical retinoid preparation in a gel vehicle is Retin-A™, which contains 0.01% to 0.1% by weight of active ingredient, produced by Ortho Pharmaceutical Corporation. The retinoid may be employed in combination with a glucocorticoid in the same vehicle, to treat skin which has previously been treated with a glucocorticoid.

The following example describes the invention in greater particularity, and is intended to be a way of illustrating but not limiting the invention.

EXAMPLE

Skin atrophy was produced in SKH-hairless-I albino mice by the topical application of various glucocorticoids one time daily, five days per week for three weeks to their dorsal flanks. The glucocorticoids included: clobetasol propionate (0.05%); triamcinolone acetonide (0.5%) or fluocinolone acetonide (0.05%) dissolved in an alcohol: propylene glycol vehicle (70:30, v/v). The atrophied mice were divided into various treatment groups and either vehicle or all-trans-retinoic acid (0.1%) in vehicle was topically applied one time daily, five days per week for two weeks to the dorsal flank skin previously treated with glucocorticoids. Skin-fold thickness measurements of the treated sites were taken with an electronic digital caliper prior to initial treatment and approximately 72 hours following one week and two weeks of treatments. The results are given in Table II.



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TABLE II

| REPAIR/REVERSAL OF GLUCOCORTICOID-INDUCED SKIN ATROPHY BY ALL-TRANS-RETINOIC ACID (RA) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SKIN ATROPHY | | | | REPAIR/REVERSAL OF SKIN ATROPHY | | | | |
| TREATMENT | DOSE (%) | N | PERCENT SKIN ATROPHY | TREATMENT | DOSE (%) | N | % REPAIR/REVERSAL | |
| | | | | | | | WEEK 1 | WEEK 2 |
| CLOBETASOL PROPIONATE | 0.05 | 6 | 34.8 | VEHICLE | - | 3 | 9.5 | 20.0 |
| | | | | RA | 0.1 | 3 | 36.4 | 45.5 |
| TRIAMCINOLONE ACETONIDE | O.5 | 6 | 39.2 | VEHICLE | - | 3 | 15.2 | 28.3 |
| | | | | RA | 0.1 | 3 | 40.2 | 53.3 |
| FLUOCINOLONE ACETONIDE | 0.05 | 6 | 38.6 | VEHICLE | - | 3 | 29.5 | 34.7 |
| | | | | RA | 0.1 | 3 | 30.6 | 50.0 |
| ALL THREE GLUCOCORTICOIDS INDUCED SKIN ATROPHY TO SIMILAR DEGREE IN THE HAIRLESS MOUSE, (E.G., 34.8% BY CLOBETASOL PROPIONATE, 39.2% BY TRIAMCINOLONE ACETONIDE AND 38.6% BY FLUOCINOLONE ACETONIDE). TOPICAL ALL-TRANS-RETINOIC ACID PRODUCED INCREASES IN SKIN-FOLD THICKNESS OVER VEHICLE CONTROL AND CLEARLY ENHANCED THE REPAIR/REVERSAL OF GLUCOCORTICOID-INDUCED SKIN ATROPHY.<br>N = NO. OF MICE | | | | | | | | |

The results shown in Table II clearly demonstrate that the administration of all-trans-retinoic acid reverses the effects of skin atrophy induced by topical glucocorticoid therapy.

## Claims

1. The use of a retinoid in the manufacture of a topical medicament for reversing skin atrophy induced by prior application of a glucocorticoid.

2. The use of a retinoid as claimed in claim 1 wherein said retinoid comprises from about 0.00001% by weight to about 3.0% by weight of said medicament.

3. The use of a retinoid as claimed in claim 1 or claim 2, wherein said medicament further comprises a glucocorticoid.

4. The use of a retinoid as claimed in claim 3 wherein the glucocorticoid is dexamethasone.

5. The use of a retinoid as claimed in any preceding claim wherein said retinoid is selected from all-trans-retinoic acid, 13-cis-retinoic acid, (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester, (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid, N-ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamide, (E,E)-9-(2,6-dichloro-4-methoxy-3-methylphenyl)-3,7-dimethyl-2,4,6,8-nonaetraenoic acid ethyl ester, 7,8-didehydroretinoic acid, (E,E)-4-[2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadienyl]benzoic acid, (E)-4-[4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl]benzoic acid, (all-E)-3,7-dimethyl-3-thienyl)-2,4,6,8-nonatetraenoic acid, (E,E,E)-3-methyl-7-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2,4,6-octatrienoic acid, (E)-6-[2-(2,6,6-trimethyl-1-cyclohexen-1-yl)ethenyl]-2-naphthalenecarboxylic acid, (E,E,E)-7-(2,3,-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-3-methyl-2,4,6-octatrienoic acid, (E)-4-[2-(2,3-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-1-propenyl]-benzoic acid, (E)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl-1-propenyl]benzoic acid, (E)-4-[2-(5,6,7,8-tetrahydro-3-methyl-5,5,8,8-tetramethyl-2-naphthalenyl-1- propenyl] benzoic acid, (E)-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-(1-methyl-2-phenylethenyl)-naphthalene, 6-(1,2,3,4,-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)-2-naphthalenecarboxylic acid, (E)-6-[2-(4-(ethylsulfonyl)phenyl]-1-methylethenyl]-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)ethynyl]benzoic acid, (E)-2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl-[4-tetrazol-5-yl)phenyl]-1-propene, (E)-4-[2-(5,6,7,8-tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzyl alcohol, retinoyl palmitate, retinyl palmitate, retinyl propionate and (6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoic acid).



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6. The use of a retinoid as claimed in any of claims 1 to 4 wherein said retinoid is all-trans-retinoic acid.

7. The use of a retinoid as claimed in any of claims 1 to 4 wherein said retinoid is 13-cis-retinoic acid.

8. The use of a retinoid as claimed in any of claims 1 to 4 wherein said retinoid is selected from (E)-4-[4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl]benzoic acid, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)ethynyl]benzoic acid, and (E)-4-[2-(5,6,7,8-tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]-benzyl alcohol.

**Patentansprüche**

1. Verwendung eines Retinoids bei der Herstellung eines topischen Arzneimittels zur Umkehr der durch vorherige Verwendung eines Glucocorticoids induzierten Hautatrophie.

2. Verwendung eines Retinoids nach Anspruch 1, wobei das Retinoid etwa 0,00001 Gew.-% bis etwa 3,0 Gew.-% des Arzneimittels ausmacht.

3. Verwendung eines Retinoids nach Anspruch 1 oder 2, wobei das Arzneimittel ferner ein Glucocorticoid umfaßt.

4. Verwendung eines Retinoids nach Anspruch 3, wobei es sich bei dem Glucocorticoid um Dexamethason handelt.

5. Verwendung eines Retinoids nach einem der vorstehenden Ansprüche, wobei das Retinoid ausgewählt ist unter: all-trans-Retinoesäure, 13-cis-Retinoesäure, (all-E)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8,-nonatetraensäureethylester, (all-E)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraensäure, N-Ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamid, (E,E)-9-(2,6-Dichlor-4-methoxy-3-methylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraensäureethylester, 7,8-Didehydroretinoesäure, (E,E)-4-[2-Methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadienyl]-benzoesäure, (E)-4-[4-Methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl]-benzoesäure, (all-E)-3,7-Dimethyl-3-thienyl)-2,4,6,8-nonatetraensäure, (E,E,E)-3-Methyl-7-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalinyl)-2,4,6-octatriensäure, (E)-6-[2-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-ethenyl]-2-naphthalincarbonsäure, (E,E,E)-7-(2,3-Dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-3-methyl-2,4,6-octatriensäure, (E)-4-[2-(2,3-Dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-1-propenyl]-benzoesäure, (E)-4-[2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalinyl-1-propenyl]-benzoesäure, (E)-4-[2-(5,6,7,8-tetrahydro-3-methyl-5,5,8,8-tetramethyl-2-naphthalinyl-1-propenyl]-benzoesäure, (E)-1,2,3,4-Tetrahydro-(1,1,4,4-tetramethyl-6-(1-methyl-2-phenylethenyl)-naphthalin, 6-(1,2,3,4-Tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)-2-naphthalincarbonsäure, (E)-6-[2-(4-Ethylsulfonyl)-phenyl]-1-methylethenyl]-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalin, 4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalinyl)-ethinyl]-benzoesäure, (E)-2-(1,1,4,4-Tetramethyl-1,2,3,4-tetrahydronaphth-7-yl-[4-tetrazol-5-yl)-phenyl]-1-propen, (E)-4-[2-(5,6,7,8-Tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthalinyl)-1-propenyl]-benzylalkohol, Retinoylpalmitat, Retinylpalmitat, Retinylpropionat und 6-(3-(1-Adamantyl)-4-methoxyphenyl)-2-naphtoesäure.

6. Verwendung eines Retinoids nach einem der Ansprüche 1 bis 4, wobei es sich bei dem Retinoid um all-trans-Retinoesäure handelt.

7. Verwendung eines Retinoids nach einem der Ansprüche 1 bis 4, wobei es sich bei dem Retinoid um 13-cis-Retinoesäure handelt.

8. Verwendung eines Retinoids nach einem der Ansprüche 1 bis 4, wobei das Retinoid ausgewählt ist unter (E)-4-[4-Methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl]-benzoesäure, 4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalinyl)-ethinyl]-benzoesäure und (E)-4-[2-(5,6,7,8-Tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthalinyl)-1-propenyl]-benzylalkohol.

**Revendications**

1. Utilisation d'un rétinoïde dans la fabrication d'un médicament topique pour faire régresser l'atrophie cutanée provoquée par une application précédente d'un glucocorticoïde.

2. Utilisation d'un rétinoïde selon la revendication 1, dans laquelle ledit rétinoïde représente d'environ 0,00001 % en poids à environ 3,0 % en poids dudit médicament.



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3. Utilisation d'un rétinoïde selon la revendication 1 ou 2, dans laquelle ledit médicament comprend en outre un glucocorticoïde.

4. Utilisation d'un rétinoïde selon la revendication 3, dans laquelle le glucocorticoïde est la dexaméthasone.

5. Utilisation d'un rétinoïde selon l'une quelconque des revendications précédente, dans laquelle ledit rétinoïde est choisi parmi l'acide tout-trans-rétinoïque, l'acide 13-cis-rétinoïque, le (tout-E)-9-(4-méthoxy-2,3,6-triméthylphényl)-3,7-diméthyl-2,4,6,8-nonatétraénoate d'éthyle, l'acide (tout-E)-9-(4-méthoxy-2,3,6-triméthylphényl)-3,7-diméthyl-2,4,6,8-nonatétraénoïque, le N-éthyl-9-(4-méthoxy-2,3,6-triméthylphényl)-3,7-diméthyl-2,4,6,8-nonatétraénamide, le (E,E)-9-(2,6-dichloro-4-méthoxy-3-méthylphényl)-3,7-diméthyl-2,4,6,8-nonatétraénoate d'éthyle, l'acide 7,8-didéhydrorétinoïque, l'acide (E,E)-4-[2-méthyl-4-(2,6,6-triméthyl-1-cyclohexène-1-yl)-1,3-butadiényl]-benzoïque, l'acide (E)-4-[4-méthyl-6-(2,6,6-triméthyl-1-cyclohexène-1-yl)-1,3,5-hexatriényl]-benzoïque, l'acide (tout-E)-3,7-diméthyl-(3-thiényl)-2,4,6,8-nonatétraénoïque, l'acide (E,E,E)-3-méthyl-7-(5,6,7,8-tétrahydro-5,5,8,8-tétraméthyl-2-naphtalényl)-2,4,6-octatriénoïque, l'acide (E)-6-[2-(2,6,6-triméthyl-1-cyclohexène-1-yl)-éthényl]-2-naphtalènecarboxylique, l'acide (E,E,E)-7-(2,3-dihydro-1,1,3,3-tétraméthyl-IH-indène-5-yl)-3-méthyl-2,4,6-octatriénoïque, l'acide (E)-4-[2-(2,3-dihydro-1,1,3,3-tétraméthyl-IH-indène-5-yl)-1-propényl]-benzoïque, l'acide (E)-4-[2-(5,6,7,8-tétrahydro-5,5,8,8-tétraméthyl-2-naphtalényl-1-propényl]-benzoïque, l'acide (E)-4-[2-(5,6,7,8-tétrahydro-3-méthyl-5,5,8,8-tétraméthyl-2-naphtalényl-1-propényl]-benzoïque, le (E)-1,2,3,4-tétrahydro-1,1,4,4-tétraméthyl-6-(1-méthyl-2-phényléthényl)-naphtalène, l'acide 6-(1,2,3,4-tétrahydro-1,1,4,4-tétraméthyl-6-naphtyl)-2-naphtalènecarboxylique, le (E)-6-[2-[4-(éthylsulfonyl)-phényl]-1-méthyléthényl]-1,2,3,4-tétrahydro-1,1,4,4-tétraméthylnaphtalène, l'acide 4-[(5,6,7,8-tétrahydro-5,5,8,8-tétraméthyl-2-naphtalényl)-éthynyl]-benzoïque, le (E)-2-[1,1,4,4-tétraméthyl-1,2,3,4-tétrahydronapht-7-yl-(4-tétrazol-5-yl)-phényl]-1-propène, l'alcool (E)-4-[2-(5,6,7,8-tétrahydro-7-hydroxy-5,5,8,8-tétraméthyl-2-na phtalényl)-1-propényl]-benzylique, le palmitate de rétinoyle, le palmitate de rétinyle, le propionate de rétinyle et l'acide 6-[3-(1-adamantyl)-4-méthoxyphényl]-2-naphtoïque.

6. Utilisation d'un rétinoïde selon l'une quelconque des revendications 1 à 4, dans laquelle ledit rétinoïde est l'acide tout-trans-rétinoïque.

7. Utilisation d'un rétinoïde selon l'une quelconque des revendications 1 à 4, dans laquelle ledit rétinoïde est l'acide 13-*cis*-rétinoïque.

8. Utilisation d'un rétinoïde selon l'une quelconque des revendications 1 à 4, dans laquelle ledit rétinoïde est choisi parmi l'acide (E)-4-[4-méthyl-6-(2,6,6-triméthyl-1-cyclohexène-1-yl)-1,3,5-hexatriényl]-benzoïque, l'acide 4-[(5,6,7,8-tétrahydro-5,5,8,8-tétraméthyl-2-naphtalényl)-éthynyl]-benzoïque et l'alcool (E)-4-[2-(5,6,7,8-tétrahydro-7-hydroxy-5,5,8,8-tétraméthyl-2-naphtalényl)-1-propényl]-benzylique.



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(54) **Title:** DJCARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF

(57) **Abstract:** The present invention teaches a foamable pharmaceutical carrier comprising a benefit agent, selected from the group consisting of a dicarboxylic acid and a dicarboxylic acid ester; a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; a solvent selected from the group consisting of water, a hydrophilic solvent, a hydrophobic solvent, a potent solvent, a polar solvent, a silicone, an emollient, and mixtures thereof, wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients. The invention further relates to a foamable composition further containing a liquefied hydrocarbon gas propellant.



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# DICARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF

## BACKGROUND OF THE INVENTION

**[0001]** This invention relates to foamable pharmaceutical and cosmetic compositions.

**[0002]** External topical administration is an important route for the administration of drugs in disease treatment. Many groups of drugs, including, for example, antibiotic, anti-fungal, anti-inflammatory, anesthetic, analgesic, anti-allergic, corticosteroid, retinoid and anti-proliferative medications are preferably administered in hydrophobic media, namely ointment. However, ointments often form an impermeable barrier, so that metabolic products and excreta from the wounds to which they are applied are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the wound tissue, so the efficacy of the drug is reduced. In addition, ointments and creams often do not create an environment for promoting respiration of the wound tissue and it is not favorable to the normal respiration of the skin. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds.

**[0003]** Foams are considered a more convenient vehicle for topical delivery of active agents. There are several types of topical foams, including aqueous foams, such as commonly available shaving foams; hydroalcoholic foams, emulsion-based foams, comprising oil and water components, and oleaginous foams, which consist of high oil content. In skin therapy, oil containing foams are preferred, since oil contributes to skin protection and moisturization, which improve the therapeutic effect of the formulation.



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[0004] Dicarboxylic acids are known to possess therapeutic properties. Dicarboxylic acids, and their mercapto, ester and salt derivatives have been used in the treatment of a variety of skin disorders and/or conditions.

[0005] Azelaic acid (AZA) is a naturally occurring nine carbon straight chain molecule with two terminal carboxyl groups. AZA is an anti-keratinizing agent, displaying antiproliferative effects on keratinocytes and modulating the early and terminal phases of epidermal differentiation. AZA is a competitive inhibitor of the reduction of testosterone to dihydrotestosterone, and as such is supposed to reduce the production of sebum in the sebaceous gland. Furthermore, recent investigations have demonstrated that AZA and sebacic acid also have anti-bacterial and anti-fungal properties. Structure-activity relationship studies have revealed that these effects are retained when the dicarboxylic acid has a backbone of about 6 to about 14 carbons.

[0006] Dicarboxylic acid esters are also known to contribute to the skin penetration of an active agent. Enhancing effects on skin penetration of methyl nicotinate have been observed with dibutyl adipate and dioctyl adipate. Diisopropyl sebacate also markedly enhances the skin penetration of the erythromycin. The skin penetration enhancing properties of mono- or di-esters of dicarboxylic acid, including dibutyl adipate, diethyl sebacate, diisopropyl dimerate, diisopropyl adipate, diisopropyl sebacate and dioctyl succinate have been recognized.

[0007] There remains an unmet need for improved, easy to use, stable oil-containing foam formulations, containing oils, which effectively deliver and/or deposit various benefit agents into and onto the skin and/or other target sites and are relatively non-irritating and thus suitable for use by people having sensitive skin and eyes.

## SUMMARY

[0008] The present invention relates to aqueous and non aqueous stable compositions comprising a dicarboxylic acid or ester derivative thereof in which

the dicarboxylic acid or ester derivative is a stabilizing emollient and or has a therapeutic effect.

**[0009]** There is provided a pharmaceutical or cosmetic composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

   i. a dicarboxylic acid; and

   ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

c. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.



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**[0010]** There is also provided a foamable composition as described above wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

**[0011]** There is also provided a therapeutic composition comprising:

a. a therapeutically effective amount of an active agent;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

**[0012]** There is also provided a method of treating a disorder of a mammalian subject, comprising:

administering a foamable therapeutic composition to a target site, the composition comprising:

e. a therapeutically effective amount of an active agent;

f. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

g. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

h. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

**[0013]** There is also provided a pharmaceutical or cosmetic non aqueous composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

   i. a dicarboxylic acid; and

   ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0014] There is also provided a therapeutic composition comprising:

a. a therapeutically effective amount of an active agent wherein the active agent is substantially insoluble in water;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, comprising a dicarboxylic acid ester in which the active agent is substantially soluble;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

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wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

**[0015]** There is also provided a foamable composition comprising:

a. a liquid dicarboxylic acid ester, said ester having emollient properties;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

c. an active agent, said active agent soluble in or having enhanced penetration due to the dicarboxylic acid;

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

**[0016]** There is also provided a foamable composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. an ester-based or ether-based surfactant;

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the composition is substantially free of polymeric material, and

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

**[0017]** There is also provided a pharmaceutical or cosmetic composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the composition is substantially free of water; and

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

**[0018]** There is also provided a formulation of any of the compositions described above wherein the composition is in a non foam state.

**[0019]** There is also provided a formulation of any of the compositions described above for use in the manufacture of a medicament.

## DETAILED DESCRIPTION

**[0020]** The present invention relates to a composition comprising a benefit agent, selected from the group consisting of (i) a dicarboxylic acid; and (ii) a dicarboxylic acid ester for use as vehicle composition.

**[0021]** According to one or more embodiments of the present invention, the composition includes:

a. a benefit agent, selected from the group consisting of

   i. a dicarboxylic acid; and

   ii. a dicarboxylic acid ester;

b. a surface-active agent;

c. about 0.01% to about 5% by weight of at least one polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent; and

d. water.

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**[0022]** The present invention further relates to a foamable composition including:

a. a benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a surface-active agent;

c. about 0.01% to about 5% by weight of at least one polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

d. water; and

e. liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

**[0023]** In one or more embodiments there is provided a pharmaceutical or cosmetic composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

c. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients;

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

**[0024]** In one or more embodiments there is provided a foamable composition which produces a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

**[0025]** In one or more embodiments there is provided a composition wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that is substantially resistant to phase reversal.

**[0026]** In one or more embodiments there is provided a composition wherein, the benefit agent, stabilizer and solvent are selected to generate a single phase.

**[0027]** In one or more embodiments there is provided a composition wherein, the benefit agent, stabilizer and solvent are selected to generate a substantially uniform suspension of benefit agent crystals.

**[0028]** In one or more embodiments there is provided a composition, wherein the breakable foam comprises micro or nano particles, crystals or bodies.

**[0029]** In one or more embodiments there is provided a composition, which is substantially resistant to one or more Freeze-Thaw cycles (FTC).

**[0030]** In one or more embodiments there is provided a composition wherein the surface-active agent is a solid, a liquid or a mixture thereof.

**[0031]** In one or more embodiments there is provided a composition wherein the surface active agent is selected from the group consisting of a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59; a polyoxyethylene alkylyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol, sorbitan monolaurate, sorbitan monolaurate a monoglyceride, a diglyceride, isoceteth-20, a sucrose ester, or selected from the group consisting of steareth 2, glyceryl monostearate/PEG 100 stearate, Glyceryl Stearate, Steareth-21, peg 40 stearate, polysorbate 60, polysorbate 80, sorbitan stearate, laureth 4, Sorbitan monooleate, ceteareth 20, steareth 20, ceteth 20, Macrogol Cetostearyl Ether, ceteth 2, PEG-30 Dipolyhydroxystearate, sucrose distearate, polyoxyethylene (100) stearate, PEG 100 stearate, laureth 4, cetomacrogol ether, Cetearyl alcohol, Cetearyl glucoside, Oleyl alcohol, Steareth-2, Diisopropyl adipate, Capric/caprilic triglicerides, Polysorbate 20; Montanov 68 (CETEARYL ALCOHOL (and) CETEARYL GLUCOSIDE.), Sharonmix 824(a liquid blend of methyl paraben, ethyl paraben and propyl paraben - in phenoxyethanol), Simusol 165 (Glyceryl stearate and PEG-100 stearate). Methyl glucose sequistearate, Peg 30 dipolyhydroxystearate, sucrose stearic acid esters, sorbitan laureth, sorbitan stearate and mixtures thereof.

**[0032]** In one or more embodiments there is provided a composition wherein the surface active agent comprises at least one ester based surfactant or at least one ether based surfactant.

**[0033]** In one or more embodiments there is provided a composition wherein the surface active agent is reduced about in proportion to the increase in dicarboxylic ester.

**[0034]** In one or more embodiments there is provided a composition wherein the stabilizer is not a polymeric agent.

**[0035]** In one or more embodiments there is provided a composition wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

**[0036]** In one or more embodiments there is provided a composition wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester, a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

**[0037]** In one or more embodiments there is provided a composition wherein the polymeric agent is selected from the group consisting of carbopol 934, pemulen TR2, klucel EF, xanthan gum, methocel A4M, and carboxy methyl cellulose or selected from the group consisting of locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, cationic guars, hydroxypropyl guar gum, starch, an amine-bearing polymer, chitosan, alginic acid, hyaluronic acid, a chemically modified starch, a carboxyvinyl polymer, polyvinylpyrrolidone, polyvinyl alcohol, a polyacrylic acid polymer, a polymethacrylic acid polymer, polyvinyl acetate, a polyvinyl chloride polymer, a

polyvinylidene chloride polymer, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxy propylmethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylcellulose carboxymethylhydroxyethylcellulose, a cationic cellulose aluminum starch octenylsuccinate (ASOS), PEG 1000, PEG 4000, PEG 6000 and PEG 8000.

**[0038]** In one or more embodiments there is provided a composition wherein the polymeric agent is a derivatized polymer.

**[0039]** In one or more embodiments there is provided a composition wherein the derivatized polymer is a polymeric emulsifier.

**[0040]** In one or more embodiments there is provided a composition wherein the benefit agent is selected from the group consisting of diisopropyl adipate, dimethyl sebacate, dioctyl malate, diethyl sebacate, azelaic acid and TU-2100.

**[0041]** In one or more embodiments there is provided a composition wherein, further comprising an additional active agent.

**[0042]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid has the molecular formula $HOOC-(CH_2)_n-COOH$; and wherein n is in the range between 0 and 32.

**[0043]** In one or more embodiments there is provided a composition wherein n is in the range between 4 and 10.

**[0044]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid is selected from the group consisting of oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid and dodecanedioic acid, maleic acid and fumaric acid.

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**[0045]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid is selected from the group consisting of adipic acid, azelaic acid and sebacic acid.

**[0046]** In one or more embodiments there is provided a composition wherein further containing a foam adjuvant selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain; a fatty acid having 16 or more carbons in their carbon chain; fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; a fatty alcohol having at least one double bond; a fatty acid having at least one double bond; a branched fatty alcohol; a branched fatty acid and a fatty acid substituted with a hydroxyl group.

**[0047]** In one or more embodiments there is provided a composition wherein further containing at least one organic carrier selected from the group consisting of a hydrophobic organic carrier, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight.

**[0048]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid or dicarboxylic acid ester is in a concentration between about 0.1% and about 60%.

**[0049]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid, and wherein the concentration of azelaic acid is between 5% and 25%.

**[0050]** In one or more embodiments there is provided a composition wherein the pH of the composition is below the first pKa of the dicarboxylic acid.

**[0051]** In one or more embodiments there is provided a composition wherein the pH of the composition is between the first and second pKa of the dicarboxylic acid.

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**[0052]** In one or more embodiments there is provided a composition wherein the pH of the composition is above the second pKa of the dicarboxylic acid.

**[0053]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid the pH of the composition is below 5.3.

**[0054]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid the pH of the composition is between about 4.5 and about 5.3.

**[0055]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid ester is selected from the group consisting of a mono ester of said dicarboxylic acid, and a diester of the dicarboxylic acid.

**[0056]** In one or more embodiments there is provided a composition wherein the alcohol moiety of the dicarboxylic acid ester is selected from the group consisting of an alkyl alcohol, an aryl alcohol, methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, isobutyl alcohol, t-butyl alcohol, pentyl alcohol, hexyl alcohol, octyl alcohol, decyl alcohol, capryl alcohol, phenol and benzyl alcohol.

**[0057]** In one or more embodiments there is provided a composition wherein the alcohol moiety of the dicarboxylic acid ester is a biologically active alcohol.

**[0058]** In one or more embodiments there is provided a composition wherein the biologically active alcohol is selected from the group consisting of a hydroxyalkylbenzoate, salicylic acid, a dihydroxybenzene, hydroxytoluene, an alpha-hydroxy acid, retinol, a vitamin A derivative, a steroid, vitamin E, a vitamin E derivative, vitamin D and a vitamin D derivative.



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**[0059]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid ester is selected from the group consisting of diisobutyl adipate, diisopropyl adipate, diisopropyl sebacate, diisosteary dimer dilinoleate, diisostearyl fumerate, diisopropyl dimerate, diethyl adipate, diethyl sebacate, diethylhexyl adipate, diethylhexyl malate, dioctyl malate, diethyl succinate, and dioctyl sebacate.

**[0060]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid ester is diisopropyl adipate, in an amount from about 0.1% to about 60%

**[0061]** In one or more embodiments there is provided a composition wherein the organic carrier is selected from the group consisting of mineral oil, triglycerides, medium chain triglyceride (MCT) oil, capric/caprylic triglyceride, alkyl esters of fatty acids such as isopropyl palmitate, isopropyl myristate, isopropyl isostearate, poly propylene glycol 15-stearly ether, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, maleated soybean oil, unsaturated or polyunsaturated oils, such as olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzigium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils; essential oils; and silicone oils, such as dimethicone, cyclomethicone, polyalkyl siloxane, polyaryl siloxane, polyalkylaryl siloxane, a polyether siloxane copolymer and a poly(dimethylsiloxane)-(diphenyl-siloxane) copolymer.

**[0062]** In one or more embodiments there is provided a composition wherein the organic carrier comprises a polypropylene glycol alkyl ether.



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**[0063]** In one or more embodiments there is provided a composition further containing at least one polar solvent.

**[0064]** In one or more embodiments there is provided a composition wherein the polar solvent is selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, oleyl alcohol, alpha-hydroxy acids, such as lactic acid and glycolic acid, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, alkanols, such as dialkylamino acetates, and admixtures thereof.

**[0065]** In one or more embodiments there is provided a composition wherein the organic carrier is capric/caprylic triglyceride and wherein the dicarboxylic acid is azelaic acid.

**[0066]** In one or more embodiments there is provided a composition wherein the polar solvent is selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid wherein the dicarboxylic acid is azelaic acid.

**[0067]** In one or more embodiments there is provided a composition wherein the organic carrier is capric/caprylic triglyceride.

**[0068]** In one or more embodiments there is provided a composition wherein the organic solvent comprises at least one organic carrier, selected from the group capric/caprylic triglyceride, a polypropylene glycol alkyl ether an ester of a fatty acid and mineral oil and wherein the dicarboxylic acid ester is diisopropyl adipate .

**[0069]** In one or more embodiments there is provided a composition further comprising a polar solvent, selected from the group consisting of dimethyl

isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

**[0070]** In one or more embodiments there is provided a composition wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that can produce a substantially strong and closed packed barrier between the oil and the water phases whilst maintaining a fluid constitution

**[0071]** In one or more embodiments there is provided a composition further comprising an additional component selected from the group consisting of a modulating agent, a polar solvent, an anti perspirant, an anti-static agent, a buffering agent, a bulking agent, a chelating agent, a colorant, a conditioner, a deodorant, a diluent, a dye, an emollient, fragrance, a humectant, an occlusive agent, a penetration enhancer, a perfuming agent, a permeation enhancer, a pH-adjusting agent, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent, and a vitamin.

**[0072]** In one or more embodiments there is provided a composition wherein the organic carrier is selected from the group consisting of PPG 15-stearyl ether, isopropyl myristate and medium chain triglyceride oil and capric/caprylic triglyceride and the benefit agent is a solid at ambient temperature.

**[0073]** In one or more embodiments there is provided a therapeutic composition comprising therapeutically effective amount of an active agent; and a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of:

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester

wherein the active agent is selected from the group consisting of active herbal extracts, acaricides, age spot and keratose removing agents, allergen,

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analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, antiyeast agents, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hair growth regulators, hormones, hydroxy acids, immunosuppressants, immunoregulating agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, self tanning agents, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, wound healing agents and wart removers.

**[0074]** In one or more embodiments there is provided a foamable therapeutic composition wherein the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the active agent.

**[0075]** In one or more embodiments there is provided a foamable therapeutic composition wherein the active agent is a steroid.

**[0076]** In one or more embodiments there is provided a foamable therapeutic composition wherein the steroid is selected from the group consisting of bydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethsone dipropionate, clobetasol valemate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone,



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halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortmate, mepreddisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone.

**[0077]** In one or more embodiments there is provided a foamable therapeutic composition wherein the active agent is an immunomodulator.

**[0078]** In one or more embodiments there is provided a foamable therapeutic composition, wherein the immunomodulator is selected from the group consisting of a cyclic peptides, cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus, verolimus, laflunimus, laquinimod and imiquimod.

**[0079]** In one or more embodiments there is provided a foamable therapeutic composition, wherein the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the immunomodulator.

**[0080]** In one or more embodiments there is provided a foamable therapeutic composition, wherein the dicarboxylic acid ester is diisopropyl adipate.

**[0081]** In one or more embodiments there is provided a composition wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

**[0082]** In one or more embodiments there is provided a composition wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester,a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan



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monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

**[0083]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid.

**[0084]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid and further comprising an organic solvent comprising capric/caprylic triglyceride.

**[0085]** In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid and further comprising an organic solvent comprising capric/caprylic triglyceride and further comprising at least one polar carrier, selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

**[0086]** In one or more embodiments there is provided a method of treating a disorder of a mammalian subject, comprising:

administering a foamable therapeutic composition to a target site, the composition comprising a therapeutically effective amount of an active agent; and a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

wherein the target site is selected from the group consisting of the skin, a body cavity, a mucosal surface, the nose, the mouth, the eye, the ear canal, the respiratory system, the vagina and the rectum.

**[0087]** In one or more embodiments there is provided a method of treating a disorder of a mammalian subject,wherein the disorder is selected from the group consisting of dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychial infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, granuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callouses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo; and wherein the active agent is suitable for treating said disorderm or is selected from the group consisting of chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis,



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pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum; and wherein the active agent is suitable for treating said disorder.

**[0088]** In one or more embodiments there is provided a method of treating a disorder of a mammalian subject,wherein the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid or dicarboxylic acid ester.

**[0089]** In one or more embodiments there is provided a method of treating a disorder of a mammalian subject, wherein the disorder is a dermatological disorder, which can be treated by a topical steroid, an immunomodulator or an anti-infective agent.

**[0090]** In one or more embodiments there is provided a method of treating a disorder of a mammalian subject, wherein the disorder is selected from atopic dermatitis and psoriasis; and the active agent is selected from (i) steroid; and (ii) a combination of steroid and an additional non-steroidal active agent.

**[0091]** In one or more embodiments there is provided a method of treating a disorder of a mammalian subject, wherein the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises an immunomodulator.

**[0092]** In one or more embodiments there is provided a therapeutic composition comprising: a therapeutically effective amount of an active agent wherein the active agent is substantially insoluble in water; and a beneficially or therapeutically effective concentration of at least one benefit agent, comprising a dicarboxylic acid ester in which the active agent is substantially soluble; wherein the benefit agent, stabilizer and solvent are selected to

generate an emulsion that can produce a substantially strong and closed packed barrier between the oil and the water phases whilst maintaining a fluid constitution.

**[0093]** In one or more embodiments there is provided a foamable composition comprising: a liquid dicarboxylic acid ester, said ester having emollient properties; a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof, an active agent, said active agent soluble in or having enhanced penetration due to the dicarboxylic acid; wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release

**[0094]** In one or more embodiments the stabilizer comprises a ether-based or ester-based surfactant.

**[0095]** In one or more embodiments the stabilizer comprises an alkyl-derivatized polymer having polymeric emulsifying properties.

**[0096]** In one or more embodiments the composition is an oil in water emulsion.

**[0097]** In one or more embodiments the dicarboxylic acid ester comprises about or more than 50 wt% of the composition.

**[0098]** In one or more embodiments the active agent is otherwise insoluble or unstable, but is solubilized or stabilized by DCA.

**[0099]** In one or more embodiments the composition is substantially free of water

In one or more embodiments the composition is in a non foam state.

**[0100]** In one or more embodiments there is provided a pharmaceutical or cosmetic composition comprising:

a. a benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a surface-active agent;

c. about 0.01% to about 5% by weight of at least one polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent; and

d. water.

**[0101]** All % values are provided on a weight (w/w) basis.

**Dicarboxylic acid and esters thereof**

**[0102]** In an embodiment of the present invention, the organic carrier comprises an ester of a dicarboxylic acid. In the context of the present invention, a dicarboxylic acid is an organic material, having two carboxylic acid moieties on its carbon atom skeleton. They have the general molecular formula HOOC-$(CH_2)_n$-COOH.

**[0103]** Non limiting examples of some elementary dicarboxylic acids (DCA's) are succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, phthalic acid, isophthalic acid, terephthalic acid.

**[0104]** In an embodiment of the present invention, the dicarboxylic acid is a short-chain dicarboxylic acid. The simplest Short-chain dicarboxylic acid are oxalic acid (n=0), malonic acid (n=1), succinic acid (n=2) and glutaric acid (n=3).

**[0105]** Additional members of dicarboxylic acid group are derived from natural products or from synthesis, having "n" value from 4 up to 21. In one or more

embodiments of the present invention, the dicarboxylic acid is selected from the group consisting of adipic acid (hexanedioic acid; n=4), pimelic acid (heptanedioic acid; n=5), suberic acid (octanedioic acid; n=6), azelaic acid (nonanedioic acid; n=7), sebacic acid (decanedioic acid; n=8) and dodecanedioic acid (n=10).

**[0106]** In an additional embodiment, the dicarboxylic acid contains 10 to 32 carbon atoms in their carbon atom skeleton, such as brassylic acid (n=11), thapsic acid (n=14), 14-methylnonacosanedioic acid (C29) and 14,15-dimethyltriacontanedioic acid (C30).

**[0107]** The carbon atom skeleton of the dicarboxylic acid can be saturated or unsaturated, such as in the case of maleic acid and fumaric acid.

**[0108]** In general terms non-esterified dicarboxylic acids are usually solid at ambient temperature. Non limiting examples of solid DCA's are oxalic, malonic glutaric, sebacic , phthalic and azaleic acid. Similarly, in general terms DCA's with short carbon chain skeleton are water soluble, such as oxalic, malonic, and succinic acid. Longer chain DCA's like adipic acid and having up to 10 carbon atoms in the carbon chain are slightly soluble in water. Also non "simple" DCA's are generally solid at ambient temperature , insoluble in water, and are usually more oil soluble than their parent DCA's

**[0109]** An ester of a dicarboxylic acid is a chemical compound produced by the reaction between a dicarboxylic acid and at least one alcohol, with the elimination of a molecule of water. The reaction of a dicarboxylic acid with one alcohol molecule results in a mono ester of a dicarboxylic acid. The reaction of a dicarboxylic acid with two alcohol molecules results in a diester of the dicarboxylic acid.

**[0110]** DCA esters are typically hydrophobic and generally insoluble in water. Most simple esters of DCA are liquid. By simple it is meant that the alcohol moiety linked to the DCA is a straight or branched alkyl chain. Examples of liquid simple diesters are dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diethyl



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sebacate, dibutyl sebacate, and diisopropyl adipate. Aromatic diesters of pthalic, isopthalic and therephalic acids are in the range of slightly soluble to insoluble.

**[0111]** The alcohol molecule, to be linked to the dicarboxylic acid, can be selected from the group of an alkyl an aryl alcohol. Exemplary alcohol, suitable according to the present invention include methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, isobutyl alcohol, t-butyl alcohol, pentyl alcohol, hexyl alcohol, octyl alcohol, decyl alcohol, capryl alcohol, phenol, benzyl alcohol and the like.

**[0112]** In one or more embodiments, the alcohol is a biologically active alcohol. In an embodiment, biologically active alcohol possesses keratolytic activities. Examples of keratolytically active alcohol suitable according to the present invention include ortho-, meta- and para-hydroxyalkylbenzoate, salicylic acid, ortho-, meta-, and para-dihydroxybenzene, ortho-, meta-, and para-hydroxytoluene, alpha-hydroxy acid, retinol, and derivatives thereof such as provided in U.S. Pat. 6,180,669, which is incorporated herein by reference. In another embodiment, the biologically active alcohol is selected from the group consisting of steroidal hormones, steroidal anti-inflammatory agents, vitamin E and vitamin D, such as provided in U.S. Pat. Appl. 20040191196, which is incorporated herein by reference.

**[0113]** In an embodiment of the present invention, the dicarboxylic acid is incorporated in the foamable composition in a safe and effective amount. The term "safe and effective" means an amount of an active agent that exerts a therapeutic effect on a specific disorder, without causing adverse effects that may prohibit the use of said active agent in the treatment of said disorder. The dicarboxylic acid can be incorporated in the foamable composition of the present invention in a concentration between about 0.1% and about 25%, more preferably between about 1% and about 20%.

**[0114]** In an embodiment of the present invention, the dicarboxylic acid is azelaic acid, and its concentration in the composition is between 5% and 25%, or between 10% and 20%.

**[0115]** In one or more embodiment, the dicarboxylic acid is present in the composition in an ionized state. The first and second pKa values for a dicarboxylic acid are different from one another. Depending on the pH of the composition and the specific first and second pKa of the dicarboxylic acid, said dicarboxylic acid can be non-ionized (both carboxy groups are in their acid state); semi-ionized (one carboxy group is in an acid state and the second is in an anionic state); or doubly-ionized, wherein both carboxy groups are anionic. For example, in maleic acid the first pKa is 1.9 and the second pKa is 4.4. Therefore, if the pH of the composition is between about 2 and about 4.3, the maleic acid is mostly semi-ionized and at pH above 4.5 the maleic acid is mostly doubly-ionized. Likewise, in the case of azelaic acid the first pKa is about 4.5 and the second pKa is about 5.3. Therefore, if the pH of the composition is below 4.5, the azelaic acid is non-ionized; between about 4.5 and about 5.3, it is mostly semi-ionized and at a pH above 5.3, the azelaic acid is mostly doubly-ionized.

**[0116]** The ionization state of the dicarboxylic acid has influence on its therapeutic potential. On one hand, if the dicarboxylic acid is doubly anionic, its penetration into the skin will be very low, due to the lipophilic nature of the skin. On the other hand, the non-ionic state is available at very low (acidic) pH values, which can cause skin irritation.

**[0117]** Hence, in one or more embodiments, the pH of the composition is adjusted to a value between the first and second pKa values of the dicarboxylic acid. For example, in the case of azelaic acid, the pH is adjusted in the range from about 2.0 to about 4.5, preferably in the range from about 3.0 to about 4.5. Thus, in an embodiment of the present invention, the dicarboxylic acid is azelaic acid, and the pH of the composition is adjusted in the range from about 4.0 to about 6.0, preferably in the range from about 4.5.0 to about 5.3.

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**[0118]** Dicarboxylic acid esters are considered excellent emollients and their inclusion in a composition which is intended for topical application contributes to the overall improvement of skin condition. Emollient dicarboxylic esters typically include an alkyl alcohol moiety, wherein said alkyl alcohol has a carbon chain of at least one or two or more carbon atoms. In certain embodiments, the alkyl alcohol is a branched alkyl, such as isopropyl alcohol; and in other embodiments the alkyl alcohol has a long carbon backbone, e.g., a carbon chain length of 6-18.

**[0119]** Dicarboxylic acid esters can be complex substances. One example is TU 2100 (Nonanedioic acid, bis[(2-(ethoxycarbonyl)phenyl] ester). It is also known as Azelaoyl di(ethyl salicylate) and has a CAS Registry Number: [207972-39-2] and is a solid. TU-2100 is a "non-simple" diester; with a high molecular weight, and a melting point of 34-36, which is relatively low with reference to its molecular weight.

**[0120]** Non-limiting examples of emollient dicarboxylic acid esters include diisobutyl adipate, diisopropyl adipate, diisopropyl sebacate, diisosteary dimer dilinoleate, diisostearyl fumerate, diisopropyl dimerate, diethyl adipate, diethyl sebacate, diethylhexyl adipate, diethylhexyl malate, dioctyl malate, diethyl succinate, and dioctyl sebacate. Other diccarboxylic acid esters are dimethyl phthalate, diethyl phthalate, diethyl sebacate, diisopropyl dimerate, dibutyl sebacate, dibutyl phthalate and dioctyl phthalate. Additionally dicarboxylic acid esters are capable of solubilizing active components which are difficult to dissolve by other oils. Furthermore, certain dicarboxylic acid esters, such as diisopropyl adipate and dimethyl sebacate are known to enhance the skin penetration of active agents. Hence in an embodiment of the present invention, the dicarboxylic acid ester is incorporated in the foamable composition in an amount, suitable to exert its emollient effect, solubilizing effect or skin penetration enhancing effect. In one or more embodiments, the dicarboxylic acid ester is incorporated in the foamable composition of the present invention in a concentration between about 0.1% and about 30%, more preferably between about 1% and about 25%.

**[0121]** In one embodiment, the dicarboxylic acid ester is diisopropyl adipate (DISPA), in an amount between about 0.1% and about 30%, or about 1% and about 25%.

**[0122]** As can be appreciated by the discussion above, there is a varied range of dicarboxylic acids and esters; some are soild, some are liquid, some are water soluble, some are slightly soluble and others are insoluble in water. There is also a varied range of functions and physical properties. Some are active agents and others are solvents and some are penetration enhancers. The challenges of making a uniform solution of solid DCA's wihout crystal formation or precipitation or a uniform suspension of insoluble agent, or using a DCA to solubilise a substance which is otherwise insoluble or as an emollient or as a penetration enhancer or more than one of them are as varied as their different natures and properties as may be appreciated by a man of the art. In other words each agent has its own properties and challenges which are interrelated to the objectives and other ingredients of the formulation

**[0123]** The sensory properties of foams containing a dicarboxylic acid or a dicarboxylic acid ester are favorable, as revealed by consumer panel tests.

**Foam adjuvant**

**[0124]** Optionally, the foamable vehicle further includes a foam adjuvant selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain; a fatty acid having 16 or more carbons in their carbon chain; fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; a fatty alcohol having at least one double bond; a fatty acid having at least one double bond; a branched fatty alcohol; a branched fatty acid and a fatty acid substituted with a hydroxyl group.



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**Additional organic carrier**

**[0125]** Optionally, the foamable vehicle further includes at least one additional organic carrier selected from the group consisting of a hydrophobic organic carrier, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight. The hydrophobic solvent and/or the emollient can be selected from the group consisting of mineral oil, triglycerides, capric/caprylic triglyceride, alkyl esters of fatty acids such as isopropyl palmitate, isopropyl isostearate, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, maleated soybean oil, unsaturated or polyunsaturated oils, such as olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzigium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils; essential oils; and silicone oils, such as dimethicone, cyclomethicone, polyalkyl siloxane, polyaryl siloxane, polyalkylaryl siloxane, a polyether siloxane copolymer and a poly(dimethylsiloxane)-(diphenyl-siloxane) copolymer.

**[0126]** In an embodiment of the present invention, the organic carrier is a polypropylene glycol alkyl ether (PPG alkyl ether). PPG alkyl ethers are liquid, water-insoluble propoxylated fatty alcohols, having the molecular formula of $RO(CH_2CHOCH_3)_n$; wherein "R" is a straight-chained or branched $C_4$ to $C_{22}$ alkyl group; and "n" is in the range between 4 and about 50. They are organic liquids that function as skin-conditioning agent in pharmaceutical and cosmetic formulations. Non-limiting exemplary PPG alkyl ethers include PPG stearyl ethers and PPG Butyl Ether. Preferred PPG alky ethers according to the present invention include PPG-15 Stearyl Ether, PPG-2 Butyl Ether, PPG-9-13 Butyl Ether and PPG-40 Butyl Ether.



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[0127] According to a preferred embodiment, the organic carrier does not contain petrolatum, which is also termed "white petrolatum" and "Vaseline". Petrolatum often forms an impermeable occlusive barrier, so that metabolic products and excreta from damaged tissue are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the treated tissue, so the efficacy of the drug is reduced. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds causing inconvenience to the user, thereby decreasing treatment compliance.

**Polymeric agent**

[0128] The composition of the present invention contains a polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent. A polymeric agent enhances the creation of foam having fine bubble structure, which does not readily collapse upon release from the pressurized aerosol can. The polymeric agent serves to stabilize the foam composition and to control drug residence in the target organ.

[0129] Exemplary polymeric agents include, in a non-limiting manner, naturally-occurring polymeric materials, such as locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, cationic guars, hydroxypropyl guar gum, starch, amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid and hyaluronic acid; chemically modified starches and the like, carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like.

[0130] Additional exemplary polymeric agents include semi-synthetic polymeric materials such as cellulose ethers, such as methylcellulose,

hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxy propylmethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylcellulose carboxymethylhydroxyethylcellulose, and cationic celluloses, carbomer (homopolymer of acrylic acid is crosslinked with an allyl ether pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene, such as Carbopol® 934, Carbopol® 940, Carbopo® 941, Carbopol® 980 and Carbopol® 981, pemulen and aluminum starch octenylsuccinate (ASOS). Polyethylene glycol, having molecular weight of 1000 or more (e.g., PEG 1,000, PEG 4,000, PEG 6,000 and PEG 10,000) also have gelling capacity and while they are considered herein as "secondary polar solvents", as detailed herein, they are also considered polymeric agents.

**[0131]** In one or more embodiments the polymeric agents have emulsifying properties. In certain preferred embodiments the polymeric agent is a derivatized hydrophilic polymer with hydrophobic alkyl moieties Other types that may also a similar stabilizing effect are silicone copolymers and derivatized starch ASOS.

**[0132]** Mixtures of the above polymeric agents are contemplated.

**[0133]** The concentration of the polymeric agent should be selected so that the composition, after filling into aerosol canisters, is flowable, and can be shaken in the canister. In one or more embodiments, the concentration of the polymeric agent is selected such that the viscosity of the composition, prior to filling of the composition into aerosol canisters, is less than 12,000 CPs, and more preferably, less than 10,000 CPs.

**Surface Active Agent**

**[0134]** The composition of the present invention further contains a surface-active agent. Surface-active agents (also termed "surfactants") include any agent linking oil and water in the composition, in the form of emulsion. A surfactant's hydrophilic/lipophilic balance (HLB) describes the emulsifier's affinity toward

water or oil. HLB is defined for non-ionic surfactants. The HLB scale ranges from 1 (totally lipophilic) to 20 (totally hydrophilic), with 10 representing an equal balance of both characteristics. Lipophilic emulsifiers form water-in-oil (w/o) emulsions; hydrophilic surfactants form oil-in-water (o/w) emulsions. The HLB of a blend of two emulsifiers equals the weight fraction of emulsifier A times its HLB value plus the weight fraction of emulsifier B times its HLB value (weighted average). In many cases a single surfactant may suffice. In other cases a combination of two or more surfactants is desired. Reference to a surfactant in the specification can also apply to a combination of surfactants or a surfactant system. As will be appreciated by a person skilled in the art which surfactant or surfactant system is more appropriate is related to the vehicle and intended purpose. In general terms a combination of surfactants is usually preferable where the vehicle is an emulsion. In an emulsion environment a combination of surfactants can be significant in producing breakable forms of good quality. It has been further discovered that the generally thought considerations for HLB values for selecting a surfactant or sufactant combination are not always binding for emulsions and that good quality foams can be produced with a surfactant or surfactant combination both where the HLB values are in or towards the lipophilic side of the scale and where the HLB values are in or towards the hydrophilic side of the scale. Surfactants also play a role in foam formation where the foamable formulation is a single phase composition.

**[0135]** According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 2 and 9, or more than one surface active agent and the weighted average of their HLB values is between about 2 and about 9. Lower HLB values may in certain embodiments be more applicable to water in oil emulsions.

**[0136]** According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 7 and 14, or more than one surface active agent and the weighted average of their HLB

values is between about 7 and about 14. Mid range HLB values may in certain embodiments be more suitable for oil in water emulsions.

**[0137]** According to one or more other embodiments the composition contains a single surface active agent having an HLB value between about 9 and about 19, or more than one surface active agent and the weighted average of their HLB values is between about 9 and about 19. In a waterless or substantially waterless environment a wide range of HLB values may be suitable.

**[0138]** Preferably, the composition of the present invention contains a non-ionic surfactant. Nonlimiting examples of possible non-ionic surfactants include a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59; a polyoxyethylene alkyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, steareths such as steareth 2, brij 21, brij 721, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol and its anhydrides, sorbitan monolaurate, sorbitan monolaurate, a monoglyceride, a diglyceride, isoceteth-20 and mono-, di- and tri-esters of sucrose with fatty acids. In certain embdiments, suitable sucrose esters include those having high monoester content, which have higher HLB values.

**[0139]** In certain embodimens with DCA esters as emollient, surfactants are selected which can provide a close packed sufacant layer separating the oil and water phases. To achieve such objectives combinations of at least two surfactants are selected. Preferrably, they should be complex emulgators and more preferably they should both be of a similar molecular type. For example, a pair of ethers like steareth 2 and steareth 21, or a pair of esters for example, PEG-40 stearate and polysorbate 80. In Certain circumstances POE esters cannot be used and a combination of sorbitan laurate and sorbitan stearate or a combination of sucrose stearic acid ester mixtures and sodium laurate may be used. All these combinations due to heir versatility and strength may also be used satisfactorily and effectively with solutions of DCA's and with

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solid/crystalline suspensions, although the amounts and proportion may be varied according to the formulation and its objectives as will be appreciated by a man of the art.

**[0140]** It has been discovered also that by using a derivatized hydrophilic polymer with hydrophobic alkyl moieties as a polymeric emulsifier such as pemulen it is possible to stabilize the emulsion better about or at the region of phase reversal tension. Other types of derivatized polymers like silicone copolymers, derivatized starch [Aluminum Starch Octenylsuccinate (ASOS)] / [DRY-FLO AF Starch], and derivatized dexrin may also a similar stabilizing effect.

**[0141]** A series of dextrin derivative surfactants prepared by the reaction of the propylene glycol polyglucosides with a hydrophobic oxirane-containing material of the glycidyl ether are highly biodegradable. [Hong-Rong Wang and Keng-Ming Chen, Colloids and Surfaces A: Physicochemical and Engineering Aspects Volume 281, Issues 1-3, 15 June 2006, Pages 190-193] .

**[0142]** Non-limiting examples of non-ionic surfactants that have HLB of about 7 to about 12 include steareth 2 (HLB~4.9); glyceryl monostearate/PEG 100 stearate ( Av HLB~11.2); stearate Laureth 4 (HLB~9.7) and cetomacrogol ether (e.g., polyethylene glycol 1000 monocetyl ether).

**[0143]** Non-limiting examples of preferred surfactants, which have a HLB of 4-19 are set out in the Table below:



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| Surfactant | HLB |
|---|---|
| steareth 2 | ~4.9 |
| glyceryl monostearate/PEG 100 stearate | Av ~11.2 |
| Glyceryl Stearate | ~4 |
| Steareth-21 | ~15.5 |
| peg 40 stearate | ~16.9 |
| polysorbate 80 | ~15 |
| sorbitan stearate | ~4.7 |
| laureth 4 | ~9.7 |
| Sorbitan monooleate (span 80) | ~4.3 |
| ceteareth 20 | ~15.7 |
| steareth 20 | ~15.3 |
| ceteth 20 | ~15.7 |
| Macrogol Cetostearyl Ether | ~15.7 |
| ceteth 2 (Lipocol C-2) | ~5.3 |
| PEG-30 Dipolyhydroxystearate | ~5.5 |
| sucrose distearate (Sisterna SP30) | ~6 |
| polyoxyethylene (100) stearate | ~18.8 |

**[0144]** More exemplary stabilizing surfactants which may be suitable for use in the present invention are found below.

**PEG-Fatty Acid Monoester Surfactants**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-30 stearate | Myrj 51 | >10 |
| PEG-40 laurate | Crodet L40 (Croda) | 17.9 |
| PEG-40 oleate | Crodet O40 (Croda) | 17.4 |
| PEG-45 stearate | Nikkol MYS-45 (Nikko) | 18 |
| PEG-50 stearate | Myrj 53 | >10 |
| PEG-100 stearate | Myrj 59, Arlacel 165 (ICI) | 19 |

**PEG-Fatty Acid Diester Surfactants:**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-4 dilaurate | Mapeg .RTM. 200 DL (PPG), Kessco .RTM.PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.) | 7 |
| PEG-4 | distearate Kessco .RTM. 200 DS (Stepan.sub) | 5 |
| PEG-32 dioleate | Kessco .RTM. PEG 1540 DO (Stepan) | 15 |
| PEG-400 dioleate | Cithrol 4DO series (Croda) | >10 |
| PEG-400 disterate | Cithrol 4DS series (Croda) | >10 |
| PEG-20 glyceryl oleate | Tagat .RTM. O (Goldschmidt) | >10 |

**Transesterification Products of Oils and Alcohols**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-30 castor oil | Emalex C-30 (Nihon Emulsion) | 11 |
| PEG-40 hydrogenated castor oil | Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel) | 13 |

**Polyglycerized Fatty Acids, such as:**

| Chemical name | Product example name | LB |
|---|---|---|
| Polyglyceryl-6 dioleate | Caprol .RTM. 6G20 (ABITEC); PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)Hodag | 8.5 |

**PEG-Sorbitan Fatty Acid Esters**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-20 sorbitan monolaurate | Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea) | 17 |
| PEG-20 sorbitan Monopalmitate | Tween 40 (Atlas/ICI), Crillet 2 (Croda) | 16 |
| PEG-20 sorbitan monostearate | Tween-60 (Atlas/ICI), Crillet 3 (Croda) | 15 |
| PEG-20 sorbitan monooleate | Tween-80 (Atlas/ICI), Crillet 4 (Croda) | 15 |

**Polyethylene Glycol Alkyl Ethers**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-2 oleyl ether | oleth-2 Brij 92/93 (Atlas/ICI) | 4.9 |
| PEG-3 oleyl ether | oleth-3 Volpo 3 (Croda) | <10 |
| PEG-5 oleyl ether | oleth-5 Volpo 5 (Croda) | <10 |
| PEG-10 oleyl ether | oleth-10 Volpo 10 (Croda), Brij 96/97 (Atlas/ICI) | 12 |
| PEG-20 oleyl ether | oleth-20 Volpo 20 (Croda), Brij 98/99 (Atlas/ICI) | 15 |
| PEG-4 lauryl ether | laureth-4Brij 30 (Atlas/ICI) | 9.7 |
| PEG-23 lauryl ether | laureth-23Brij 35 (Atlas/ICI) | 17 |
| PEG-10 stearyl ether | Brij 76 (ICI) | 12 |
| PEG-2 cetyl ether | Brij 52 (ICI) | 5.3 |

**Sugar Ester Surfactants**

| Chemical name | Product example name | HLB |
|---|---|---|
| Sucrose distearate | Sisterna SP50, Surfope 1811 | 11 |

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**Sorbitan Fatty Acid Ester Surfactants**

| Chemical name | Product example name | HLB |
|---|---|---|
| Sorbitan monolaurate | Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI) | 8.6 |
| Sorbitan monopalmitate | Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko) | 6.7 |
| Sorbitan monooleate | Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda) | 4.3 |
| Sorbitan monostearate | Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko) | 4.7 |

**[0145]** In one or more embodiments the surface active agent is a complex emulgator in which the combination of two or more surface active agents can be more effective than a single surfactant and provides a more stable emulsion or improved foam quality than a single surfactant. For example and by way of non-limiting explanation it has been found that by choosing say two surfactants, one hydrophobic and the other hydrophilic the combination can produce a more stable emulsion than a single surfactant. Preferably, the complex emulgator comprises a combination of surfactants wherein there is a difference of about 4 or more units between the HLB values of the two surfactants or there is a significant difference in the chemical nature or structure of the two or more surfactants.

**[0146]** Specific non limiting examples of surfactant systems are, combinations of polyoxyethylene alkyl ethers, such as Brij 59 / Brij10; Brij 52 / Brij 10; Steareth 2 / Steareth 20; Steareth 2 / Steareth 21 (Brij 72 / Brij 721); combinations of polyoxyethylene stearates such as Myrj 52 / Myrj 59; combinations of sucrose esters, such as Surphope 1816 / Surphope 1807; combinations of sorbitan esters, such as Span 20 / Span 80; Span 20 / Span 60; combinations of sucrose esters and sorbitan esters, such as Surphope 1811 and Span 60; combinations of liquid polysorbate detergents and PEG compounds, such as Tween 80 / PEG-40 stearate; methyl glucaso sequistearate; polymeric emulsifiers, such as



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Permulen (TRI or TR2); liquid crystal systems, such as Arlatone (2121), Stepan (Mild RM1), Nikomulese (41) and Montanov (68) and the like.

**[0147]** In certain embodiments the surfactant is preferably one or more of the following: a combination of steareth-2 and steareth-21 on their own or in combination with glyceryl monostearate (GMS); in certain other embodiments the surfactant is a combination of polysorbate 80 and PEG-40 stearate. In certain other embodiments the surfactant is a combination of glyceryl monostearate/PEG 100 stearate. In certain other embodiments the surfactant is a combination of two or more of stearate 21, PEG 40 stearate, and polysorbate 80. In certain orher embodiments the surfactant is a combination of two or more of laureth 4, span80, and polysorbate 80. In certain other embodiments the surfactant is a combination of two or more of GMS and ceteareth. In certain other embodiments the surfactant is a combination of two or more of steareth 21, ceteareth 20, ceteth 2 and laureth 4 In certain other embodiments the surfactant is a combination of ceteareth 20 and polysorbate 40 stearate. In certain orther embodiments the surfactant is a combination of span 60 and GMS.

**[0148]** In certain other embodiments the surfactant is one or more of sucrose stearic acid esters, sorbitan laureth, and sorbitan stearate.

**[0149]** In one or more embodiments the stability of the composition can be improved when a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed. The ratio between the at least one non-ionic surfactant having HLB of less than 9 and the at least one non-ionic surfactant having HLB of equal or more than 9, is between 1:8 and 8:1, or at a ratio of 4:1 to 1:4. The resultant HLB of such a blend of at least two emulsifiers is preferably between about 9 and about 14.

**[0150]** Thus, in an exemplary embodiment, a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed, at a ratio of between 1:8 and

8:1, or at a ratio of 4:1 to 1:4, wherein the HLB of the combination of emulsifiers is preferably between about 5 and about 18.

**[0151]** In certain cases, the surface active agent is selected from the group of cationic, zwitterionic, amphoteric and ampholytic surfactants, such as sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, sodium lauryl sulfate, triethanolamine lauryl sulfate and betaines.

**[0152]** Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two incompatible components on a nanometer scale. Soap is an everyday example of a lyotropic liquid crystal. Certain types of surfactants tend to form lyotropic liquid crystals in emulsions interface (oil-in-water) and exert a stabilizing effect

**[0153]** In one or more embodiments the surfactant is a surfactant or surfactant combination is capable of or which tends to form liquid crystals. Surfactants which tend to form liquid crystals may improve the quality of foams. Non limiting examples of surfactants with postulated tendency to form interfacial liquid crystals are: phospholipids, alkyl glucosides, sucrose esters, sorbitan esters.

**[0154]** In one or more embodiments the at least one surface active agent is liquid.

**[0155]** In one or more embodiments the at least one surface active agent is solid, semi solid or waxy.

**[0156]** It should be noted that HLB values may not be so applicable to non ionic surfactants, for example, with liquid crystals or with silicones. Also HLB



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values may be of lesser significance in a waterless or substantially non-aqueous environment.

**[0157]** In one or more embodiments the surfactant can be, a surfactant system comprising of a surfactant and a co surfactant, a waxy emulsifier, a liquid crystal emulsifier, an emulsifier which is solid or semi solid at room temperature and pressure, or combinations of two or more agents in an appropriate proportion as will be appreciated a person skilled in the art. Where a solid or semi solid emulsifier combination is used it can also comprise a solid or semi solid emulsifier and a liquid emulsifier.

**[0158]** In one or more embodiments of the present invention, the surface-active agent includes at least one non-ionic surfactant. Ionic surfactants are known to be irritants. Therefore, non-ionic surfactants are preferred in applications including sensitive tissue such as found in most mucosal tissues, especially when they are infected or inflamed. Non-ionic surfactants alone can provide formulations and foams of good or excellent quality in the carriers and compositions of the present invention.

**[0159]** Thus, in a preferred embodiment, the surface active agent, the composition contains a non-ionic surfactant. In another preferred embodiment the composition includes a mixture of non-ionic surfactants as the sole surface active agent. Yet, in additional embodiments, the foamable composition includes a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio in the range of about 100:1 to 6:1. In one or more embodiments, the non-ionic to ionic surfactant ratio is greater than about 6:1, or greater than about 8:1; or greater than about 14:1, or greater than about 16:1, or greater than about 20:1. In further embodiments, surface active agent comprises a combination of a non-ionic surfactant and an ionic surfactant, at a ratio of between 1:1 and 20:1

**[0160]** In one or more embodiments of the present invention, a combination of a non-ionic surfactant and an ionic surfactant (such as sodium lauryl sulphate and cocamidopropylbetaine) is employed, at a ratio of between 1:1 and 20:1, or

at a ratio of 4:1 to 10:1; for example, about 1:1, about 4:1, about 8:1, about 12:1, about 16:1and about 20:1 or at a ratio of 4:1 to 10:1, for example, about 4:1, about 6:1, about 8:1 and about 10:1.

**[0161]** In selecting a suitable surfactant or combination thereof it should be borne in mind that the upper amount of surfactant that may be used may be limited by the shakability of the composition. If the surfactant is non liquid, it can make the formulation to viscous or solid. This can be particularly significant if the formulation has high molecular weight, e.g., a high molecular weight PEG or polymeric agents or petroleum or if the surfactants are large. Solvents and polymeric agents which have high molecular weight and are very viscous or solid or waxy (e.g., Peg 1500, 2000, etc. or petrolatum) can exacerbate the effect of a waxy or solid surfactant on shakability or flowability In general terms, as the amount of non-liquid surfactant is increased the shakability of the formulation reduces until a limitation point is reached where the formulation becomes non shakable and unsuitable. Thus in one embodiment, an effective amount of surfactant may be used provided the formulation remains shakable. In other certain exceptional embodiments the upper limit may be determined by flowability such as in circumstances where the composition is marginally or apparently non-shakable. The formulation is sufficiently flowable to be able to flow through an actuator valve and be released and still expand to form a good quality foam.

**[0162]** In certain embodiments of the present invention the amount of surfactant or combination of surfactants is between about 0.05% to about 20%; between about 0.05% to about 15%. or between about 0.05% to about 10%. In a preferred embodiment the concentration of surface active agent is between about 0.2% and about 8%. In a more preferred embodiment the concentration of surface active agent is between about 1% and about 6%.

**[0163]** In some embodiments, it is desirable that the surface active agent does not contain a polyoxyethylene (POE) moiety, such as polysorbate surfactants, POE fatty acid esters, and POE alkyl ethers, because the active agent is incompatible with such surface active agents. For example, the active agent

pimecrolimus is not stable the presence of POE moieties, yet benefits greatly from the use of dicarboxylic esters as penetration enhancers. In such cases, alternative surface active agents are employed. In an exemplary manner, POE – free surfactants include non-ethoxylated sorbitan esters, such as sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate and sorbitan sesquioleate; glycerol fatty acid esters, such as glycerol monostearate and glycerol monooleate; mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), sucrose stearate, sucrose distearate sucrose palmitate and sucrose laurate; and alkyl polyglycosides, such as lauryl diglucoside.

**[0164]** If the composition as formulated is a substantially non shakable composition it is nevertheless possible as an exception in the scope of the present invention for the formulation to be flowable to a sufficient degree to be able to flow through an actuator valve and be released and still expand to form a good quality foam. This surprising and unusual exception may be due one or more of a number of factors such as the high viscosity, the softness, the lack of crystals, the pseudoplastic or semi pseudo plastic nature of the composition and the dissolution of the propellant into the composition.

**[0165]** In one or more embodiments of the present invention, the surface-active agent includes mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), prepared from sucrose and esters of fatty acids or by extraction from sucro-glycerides. Suitable sucrose esters include those having high monoester content, which have higher

Phase inversion and tension

**[0166]** Phase inversion is a factor in the preparation and stabilization of emulsions and can be both an aid and a detriment. Phase inversion involves the change of emulsion type from o/w to w/o or vice versa. Prior to phase inversion occurring there is a tension in the emulsion which if destabilized or driven will lead to phase inversion and if controlled or ameliorated or dissipated will result in



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a more stable emulsion. The occurrence of phase inversion during preparation can be a sign of instability. If controlled, it can result in a finer product but if due to other factors after the the emulsion was prepared it can cause problems. Inversion can occur by for example adding calcium chloride to an o/w emulsion stabilized with sodium stearate to form calcium stearate. Inversion can also occur as the product of changes to the phase- volume ratio. For example if a small amount of water is added to surfactant mixed with oil and agitated aw/o emulsion is formed As the amount of water added is gradually increased a point will be reached where the water and emulsifier envlop the oil as small droplets to form an o/w emulsion. The amount of each ingredient including the surfactants will have their part to play in the phenomenum.

Substantially Alcohol-Free

**[0167]** According to one or more embodiments, the foamable composition is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butaneol, iso-butaneol, t-butaneol and pentanol, are considered less desirable solvents or polar solvents due to their skin-irritating effect. Thus, the composition is substantially alcohol-free and includes less than about 5% final concentration of lower alcohols, preferably less than about 2%, more preferably less than about 1%.

Substantially Non Aqueous

**[0168]** In certain cases, the active agent degrades in the presence of water, and therefore, in such cases the present of water in the composition is not desirable. Thus, in certain preferred embodiments, the composition is substantially non-aqueous. The term "substantially non-aqueous" or "substantially waterless" is intended to indicate that the composition has a water content below about 5%, preferably below about 2%, such as below about 1.5%. In certain other preferred embodiments the composition is non aqueous or waterless.

**[0169]** By non aqueous or waterless is meant that the composition contains no or substantially no, free or unassociated or absorbed water. It will be understood by a person of the art that the waterless solvents and substances miscible with them of the present invention can be hydrophilic and can contain water in an associated or unfree or absorbed form and may absorb water from the atmosphere and the ability to do so is its hygroscopic water capacity. It is intended that essentially non-aqueous formulations are included within its scope such that the formulations may have present a small amount of water. In some embodiments the composition ingredients are pretreated to reduce, remove or eliminate any residual or associated or absorbed water.

Shakability

**[0170]** 'Shakability' means that the composition contains some or sufficient flow to allow the composition to be mixed or remixed on shaking. That is, it has fluid or semi fluid properties. In some very limited cases possibly aided by the presence of silicone it may exceptionally be possible to have a foamable composition which is flowable but not apparently shakable.

Breakability

**[0171]** A breakable foam is one that is thermally stable, yet breaks under sheer force.

**[0172]** The breakable foam of the present invention is not "quick breaking", i.e., it does not readily collapse upon exposure to body temperature environment. Sheer-force breakability of the foam is clearly advantageous over thermally induced breakability, since it allows comfortable application and well directed administration to the target area.

**Modulating Agent**

**[0173]** The term modulating agent is used to describe an agent which can improve the stability of or stabilize a foamable carrier or composition and or an



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active agent by modulating the effect of a substance or residue present in the carrier or composition.

**[0174]** In one or more embodiments the modulating agent is used in a water in oil or oil in water emulsion. In one or more other embodiments the modulating agent is used in a unique waterless emulsion.

**[0175]** In certain embodiments the substance or residue may for example be acidic or basic and potentially alter pH in an emulsion environment or it may be one or more metal ions which may act as a potential catalyst in an emulsion environment.

**[0176]** In certain other embodiments the substance or residue may for example be acidic or basic and potentially alter an artificial pH in a waterless or substantially non aqueous environment or it may be one or more metal ions which may act as a potential catalyst in a waterless or substantially non aqueous environment.

**[0177]** In one or more embodiments the modulating agent is used to describe an agent which can affect pH in an aqueous solution. The agent can be any of the known buffering systems used in pharmaceutical or cosmetic formulations as would be appreciated by a man of the art. It can also be an organic acid, a carboxylic acid, a fatty acid an amino acid, an aromatic acid, an alpha or beta hydroxyl acid an organic base or a nitrogen containing compound.

**[0178]** In one or more further embodiments the modulating agent is used to describe an agent, which is a chelating or sequestering or complexing agent that is sufficiently soluble or functional in the solvent to enable it to "mop up" or "lock" metal ions.

**[0179]** In an embodiment modulating agent is used to describe an agent which can effect pH in an aqueous solution the term modulating agent more particularly means an acid or base or buffer system or combinations thereof, which is introduced into or is present in and acts to modulate the ionic or polar

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characteristics and any acidity or basesity balance of an emulsion carrier, composition, foamable carrier or foamable composition or resultant foam of the present invention.

**[0180]** In other embodiments modulating agent is used to describe an agent which can effect pH in an aqueous solution the term modulating agent more particularly means an acid or base or buffer system or combinations thereof, which is introduced into or is present in and acts to modulate the ionic or polar characteristics and any acidity or basesity balance of a waterless or substantially non aqueous carrier, composition, foamable carrier or foamable composition or resultant foam of the present invention.

**[0181]** The substance or residue can be introduced into the formulation from any one or more of the ingredients, some of which themselves may have acidic or basic properties. For example the polymer or solvent may contain basic residues in which case it may be desirable or beneficial to add an acid. Alternatively the surfactant may contain some acid residues in which case the addition of a base may be desirable and beneficial. In some cases more than one ingredient may contain residues which may ameliorate or compound their significance. For example if one ingredient provided weak acid residues and another stronger acid residues the pH in an emulsion environment (or artificial pH in a waterless environment) should be lower. In contrast if one residue was acid and the other basic the net effect in the formulation maybe significantly reduced. In some circumstances the active ingredient may favor an acidic pH or more significantly may need to be maintained at a certain acidic pH otherwise it may readily isomerize, chemically react or breakdown, in which case introducing acidic components such as an acidic polymer might be of help. In an embodiment of the present invention sufficient modulating agent is added to achieve a pH in which the active agent is preferably stable. In another embodiment of the present invention sufficient modulating agent is added to achieve an artificial pH in which the active agent is preferably stable.



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**[0182]** The terms pH, pKa, and pKb, buffers and the like are used in classical measurements of an aqueous solution. Such measurements are artificial in a waterless environment. Nevertheless, reference to and description below of such terms are made for convenience and clarity, since such terms are well defined and understood with reference to aqueous solutions and further due to the lack of an appropriate uniform way of describing and identifying the artificial or virtual pH, pK etc in a waterless environment in relation to the present invention. Although predictions of artificial pH can be made using dilution techniques of measurements of waterless formulations diluted in water they are formulation sensitive and specific and have to be carefully calibrated with complex formulas.

**[0183]** Waterless medium can be polar and protic yet it does not conform to classical ionic behavior.

**[0184]** A buffer, as defined by Van Slyke [Van Slyke, *J. Biol. Chem.* 52, 525 (1922)], is "a substance which by its presence in solution increases the amount of acid or alkali that must be added to cause unit change in pH."

**[0185]** A buffer solution is a solution of a definite pH made up in such a way that this pH alters only gradually with the addition of alkali or acid. Such a solution consists of a solution of a salt of the week acid in the presence of the three acid itself. The pH of the solution is determined by the dissociation equilibrium of the free acid.

**[0186]** An acid can be a strong acid or a weak acid. A strong acid is an acid, which is a virtually 100% ionized in solution. In contrast, a week acid is one which does not ionize fully. When it is dissolved in water. The lower the value for pKa, the stronger is the acid and likewise, the higher the value for pKa the weaker is the acid.

**[0187]** A base can be a strong base or a weak base. A strong base is something, which is fully ionic with 100% hydroxide ions. In contrast, a weak base is one which does not convert fully into hydroxide ions in solution. The

lower the value for pKb, the stronger is the base and likewise, the higher the value for pKb the weaker is the base.

**[0188]** In one or more embodiments of the present invention the modulating agent comprises an organic compound.

**[0189]** In one or more preferred embodiments of the present invention the chelating agent is selected from the group consisting of ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), hydroxyethylenediaminetriacetic acid (HEDTA), nitrilotriacetic acid (NTA), O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid (EGTA), trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CyDTA) or a pharmaceutically acceptable salt thereof (normally as a sodium salt), more preferably EDTA, HEDTA and their salts; most preferably EDTA and its salts.

**[0190]** In one or more embodiments of the present invention a preferred non limiting example of the chelating agent is EDTA. Typically, the chelating and sequestering agent is present in the composition at a level of up to about 5.0%, preferably 1.0 percent, by weight, of the composition.

**[0191]** In one or more embodiments of the present invention the modulating agent may also be a preservative or an antioxidant or an ionization agent. Any preservative, antioxidant or ionization agents suitable for pharmaceutical or cosmetic application may be used. Non limiting examples of antioxidants are tocopherol succinate, propyl galate, butylated hydroxy toluene and butyl hydroxy anisol. Ionization agents may be positive or may be negative depending on the environment and the active agent or composition that is to be protected. Ionization agents may for example act to protect or reduce sensitivity of active agents. Non limiting examples of positive ionization agents are benzyl conium chloride, and cetyl pyridium chloride. Non limiting examples of negative ionization agents are sodium lauryl sulphate, sodium lauryl lactylate and phospholipids.

**Humectant**

**[0192]** A humectant is a substance that helps retain moisture and also prevents rapid evaporation. Non limiting examples are propylene glycol, propylene glycol derivatives, glycerin, hydrogenated starch hydrosylate, hydrogenated lanolin, lanolin wax, D manitol, sorbitol, sodium 2-pyrrolidone-5-carboxylate, sodium lactate, sodium PCA, soluble collagen, dibutyl phthalate, and gelatin. Other examples may be found in the Handbook of Pharmaceutical Additives published by Gower.

**Moisturizers**

**[0193]** A moisturizer, is a substance that helps retain moisture or add back moisture to the skin. Examples are allantoin, petrolatum, urea, lactic acid, sodium PCV, glycerin, shea butter, caprylic/capric/stearic triglyceride, candelilla wax, propylene glycol, lanolin, hydrogenated oils, squalene, sodium hyaluronate and lysine PCA. Other examples may be found in the *Handbook of Pharmaceutical Additives* published by Gower.

**[0194]** Pharmaceutical compositions of the present invention may in one or more embodiments usefully comprise in addition a heumectant or a moisturizer or combinations thereof.

**Polar solvent**

**[0195]** Optionally, the foamable vehicle further includes at least one polar solvent.

**[0196]** A "polar solvent" is an organic solvent, typically soluble in both water and oil. Certain polar solvents, for example propylene glycol and glycerin, possess the beneficial property of a heumectant.

**[0197]** In one or more embodiments, the polar solvent is a heumectant.



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[0198] In one or more embodiments, the polar solvent is a polyol. Polyols are organic substances that contain at least two hydroxy groups in their molecular structure.

[0199] In one or more embodiments, the polar solvent contains an diol (a compound that contains two hydroxy groups in its molecular structure), such as propylene glycol (e.g., 1,2-propylene glycol and 1,3-propylene glycol), butaneediol (e.g., 1,4-butaneediol), butaneediol (e.g., 1,3-butaneediol and 1,4-butenediol), butynediol, pentanediol (e.g., 1,5-pentanediol), hexanediol (e.g., 1,6-hexanediol), octanediol (e.g., 1,8-octanediol), neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol.

[0200] In one or more embodiments, the polar solvent contains a triol (a compound that contains three hydroxy groups in its molecular structure), such as glycerin and 1,2,6-Hexanetriol.

[0201] Other non-limiting examples of polar solvents include pyrrolidones, (such as N-methyl-2-pyrrolidone and 1-methyl-2-pyrrolidinone), dimethyl isosorbide, 1,2,6-hexapetriol, dimethyl sulfoxide (DMSO), ethyl proxitol, dimethylacetamide (DMAc) and alpha hydroxy acids, such as lactic acid and glycolic acid.

[0202] According to still other embodiments, the polar solvent is a polyethylene glycol (PEG) or PEG derivative that is liquid at ambient temperature, including PEG200 (MW (molecular weight) about 190-210 kD), PEG300 (MW about 285-315 kD), PEG400 (MW about 380-420 kD), PEG600 (MW about 570-630 kD) and higher MW PEGs such as PEG 4000, PEG 6000 and PEG 10000 and mixtures thereof.

[0203] Polar solvents are known to enhance the penetration of active agent into the skin and through the skin, and therefore, their inclusion in the composition of the present invention can be desirable, despite their undesirable skin drying and irritation potential. There is at one level a commonality between



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the different polar solvents and their penetration enhancement properties. Lower molecular weight alcohols can sometimes be more potent as a solvent, for example by extracting lipids from the skin layers more effectively, which characteristic can adversely affect the skin structure and cause dryness and irritation. Therefore the selection of lower molecular weight alcohols is ideally avoided.

**[0204]** Polar solvents, such as detailed below possess high solubilizing capacity and contribute to the skin penetration of an active agent. Non limiting examples include dimethyl isosorbide polyols, such as glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, oleyl alcohol, alpha-hydroxy acids, such as lactic acid and glycolic acid, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, alkanols, such as dialkylamino acetates, and admixtures thereof. In certain preferred embodiments, the polar solvent is selected from the group consisting of dimethyl isosorbide glycerol (glycerin), propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

**Skin penetration enhancer**

**[0205]** A "skin penetration enhancer", also termed herein "penetration enhancer," is an organic solvent, typically soluble in both water and oil. Examples of penetration enhancer include polyols, such as glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, terpen-ols, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, hexylene glycol, other glycols, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, dimethylisosorbide, monooleate of ethoxylated glycerides (with 8 to 10 ethylene oxide units), azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, esters, such as isopropyl myristate/palmitate, ethyl acetate,



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butyl acetate, methyl proprionate, capric/caprylic triglycerides, octylmyristate, dodecyl-myristate; myristyl alcohol, lauryl alcohol, lauric acid, lauryl lactate ketones; amides, such as acetamide oleates such as triolein; various alkanoic acids such as caprylic acid; lactam compounds, such as azone; alkanols, such as dialkylamino acetates, and admixtures thereof.

**[0206]** According to one or more embodiments, the penetration enhancer is a polyethylene glycol (PEG) or PEG derivative that is liquid at ambient temperature

**Potent Solvent**

**[0207]** In one or more embodiments of the present invention, the foamable composition includes a potent solvent, in addition to or in place of one of the hydrophobic solvents, polar solvents or emollients of the composition. A potent solvent is a solvent other than mineral oil that solubilizes a specific active agent substantially better than a hydrocarbon solvent such as mineral oil or petrolatum. For example, a potent solvent solubilizes the active agent 5 fold better than a hydrocarbon solvent; or even solubilizes the active agent 10-fold better than a hydrocarbon solvent.

**[0208]** In one or more embodiments of the present invention, the composition includes at least one active agent in a therapeutically effective concentration; and at least one potent solvent in a sufficient amount to substantially solubilize the at least one active agent in the composition. The term "substantially soluble" means that at least 95% of the active agent has been solubilized, i.e., 5% or less of the active agent is present in a solid state. In one or more embodiments, the concentration of the at least one potent solvent is more than about 40% of the at least one solvent of the composition of the present invention; or even more than about 60%.

**[0209]** Non-limiting examples of pairs of active agent and potent solvent include: Betamethasone valerate: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol; Hydrocortisone butyrate: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol; Metronidazole:

Practically insoluble in mineral oil (<0.01%); soluble more than 1% in dimethyl isosrbide; Ketoconazole: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol, propylene glycol and dimethyl isosrbide; Mupirocin: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol, hexylene glycol, dimethyl isosorbide, propylene glycol and polyethylene glycol 400 (PEG 400); Meloxicam, a nonsteroidal anti-inflammatory agent: Practically insoluble in mineral oil (<0.001%); soluble in propylene glycol: 0.3 mg/mL; and in PEG 400: 3.7 mg/mL; and Progesterone: Practically insoluble in mineral oil (<0.001%); soluble in PEG 400: 15.3 mg/mL.

**[0210]** A non-limiting exemplary list of solvents that can be considered as potent solvents includes polyethylene glycol, propylene glycol, hexylene glycol, butaneediols and isomers thereof, glycerol, benzyl alcohol, DMSO, ethyl oleate, ethyl caprylate, diisopropyl adipate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, isosorbide derivatives, such as dimethyl isosorbide, glycofurol and ethoxydiglycol (transcutol) and laurocapram .

**[0211]** The use of a potent solvent in a foam composition provides an improved method of delivering poorly soluble therapeutic agents to a target area. It is known that low drug solubility results in poor bioavailability, leading to decreased effectiveness of treatment. Foam compositions of the present invention, for which the solvent includes a potent solvent, increase the levels of the active agent in solution and thus, provide high delivery and improved therapy.

**[0212]** Potent solvents, as defined herein, are usually liquid. Formulations comprising potent solvents and active agents are generally disadvantageous as therapeutics, since their usage involves unwanted dripping and inconvenient method of application; resulting in inadequate dosing. Surprisingly, the foams of the present invention, which are drip-free, provide a superior vehicle for such active agents, enabling convenient usage and accurate effective dosing.

**[0213]** In one or more embodiments of the present invention the present invention the foamable pharmaceutical composition may additionally include a

mixture of two or more of the solvents selected from the group of hydrophobic solvents, silicone oils, emollients, polar solvents and potent solvents in an appropriate proportion as would be appreciated to a person skilled in the art.

**[0214]** In one or more embodiments of the present invention, the PPG alkyl ether may act as a potent solvent

**Additional components**

**[0215]** In an embodiment of the present invention, a composition of the present invention includes one or more additional components. Such additional components include but are not limited to anti perspirants, anti-static agents, buffering agents, bulking agents, chelating agents, cleansers, colorants, conditioners, deodorants, diluents, dyes, emollients, fragrances, hair conditioners, humectants, pearlescent aids, perfuming agents, permeation enhancers, pH-adjusting agents, preservatives, protectants, skin penetration enhancers, softeners, solubilizers, sunscreens, sun blocking agents, sunless tanning agents, viscosity modifiers and vitamins. As is known to one skilled in the art, in some instances a specific additional component may have more than one activity, function or effect.

**Propellants**

**[0216]** Suitable propellants include volatile hydrocarbons such as butane, propane, isobutane and fluorocarbon gases, or mixtures thereof.

**[0217]** The propellant makes up about 5-25 wt% of the foamable composition. The propellants are used to generate and administer the foamable composition as a foam. The total composition including propellant, foamable compositions and optional ingredients is referred to as the foamable composition.

**[0218]** Alcohol and organic solvents render foams inflammable. It has been surprisingly discovered that fluorohydrocarbon propellants, other than chloro-fluoro carbons (CMCs), which are non-ozone-depleting propellants, are

particularly useful in the production of a non-flammable foamable composition. A test according to European Standard prEN 14851, titled "Aerosol containers - Aerosol foam flammability test" revealed that compositions containing an organic carrier that contains a hydrophobic organic carrier and/or a polar solvent, which are detected as inflammable when a hydrocarbon propellant is used, become non-flammable, while the propellant is an HFC propellant.

**[0219]** Such propellants include, but are not limited to, hydrofluorocarbon (HFC) propellants, which contain no chlorine atoms, and as such, fall completely outside concerns about stratospheric ozone destruction by chlorofluorocarbons or other chlorinated hydrocarbons. Exemplary non-flammable propellants according to this aspect of the invention include propellants made by DuPont under the registered trademark Dymel, such as 1,1,1,2 tetrafluorethane (Dymel 134), and 1,1,1,2,3,3,3 heptafluoropropane (Dymel 227). HFCs possess Ozone Depletion Potential of 0.00 and thus, they are allowed for use as propellant in aerosol products.

**[0220]** Notably, the stability of foamable emulsions including HFC as the propellant can be improved in comparison with the same composition made with a hydrocarbon propellant.

**[0221]** In one or more embodiments foamable compositions comprise a combination of a HFC and a hydrocarbon propellant such as n-butanee or mixtures of hydrocarbom propellants such as propane , ispbutane and butane.

**MICROEMULSIONS AND NANOEMULSIONS**

**[0222]** Microemulsions and nanoemulsion are monophasic, transparent (or slightly translucent) dispersions of oil and water. Unlike conventional emulsions, microemulsions and nanoemulsion are thermodynamically stable, making them a favorable vehicle for pharmaceutical compositions, which have to maintain stability for long periods of time. They and a method of manufacture are more particularly described in US2006/0233721 which is incorporated herein by way of



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reference. As will be appreciated by a man of the art the methodology may be adapted according to the type of carrier composition.

**AGING**

**[0223]** In order to project the potential shelf life and stability of the compositions and their ingredients particularly active or benefit agents the compositions can subjected to a number of tests, including centrifugation to look for resistance to creaming, phase separation; one or more freeze thaw cycles, standing at room and higher temperatures as an indicator of resistance to aging.

**Composition and Foam Physical Characteristics and Advantages**

**[0224]** A pharmaceutical or cosmetic composition manufactured using the foamable carrier of the present invention is very easy to use. When applied onto the afflicted body surface of mammals, i.e., humans or animals, it is in a foam state, allowing free application without spillage. Upon further application of a mechanical force, e.g., by rubbing the composition onto the body surface, it freely spreads on the surface and is rapidly absorbed.

**[0225]** The foamable composition of the present invention is stable, having an acceptable shelf-life of at least one year, or preferably, at least two years at ambient temperature, as revealed in accelerated stability tests. The foamable compositions according to the present invention are stable. Following accelerated stability studies, they demonstrate desirable texture; they form fine bubble structures that do not break immediately upon contact with a surface, spread easily on the treated area and absorb quickly.

**[0226]** The composition should also be free flowing, to allow it to flow through the aperture of the container, e.g., and aerosol container, and create an acceptable foam.

**[0227]** Foam quality can be graded as follows:



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Grade E (excellent): very rich and creamy in appearance, does not show any bubble structure or shows a very fine (small) bubble structure; does not rapidly become dull; upon spreading on the skin, the foam retains the creaminess property and does not appear watery.

Grade G (good): rich and creamy in appearance, very small bubble size, "dulls" more rapidly than an excellent foam, retains creaminess upon spreading on the skin, and does not become watery.

Grade FG (fairly good): a moderate amount of creaminess noticeable, bubble structure is noticeable; upon spreading on the skin the product dulls rapidly and becomes somewhat lower in apparent viscosity.

Grade F (fair): very little creaminess noticeable, larger bubble structure than a "fairly good" foam, upon spreading on the skin it becomes thin in appearance and watery.

Grade P (poor): no creaminess noticeable, large bubble structure, and when spread on the skin it becomes very thin and watery in appearance.

Grade VP (very poor): dry foam, large very dull bubbles, difficult to spread on the skin.

**[0228]** Topically administrable foams are typically of quality grade E or G, when released from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously immediately upon discharge from the container. The finer foam structure looks and feels smoother, thus increasing its usability and appeal.

**[0229]** As further aspect of the foam is breakability. The breakable foam is thermally stable, yet breaks under sheer force. Sheer-force breakability of the foam is clearly advantageous over thermally induced breakability. Thermally sensitive foams immediately collapse upon exposure to skin temperature and,

therefore, cannot be applied on the hand and afterwards delivered to the afflicted area.

**[0230]** Another property of the foam is specific gravity, as measured upon release from the aerosol can. Typically, foams have specific gravity of less than 0.12 g/mL; or less than 0.10 g/mL; or less than 0.08 g/mL, depending on their composition and on the propellant concentration.

**Pharmaceutical composition**

**[0231]** The foamable carrier of the present invention is an ideal vehicle for active pharmaceutical ingredients and active cosmetic ingredients. In the context of the present invention, active pharmaceutical ingredients and active cosmetic ingredients are collectively termed "active agent" or "active agents."

**[0232]** In one or more embodiments, the dicarboxylic acid or dicarboxylic ester is the active ingredient. It can be used in the formulation as a suspended solid or in solution, alone or in combination with other active agents. As is known to one skilled in the art, in some instances a specific active agent may have more than one activity, function or effect.

**[0233]** In one embodiment, the dicarboxylic acid or dicarboxylic acid ester is useful as an antibiotic, an antifungal agent, a keratolytic agent, an inhibitor of the reduction of testosterone to dihydrotestosterone, an inhibitor of the production of sebum in the sebaceous gland, an anti-acne agent, by way of example. Dicarboxylic acids, and azxelaic acid in particular, may be used for the treatment of diaper rash, hyperpigmentary drmatoses, acne, presbyderma of aging skin, hyperhydrosis, ischthyosis, and wrinkling of the skin, anti-tumor agents (for example, in conjunction with vitamins A, E and D), rosacea, a pigmentation disorder, a cell proliferation abnormality a skin infection and a skin inflammation and treatment of corns and callouses due to the anti-keratolytic effects.

**[0234]** In one or more embodiments, the dicarboxylic acid or dicarboxylic ester is used as a solvent for an active agent or as a penetration enhancer for an active agent.

**[0235]** Suitable active agents for use in conjunction with a dicarboxylic acid or a dicarboxylic ester include, but are not limited to, active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, antiyeast agents, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hair growth regulators, hormones, hydroxy acids, immunosuppressants, immunoregulating agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, self tanning agents, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, wound healing agents and wart removers. As is known to one skilled in the art, in some instances a specific active agent may have more than one activity, function or effect.

**[0236]** In one or more embodiments, the formulation additionally includes a steroidal anti-inflammatory agent. The dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the steroid. Exemplary steroidal anti-inflammatory agents include, but are not limited to, corticosteroids such as bydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethsone dipropionate, clobetasol valemate,

desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortmate, mepreddisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof. In an embodiment of the present invention, the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the steroid.

**[0237]** In one embodiment, the formulation additionally includes an immunomodulator. The dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the immunomodulator. Immunomodulators are chemically or biologically-derived agents that modify the immune response or the functioning of the immune system (as by the stimulation of antibody formation or the inhibition of white blood cell activity). Immunomodulators include, among other options, cyclic peptides, such as cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus (rapamycin), verolimus, laflunimus, laquinimod and imiquimod. Such compounds, delivered in the foam of the present invention, are especially advantageous in skin disorders such as psoriasis, eczema and atopic dermatitis, where the large skin areas are to be treated.

**[0238]** In an embodiment of the present invention, the active agent is selected from a dicarboxylic acid and a dicarboxylic acid ester.

**[0239]** Because of the multiple therapeutic properties of dicarboxylic acids and their respective esters, the combination of such dicarboxylic acids or their

respective esters with another active agents can result in a synergistic therapeutic benefit. For example, psoriasis is characterized by a heperkeratinization aspect and an inflammation, and therefore, its treatment can benefit from the combination of a dicarboxylic acid, which is keratolytic and a steroid.

**Fields of Applications**

**[0240]** The foamable carrier of the present invention is suitable for treating any inflicted surface. In one or more embodiments, foamable carrier is suitable for administration to the skin, a body surface, a body cavity or mucosal surface, e.g., the cavity and/or the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum (severally and interchangeably termed herein "target site").

**[0241]** In one embodiment, the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid.

**[0242]** In another embodiment, the disorder is a dermatological disorder that benefits from the use of a dicarboxylic acid or dicarboxylic ester in conjunction with another active agent. The dicarboxylic acid or dicarboxylic ester may benefit by improving the solubility of the active agent or increasing the penetration of the active agent. The dicarboxylic acid or dicarboxylic ester may also provide a synergistic therapeutic effect in combination with the active agent.

**[0243]** By selecting a suitable active agent, or a combination of two or more active agents, the foamable composition of the present invention is useful in treating an animal or a human patient having any one of a variety of dermatological disorders, including dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa,



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carbuncles, paronychial infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, granuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callouses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo.

**[0244]** Likewise, the foamable composition of the present invention is suitable for treating a disorder of a body cavity or mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum. Non limiting examples of such conditions include chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum.



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**[0245]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid.

**[0246]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid ester.

**[0247]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by a topical steroid, and the dicarboxylic acid or dicarboxylic ester provides a beneficial effect by increasing the solubility or penetration of the topical steroid.

**[0248]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by an immunomodulator and the dicarboxylic acid or dicarboxylic ester provides a beneficial effect by increasing the solubility or penetration of the topical immunomodulator.

**[0249]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by an anti-infective agent, such as an antibacterial agent, and antibiotic, an antifungal agent and an antiviral agent, and the dicarboxylic acid or dicarboxylic ester provides a beneficial effect as an anti-infective agent or by increasing the solubility or penetration of the anti-infective agent.

**[0250]** In an embodiment of the present invention, the disorder is a dermatological disorder, which is common in children. Foam is advantageous in the topical treatment of children, who are sensitive to treatment with a cream or ointment.

**[0251]** In an embodiment of the present invention, the disorder is atopic dermatitis and the active agent is a steroid, further including a dicarboxylic acid (DCA) or DCA ester to stabilize or solubilize the topical steroid.

**[0252]** In an embodiment of the present invention, the disorder is psoriasis and the active agent is a steroid, further including a DCA or DCA ester to stabilize or solubilize the topical steroid.

**[0253]** In an embodiment of the present invention, the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises a steroid and an additional non-steroidal active agent, such as a vitamin D derivative, further including a DCA or DCA ester to stabilize or solubilize the topical steroid and/or non-steroidal active agent.

**[0254]** In an embodiment of the present invention, the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises an immunomodulator, further including a DCA or DCA ester to stabilize or solubilize the immunomodulator.

**[0255]** In an embodiment of the present invention, the composition is useful for the treatment of an infection. In one or more embodiments, the composition is suitable for the treatment of an infection, selected from the group of a bacterial infection, a fungal infection, a yeast infection, a viral infection and a parasitic infection.

**[0256]** In an embodiment of the present invention, the composition is useful for the treatment of wound, ulcer and burn.

**[0257]** The composition of the present invention is also suitable for administering a hormone to the skin or to a mucosal membrane or to a body cavity, in order to deliver the hormone into the tissue of the target organ, in any disorder that responds to treatment with a hormone.

**[0258]** Other foamable compositions are described in: U.S. Publication No. 05-0232869, published on October 20, 2005, entitled NONSTEROIDAL IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0205086, published on September 22, 2005, entitled RETINOID IMMUNOMODULATING KIT AND COMPOSITION AND USES

THEREOF; U.S. Publication No. 06-0018937, published on January 26, 2006, entitled STEROID KIT AND FOAMABLE COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0271596, published on December 8, 2005, entitled VASOACTIVE KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0269485, published on November 30, 2006, entitled ANTIBIOTIC KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 07-0020304, published on January 25, 2007, entitled NON-FLAMMABLE INSECTICIDE COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0193789, published on August 31, 2006, entitled FILM FORMING FOAMABLE COMPOSITION; U.S. Patent Application No. 11/732547, filed on April 4, 2007, entitled ANTI-INFECTION AUGMENTATION OF FOAMABLE COMPOSITIONS AND KIT AND USES THEREOF; U.S. Provisional Patent Application No. 60/789186, filed on April 4, 2006, KERATOLYTIC ANTIFUNGAL FOAM; U.S. Provisional Patent Application No. 0/815948, filed on June 23, 2006, entitled FOAMABLE COMPOSITIONS COMPRISING A CALCIUM CHANNEL BLOCKER, A CHOLINERGIC AGENT AND A NITRIC OXIDE DONOR; U.S. Provisional Patent Application No. 60/818634, filed on July 5, 2006, entitled DICARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF; U.S. Provisional Patent Application No. 60/843140, filed on September 8, 2006, entitled FOAMABLE VEHICLE AND VITAMIN PHARMACEUTICAL COMPOSITIONS THEREOF, all of which are incorporated herein by reference in their entirety. More particularly any of the active ingredients; the solvents; the surfactants; foam adjuvants; penetration enhancers; humectants; moisturizers; and other excipients as well as the propellants listed therein can be applied herein and are incorporated by reference.

**[0259]** The following examples further exemplify the benefit agent foamable pharmaceutical carriers, pharmaceutical compositions thereof, methods for preparing the same, and therapeutic uses of the compositions. The examples are for the purposes of illustration only and are not intended to be limiting of the invention. Many variations may be carried out by one of ordinary skill in the art and are contemplated within the full scope of the present invention.

## METHODOLOGY

**[0260]** A general procedure for preparing foamable compositions is set out in WO 2004/037225, which is incorporated herein by reference.

### Emulsion Foam

1. Mix oily phase ingredients and heat to 75°C to melt all ingredients and obtain homogeneous mixture.
2. Mix polymers in water with heating or cooling as appropriate for specific polymer.
3. Add all other water soluble ingredients to water-polymer solution and heat to 75°C.
4. Add slowly internal phase to external phase at 75°C under vigorous mixing and homogenize to obtain fine emulsion. Alternatively the external phase is added slowly to the internal phase.
5. Cool to below 40°C and add sensitive ingredients with mild mixing.
6. Cool to room temperature.

### Waterless Foam

1. Dissolve the polymers in the main solvent with heating or cooling as appropriate for specific polymer. Add the all other ingredients and heat to 75°C to melt and dissolve the various ingredients.
2. Cool to below 40°C and add sensitive ingredients with mild mixing.
3. Cool to room temperature.

**Oily Waterless Foam**

1. Mix all ingredients excluding polymers and heat to 75°C to melt and dissolve and obtain homogeneous mixture.
2. Mix well and cool to below 40°C and add the polymers and sensitive ingredients with moderate mixing.
3. Cool to room temperature.

**Oily Foam with phospholipids and/or water**

1. Swell the phospholipids in the main oily solvent under mixing for at least 20 minutes until uniform suspension is obtained.
2. Add all other ingredients excluding polymers and heat to 75°C to melt and dissolve and obtain homogeneous mixture.
3. Mix well and cool to below 40°C and add the polymers and sensitive ingredients with moderate mixing.
4. Cool to room temperature.
5. In case of polymers dissolved in water or organic solvent, dissolve the polymers in the solvent with heating or cooling as appropriate for specific polymer and add to the oily mixture under vigorous mixing at ~40°C.

Canisters Filling and Crimping

Each aerosol canister is filled with PFF and crimped with valve using vacuum crimping machine.

Pressurizing

Propellant Filling

Pressurizing is carried out using a hydrocarbon gas or gas mixture

Canisters are filled and then warmed for 30 sec in a warm bath at 50°C and well shaken immediately thereafter.

Closure Integrity Test.

Each pressurized canister is subjected to bubble and crimping integrity testing by immersing the canister in a 60°C water bath for 2 minutes. Canisters are observed for leakage as determined by the generation of bubbles. Canisters releasing bubbles are rejected.

**TESTS**

**[0261]** By way of non limiting example the objectives of hardness, collapse time and FTC stability tests are briefly set out below as would be appreciated by a person of the art.

**[0262]** Hardness

LFRA100 instrument is used to characterize hardness. A probe is inserted into the test material. The resistance of the material to compression is measured by a calibrated load cell and reported in units of grams on the texture analyzer instrument display. Preferably at least three repeat tests are made. The textural characteristics of a dispensed foam can effect the degree of dermal penetration, efficacy, spreadability and acceptability to the user. The results can also be looked at as an indicator of softness. Note: the foam sample is dispensed into an aluminum sample holder and filled to the top of the holder.

**[0263]** Collapse Time

Collapse time (CT) is examined by dispensing a given quantity of foam and photographing sequentially its appearance with time during incubation at 36°C. It is useful for evaluating foam products, which maintain structural stability at skin temperature for at least 1 min.

**[0264]** Viscosity

Viscosity is measured with Brookfield LVDV-II + PRO with spindle SC4-25 at ambient temperature and 10, 5 and 1 RPM. Viscosity is usually measured at 10RPM. However, at about the apparent upper limit for the spindle of ~>50,000CP, the viscosity at 1RPM may be measured, although the figures are of a higher magnitude.

**[0265]** FTC (Freeze Thaw Cycles)

To check the foam appearance under extreme conditions of repeated cycles of cooling, heating, (first cycle) cooling, heating (second cycle) etc., commencing with -100°C (24hours) followed by +400°C (24hours) measuring the appearance and again repeating the cycle for up to three times.

**[0266]** Creaming by centrifugation:

1. Principle of test

   The centrifugation used in this procedure serves as a stress condition simulating the aging of the liquid dispersion under investigation. Under these conditions, the centrifugal force applied facilitates the coalescence of dispersed globules or sedimentation of dispersed solids, resulting in loss of the desired properties of the formulated dispersion.

2. Procedure

   2.1. Following preparation of the experimental formulation/s, allow to stand at room temperature for ≥ 24 h.

   2.2. Handle pentane in the chemical hood. Add to each experimental formulation in a 20-mL glass vial a quantity of pentane equivalent to the specified quantity of propellant for that formulation, mix and allow formulation to stand for at least 1 h and not more than 24 h.



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2.3. Transfer each mixture to 1.5 mL microtubes. Tap each microtube on the table surface to remove entrapped air bubbles.

2.4. Place visually balanced microtubes in the centrifuge rotor and operate the centrifuge at 3,000 rpm for 10 min or at 1,000 rpm for 10 min.

**[0267]** Intra-canister uniformity

1. Representative product containers are collected, sample test solutions are prepared and the content of the analyte is determined according to standard methods in the art. Variability of content is characterized as percent difference or relative standard deviation, as appropriate, according to the number of samples evaluated.

2. The results ascertain variability or uniformity within a given container in content of analytes (primarily active pharmaceutical ingredients, but also preservatives) taken from different parts of a pressurized canister drug products

3. Two full canisters were shaken according to product instructions. About 1-3g of Foam was dispensed from each canister and discarded. Foam sufficient for two replicate sample solution preparations was then dispensed into a glass beaker. This represents the initial sample. A middle portion is then dispensed from each canister being about half the canister contents. This middle dispensed portion may be discarded or collected for testing purposes, as necessary. Foam sufficient for two replicate sample solution preparations was then dispensed into a glass beaker. This represents the final sample. A small amount of formulation remains in the canister. The foam samples were stirred to remove gas / air bubbles. From both the initial and final foam portions from each canister 4 separate sample solutions are prepared and analyzed, 2 from the initial portion and 2 from the final portion. The percent difference is calculated as follows:

$$\frac{\text{Difference between content determined in initial \& final portions}}{\text{Mean of content of initial \& final portions}} \times 100$$

and the intra canister uniformity evaluated from the results.

**STOCK COMPOSITIONS**

**[0268]** Non-limiting examples of how stock solutions are made up with and without API. Other stock solutions may be made using the same methodology by simply varying adding or omitting ingredients as would be appreciated by one of the ordinary skills in the art.

**Examples**

**[0269]** The invention is described with reference to the following examples. This invention is not limited to these examples and experiments. Many variations will suggest themselves and are within the full intended scope of the appended claims.

**SECTION A – AQUEOUS**

**A1 – EMOLLIENT FORMULATIONS**

**A1 -** Example 1 – Vehicle composition containing diisopropyl adipate (DISPA)

The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| PHASE | Ingredient | GOG 08 | GOG 09 | GOG 10 | GOG 11 |
|---|---|---|---|---|---|
| | | %w/w | %w/w | %w/w | %w/w |
| Oil Phase (A) | Capric/caprylic triglyceride | | | 10.00 | 10.00 |
| | Diisopropyladipate (DISPA) | 20.00 | 20.00 | 20.00 | 20.00 |
| | Benzyl alcohol | 2.00 | 2.00 | 2.00 | 2.00 |
| | Oleyl alcohol | 20.00 | 20.00 | 10.00 | 10.00 |
| | PPG 15 stearyl ether | 2.00 | 2.00 | 2.00 | 2.00 |
| | Sorbitan laurate | | | | 1.50 |
| | Sorbitan stearate | 4.00 | 4.00 | 2.00 | 2.00 |
| | Stearic acid | 4.00 | 4.00 | 2.00 | |
| | Stearyl alcohol | | | | 3.00 |
| | Pemulen TR2 | 0.05 | | 0.05 | |
| Water Phase (B) | Hydroxypropyl methyl cellulose | | | | 0.15 |
| | Xanthan gum | | | | 0.15 |
| | Sucrose ester | 2.00 | 2.00 | 1.00 | 2.00 |
| | Propylene glycol | 8.00 | 8.00 | 8.00 | 8.00 |
| | Glycerin | 5.00 | 5.00 | 5.00 | 8.00 |
| | TEA | 0.10 | 0.10 | 0.10 | |
| | Water | 37.85 | 32.90 | 37.85 | 31.20 |
| | Foam quality | E | E | G | E |
| | Emulsion stability (10000 RPM) | Stable | Stable | Stable | Stable |

**[0270]** Notes:

- Compositions GOG 08 and GOG 09 contain 20% DISPA and 20% oleyl alcohol to provide (1) high emolliency; (2) high solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.
- Compositions GOG 10 and GOG 11 contain 20% DISPA, 20% oleyl alcohol and 10% capric/caprylic triglyceride to provide (1) enhanced emolliency; (2) high solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.

- The compositions contain about 30% water. Therefore, they provide high skin barrier build-up effect.

- The compositions are oil in water emulsions, despite the fact that there is oil more than water in the formulation. Oil in water emulsion is maintained and stabiized by selecting a surfactant that favors oil in water emulsions over water in oil emulsions. Hence, the skin feeling of the composition is favorable.

- The surfactants, sorbitan laurate, sorbitan stearate and sucrose esters, are POE-free and hence this formulation may be used with active agents that are not compatible with POE.

- The compositions can be used as lotions for topical therapy of an inflammatory skin diorder.

- In order to create a foamable composition, the composition is filled into an aerosol canister and pressurized using a liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

**A1** - Example 2 –Vehicle composition containing diisopropyl adipate (DISPA)

The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.



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| PHASE | Ingredient | GOG 13 %w/w | GOG 14 %w/w | GOG 15 %w/w |
|---|---|---|---|---|
| Oil Phase (A) | Capric/caprylic triglyceride | 10.00 | 10.00 | 10.00 |
| | Diisopropyladipate | 20.00 | | |
| | Dimethyl sebacate | | 20.00 | |
| | Dioctyl malate | | | 20.00 |
| | Benzyl alcohol | 2.00 | 2.00 | 2.00 |
| | Oleyl alcohol | 10.00 | 10.00 | 10.00 |
| | PPG 15 stearyl ether | 2.00 | 2.00 | 2.00 |
| | Sorbitan laurate | | 2.00 | 2.00 |
| | Sorbitan stearate | 2.00 | | |
| | Stearic acid | | | 1.20 |
| | Stearyl alcohol | 3.00 | 1.00 | |
| Water Phase (B) | Hydroxypropyl methyl cellulose | 0.15 | 0.15 | 0.15 |
| | Xanthan gum | 0.15 | 0.15 | 0.15 |
| | Sucrose ester HLB 16 | | | |
| | Sucrose ester HLB 11 | 3.00 | 2.00 | 2.00 |
| | Propylene glycol | 17.70 | 17.70 | 17.70 |
| | Glycerin | | | |
| | TEA | | | 0.06 |
| | Water | 30.00 | 33.00 | 32.74 |

| | | | |
|---|---|---|---|
| Foam quality | E | G | E |
| Emulsion stability (10000 RPM) | Stable | Stable | Stable |

**[0271]** Notes:

- Composition GOG 13 contains 20% DISPA, 10% oleyl alcohol and 10% capric/caprylic triglyceride, to provide (1) enhanced emolliency; (2) high solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.

- Composition GOG 14 contains 20% diethyl sebacate, 10% oleyl alcohol and 10% capric/caprylic triglyceride, to provide (1) enhanced emolliency; (2) high

solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.

- Composition GOG 15 contains 20% dioctyl malate, 10% oleyl alcohol and 10% capric/caprylic triglyceride, to provide (1) enhanced emolliency; (2) high solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.
- The compositions contain about 30% water. Therefore, they provide high skin barrier build-up effect
- The compositions are oil in water emulsions, despite the fact that there is oil more than water in the formulation. Hence, the skin feeling of the composition is favorable.
- The surfactants are POE-free: sorbitan laurate, sorbitan stearate and sucrose esters.
- The compositions can be used as lotions for topical therapy of an inflammatory skin diorder.
- In order to create a foamable composition, the composition is filled into an aerosol canister and pressurized using a liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

**A1** - Example 3 –Vehicle compositions containing 10% to 50% diisopropyl adipate (DISPA) as solvent

**[0272]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | DCA001 | DCA002 | DCA003 | DCA011 |
|---|---|---|---|---|
| diisopropyl adipate (DISPA) | 10.00 | 20.00 | 30.00 | 40.00 |
| Steareth 2 | 3.06 | 3.67 | 4.89 | 4.89 |
| Steareth 21 | 1.94 | 2.33 | 3.11 | 3.11 |
| Carboxy methyl cellulose | 0.50 | 0.50 | 0.50 | 0.50 |
| Water purified | 84.50 | 73.50 | 61.50 | 51.50 |
| **Total** | **100.00** | **100.00** | **100.00** | **100.00** |
| Propellant propane, isobutene and butane mixture | 8.00 | 8.00 | 8.00 | 8.00 |
| | | | | |
| **Appearance:** | | | | |
| foam quality | E | E | E | E |
| color | White | White | White | White |
| odor | No odor | No odor | No odor | No odor |
| density | 0.049 | 0.045 | 0.064 | |
| collapse time | | >300 | >300 | |
| Hardness | | 18.76 | 31.77 | |

**[0273]** Excellent foam formulations were prepared with DISPA, surfactant, and a nominal amount of polymeric agent.

**[0274]** In foamable compositions using less than 40 wt% DISPA, no solvent other than water is required to make foamable composition with resultant excellent foams. The use of a combination of ether-based or ester-based surfactants was found to be useful in forming excellent foams with a minimal number of ingredients. Without being bound by any particular theory or mode of operation, it is believed that the use of non-ionic surfactants with significant hydrophobic and hydrophilic components, increase the emulsifier or foam stabilization characteristics of the composition. Similarly, without being bound by any particular theory or mode of operation,using combinations of surfactants with high and low HLB's to provide a relatively close packed surfactant layer may strengthen the emulsion.

**[0275]** Visual test after addition of water indicated that DCA011 is an oil in water emulsion.

**A1** - Example 4 – Minimal vehicle compositions, containing 40% diisopropyl adipate (DISPA) with and without polymer

**[0276]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | DCA011 | DCA011A |
|---|---|---|
| diisopropyl adipate (DISPA) | 40.00 | 40.00 |
| Steareth 2 | 4.89 | 4.89 |
| Steareth 21 | 3.11 | 3.11 |
| Carboxy methyl cellulose | 0.50 | |
| Water purified | 51.50 | 52.00 |
| **Total** | **100.00** | **100.00** |
| Propellant propane, isobutene and butane mixture | 8.00 | 8.00 |

| **Appearance:** | | |
|---|---|---|
| foam quality | E | E |
| color | White | White |
| odor | No odor | No odor |

**[0277]** Polymeric agents are introduced to improve foam. Surprisingly, it was possible to prepare excellent foam formulations without a polymeric agent from DISPA, surfactant, and water (and without a foam adjuvant or another solvent). This is especially surprising as the use of water in the composition is understood to benefit from the use of a polymeric agent that can thicken or increase the viscosity of the compositions and improve the resultant foam strength.

**[0278]** As in Example 3 and in Example 6, the combination of ether-based or ester-based surfactants was found to be useful in forming excellent foams with a minimal number of ingredients.

**A1** - Example 5 –Vehicle compositions containing about 50% diisopropyl adipate (DISPA) with polymer

**[0279]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | **DCA012** | **DCA013** |
|---|---|---|
| diisopropyl adipate (DISPA) | 46.00 | 50.00 |
| Steareth 2 | 4.58 | |
| Steareth 21 | 2.92 | |
| Isoceteth 20 | | 3.00 |
| Pemulen TR2 | | 0.22 |
| TEA | | 0.12 |
| Carboxy methyl cellulose | 0.50 | |
| Water purified | 46.00 | 46.66 |
| **Total** | **100.00** | **100.00** |
| Propellant propane, isobutene and butane mixture | 8.00 | 8.00 |
| | | |
| **Appearance:** | | |
| foam quality | E | E |
| color | White | White |
| odor | No odor | No odor |

- Increasing the amount of DISPA above 46% resulted in a poor foam and precipitation in formulations containing a polymer. Changing the surfactant to GMS eliminated the precipitation but the foam remained poor. Replacing the carboxy methyl cellulose polymeric agent with carbopol did not result in any improvement.

- Surprisingly, removal of the polymer at 50% DISPA, and steareth 21 and steareth 2 improved the foam quality but did not eliminate the precipitation.

- However, by changing the surfactants and polymeric agents it was possible to increase the level of the DISPA and achieve excellent foams without precipitation.



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- A combination of ether-based or ester-based surfactants was found to be useful in forming excellent foams with a minimal number of ingredients

- It has been discovered also that by using a derivatized hydrophilic polymer with hydrophobic alkyl moieties as a polymeric emulsifier it is possible to stabilize the emulsion better about or at the region of phase reversal tension. Other types of derivatized polymers like silicone copolymers, derivatized starch and derivatized dexrin may also a similar stabilizing effect.

**A1 -** Example 6–Vehicle compositions containing 60% diisopropyl adipate (DISPA) without polymer

**[0280]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | DCA028 | DCA029 | DCA030 | DCA031 |
|---|---|---|---|---|
| diisopropyl adipate | | 60.00 | | 60.00 |
| diethyl sebacate | 60.00 | | 60.00 | |
| Steareth 2 | | | 3.00 | 3.00 |
| Steareth 21 | | | 2.00 | 2.00 |
| PEG-40 Stearate | 4.00 | 4.00 | | |
| Polysorbate 80 | 2.00 | 2.00 | | |
| Water purified | 34.00 | 34.00 | 35.00 | 35.00 |
| **Total** | **100.00** | **100.00** | **100.00** | **100.00** |
| Propellant (1681) | 8.00 | 8.00 | 8.00 | 8.00 |
| | | | | |
| **Appearance:** | | | | |
| foam quality | E | E | E | E |
| color | White | White | White | White |
| odor | No odor | No odor | No odor | No odor |
| 1000 rpm for 10 mins | stable | stable | stable | stable |
| 3000 rpm for 10 mins % creaming | 80% | 80% | stable | 75% |

DCA 028-80% Creaming, 029-80% Creaming, 030-Homogenous, 031-75% Creaming at 3K.

**[0281]** More surprisingly, by removal of the polymer and by reducing the levels of steareth 21 and steareth 2 (ethers) (by about 40 to 50%) it was possible to obtain excellent foams without precipitation at 60% DISPA and at 60% diethyl sebacate. .

**[0282]** Without being bound to any particular theory the physical change in the formulation may be due to DISPA reaching a concentration where phase reversal from o/w to w/o emulsion is possible. Also at this concentration range of DISPA removal of the polymeric agent, which itself can absorb water may –without being bound by any theory - have resulted in additional water being available and perhaps reducing internal emulsion tensions including any resulting from the presence of the polymeric agent and thereby unexpectedly resulting in improved foam quality even though polymeric agents are normally added to strengthen foam quality. Also as the concentration of DISPA increased and consequently the amount of water decreased it appears that the amount of surfactant required reduction as the external water phase is thinner.

**[0283]** It has also been discovered by using a different surfactant (ester based in place of an ether based) system it was possible to achieve compositions that can generate good quality foam and without precipitation with 60% DISPA or 60% diethyl sebacate in the absence of polymer. Addition of small amounts of xantham gum and methocel with 60% DISPA and the ester based surfactants resulted in poor foam.

**[0284]** It further appears to be the case that - without being limited by any theory - for any given emulsion system as the oil phase is increased with a corresponding decrease in the water phase the internal tension or pressure for phase reversal will increase and the point at which the phase reversal can occur can be retarded by selective use of non traditional derivatized polymeric agents with emulsifying properties, such as permulen that can stabilize the formulation and push back the point at which pressure for phase reversal might otherwise occur.

**[0285]** Surprisingly it was observed that more traditional polymeric agents like carboxy methyl cellulose or carbopol or combinations like xantham gum and methocel can interfere with foam formulation at higher levels of dicarboxylic esters.- all these formulations were examined by conductivity, by water addition test and by microscopic examination and were found to be oil in water emulsions despite the fact that the amount of oil phase was approximately double that of the aqueous phase.

**A1 -** Example 7 –Vehicle compositions containing 10% to 45% diethyl sebacate.

**[0286]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | **DCA004** | **DCA005** | **DCA006** | **DCA024** | **DCA025** |
|---|---|---|---|---|---|
| diethyl sebacate | 10.00 | 20.00 | 30.00 | 40.00 | 45.00 |
| Steareth 2 | 4.00 | 5.00 | 5.33 | 6.00 | 6.00 |
| Steareth 21 | 2.00 | 2.50 | 2.67 | 3.00 | 3.00 |
| Carboxy methyl cellulose | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 |
| Water purified | 83.50 | 72.00 | 61.50 | 50.50 | 45.50 |
| **Total** | **100.00** | **100.00** | **100.00** | **100.00** | **100.00** |
| Propellant (1681) | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| | | | | | |
| **Appearance:** | | | | | |
| foam quality | E | E | E | E | E |
| color | White | White | White | White | White |
| odor | No odor | No odor | No odor | No odor | No odor |
| density | 0.065 | 0.063 | 0.063 | | |
| collapse time | >300 | >300 | >300 | | |
| Hardness | 17.23 | 24.67 | 27.39 | | |

**[0287]** Excellent foam formulations were prepared with diethyl sebacate, surfactant, a nominal amount of polymeric agent and water (and without any foam adjuvant or another solvent).

**A1** – Example 8 - DISPA Formulation to provide stable environment for Pimecrolimus

**Part 1-Composition of Placebo or Stock Formulation PIMF-001P**

| Material | %w/w |
|---|---|
| Caprylic/capric triglyceride | 10.00 |
| Diisopropyl adipate (DISPA) | 20.00 |
| Oleyl alcohol | 10.00 |
| PPG-15 stearyl ether | 2.00 |
| Stearic acid | 1.20 |
| Sorbitan laurate | 2.00 |
| Benzyl alcohol | 2.00 |
| Methocel A4M (methylcellulose) | 0.15 |
| Xanthan gum | 0.15 |
| Sucrose stearic acid esters, mixture | 2.00 |
| Propylene glycol | 17.70 |
| Water purified | 32.74 |
| Trolamine (TEA) | 0.06 |
| **Total** | **100.00** |
| Propellant | 8.00 |

**[0288]** Pimecrolimus is sensitive to polyethylene glycol polymers so it was necessary to develop formulations with emulsifying agents other than for example Twin, Myrj, or Brij surfactants, which are mainstream surfactants for pharmaceutical formulations. The combination of sorbitan laurate with sucrose stearic acid esters was found to be effective. Pimecrolimus is insoluble in water but is soluble in DISPA.

**Part 2 - Pimecrolimus Content Determined by HPLC in PFF and Foam Formulation**

**Samples at Various Times and Storage Conditions**

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**[0289]** The formulations were comprised of 98.8%; 98.6% and 98.4% stock plus 1.2%, 1.4% and 1.6% pimecrolimus respectively.

| Sample name | | Zero time | 14 days, 50°C, glass vials, PFF | 30 days, 40°C, Foam | 30 days, 50°C glass vials, PFF | 30 days, 50°C canisters PFF |
|---|---|---|---|---|---|---|
| PIM 1.2%: batch PIMF001-060620 | Result 1 | 1.12 | 1.14 | 1.22 | 1.05 | 1.13 |
| | Result 2 | 1.12 | 1.13 | 1.22 | 1.05 | 1.13 |
| | Average | 1.12 | 1.14 | 1.22 | 1.05 | 1.13 |
| PIM 1.4%: batch PIMF002-060620 | Result 1 | 1.45 | 1.31 | 1.41 | 1.39 | 1.37 |
| | Result 2 | 1.41 | 1.33 | 1.41 | 1.39 | 1.37 |
| | Average | 1.41 | 1.32 | 1.41 | 1.39 | 1.37 |
| PIM 1.6%: batch PIMF003-060620 | Result 1 | 1.58 | 1.5 | 1.59 | 1.56 | 1.55 |
| | Result 2 | 1.58 | 1.5 | 1.59 | 1.56 | 1.56 |
| | Average | 1.58 | 1.5 | 1.59 | 1.56 | 1.56 |

**[0290]** As can be seen from the above there is no significant breakdown of the active agent after a month when solubilized in DISPA.

**Part 3 - Physical Properties of PFF and Foam Preparations**

| | PFF | | Foam Appearance | | |
|---|---|---|---|---|---|
| **Formula Name** | **Centrifugation, 3000 rpm** | **Centrifugation, 10,000 rpm** | **Quality** | **Color** | **Odor** |
| PIMF001 | stable | 80% creaming | good | white | no odor |
| PIMF002 | stable | stable | good | white | no odor |
| PIMF003 | stable | 95% creaming | excellent | white | no odor |

**[0291]** The basic formulation is a liquid emulsion which is inherently not stable with a tendency to cream or separate. Two contradictory forces had to be overcome to produce a good to excellent stable foam. One is to have a liquid formulation that stabilizes the active agent and the other is to have a thick almost solid like constitution which resists or retards creaming and or separation. Nevertheless, by introducing into the formulation a mixture of non-poly ethylene glycol polymer surfactants, which can produce a strong and closed packed

barrier between the oil and the water that stabilizes the emulsion, together with polymeric agents that retard creaming and or separation whilst maintaining a fluid constitution, it was possible to stabilize the foam and active agent.

**[0292]** Microscopic examination disclosed that there were no crystals and that Pimecrolimus was solubilized.

**A2 – SUSPENSIONS**

**A2** –Example 9 – Dicarboxylic acid composition

**[0293]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

Part A -Formulation

| Ingredient | %w/w |
|---|---|
| Azelaic Acid | 15.00 |
| Water | 51.90 |
| Caprylic/Capric triglyceride | 10.87 |
| Propylene glycol | 10.87 |
| Dimethyl isosorbide | 5.44 |
| PEG-40 stearate | 2.83 |
| Cetostearyl alcohol | 1.09 |
| Polysorbate 80 | 0.98 |
| Glyceryl stearate | 0.54 |
| Xanthan gum | 0.27 |
| Methylcellulose A4M | 0.11 |
| Benzoic acid | 0.10 |
| NaOH (18% Solution) | to pH=4.5 |
| Total: | 100 |

**[0294]** Notes

– The composition contains azelaic acid as a benefit agent, which is suitable for treating a skin disorder, selected from acne, rosacea, a pigmentation disorder, a cell proliferation abnormality a skin infection and a skin inflammation.

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- The composition contains about 10% capric/caprylic triglyceride to provide emolliency and about 10% propylene glycol and 10% dimethyl isosorbide, to provide (1) enhanced emolliency; (2) improved solubilizing capacity of the azelaic acid; and (3) enhanced skin delivery.

- The compositions contain about 50% water. Therefore, they provide high skin barrier build-up effect.

- The composition can be used as a cream/lotion for topical therapy of a skin diorder.

- In order to create a foamable composition, the composition is filled into an aerosol canister and pressurized using a liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

Part B – 12 month stability test

| Test parameter | | T-0 | T-12 | |
|---|---|---|---|---|
| | | | upright | inverted |
| API* assay by HPLC (%) | % amount of label<br>% w/w | 99.3<br>14.90 | 100.5<br>15.07 | 101.7<br>15.26 |
| Product content uniformity (Intra canister) of API (%) | | 1.79 | 0.10 | 0.88 |

*API = active pharmaceutical ingredient

**[0295]** The total amount of active agent at T-0 and at T-12 months as a percentage of 100% of ingredient that should be present according to the label and as a percentage in the formulation w/w, respectively was determined. As can be seen, no reduction in API content was observed within the limits of detection and that the content remained uniform. The differences between samples taken from the top of the canisters and from samples taken from the bottom of the canisters were not significant and were well within the acceptable range.

**[0296]** Furthermore, the formulation comprising active ingredient azaleic acid - despite being a suspension and subject to graviational effect - was able to withstand sedimentation and degredation such that it has remained stable and



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uniformly distributed in the formulation as a suspension over a prolonged period of 12 months, whilst remaining flowable and shakable.

Example 10 – Additional dicarboxylic acid compositions

**[0297]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| Formulation : | AZL018 | AZL034 | AZL035 | AZL036 | AZL037 | AZL038 | AZL039 |
|---|---|---|---|---|---|---|---|
| | %w/w | %w/w | %w/w | %w/w | %w/w | %w/w | %w/w |
| Azelaic Acid | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Caprylic/capric triglyceride | 5.00 | 10.00 | 5.00 | 5.00 | 5.00 | 5.00 | 10.00 |
| Cetostearyl alcohol | 0.90 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Glyceryl stearate | 0.45 | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 |
| Cholesterol | 1.00 | --- | --- | --- | --- | 1.00 | --- |
| Benzoic acid | | 0.20 | --- | 0.20 | 0.20 | 0.20 | --- |
| Benzyl alcohol | 1.00 | --- | 1.00 | --- | --- | --- | 1.00 |
| PEG-40 stearate | | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 |
| Methylcellulose | | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 |
| Hydroxypropyl methylcellulose | 0.10 | --- | --- | --- | --- | --- | --- |
| Xanthan gum | 0.25 | 0.10 | 0.25 | 0.10 | 0.25 | 0.10 | 0.10 |
| Polysorbate 80 | 0.90 | 0.90 | 0.90 | 0.90 | 0.90 | 0.90 | 0.90 |
| EDTA disodium dehydrate | 0.10 | --- | --- | --- | --- | --- | --- |
| PEG-400 | --- | --- | --- | --- | 5.00 | --- | --- |
| Dimethyl isosorbide | 10.00 | --- | --- | 5.00 | --- | --- | 5.00 |
| 50% phosphotidylcholine in propylene glycol | --- | 2.80 | 2.80 | --- | 2.80 | --- | 2.80 |
| propylene glycol | 6.00 | 5.00 | 10.00 | 10.00 | --- | --- | --- |
| Sodium hydroxide | to pH=4.5 | to pH=4.5 | to pH=5.3 | to pH=4.5 | to pH=4.5 | to pH=4.5 | to pH=5.3 |
| Propellant (butane+ isobutane + propane) | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| Purified water | to 100 | to 100 | to 100 | to 100 | to 100 | to 100 | to 100 |

Example 11 –Compositions with azalaic acid with and without different polymeric agents

**[0298]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | DCA021 | DCA023 | DCA023A | DCA026 | DCA026a |
|---|---|---|---|---|---|
| Isopropyl myristate | | | | 11.00 | 11.00 |
| MCT oil | | 35.00 | 35.00 | | |
| Azelaic acid | 20.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Propylene glycol | 30.00 | | | | |
| Steareth 2 | | 8.00 | 8.00 | | |
| Steareth 21 | | 2.00 | 2.00 | | |
| PEG-40 Stearate | | | | 4.00 | 6.00 |
| Polysorbate 80 | 30.00 | | | 1.40 | 2.10 |
| Xanthan gum | 0.30 | | | 0.27 | |
| Methocel A4M | 0.30 | | | 0.11 | |
| Carboxy methyl cellulose | | 0.50 | | | |
| Water purified | 19.40 | 39.50 | 40.00 | 68.22 | 65.90 |
| **Total** | **100.00** | **100.00** | **100.00** | **100.00** | **100.00** |
| Propellant ( propane, isobutene and butane mixture | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| | | | | | |
| **Appearance:** | | | | | |
| foam quality | G-E | G-E | G-E | E | E |
| color | White | White | White | White | White |
| odor | No odor | No odor | No odor | No odor | No odor |
| Microscope | Crystals | Crystals | Crystals | Crystals | Crystals |

**[0299]** Good to excellent foam formulations were prepared with azelaic acid, surfactant, polymeric agent, and either another oil or propylene glycol water (and without any foam adjuvant). Reducing the levels of azelaic acid to lower levels eliminated the appearance of crystals (See below).

**[0300]** Surprisingly, it was possible to prepare good to excellent foam after removal of the polymeric agent. Thus, the presence of a polymeric agent, is surprisingly not essential for foam quality. Nonetheless, polymeric agents may still contribute to and can be significant with respect to foam and active agent stability.

**A3 – IN SOLUTION**

Example 12 – Azalaic acid composition

**[0301]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | **DCA022** |
|---|---|
| Azelaic acid | 6.00 |
| Propylene glycol | 50.00 |
| Polysorbate 80 | 20.00 |
| Xanthan gum | 0.30 |
| Methocel A4M | 0.30 |
| Water purified | 23.40 |
| **Total** | **100.00** |
| Propellant ) propane, isobutene and butane mixture | 8.00 |
| | |
| **Appearance:** | |
| foam quality | G-E |
| Color | White |
| Odor | No odor |
| Microscope | No crystals |

Lower azaleic acid levels provide a soluble composition. No solids or precipitates are observed. No crystals were observed at the level of microscopic examination. By no crystals means the ingredients dissolve and it is not a suspension.



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Example 13 –Compositions with diethyl salicylates azelate (TU-2100)

| | DCA016 | DCA017 | DCA016A |
|---|---|---|---|
| PPG 15-Stearyl Ether (PPG) | 40.00 | | 40.00 |
| Isopropyl myristate (IPM) | | 40.00 | |
| TU-2100 | 10.00 | 10.00 | 10.00 |
| Steareth 2 | 6.00 | 4.95 | 6.00 |
| Steareth 21 | 1.50 | 3.00 | 1.50 |
| Carboxy methyl cellulose | 0.50 | 0.50 | |
| Water purified | 42.00 | 41.55 | 42.50 |
| **Total** | **100.00** | **100.00** | **100.00** |
| Propellant propane, isobutene and butane mixture | 8.00 | 8.00 | 8.00 |

| **Appearance:** | | | |
|---|---|---|---|
| foam quality | G-E | G- | G-E |
| color | White | White | White |
| odor | No odor | No odor | No odor |
| Microscope | No crystals | No crystals | No crystals |

**[0302]** When medium chain triglycerides were used as the emollient the formulation was poor. However, when they were substituted by PPG or IPM the foam quality increased substantially. Without being bound by any particular theory this may be because the formulations are close to phase reversal and or is due to internal tensions.

**[0303]** Good to excellent foam formulations were prepared with TU-2100, PPG or IPM, surfactant, polymeric agent, and water (and without any foam adjuvant). Surprisingly a good to excellent foam was produced even after removal of polymer.

**SECTION B – NON AQUEOUS**

**B1** – Example 14 - PEG based non aqueous formulations with TU 2100

**[0304]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | DCA014 | DCA014A | DCA014B |
|---|---|---|---|
| TU-2100 | 10.00 | 10.00 | 10.00 |
| PEG 400 | 87.50 | 85.00 | 88.00 |
| Steareth 2 | 2.00 | 5.00 | |
| Klucel EF | 0.50 | | 2.00 |
| **Total** | **100.00** | **100.00** | **100.00** |
| Propellant propane, isobutene and butane mixture | 8.00 | 8.00 | 8.00 |

| **Appearance:** | | | |
|---|---|---|---|
| foam quality | G-E | G-E | G-E |
| Color | White | White | White |
| Odor | No odor | No odor | No odor |
| Microscope | No crystals | No crystals | No crystals |

**[0305]** Surprisingly it was possible to make non aqueous PEG based minimal foam compositions of good to excellent quality with a) active ingredient , PEG, a single surfactant and optionally a polymeric agent and also with b) active ingredient , PEG, and a polymeric agent.

**B2** – Example 15 - PG based non aqueous formulation with TU 2100 and with Azaleic acid

**[0306]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.



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| | DCA015 | DCA020 |
|---|---|---|
| TU-2100 | 10.00 | |
| Azelaic acid | | 9.00 |
| PEG 400 | | |
| Propylene glycol | 87.50 | 88.50 |
| Steareth 2 | 2.00 | 2.00 |
| Klucel EF | 0.50 | 0.50 |
| **Total** | **100.00** | **100.00** |
| Propellant propane, isobutene and butane mixture | 8.00 | 8.00 |

| **Appearance:** | | |
|---|---|---|
| foam quality | G-E | G-E |
| color | White | White |
| odor | No odor | No odor |
| Microscope | crystals | No crystals |

**[0307]** Surprisingly it was possible to make non aqueous PG based minimal foam compositions of good to excellent quality with active ingredient , PG, a single surfactant and a polymeric agent. Whilst TU 2100 was not soluble in the non aqueous PG based composition, azelaic acid was soluble.

## Claims

What is claimed is:

1. A pharmaceutical or cosmetic composition comprising:

    e. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

    iii. a dicarboxylic acid; and

    iv. a dicarboxylic acid ester;

    f. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

    g. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients;

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.



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2. The composition of claim 1, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

3. The composition of claim 1, wherein the benefit agent comprises azelaic acid at a concentration of less than 6 wt%

4. The composition of claim 1, wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that is substantially resistant to phase reversal.

5. The composition of claim 1, the benefit agent, stabilizer and solvent are selected to generate a single phase.

6. The composition of claim 1, the benefit agent, stabilizer and solvent are selected to generate a substantially uniform suspension of benefit agent crystals.

7. The composition of claim 1, wherein the breakable foam comprises micro or nano particles, crystals or bodies.

8. The composition of claim 1, which is substantially resistant to one or more Freeze-Thaw cycles (FTC).

9. The composition of claim 1 wherein the surface-active agent is a solid, a liquid or a mixture thereof.

10. The composition of claim 1, wherein the surface active agent is selected from the group consisting of a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a





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polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59, a polyoxyethylene alkylyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol, sorbitan monolaurate, sorbitan monolaurate a monoglyceride, a diglyceride, isoceteth-20, a sucrose ester, or selected from the group consisting of steareth 2, glyceryl monostearate/PEG 100 stearate, Glyceryl Stearate, Steareth-21, peg 40 stearate, polysorbate 60, polysorbate 80, sorbitan stearate, laureth 4, Sorbitan monooleate, ceteareth 20, steareth 20, ceteth 20, Macrogol Cetostearyl Ether, ceteth 2, PEG-30 Dipolyhydroxystearate, sucrose distearate, polyoxyethylene (100) stearate, PEG 100 stearate, laureth 4, cetomacrogol ether, Cetearyl alcohol, Cetearyl glucoside, Oleyl alcohol, Steareth-2, Diisopropyl adipate, Capric/caprilic triglicerides, Polysorbate 20; Montanov 68.(CETEARYL ALCOHOL (and) CETEARYL GLUCOSIDE.), Sharonmix 824(a liquid blend of methyl paraben, ethyl paraben and propyl paraben - in phenoxyethanol), Simusol 165 (Glyceryl stearate and PEG-100 stearate). Methyl glucose sequistearate, Peg 30 dipolyhydroxystearate, sucrose stearic acid esters, sorbitan laureth, sorbitan stearate and mixtures thereof.

11. The composition of claim 1, wherein the surface active agent comprises at least one ester-based surfactant or at least one ether-based surfactant.

12. The composition of claim 1, wherein the surface active agent is reduced about in proportion to the increase in dicarboxylic ester.

13. The composition of claim 1 wherein the stabilizer is not a polymeric agent.



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14. The composition of claim 1, wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

15. The composition of claim 13, wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester, a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

16. The composition of claim 1 wherein the polymeric agent is selected from the group consisting of carbopol 934, pemulen TR2, klucel EF, xanthan gum, methocel A4M, and carboxy methyl cellulose or selected from the group consisting of locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, cationic guars, hydroxypropyl guar gum, starch, an amine-bearing polymer, chitosan, alginic acid, hyaluronic acid, a chemically modified starch, a carboxyvinyl polymer, polyvinylpyrrolidone, polyvinyl alcohol, a polyacrylic acid polymer, a polymethacrylic acid polymer, polyvinyl acetate, a polyvinyl chloride polymer, a polyvinylidene chloride polymer, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxy propylmethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylcellulose carboxymethylhydroxyethylcellulose, a cationic cellulose aluminum starch octenylsuccinate (ASOS), PEG 1000, PEG 4000, PEG 6000 and PEG 8000.

17. The composition of claim 1 wherein the polymeric agent is a derivatized polymer.

18. The composition of claim 1 wherein the derivatized polymer is a polymeric emulsifier.

19. The composition of claim 1 wherein the benefit agent is selected from the group consisting of diisopropyl adipate, dimethyl sebacate, dioctyl malate, diethyl sebacate, azelaic acid and TU-2100.

20. The composition of claim 1 further comprising an additional active agent.

21. The composition of claim 1, wherein the dicarboxylic acid has the molecular formula $HOOC-(CH_2)_n-COOH$; and wherein n is in the range between 0 and 32.

22. The composition of claim 21, wherein n is in the range between 4 and 10.

23. The composition of claim 1, wherein the dicarboxylic acid is selected from the group consisting of oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid and dodecanedioic acid, maleic acid and fumaric acid.

24. The composition of claim 1, wherein the dicarboxylic acid is selected from the group consisting of adipic acid, azelaic acid and sebacic acid.

25. The composition of claim 2, further containing a foam adjuvant selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain; a fatty acid having 16 or more carbons in their carbon chain; fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; a fatty alcohol having at least one double bond; a fatty acid having at least one double bond; a branched fatty alcohol; a branched fatty acid and a fatty acid substituted with a hydroxyl group.



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26. The composition of claim 1 further containing at least one organic carrier selected from the group consisting of a hydrophobic organic carrier, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight.

27. The composition of claim 1, wherein the dicarboxylic acid or dicarboxylic acid ester is in a concentration between about 0.1% and about 60%.

28. The composition of claim 1, wherein the dicarboxylic acid is azelaic acid, and wherein the concentration of azelaic acid is between 5% and 25%.

29. The composition of claim 1, wherein the pH of the composition is below the first pKa of the dicarboxylic acid.

30. The composition of claim 1, wherein the pH of the composition is between the first and second pKa of the dicarboxylic acid.

31. The composition of claim 1, wherein the pH of the composition is above the second pKa of the dicarboxylic acid.

32. The composition of claim 1, wherein the dicarboxylic acid is azelaic acid the pH of the composition is below 5.3.

33. The composition of claim 1, wherein the dicarboxylic acid is azelaic acid the pH of the composition is between about 4.5 and about 5.3.

34. The composition of claim 1, wherein the dicarboxylic acid ester is selected from the group consisting of a mono ester of said dicarboxylic acid, and a diester of the dicarboxylic acid.

35. The composition of claim 33, wherein the alcohol moiety of the dicarboxylic acid ester is selected from the group consisting of an alkyl alcohol, an aryl alcohol, methyl alcohol, ethyl alcohol, propyl alcohol,



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isopropyl alcohol, butyl alcohol, isobutyl alcohol, t-butyl alcohol, pentyl alcohol, hexyl alcohol, octyl alcohol, decyl alcohol, capryl alcohol, phenol and benzyl alcohol.

36. The composition of claim 33, wherein the alcohol moiety of the dicarboxylic acid ester is a biologically active alcohol.

37. The composition of claim 35, wherein the biologically active alcohol is selected from the group consisting of a hydroxyalkylbenzoate, salicylic acid, a dihydroxybenzene, hydroxytoluene, an alpha-hydroxy acid, retinol, a vitamin A derivative, a steroid, vitamin E, a vitamin E derivative, vitamin D and a vitamin D derivative.

38. The composition of claim 33, wherein the dicarboxylic acid ester is selected from the group consisting of diisobutyl adipate, diisopropyl adipate, diisopropyl sebacate, diisosteary dimer dilinoleate, diisostearyl fumerate, diisopropyl dimerate, diethyl adipate, diethyl sebacate, diethylhexyl adipate, diethylhexyl malate, dioctyl malate, diethyl succinate, and dioctyl sebacate.

39. The composition of claim 33, wherein the dicarboxylic acid ester is diisopropyl adipate, in an amount from about 0.1% to about 60%

40. The composition of claim 25, wherein the organic carrier is selected from the group consisting of mineral oil, triglycerides, medium chain triglyceride (MCT) oil, capric/caprylic triglyceride, alkyl esters of fatty acids such as isopropyl palmitate, isopropyl myristate, isopropyl isostearate, poly propylene glycol 15-stearly ether, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, maleated soybean



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oil, unsaturated or polyunsaturated oils, such as olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzigium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils; essential oils; and silicone oils, such as dimethicone, cyclomethicone, polyalkyl siloxane, polyaryl siloxane, polyalkylaryl siloxane, a polyether siloxane copolymer and a poly(dimethylsiloxane)-(diphenyl-siloxane) copolymer.

41. The composition of claim 25, wherein the organic carrier comprises a polypropylene glycol alkyl ether.

42. The composition of claim 1 further containing at least one polar solvent.

43. The composition of claim 41, wherein the polar solvent is selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, oleyl alcohol, alpha-hydroxy acids, such as lactic acid and glycolic acid, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, alkanols, such as dialkylamino acetates, and admixtures thereof.

44. The composition of claim 39, wherein the organic carrier is capric/caprylic triglyceride and wherein the dicarboxylic acid is azelaic acid.

45. The composition of claim 41, wherein the polar solvent is selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid wherein the dicarboxylic acid is azelaic acid.



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46. The composition of claim 44, wherein the organic carrier is capric/caprylic triglyceride.

47. The composition of claim 39, wherein the organic solvent comprises at least one organic carrier, selected from the group capric/caprylic triglyceride, a polypropylene glycol alkyl ether an ester of a fatty acid and mineral oil and wherein the dicarboxylic acid ester is diisopropyl adipate .

48. The composition of claim 46, further comprising a polar solvent, selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

49. The composition of claim 1, wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that can produce a substantially strong and closed packed barrier between the oil and the water phases whilst maintaining a fluid constitution

50. The composition of claim 1, further comprising an additional component selected from the group consisting of a modulating agent, a polar solvent, an anti perspirant, an anti-static agent, a buffering agent, a bulking agent, a chelating agent, a colorant, a conditioner, a deodorant, a diluent, a dye, an emollient, fragrance, a humectant, an occlusive agent, a penetration enhancer, a perfuming agent, a permeation enhancer, a pH-adjusting agent, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent, and a vitamin.

51. The composition of claim 39, wherein the organic carrier is selected from the group consisting of PPG 15-stearyl ether, isopropyl myristate and medium chain triglyceride oil and capric/caprylic triglyceride and the benefit agent is a solid at ambient temperature.

52. A therapeutic composition comprising:



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a. a therapeutically effective amount of an active agent;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

53. The therapeutic composition of claim 52, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25%



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by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

54. The therapeutic composition of claim 52, wherein the active agent is selected from the group consisting of active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, antiyeast agents, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hair growth regulators, hormones, hydroxy acids, immunosuppressants, immunoregulating agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, self tanning agents, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, wound healing agents and wart removers.

55. The foamable therapeutic composition of claim 52, wherein the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the active agent.

56. The foamable therapeutic composition of claim 52, wherein the active agent is a steroid.



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57. The foamable therapeutic composition of claim 55, wherein the steroid is selected from the group consisting of bydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethsone dipropionate, clobetasol valemate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortmate, mepreddisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone.

58. The foamable therapeutic composition of claim 52, wherein the active agent is an immunomodulator.

59. The foamable therapeutic composition of claim 58, wherein the immunomodulator is selected from the group consisting of a cyclic peptides, cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus, verolimus, laflunimus, laquinimod and imiquimod.

60. The foamable therapeutic composition of claim 58, wherein the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the immunomodulator.

61. The foamable therapeutic composition of claim 60, wherein the dicarboxylic acid ester is diisopropyl adipate.



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62. The composition of claim 52, wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

63. The composition of claim 62, wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester,a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

64. The composition of claim 52, wherein the dicarboxylic acid is azelaic acid.

65. The composition of claim 64, further comprising an organic solvent comprising capric/caprylic triglyceride.

66. The composition of claim 65, further comprising at least one polar carrier, selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

67. A method of treating a disorder of a mammalian subject, comprising:

administering a foamable therapeutic composition to a target site, the composition comprising:

a. a therapeutically effective amount of an active agent;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of



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i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

68. The method of claim 67, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.



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69. The method of claim 67, wherein the target site is selected from the group consisting of the skin, a body cavity, a mucosal surface, the nose, the mouth, the eye, the ear canal, the respiratory system, the vagina and the rectum.

70. The method of claim 67, wherein the disorder is selected from the group consisting of dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychial infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, granuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callouses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo; and wherein the active agent is suitable for treating said disorderm or is selected from the group consisting of chlamydia infection, gonorrhea infection, hepatitis B,



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herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum; and wherein the active agent is suitable for treating said disorder.

71. The method of claim 67, wherein the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid or dicarboxylic acid ester.

72. The method of claim 67, wherein the disorder is a dermatological disorder, which can be treated by a topical steroid, an immunomodulator or an anti-infective agent.

73. The method of claim 67, wherein the disorder is selected from atopic dermatitis and psoriasis; and the active agent is selected from (i) steroid; and (ii) a combination of steroid and an additional non-steroidal active agent.

74. The method of claim 67, wherein the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises an immunomodulator.

75. A pharmaceutical or cosmetic non aqueous composition comprising:



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a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

76. The composition of claim 75, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon



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release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

77. A therapeutic composition comprising:

a. a therapeutically effective amount of an active agent wherein the active agent is substantially insoluble in water;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, comprising a dicarboxylic acid ester in which the active agent is substantially soluble;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

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78. The therapeutic composition of claim 77, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

79. The composition of claim 78, wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that can produce a substantially strong and closed packed barrier between the oil and the water phases whilst maintaining a fluid constitution.

80. A foamable composition comprising:

a. a liquid dicarboxylic acid ester, said ester having emollient properties;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

c. an active agent, said active agent soluble in or having enhanced penetration due to the dicarboxylic acid;

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

81. The composition of claim 80, wherein the stabilizer comprises a ether-based or ester-based surfactant.

82. The composition of claim 80 wherein the stabilizer comprises an alkyl-derivatized polymer having polymeric emulsifying properties.



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83. The composition of claim 80, further comprising water, wherein the composition is an oil in water emulsion.

84. The composition of claim 83, wherein the dicarboxylic acid ester comprises about or more than 50 wt% of the composition.

85. A foamable composition comprising:

i. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

j. an ester-based or ether-based surfactant;

k. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the composition is substantially free of polymeric material, and

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

86. The composition of claim 85, further comprising an active agent.

87. The composition of claim 86, wherein active agent is otherwise insoluble or unstable, but is solubilized or stabilized by DCA.

88. A pharmaceutical or cosmetic composition comprising:



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a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the composition is substantially free of water

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release

89. The composition of claim 88, further comprising an additional component selected from the group consisting of a modulating agent, a polar solvent, an anti perspirant, an anti-static agent, a buffering agent, a bulking agent, a chelating agent, a colorant, a conditioner, a deodorant, a diluent, a dye, an emollient, fragrance, a humectant, a moisturizer, an occlusive agent, a penetration enhancer, a perfuming agent, a permeation enhancer, a pH-adjusting agent, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent,

90. The composition of claim 1 in a non foam state.

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(54) **Dicarboxylic acid foamable vehicle and pharmaceutical compositions thereof**

Dicarbonsäureschäumbare Trägersubstanz und pharmazeutische Zusammensetzungen daraus

Véhicule moussant à base d'acide dicarboxylique et ses compositions pharmaceutiques

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## Description

### BACKGROUND OF THE INVENTION

**[0001]** This invention relates to foamable pharmaceutical and cosmetic compositions.

**[0002]** External topical administration is an important route for the administration of drugs in disease treatment. Many groups of drugs, including, for example, antibiotic, anti-fungal, anti-inflammatory, anesthetic, analgesic, anti-allergic, corticosteroid, retinoid and anti-proliferative medications are preferably administered in hydrophobic media, namely ointment. However, ointments often form an impermeable barrier, so that metabolic products and excreta from the wounds to which they are applied are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the wound tissue, so the efficacy of the drug is reduced. In addition, ointments and creams often do not create an environment for promoting respiration of the wound tissue and it is not favorable to the normal respiration of the skin. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds.

**[0003]** Foams are considered a more convenient vehicle for topical delivery of active agents. There are several types of topical foams, including aqueous foams, such as commonly available shaving foams; hydroalcoholic foams, emulsion-based foams, comprising oil and water components, and oleaginous foams, which consist of high oil content. In skin therapy, oil containing foams are preferred, since oil contributes to skin protection and moisturization, which improve the therapeutic effect of the formulation.

**[0004]** Dicarboxylic acids are known to possess therapeutic properties. Dicarboxylic acids, and their mercapto, ester and salt derivatives have been used in the treatment of a variety of skin disorders and/or conditions.

**[0005]** Azelaic acid (AZA) is a naturally occurring nine carbon straight chain molecule with two terminal carboxyl groups. AZA is an anti-keratinizing agent, displaying antiproliferative effects on keratinocytes and modulating the early and terminal phases of epidermal differentiation. AZA is a competitive inhibitor of the reduction of testosterone to dihydrotestosterone, and as such is supposed to reduce the production of sebum in the sebaceous gland. Furthermore, recent investigations have demonstrated that AZA and sebacic acid also have anti-bacterial and anti-fungal properties. Structure-activity relationship studies have revealed that these effects are retained when the dicarboxylic acid has a backbone of about 6 to about 14 carbons.

**[0006]** Dicarboxylic acid esters are also known to contribute to the skin penetration of an active agent. Enhancing effects on skin penetration of methyl nicotinate have been observed with dibutyl adipate and dioctyl adipate. Diisopropyl sebacate also markedly enhances the skin penetration of the erythromycin. The skin penetration enhancing properties of mono- or di-esters of dicarboxylic acid, including dibutyl adipate, diethyl sebacate, diisopropyl dimerate, diisopropyl adipate, diisopropyl sebacate and dioctyl succinate have been recognized.

**[0007]** There remains an unmet need for improved, easy to use, stable oil-containing foam formulations, containing oils, which effectively deliver and/or deposit various benefit agents into and onto the skin and/or other target sites and are relatively non-irritating and thus suitable for use by people having sensitive skin and eyes.

### SUMMARY

**[0008]** The present invention relates to aqueous and non aqueous stable compositions comprising azelaic acid.

**[0009]** There is provided a pharmaceutical or cosmetic composition as defined in Claim 1.There is also provided a foamable composition as described above wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the azelaic acid, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

**[0010]** The compositions described above may be in a non foam state.

**[0011]** There is also provided the use of the compositions in the preparation of a medicament for use in the treatment of dermatological disorders.

### DETAILED DESCRIPTION

**[0012]** According to one or more embodiments of the present invention, the composition includes:

a. a benefit agent which is azelaic acid;
b. a surface-active agent;
c. about 0.01 % to about 5% by weight of at least one polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent; and



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d. water.

**[0013]** The present invention further relates to a foamable composition including:

a. a benefit agent which is azelaic acid;
b. a surface-active agent;
c. about 0.01 % to about 5% by weight of at least one polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;
d. water; and
e. liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

**[0014]** In one or more embodiments there is provided a foamable composition which produces a foam upon release and wherein the azelaic acid, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

**[0015]** In one or more embodiments there is provided a composition wherein the azelaic acid, stabilizer and solvent are selected to generate an emulsion that is substantially resistant to phase reversal.

**[0016]** In one or more embodiments there is provided a composition wherein, the azelaic acid, stabilizer and solvent are selected to generate a single phase.

**[0017]** In one or more embodiments there is provided a composition wherein, the azelaic acid, stabilizer and solvent are selected to generate a substantially uniform suspension of benefit agent crystals.

**[0018]** In one or more embodiments there is provided a composition, wherein the breakable foam comprises micro or nano particles, crystals or bodies.

**[0019]** In one or more embodiments there is provided a composition, which is substantially resistant to one or more Freeze-Thaw cycles (FTC).

**[0020]** In one or more embodiments there is provided a composition wherein the surface-active agent is a solid, a liquid or a mixture thereof.

**[0021]** In one or more embodiments there is provided a composition wherein the surface active agent is selected from the group consisting of a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59; a polyoxyethylene alkyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol, sorbitan monolaurate, a monoglyceride, a diglyceride, isoceteth-20, steareth 2, glyceryl monostearate/PEG 100 stearate, glyceryl stearate, steareth-21, PEG 40 stearate, polysorbate 60, polysorbate 80, sorbitan stearate, laureth 4, sorbitan monooleate, ceteareth 20, steareth 20, ceteth 20, macrogol cetostearyl ether, ceteth 2, PEG-30 dipolyhydroxystearate, sucrose distearate, polyoxyethylene (100) stearate, PEG 100 stearate, cetomacrogol ether, cetearyl glucoside, steareth-2, polysorbate 20; Montanov 68 (cetearyl alcohol (and) cetearyl glucoside), Simusol 165 (glyceryl stearate and PEG-100 stearate), methyl glucose sequistearate, PEG 30 dipolyhydroxystearate, sucrose stearic acid esters, sorbitan laureth, and mixtures thereof.

**[0022]** In one or more embodiments there is provided a composition wherein the surface active agent comprises at least one ester based surfactant or at least one ether based surfactant.

**[0023]** In one or more embodiments there is provided a composition wherein the surface active agent is reduced about in proportion to the increase in dicarboxylic ester.

**[0024]** In one or more embodiments there is provided a composition wherein the stabilizer is not a polymeric agent.

**[0025]** In one or more embodiments there is provided a composition wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

**[0026]** In one or more embodiments there is provided a composition wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester, a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

**[0027]** In one or more embodiments there is provided a composition wherein the polymeric agent is selected from the group consisting of carbopol 934, pemulen TR2, klucel EF, xanthan gum, methocel A4M, and carboxy methyl cellulose or selected from the group consisting of locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, cationic guars, hydroxypropyl guar gum, starch, an amine-bearing polymer, chitosan, alginic acid, hyaluronic acid, a chemically modified starch, a carboxyvinyl polymer, polyvinylpyrrolidone, polyvinyl alcohol, a polyacrylic acid polymer, a polymethacrylic acid polymer, polyvinyl acetate, a polyvinyl chloride polymer, a polyvinylidene chloride polymer, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxy propylmethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylhydroxyethylcellulose, a cationic cellulose aluminum starch octenylsuccinate (ASOS), PEG 1000, PEG 4000,



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PEG 6000 and PEG 8000.

**[0028]** In one or more embodiments there is provided a composition wherein the polymeric agent is a derivatized polymer.

**[0029]** In one or more embodiments there is provided a composition wherein the derivatized polymer is a polymeric emulsifier.

**[0030]** In one or more embodiments there is provided a composition wherein, further comprising an additional active agent.

**[0031]** In one or more embodiments there is provided a composition wherein further containing a foam adjuvant selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain; a fatty acid having 16 or more carbons in their carbon chain; fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; a fatty alcohol having at least one double bond; a fatty acid having at least one double bond; a branched fatty alcohol; a branched fatty acid and a fatty acid substituted with a hydroxyl group.

**[0032]** In one or more embodiments there is provided a composition wherein further containing at least one organic carrier selected from the group consisting of a hydrophobic organic carrier, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight.

**[0033]** In one or more embodiments there is provided a composition wherein the azelaic acid is in a concentration between about 0.1 % and about 60%.

**[0034]** In one or more embodiments there is provided a composition wherein the concentration of azelaic acid is between 5% and 25%.

**[0035]** In one or more embodiments there is provided a composition wherein the pH of the composition is below the first pKa of the azelaic acid.

**[0036]** In one or more embodiments there is provided a composition wherein the pH of the composition is between the first and second pKa of the azelaic acid.

**[0037]** In one or more embodiments there is provided a composition wherein the pH of the composition is above the second pKa of the azelaic acid.

**[0038]** In one or more embodiments there is provided a composition wherein the pH of the composition is below 5.3.

**[0039]** In one or more embodiments there is provided a composition wherein the pH of the composition is between about 4.5 and about 5.3.

**[0040]** In one or more embodiments there is provided a composition wherein the azelaic acid, stabilizer and solvent are selected to generate an emulsion that can produce a substantially strong and closed packed barrier between the oil and the water phases whilst maintaining a fluid constitution

**[0041]** In one or more embodiments there is provided a composition further comprising an additional component selected from the group consisting of a modulating agent, a polar solvent, an anti perspirant, an anti-static agent, a buffering agent, a bulking agent, a chelating agent, a colorant, a conditioner, a deodorant, a diluent, a dye, an emollient, fragrance, a humectant, an occlusive agent, a penetration enhancer, a perfuming agent, a permeation enhancer, a pH-adjusting agent, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent, and a vitamin.

**[0042]** In one or more embodiments there is provided a therapeutic composition comprising therapeutically effective amount of an active agent; and a beneficially or therapeutically effective concentration of azelaic acid wherein the active agent is selected from the group consisting of active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, antiyeast agents, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hair growth regulators, hormones, hydroxy acids, immunosuppressants, immunoregulating agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, self tanning agents, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, wound healing agents and wart removers.

**[0043]** In one or more embodiments there is provided a foamable therapeutic composition wherein a dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the active agent.

**[0044]** In one or more embodiments there is provided a foamable therapeutic composition wherein the active agent is a steroid.

**[0045]** In one or more embodiments there is provided a foamable therapeutic composition wherein the steroid is selected from the group consisting of bydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexameth-

asone-phosphate, beclomethsone dipropionate, clobetasol valemate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortmate, mepreddisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone.

**[0046]** In one or more embodiments there is provided a foamable therapeutic composition wherein the active agent is an immunomodulator.

**[0047]** In one or more embodiments there is provided a foamable therapeutic composition, wherein the immunomodulator is selected from the group consisting of a cyclic peptides, cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus, verolimus, laflunimus, laquinimod and imiquimod.

**[0048]** In one or more embodiments there is provided a foamable therapeutic composition, wherein the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the immunomodulator.

**[0049]** In one or more embodiments there is provided a foamable therapeutic composition, wherein the dicarboxylic acid ester is diisopropyl adipate.

**[0050]** In one or more embodiments there is provided a composition wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

**[0051]** In one or more embodiments there is provided a composition wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester, a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

**[0052]** In one or more embodiments, the composition of the invention may be used in a method of treating a disorder of a mammalian subject, comprising:

> administering a foamable therapeutic composition to a target site, the composition comprising a therapeutically effective amount of an active agent; and a beneficially or therapeutically effective concentration of azelaic acid; wherein the target site is selected from the group consisting of the skin, a body cavity, a mucosal surface, the nose, the mouth, the eye, the ear canal, the respiratory system, the vagina and the rectum.

**[0053]** The disorder may be selected from the group consisting of dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychial infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, granuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callouses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo; wherein the active agent is suitable for treating said disorder or may be selected from the group consisting of chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum; wherein the active agent is suitable for treating said disorder.

**[0054]** The disorder may be a dermatological disorder, which can be treated by a dicarboxylic acid or dicarboxylic acid



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ester.

**[0055]** The disorder may be a dermatological disorder, which can be treated by a topical steroid, an immunomodulator or an anti-infective agent.

**[0056]** The disorder may be selected from atopic dermatitis and psoriasis; and the active agent is selected from (i) steroid; and (ii) a combination of steroid and an additional non-steroidal active agent.

**[0057]** The disorder may be selected from psoriasis and atopic dermatitis and the active agent comprises an immunomodulator.

In one or more embodiments there is provided a foamable composition comprising: a liquid dicarboxylic acid ester, said ester having emollient properties; a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof, an active agent, said active agent soluble in or having enhanced penetration due to the dicarboxylic acid; wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release

**[0058]** In one or more embodiments the stabilizer comprises a ether-based or ester-based surfactant.

**[0059]** In one or more embodiments the stabilizer comprises an alkyl-derivatized polymer having polymeric emulsifying properties.

**[0060]** In one or more embodiments the composition is an oil in water emulsion.

**[0061]** In one or more embodiments the dicarboxylic acid ester comprises about or more than 50 wt% of the composition.

**[0062]** In one or more embodiments the active agent is otherwise insoluble or unstable, but is solubilized or stabilized by DCA.

**[0063]** In one or more embodiments the composition is substantially free of water In one or more embodiments the composition is in a non foam state.

**[0064]** All % values are provided on a weight (w/w) basis.

**Dicarboxylic acid and esters thereof**

**[0065]** In an embodiment of the present invention, the organic carrier comprises an ester of a dicarboxylic acid. In the context of the present invention, a dicarboxylic acid is an organic material, having two carboxylic acid moieties on its carbon atom skeleton. They have the general molecular formula $HOOC-(CH_2)_n-COOH$.

**[0066]** Non limiting examples of some elementary dicarboxylic acids (DCA's) are succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, phthalic acid, isophthalic acid, terephthalic acid.

**[0067]** In an embodiment of the present invention, the dicarboxylic acid is a short-chain dicarboxylic acid. The simplest Short-chain dicarboxylic acid are oxalic acid (n=0), malonic acid (n=1), succinic acid (n=2) and glutaric acid (n=3).

**[0068]** Additional members of dicarboxylic acid group are derived from natural products or from synthesis, having "n" value from 4 up to 21. In one or more embodiments of the present invention, the dicarboxylic acid is selected from the group consisting of adipic acid (hexanedioic acid; n=4), pimelic acid (heptanedioic acid; n=5), suberic acid (octanedioic acid; n=6), azelaic acid (nonanedioic acid; n=7), sebacic acid (decanedioic acid; n=8) and dodecanedioic acid (n=10).

**[0069]** In an additional embodiment, the dicarboxylic acid contains 1 0 to 32 carbon atoms in their carbon atom skeleton, such as brassylic acid (n=11), thapsic acid (n=14), 14-methylnonacosanedioic acid (C29) and 14,15-dimethyltriacontanedioic acid (C30).

**[0070]** The carbon atom skeleton of the dicarboxylic acid can be saturated or unsaturated, such as in the case of maleic acid and fumaric acid.

**[0071]** In general terms non-esterified dicarboxylic acids are usually solid at ambient temperature. Non limiting examples of solid DCA's are oxalic, malonic glutaric, sebacic , phthalic and azaleic acid. Similarly, in general terms DCA's with short carbon chain skeleton are water soluble, such as oxalic, malonic, and succinic acid. Longer chain DCA's like adipic acid and having up to 10 carbon atoms in the carbon chain are slightly soluble in water. Also non "simple" DCA's are generally solid at ambient temperature , insoluble in water, and are usually more oil soluble than their parent DCA's

**[0072]** An ester of a dicarboxylic acid is a chemical compound produced by the reaction between a dicarboxylic acid and at least one alcohol, with the elimination of a molecule of water. The reaction of a dicarboxylic acid with one alcohol molecule results in a mono ester of a dicarboxylic acid. The reaction of a dicarboxylic acid with two alcohol molecules results in a diester of the dicarboxylic acid.

**[0073]** DCA esters are typically hydrophobic and generally insoluble in water. Most simple esters of DCA are liquid. By simple it is meant that the alcohol moiety linked to the DCA is a straight or branched alkyl chain. Examples of liquid simple diesters are dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diethyl sebacate, dibutyl sebacate, and diisopropyl adipate. Aromatic diesters of pthalic, isopthalic and therephalic acids are in the range of slightly soluble to insoluble.

**[0074]** The alcohol molecule, to be linked to the dicarboxylic acid, can be selected from the group of an alkyl an aryl alcohol. Exemplary alcohol, suitable according to the present invention include methyl alcohol, ethyl alcohol, propyl



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alcohol, isopropyl alcohol, butyl alcohol, isobutyl alcohol, t-butyl alcohol, pentyl alcohol, hexyl alcohol, octyl alcohol, decyl alcohol, capryl alcohol, phenol, benzyl alcohol and the like.

**[0075]** In one or more embodiments, the alcohol is a biologically active alcohol. In an embodiment, biologically active alcohol possesses keratolytic activities. Examples of keratolytically active alcohol suitable according to the present invention include ortho-, meta- and para-hydroxyalkylbenzoate, salicylic acid, ortho-, meta-, and para-dihydroxybenzene, ortho-, meta-, and para-hydroxytoluene, alpha-hydroxy acid, retinol, and derivatives thereof such as provided in U.S. Pat. 6,180,669, which is incorporated herein by reference. In another embodiment, the biologically active alcohol is selected from the group consisting of steroidal hormones, steroidal anti-inflammatory agents, vitamin E and vitamin D, such as provided in U.S. Pat. Appl. 20040191196, which is incorporated herein by reference.

**[0076]** In an embodiment of the present invention, the azelaic acid is incorporated in the foamable composition in a safe and effective amount. The term "safe and effective" means an amount of an active agent that exerts a therapeutic effect on a specific disorder, without causing adverse effects that may prohibit the use of said active agent in the treatment of said disorder. The azelaic acid can be incorporated in the foamable composition of the present invention in a concentration between about 0.1% and about 25%, more preferably between about 1% and about 20%.

**[0077]** In an embodiment of the present invention, the dicarboxylic acid is azelaic acid, and its concentration in the composition is between 5% and 25%, or between 10% and 20%.

**[0078]** In one or more embodiment, the azelaic acid is present in the composition in an ionized state. The first and second pKa values for a dicarboxylic acid are different from one another. Depending on the pH of the composition and the specific first and second pKa of the dicarboxylic acid, said dicarboxylic acid can be non-ionized (both carboxy groups are in their acid state); semi-ionized (one carboxy group is in an acid state and the second is in an anionic state); or doubly-ionized, wherein both carboxy groups are anionic. For example, in the case of azelaic acid the first pKa is about 4.5 and the second pKa is about 5.3. Therefore, if the pH of the composition is below 4.5, the azelaic acid is non-ionized; between about 4.5 and about 5.3, it is mostly semi-ionized and at a pH above 5.3, the azelaic acid is mostly doubly-ionized.

**[0079]** The ionization state of the dicarboxylic acid has influence on its therapeutic potential. On one hand, if the dicarboxylic acid is doubly anionic, its penetration into the skin will be very low, due to the lipophilic nature of the skin. On the other hand, the non-ionic state is available at very low (acidic) pH values, which can cause skin irritation.

**[0080]** Hence, in one or more embodiments, the pH of the composition is adjusted to a value between the first and second pKa values of the dicarboxylic acid. For example, in the case of azelaic acid, the pH is adjusted in the range from about 2.0 to about 4.5, preferably in the range from about 3.0 to about 4.5. Thus, in an embodiment of the present invention, the pH of the composition is adjusted in the range from about 4.0 to about 6.0, preferably in the range from about 4.5 to about 5.3.

**[0081]** Dicarboxylic acid esters are considered excellent emollients and their inclusion in a composition which is intended for topical application contributes to the overall improvement of skin condition. Emollient dicarboxylic esters typically include an alkyl alcohol moiety, wherein said alkyl alcohol has a carbon chain of at least one or two or more carbon atoms. In certain embodiments, the alkyl alcohol is a branched alkyl, such as isopropyl alcohol; and in other embodiments the alkyl alcohol has a long carbon backbone, e.g., a carbon chain length of 6-18.

**[0082]** Dicarboxylic acid esters can be complex substances. One example is TU 2100 (Nonanedioic acid, bis[(2-(ethoxycarbonyl)phenyl] ester). It is also known as Azelaoyl di(ethyl salicylate) and has a CAS Registry Number: [207972-39-2] and is a solid. TU-2100 is a "non-simple" diester; with a high molecular weight, and a melting point of 34-36, which is relatively low with reference to its molecular weight.

**[0083]** Non-limiting examples of emollient dicarboxylic acid esters include diisobutyl adipate, diisopropyl adipate, diisopropyl sebacate, diisosteary dimer dilinoleate, diisostearyl fumerate, diisopropyl dimerate, diethyl adipate, diethyl sebacate, diethylhexyl adipate, diethylhexyl malate, dioctyl malate, diethyl succinate, and dioctyl sebacate. Other dicarboxylic acid esters are dimethyl phthalate, diethyl phthalate, diethyl sebacate, diisopropyl dimerate, dibutyl sebacate, dibutyl phthalate and dioctyl phthalate. Additionally dicarboxylic acid esters are capable of solubilizing active components which are difficult to dissolve by other oils. Furthermore, certain dicarboxylic acid esters, such as diisopropyl adipate and dimethyl sebacate are known to enhance the skin penetration of active agents. Hence in an embodiment of the present invention, the dicarboxylic acid ester is incorporated in the foamable composition in an amount, suitable to exert its emollient effect, solubilizing effect or skin penetration enhancing effect. In one or more embodiments, the dicarboxylic acid ester is incorporated in the foamable composition of the present invention in a concentration between about 0.1 % and about 30%, more preferably between about 1% and about 25%.

**[0084]** In one embodiment, the dicarboxylic acid ester is diisopropyl adipate (DISPA), in an amount between about 0.1 % and about 30%, or about 1% and about 25%.

**[0085]** As can be appreciated by the discussion above, there is a varied range of dicarboxylic acids and esters; some are soild, some are liquid, some are water soluble, some are slightly soluble and others are insoluble in water. There is also a varied range of functions and physical properties. Some are active agents and others are solvents and some are penetration enhancers. The challenges of making a uniform solution of solid DCA's wihout crystal formation or precipitation or a uniform suspension of insoluble agent, or using a DCA to solubilise a substance which is otherwise insoluble or as



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an emollient or as a penetration enhancer or more than one of them are as varied as their different natures and properties as may be appreciated by a man of the art. In other words each agent has its own properties and challenges which are interrelated to the objectives and other ingredients of the formulation

**[0086]** The sensory properties of foams containing a dicarboxylic acid or a dicarboxylic acid ester are favorable, as revealed by consumer panel tests.

**Foam adjuvant**

**[0087]** Optionally, the foamable vehicle further includes a foam adjuvant selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain; a fatty acid having 16 or more carbons in their carbon chain; fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; a fatty alcohol having at least one double bond; a fatty acid having at least one double bond; a branched fatty alcohol; a branched fatty acid and a fatty acid substituted with a hydroxyl group.

**Additional organic carrier**

**[0088]** Optionally, the foamable vehicle further includes at least one additional organic carrier selected from the group consisting of a hydrophobic organic carrier, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight. The hydrophobic solvent and/or the emollient can be selected from the group consisting of mineral oil, triglycerides, capric/caprylic triglyceride, alkyl esters of fatty acids such as isopropyl palmitate, isopropyl isostearate, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, maleated soybean oil, unsaturated or polyunsaturated oils, such as olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzigium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils; essential oils; and silicone oils, such as dimethicone, cyclomethicone, polyalkyl siloxane, polyaryl siloxane, polyalkylaryl siloxane, a polyether siloxane copolymer and a poly(dimethylsiloxane)-(diphenyl-siloxane) copolymer.

**[0089]** According to a preferred embodiment, the organic carrier does not contain petrolatum, which is also termed "white petrolatum" and "Vaseline". Petrolatum often forms an impermeable occlusive barrier, so that metabolic products and excreta from damaged tissue are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the treated tissue, so the efficacy of the drug is reduced. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds causing inconvenience to the user, thereby decreasing treatment compliance.

**Polymeric agent**

**[0090]** The composition of the present invention contains a polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent. A polymeric agent enhances the creation of foam having fine bubble structure, which does not readily collapse upon release from the pressurized aerosol can. The polymeric agent serves to stabilize the foam composition and to control drug residence in the target organ.

**[0091]** Exemplary polymeric agents include, in a non-limiting manner, naturally-occurring polymeric materials, such as locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, cationic guars, hydroxypropyl guar gum, starch, amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid and hyaluronic acid; chemically modified starches and the like, carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like.

**[0092]** Additional exemplary polymeric agents include semi-synthetic polymeric materials such as cellulose ethers, such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxy propylmethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylhydroxyethylcellulose, and cationic celluloses, carbomer (homopolymer of acrylic acid is crosslinked with an allyl ether pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene, such as Carbopol® 934, Carbopol® 940, Carbopo® 941, Carbopol® 980 and Carbopol® 981, pemulen and aluminum starch octenylsuccinate (ASOS). Polyethylene glycol, having molecular weight of 1000 or more (e.g., PEG 1,000, PEG 4,000, PEG 6,000 and PEG 10,000) also have gelling capacity and while they are considered herein as "secondary polar

solvents", as detailed herein, they are also considered polymeric agents.

**[0093]** In one or more embodiments the polymeric agents have emulsifying properties. In certain preferred embodiments the polymeric agent is a derivatized hydrophilic polymer with hydrophobic alkyl moieties. Other types that may also a similar stabilizing effect are silicone copolymers and derivatized starch ASOS.

**[0094]** Mixtures of the above polymeric agents are contemplated.

**[0095]** The concentration of the polymeric agent should be selected so that the composition, after filling into aerosol canisters, is flowable, and can be shaken in the canister. In one or more embodiments, the concentration of the polymeric agent is selected such that the viscosity of the composition, prior to filling of the composition into aerosol canisters, is less than 12,000 CPs, and more preferably, less than 10,000 CPs.

**Surface Active Agent**

**[0096]** The composition of the present invention further contains a surface-active agent. Surface-active agents (also termed "surfactants") include any agent linking oil and water in the composition, in the form of emulsion. A surfactant's hydrophilic/lipophilic balance (HLB) describes the emulsifier's affinity toward water or oil. HLB is defined for non-ionic surfactants. The HLB scale ranges from 1 (totally lipophilic) to 20 (totally hydrophilic), with 10 representing an equal balance of both characteristics. Lipophilic emulsifiers form water-in-oil (w/o) emulsions; hydrophilic surfactants form oil-in-water (o/w) emulsions. The HLB of a blend of two emulsifiers equals the weight fraction of emulsifier A times its HLB value plus the weight fraction of emulsifier B times its HLB value (weighted average). In many cases a single surfactant may suffice. In other cases a combination of two or more surfactants is desired. Reference to a surfactant in the specification can also apply to a combination of surfactants or a surfactant system. As will be appreciated by a person skilled in the art which surfactant or surfactant system is more appropriate is related to the vehicle and intended purpose. In general terms a combination of surfactants is usually preferable where the vehicle is an emulsion. In an emulsion environment a combination of surfactants can be significant in producing breakable forms of good quality. It has been further discovered that the generally thought considerations for HLB values for selecting a surfactant or sufactant combination are not always binding for emulsions and that good quality foams can be produced with a surfactant or surfactant combination both where the HLB values are in or towards the lipophilic side of the scale and where the HLB values are in or towards the hydrophilic side of the scale. Surfactants also play a role in foam formation where the foamable formulation is a single phase composition.

**[0097]** According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 2 and 9, or more than one surface active agent and the weighted average of their HLB values is between about 2 and about 9. Lower HLB values may in certain embodiments be more applicable to water in oil emulsions.

**[0098]** According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 7 and 14, or more than one surface active agent and the weighted average of their HLB values is between about 7 and about 14. Mid range HLB values may in certain embodiments be more suitable for oil in water emulsions.

**[0099]** According to one or more other embodiments the composition contains a single surface active agent having an HLB value between about 9 and about 19, or more than one surface active agent and the weighted average of their HLB values is between about 9 and about 19. In a waterless or substantially waterless environment a wide range of HLB values may be suitable.

**[0100]** Preferably, the composition of the present invention contains a non-ionic surfactant. Nonlimiting examples of possible non-ionic surfactants include a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59; a polyoxyethylene alkyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, steareths such as steareth 2, brij 21, brij 721, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol and its anhydrides, sorbitan monolaurate, sorbitan monolaurate, a monoglyceride, a diglyceride, isoceteth-20 and mono-, di- and tri-esters of sucrose with fatty acids. In certain embodiments, suitable sucrose esters include those having high monoester content, which have higher HLB values.

**[0101]** In certain embodiments with DCA esters as emollient, surfactants are selected which can provide a close packed sufacant layer separating the oil and water phases. To achieve such objectives combinations of at least two surfactants are selected. Preferrably, they should be complex emulgators and more preferably they should both be of a similar molecular type. For example, a pair of ethers like steareth 2 and steareth 21, or a pair of esters for example, PEG-40 stearate and polysorbate 80. In certain circumstances POE esters cannot be used and a combination of sorbitan laurate and sorbitan stearate or a combination of sucrose stearic acid ester mixtures and sodium laurate may be used. All these combinations due to heir versatility and strength may also be used satisfactorily and effectively with solutions of DCA's and with solid/crystalline suspensions, although the amounts and proportion may be varied according to the formulation and its objectives as will be appreciated by a man of the art.

**[0102]** It has been discovered also that by using a derivatized hydrophilic polymer with hydrophobic alkyl moieties as

a polymeric emulsifier such as pemulen it is possible to stabilize the emulsion better about or at the region of phase reversal tension. Other types of derivatized polymers like silicone copolymers, derivatized starch [Aluminum Starch Octenylsuccinate (ASOS)] / [DRY-FLO AF Starch], and derivatized dexrin may also a similar stabilizing effect.

**[0103]** A series of dextrin derivative surfactants prepared by the reaction of the propylene glycol polyglucosides with a hydrophobic oxirane-containing material of the glycidyl ether are highly biodegradable. [Hong-Rong Wang and Keng-Ming Chen, Colloids and Surfaces A: Physicochemical and Engineering Aspects Volume 281, Issues 1-3, 15 June 2006, Pages 190-193].

**[0104]** Non-limiting examples of non-ionic surfactants that have HLB of about 7 to about 12 include steareth 2 (HLB~4.9); glyceryl monostearate/PEG 100 stearate (Av HLB~11.2); stearate laureth 4 (HLB-9.7) and cetomacrogol ether (e.g., polyethylene glycol 1000 monocetyl ether).

**[0105]** Non-limiting examples of preferred surfactants, which have a HLB of 4-19 are set out in the Table below:

| Surfactant | HLB |
|---|---|
| steareth 2 | ~4.9 |
| glyceryl monostearate/PEG 100 stearate | Av ~11.2 |
| Glyceryl stearate | ~4 |
| steareth-21 | ~15.5 |
| peg 40 stearate | ~16.9 |
| polysorbate 80 | ~15 |
| sorbitan stearate | ~4.7 |
| laureth 4 | ~9.7 |
| sorbitan monooleate (span 80) | ~4.3 |
| ceteareth 20 | ~15.7 |
| steareth 20 | ~15.3 |
| ceteth 20 | ~15.7 |
| macrogol cetostearyl ether | ~15.7 |
| ceteth 2 (Lipocol C-2) | ~5.3 |
| PEG-30 Dipolyhydroxystearate | ~5.5 |
| sucrose distearate (Sisterna SP30) | ~6 |
| polyoxyethylene (100) stearate | ~18.8 |

**[0106]** More exemplary stabilizing surfactants which may be suitable for use in the present invention are found below.

**PEG-Fatty Acid Monoester Surfactants**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-30 stearate | Myrj 51 | >10 |
| PEG-40 laurate | Crodet L40 (Croda) | 17.9 |
| PEG-40 oleate | Crodet 040 (Croda) | 17.4 |
| PEG-45 stearate | Nikkol MYS-45 (Nikko) | 18 |
| PEG-50 stearate | Myrj 53 | >10 |
| PEG-100 stearate | Myrj 59, Arlacel 165 (ICI) | 19 |

**PEG-Fatty Acid Diester Surfactants:**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-4 dilaurate | Mapeg .RTM. 200 DL (PPG), Kessco .RTM.PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.) | 7 |
| PEG-4 | distearate Kessco .RTM. 200 DS (Stepan.sub) | 5 |
| PEG-32 dioleate | Kessco .RTM. PEG 1540 DO (Stepan) | 15 |
| PEG-400 dioleate | Cithrol 4DO series (Croda) | >10 |
| PEG-400 disterate | Cithrol 4DS series (Croda) | >10 |
| PEG-20 glyceryl oleate | Tagat .RTM. O (Goldschmidt) | >10 |

**Transesterification Products of Oils and Alcohols**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-30 castor oil | Emalex C-30 (Nihon Emulsion) | 11 |
| PEG-40 hydrogenated castor oil | Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel) | 13 |

**Polyglycerized Fatty Acids, such as:**

| Chemical name | Product example name | LB |
|---|---|---|
| Polyglyceryl-6 dioleate | Caprol .RTM. 6G20 (ABITEC); PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)Hodag | 8.5 |

**PEG-Sorbitan Fatty Acid Esters**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-20 sorbitan monolaurate | Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea) | 17 |
| PEG-20 sorbitan Monopalmitate | Tween 40 (Atlas/ICI), Crillet 2 (Croda) | 16 |
| PEG-20 sorbitan monostearate | Tween-60 (Atlas/ICI), Crillet 3 (Croda) | 15 |
| PEG-20 sorbitan monooleate | Tween-80 (Atlas/ICI), Crillet 4 (Croda) | 15 |

**Polyethylene Glycol Alkyl Ethers**

| Chemical name | Product example name | HLB |
|---|---|---|
| PEG-2 oleyl ether | oleth-2 Brij 92/93 (Atlas/ICI) | 4.9 |
| PEG-3 oleyl ether | oleth-3 Volpo 3 (Croda) | <10 |
| PEG-5 oleyl ether | oleth-5 Volpo 5 (Croda) | <10 |
| PEG-10 oleyl ether | oleth-10 Volpo 10 (Croda), Brij 96/97 (Atlas/ICI) | 12 |
| PEG-20 oleyl ether | oleth-20 Volpo 20 (Croda), Brij 98/99 (Atlas/ICI) | 15 |
| PEG-4 lauryl ether | laureth-4Brij 30 (Atlas/ICI) | 9.7 |
| PEG-23 lauryl ether | laureth-23Brij 35 (At)as/ICI) | 17 |
| PEG-10 stearyl ether | Brij 76 (ICI) | 12 |
| PEG-2 cetyl ether | Brij 52 (ICI) | 5.3 |

**Sugar Ester Surfactants**

| Chemical name | Product example name | HLB |
|---|---|---|
| Sucrose distearate | Sisterna SP50, Surfope 1811 | 11 |

**Sorbitan Fatty Acid Ester Surfactants**

| Chemical name | Product example name | HLB |
|---|---|---|
| Sorbitan monolaurate | Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI) | 8.6 |
| Sorbitan monopalmitate | Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko) | 6.7 |
| Sorbitan monooleate | Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda) | 4.3 |
| Sorbitan monostearate | Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko) | 4.7 |

**[0107]** In one or more embodiments the surface active agent is a complex emulgator in which the combination of two or more surface active agents can be more effective than a single surfactant and provides a more stable emulsion or improved foam quality than a single surfactant. For example and by way of non-limiting explanation it has been found that by choosing say two surfactants, one hydrophobic and the other hydrophilic the combination can produce a more stable emulsion than a single surfactant. Preferably, the complex emulgator comprises a combination of surfactants wherein there is a difference of about 4 or more units between the HLB values of the two surfactants or there is a significant difference in the chemical nature or structure of the two or more surfactants.

**[0108]** Specific non limiting examples of surfactant systems are, combinations of polyoxyethylene alkyl ethers, such as Brij 59 / Brij10; Brij 52 / Brij 10; Steareth 2 / Steareth 20; Steareth 2 / Steareth 21 (Brij 72 / Brij 721); combinations of polyoxyethylene stearates such as Myrj 52 / Myrj 59; combinations of sucrose esters, such as Surphope 1816 / Surphope 1807; combinations of sorbitan esters, such as Span 20 / Span 80; Span 20 / Span 60; combinations of sucrose esters and sorbitan esters, such as Surphope 1811 and Span 60; combinations of liquid polysorbate detergents and PEG compounds, such as Tween 80 / PEG-40 stearate; methyl glucaso sequistearate; polymeric emulsifiers, such as Permulen (TRI or TR2); liquid crystal systems, such as Arlatone (2121), Stepan (Mild RM1), Nikomulese (41) and Montanov (68) and the like.

**[0109]** In certain embodiments the surfactant is preferably one or more of the following: a combination of steareth-2 and steareth-21 on their own or in combination with glyceryl monostearate (GMS); in certain other embodiments the surfactant is a combination of polysorbate 80 and PEG-40 stearate. In certain other embodiments the surfactant is a combination of glyceryl monostearate/PEG 100 stearate. In certain other embodiments the surfactant is a combination of two or more of stearate 21, PEG 40 stearate, and polysorbate 80. In certain orher embodiments the surfactant is a combination of two or more of laureth 4, span80, and polysorbate 80. In certain other embodiments the surfactant is a combination of two or more of GMS and ceteareth. In certain other embodiments the surfactant is a combination of two or more of steareth 21, ceteareth 20, ceteth 2 and laureth 4. In certain other embodiments the surfactant is a combination of ceteareth 20 and polysorbate 40 stearate. In certain orther embodiments the surfactant is a combination of span 60 and GMS.

**[0110]** In certain other embodiments the surfactant is one or more of sucrose stearic acid esters, sorbitan laureth, and sorbitan stearate.

**[0111]** In one or more embodiments the stability of the composition can be improved when a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed. The ratio between the at least one non-ionic surfactant having HLB of less than 9 and the at least one non-ionic surfactant having HLB of equal or more than 9, is between 1:8 and 8:1, or at a ratio of 4:1 to 1:4. The resultant HLB of such a blend of at least two emulsifiers is preferably between about 9 and about 14.

**[0112]** Thus, in an exemplary embodiment, a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed, at a ratio of between 1:8 and 8:1, or at a ratio of 4:1 to 1:4, wherein the HLB of the combination of emulsifiers is preferably between about 5 and about 18.

**[0113]** In certain cases, the surface active agent is selected from the group of cationic, zwitterionic, amphoteric and ampholytic surfactants, such as sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, sodium lauryl sulfate, triethanolamine lauryl sulfate and betaines.

**[0114]** Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two incompatible components on a nanometer scale. Soap is an everyday example of a lyotropic liquid

crystal. Certain types of surfactants tend to form lyotropic liquid crystals in emulsions interface (oil-in-water) and exert a stabilizing effect.

**[0115]** In one or more embodiments the surfactant is a surfactant or surfactant combination is capable of or which tends to form liquid crystals. Surfactants which tend to form liquid crystals may improve the quality of foams. Non limiting examples of surfactants with postulated tendency to form interfacial liquid crystals are: phospholipids, alkyl glucosides, sucrose esters, sorbitan esters.

**[0116]** In one or more embodiments the at least one surface active agent is liquid.

**[0117]** In one or more embodiments the at least one surface active agent is solid, semi solid or waxy.

**[0118]** It should be noted that HLB values may not be so applicable to non ionic surfactants, for example, with liquid crystals or with silicones. Also HLB values may be of lesser significance in a waterless or substantially non-aqueous environment.

**[0119]** In one or more embodiments the surfactant can be, a surfactant system comprising of a surfactant and a co surfactant, a waxy emulsifier, a liquid crystal emulsifier, an emulsifier which is solid or semi solid at room temperature and pressure, or combinations of two or more agents in an appropriate proportion as will be appreciated a person skilled in the art. Where a solid or semi solid emulsifier combination is used it can also comprise a solid or semi solid emulsifier and a liquid emulsifier.

**[0120]** In one or more embodiments of the present invention, the surface-active agent includes at least one non-ionic surfactant. Ionic surfactants are known to be irritants. Therefore, non-ionic surfactants are preferred in applications including sensitive tissue such as found in most mucosal tissues, especially when they are infected or inflamed. Non-ionic surfactants alone can provide formulations and foams of good or excellent quality in the carriers and compositions of the present invention.

**[0121]** Thus, in a preferred embodiment, the surface active agent, the composition contains a non-ionic surfactant. In another preferred embodiment the composition includes a mixture of non-ionic surfactants as the sole surface active agent. Yet, in additional embodiments, the foamable composition includes a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio in the range of about 100:1 to 6:1. In one or more embodiments, the non-ionic to ionic surfactant ratio is greater than about 6:1, or greater than about 8:1; or greater than about 14:1, or greater than about 16:1, or greater than about 20:1. In further embodiments, surface active agent comprises a combination of a non-ionic surfactant and an ionic surfactant, at a ratio of between 1:1 and 20:1

**[0122]** In one or more embodiments of the present invention, a combination of a non-ionic surfactant and an ionic surfactant (such as sodium lauryl sulphate and cocamidopropylbetaine) is employed, at a ratio of between 1:1 and 20:1, or at a ratio of 4:1 to 10:1; for example, about 1:1, about 4:1, about 8:1, about 12:1, about 16:1 and about 20:1 or at a ratio of 4:1 to 10:1, for example, about 4:1, about 6:1, about 8:1 and about 10:1.

**[0123]** In selecting a suitable surfactant or combination thereof it should be borne in mind that the upper amount of surfactant that may be used may be limited by the shakability of the composition. If the surfactant is non liquid, it can make the formulation to viscous or solid. This can be particularly significant if the formulation has high molecular weight, e.g., a high molecular weight PEG or polymeric agents or petroleum or if the surfactants are large. Solvents and polymeric agents which have high molecular weight and are very viscous or solid or waxy (e.g., Peg 1500, 2000, etc. or petrolatum) can exacerbate the effect of a waxy or solid surfactant on shakability or flowability. In general terms, as the amount of non-liquid surfactant is increased the shakability of the formulation reduces until a limitation point is reached where the formulation becomes non shakable and unsuitable. Thus in one embodiment, an effective amount of surfactant may be used provided the formulation remains shakable. In other certain exceptional embodiments the upper limit may be determined by flowability such as in circumstances where the composition is marginally or apparently non-shakable. The formulation is sufficiently flowable to be able to flow through an actuator valve and be released and still expand to form a good quality foam.

**[0124]** In certain embodiments of the present invention the amount of surfactant or combination of surfactants is between about 0.05% to about 20%; between about 0.05% to about 15% or between about 0.05% to about 10%. In a preferred embodiment the concentration of surface active agent is between about 0.2% and about 8%. In a more preferred embodiment the concentration of surface active agent is between about 1 % and about 6%.

**[0125]** In some embodiments, it is desirable that the surface active agent does not contain a polyoxyethylene (POE) moiety, such as polysorbate surfactants, POE fatty acid esters, and POE alkyl ethers, because the active agent is incompatible with such surface active agents. For example, the active agent pimecrolimus is not stable the presence of POE moieties, yet benefits greatly from the use of dicarboxylic esters as penetration enhancers. In such cases, alternative surface active agents are employed. In an exemplary manner, POE - free surfactants include non-ethoxylated sorbitan esters, such as sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan tri-oleate, sorbitan monolaurate and sorbitan sesquioleate; glycerol fatty acid esters, such as glycerol monostearate and glycerol monooleate; mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), sucrose stearate, sucrose distearate sucrose palmitate and sucrose laurate; and alkyl polyglycosides, such as lauryl diglucoside.

**[0126]** If the composition as formulated is a substantially non shakable composition it is nevertheless possible as an

exception in the scope of the present invention for the formulation to be flowable to a sufficient degree to be able to flow through an actuator valve and be released and still expand to form a good quality foam. This surprising and unusual exception may be due one or more of a number of factors such as the high viscosity, the softness, the lack of crystals, the pseudoplastic or semi pseudo plastic nature of the composition and the dissolution of the propellant into the composition.

**[0127]** In one or more embodiments of the present invention, the surface-active agent includes mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), prepared from sucrose and esters of fatty acids or by extraction from sucro-glycerides. Suitable sucrose esters include those having high monoester content, which have higher HLB values.

Phase inversion and tension

**[0128]** Phase inversion is a factor in the preparation and stabilization of emulsions and can be both an aid and a detriment. Phase inversion involves the change of emulsion type from o/w to w/o or vice versa. Prior to phase inversion occurring there is a tension in the emulsion which if destabilized or driven will lead to phase inversion and if controlled or ameliorated or dissipated will result in a more stable emulsion. The occurrence of phase inversion during preparation can be a sign of instability. If controlled, it can result in a finer product but if due to other factors after the the emulsion was prepared it can cause problems. Inversion can occur by for example adding calcium chloride to an o/w emulsion stabilized with sodium stearate to form calcium stearate. Inversion can also occur as the product of changes to the phase- volume ratio. For example if a small amount of water is added to surfactant mixed with oil and agitated aw/o emulsion is formed. As the amount of water added is gradually increased a point will be reached where the water and emulsifier envlop the oil as small droplets to form an o/w emulsion. The amount of each ingredient including the surfactants will have their part to play in the phenomenum.

Substantially Alcohol-Free

**[0129]** According to one or more embodiments, the foamable composition is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butaneol, iso-butaneol, t-butaneol and pentanol, are considered less desirable solvents or polar solvents due to their skin-irritating effect. Thus, the composition is substantially alcohol-free and includes less than about 5% final concentration of lower alcohols, preferably less than about 2%, more preferably less than about 1%.

Substantially Non Aqueous

**[0130]** In certain cases, the active agent degrades in the presence of water, and therefore, in such cases the presence of water in the composition is not desirable. Thus, in certain preferred embodiments, the composition is substantially non-aqueous. The term "substantially non-aqueous" or "substantially waterless" is intended to indicate that the composition has a water content below about 5%, preferably below about 2%, such as below about 1.5%. In certain other preferred embodiments the composition is non aqueous or waterless.

**[0131]** By non-aqueous or waterless is meant that the composition contains no or substantially no, free or unassociated or absorbed water. It will be understood by a person of the art that the waterless solvents and substances miscible with them of the present invention can be hydrophilic and can contain water in an associated or unfree or absorbed form and may absorb water from the atmosphere and the ability to do so is its hygroscopic water capacity. It is intended that essentially non-aqueous formulations are included within its scope such that the formulations may have present a small amount of water. In some embodiments the composition ingredients are pretreated to reduce, remove or eliminate any residual or associated or absorbed water.

Shakability

**[0132]** 'Shakability' means that the composition contains some or sufficient flow to allow the composition to be mixed or remixed on shaking. That is, it has fluid or semi fluid properties. In some very limited cases possibly aided by the presence of silicone it may exceptionally be possible to have a foamable composition which is flowable but not apparently shakable.

Breakability

**[0133]** A breakable foam is one that is thermally stable, yet breaks under shear force.

**[0134]** The breakable foam of the present invention is not "quick breaking", i.e., it does not readily collapse upon

exposure to body temperature environment. Shear-force breakability of the foam is clearly advantageous over thermally induced breakability, since it allows comfortable application and well directed administration to the target area.

**Modulating Agent**

**[0135]** The term modulating agent is used to describe an agent which can improve the stability of or stabilize a foamable carrier or composition and or an active agent by modulating the effect of a substance or residue present in the carrier or composition.

**[0136]** In one or more embodiments the modulating agent is used in a water in oil or oil in water emulsion. In one or more other embodiments the modulating agent is used in a unique waterless emulsion.

**[0137]** In certain embodiments the substance or residue may for example be acidic or basic and potentially alter pH in an emulsion environment or it may be one or more metal ions which may act as a potential catalyst in an emulsion environment.

**[0138]** In certain other embodiments the substance or residue may for example be acidic or basic and potentially alter an artificial pH in a waterless or substantially non aqueous environment or it may be one or more metal ions which may act as a potential catalyst in a waterless or substantially non aqueous environment.

**[0139]** In one or more embodiments the modulating agent is used to describe an agent which can affect pH in an aqueous solution. The agent can be any of the known buffering systems used in pharmaceutical or cosmetic formulations as would be appreciated by a man of the art. It can also be an organic acid, a carboxylic acid, a fatty acid an amino acid, an aromatic acid, an alpha or beta hydroxyl acid an organic base or a nitrogen containing compound.

**[0140]** In one or more further embodiments the modulating agent is used to describe an agent, which is a chelating or sequestering or complexing agent that is sufficiently soluble or functional in the solvent to enable it to "mop up" or "lock" metal ions.

**[0141]** In an embodiment modulating agent is used to describe an agent which can effect pH in an aqueous solution. The term modulating agent more particularly means an acid or base or buffer system or combinations thereof, which is introduced into or is present in and acts to modulate the ionic or polar characteristics and any acidity or basesity balance of an emulsion carrier, composition, foamable carrier or foamable composition or resultant foam of the present invention.

**[0142]** In other embodiments modulating agent is used to describe an agent which can effect pH in an aqueous solution. The term modulating agent more particularly means an acid or base or buffer system or combinations thereof, which is introduced into or is present in and acts to modulate the ionic or polar characteristics and any acidity or basesity balance of a waterless or substantially non aqueous carrier, composition, foamable carrier or foamable composition or resultant foam of the present invention.

**[0143]** The substance or residue can be introduced into the formulation from any one or more of the ingredients, some of which themselves may have acidic or basic properties. For example the polymer or solvent may contain basic residues in which case it may be desirable or beneficial to add an acid. Alternatively the surfactant may contain some acid residues in which case the addition of a base may be desirable and beneficial. In some cases more than one ingredient may contain residues which may ameliorate or compound their significance. For example if one ingredient provided weak acid residues and another stronger acid residues the pH in an emulsion environment (or artificial pH in a waterless environment) should be lower. In contrast if one residue was acid and the other basic the net effect in the formulation maybe significantly reduced. In some circumstances the active ingredient may favor an acidic pH or more significantly may need to be maintained at a certain acidic pH otherwise it may readily isomerize, chemically react or breakdown, in which case introducing acidic components such as an acidic polymer might be of help. In an embodiment of the present invention sufficient modulating agent is added to achieve a pH in which the active agent is preferably stable. In another embodiment of the present invention sufficient modulating agent is added to achieve an artificial pH in which the active agent is preferably stable.

**[0144]** The terms pH, pKa, and pKb, buffers and the like are used in classical measurements of an aqueous solution. Such measurements are artificial in a waterless environment. Nevertheless, reference to and description below of such terms are made for convenience and clarity, since such terms are well defined and understood with reference to aqueous solutions and further due to the lack of an appropriate uniform way of describing and identifying the artificial or virtual pH, pK etc in a waterless environment in relation to the present invention. Although predictions of artificial pH can be made using dilution techniques of measurements of waterless formulations diluted in water they are formulation sensitive and specific and have to be carefully calibrated with complex formulas.

**[0145]** Waterless medium can be polar and protic yet it does not conform to classical ionic behavior.

**[0146]** A buffer, as defined by Van Slyke [Van Slyke, J. Biol. Chem. 52, 525 (1922)], is "a substance which by its presence in solution increases the amount of acid or alkali that must be added to cause unit change in pH."

**[0147]** A buffer solution is a solution of a definite pH made up in such a way that this pH alters only gradually with the addition of alkali or acid. Such a solution consists of a solution of a salt of the weak acid in the presence of the three acid itself. The pH of the solution is determined by the dissociation equilibrium of the free acid.

**[0148]** An acid can be a strong acid or a weak acid. A strong acid is an acid, which is a virtually 100% ionized in solution. In contrast, a weak acid is one which does not ionize fully when it is dissolved in water. The lower the value for pKa, the stronger is the acid and likewise, the higher the value for pKa the weaker is the acid.

**[0149]** A base can be a strong base or a weak base. A strong base is something, which is fully ionic with 100% hydroxide ions. In contrast, a weak base is one which does not convert fully into hydroxide ions in solution. The lower the value for pKb, the stronger is the base and likewise, the higher the value for pKb the weaker is the base.

**[0150]** In one or more embodiments of the present invention the modulating agent comprises an organic compound.

**[0151]** In one or more preferred embodiments of the present invention the chelating agent is selected from the group consisting of ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), hydroxyethylenediaminetriacetic acid (HEDTA), nitrilotriacetic acid (NTA), O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid (EGTA), trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CyDTA) or a pharmaceutically acceptable salt thereof (normally as a sodium salt), more preferably EDTA, HEDTA and their salts, most preferably EDTA and its salts.

**[0152]** In one or more embodiments of the present invention a preferred non limiting example of the chelating agent is EDTA. Typically, the chelating and sequestering agent is present in the composition at a level of up to about 5.0%, preferably 1.0 percent, by weight, of the composition.

**[0153]** In one or more embodiments of the present invention the modulating agent may also be a preservative or an antioxidant or an ionization agent. Any preservative, antioxidant or ionization agents suitable for pharmaceutical or cosmetic application may be used. Non limiting examples of antioxidants are tocopherol succinate, propyl galate, butylated hydroxy toluene and butyl hydroxy anisol. Ionization agents may be positive or may be negative depending on the environment and the active agent or composition that is to be protected. Ionization agents may for example act to protect or reduce sensitivity of active agents. Non limiting examples of positive ionization agents are benzyl conium chloride, and cetyl pyridium chloride. Non limiting examples of negative ionization agents are sodium lauryl sulphate, sodium lauryl lactylate and phospholipids.

**Humectant**

**[0154]** A humectant is a substance that helps retain moisture and also prevents rapid evaporation. Non limiting examples are propylene glycol, propylene glycol derivatives, glycerin, hydrogenated starch hydrosylate, hydrogenated lanolin, lanolin wax, D manitol, sorbitol, sodium 2-pyrrolidone-5-carboxylate, sodium lactate, sodium PCA, soluble collagen, dibutyl phthalate, and gelatin. Other examples may be found in the Handbook of Pharmaceutical Additives published by Gower.

**Moisturizers**

**[0155]** A moisturizer, is a substance that helps retain moisture or add back moisture to the skin. Examples are allantoin, petrolatum, urea, lactic acid, sodium PCV, glycerin, shea butter, caprylic/capric/stearic triglyceride, candelilla wax, propylene glycol, lanolin, hydrogenated oils, squalene, sodium hyaluronate and lysine PCA. Other examples may be found in the Handbook of Pharmaceutical Additives published by Gower.

**[0156]** Pharmaceutical compositions of the present invention may in one or more embodiments usefully comprise in addition a heumectant or a moisturizer or combinations thereof.

**Polar solvent**

**[0157]** Optionally, the foamable vehicle further includes at least one polar solvent.

**[0158]** A "polar solvent" is an organic solvent, typically soluble in both water and oil. Certain polar solvents, for example propylene glycol and glycerin, possess the beneficial property of a heumectant.

**[0159]** In one or more embodiments, the polar solvent is a heumectant.

**[0160]** In one or more embodiments, the polar solvent is a polyol. Polyols are organic substances that contain at least two hydroxy groups in their molecular structure.

**[0161]** In one or more embodiments, the polar solvent contains an diol (a compound that contains two hydroxy groups in its molecular structure), such as propylene glycol (e.g., 1,2-propylene glycol and 1,3-propylene glycol), butaneediol (e.g., 1,4-butaneediol), butaneediol (e.g., 1,3-butaneediol and 1,4-butenediol), butynediol, pentanediol (e.g., 1,5-pentanediol), hexanediol (e.g., 1,6-hexanediol), octanediol (e.g., 1,8-octanediol), neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol.

**[0162]** In one or more embodiments, the polar solvent contains a triol (a compound that contains three hydroxy groups in its molecular structure), such as glycerin and 1,2,6-Hexanetriol.

**[0163]** Other non-limiting examples of polar solvents include pyrrolidones, (such as N-methyl-2-pyrrolidone and 1-methyl-2-pyrrolidinone), dimethyl isosorbide, 1,2,6-hexapetriol, dimethyl sulfoxide (DMSO), ethyl proxitol, dimethyla-

cetamide (DMAc) and alpha hydroxy acids, such as lactic acid and glycolic acid.

**[0164]** According to still other embodiments, the polar solvent is a polyethylene glycol (PEG) or PEG derivative that is liquid at ambient temperature, including PEG200 (MW (molecular weight) about 190-210 kD), PEG300 (MW about 285-315 kD), PEG400 (MW about 380-420 kD), PEG600 (MW about 570-630 kD) and higher MW PEGs such as PEG 4000, PEG 6000 and PEG 10000 and mixtures thereof.

**[0165]** Polar solvents are known to enhance the penetration of active agent into the skin and through the skin, and therefore, their inclusion in the composition of the present invention can be desirable, despite their undesirable skin drying and irritation potential. There is at one level a commonality between the different polar solvents and their penetration enhancement properties. Lower molecular weight alcohols can sometimes be more potent as a solvent, for example by extracting lipids from the skin layers more effectively, which characteristic can adversely affect the skin structure and cause dryness and irritation. Therefore the selection of lower molecular weight alcohols is ideally avoided.

**[0166]** Polar solvents, such as detailed below possess high solubilizing capacity and contribute to the skin penetration of an active agent. Non limiting examples include dimethyl isosorbide, polyols, such as glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, oleyl alcohol, alpha-hydroxy acids, such as lactic acid and glycolic acid, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, alkanols, such as dialkylamino acetates, and admixtures thereof. In certain preferred embodiments, the polar solvent is selected from the group consisting of dimethyl isosorbide glycerol (glycerin), propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

**Skin penetration enhancer**

**[0167]** A "skin penetration enhancer", also termed herein "penetration enhancer," is an organic solvent, typically soluble in both water and oil. Examples of penetration enhancer include polyols, such as glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, terpenols, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, hexylene glycol, other glycols, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, dimethylisosorbide, monooleate of ethoxylated glycerides (with 8 to 10 ethylene oxide units), azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, esters, such as isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl proprionate, capric/caprylic triglycerides, octylmyristate, dodecyl-myristate; myristyl alcohol, lauryl alcohol, lauric acid, lauryl lactate ketones; amides, such as acetamide oleates such as triolein; various alkanoic acids such as caprylic acid; lactam compounds, such as azone; alkanols, such as dialkylamino acetates, and admixtures thereof.

**[0168]** According to one or more embodiments, the penetration enhancer is a polyethylene glycol (PEG) or PEG derivative that is liquid at ambient temperature

**Potent Solvent**

**[0169]** In one or more embodiments of the present invention, the foamable composition includes a potent solvent, in addition to or in place of one of the hydrophobic solvents, polar solvents or emollients of the composition. A potent solvent is a solvent other than mineral oil that solubilizes a specific active agent substantially better than a hydrocarbon solvent such as mineral oil or petrolatum. For example, a potent solvent solubilizes the active agent 5 fold better than a hydrocarbon solvent; or even solubilizes the active agent 10-fold better than a hydrocarbon solvent.

**[0170]** In one or more embodiments of the present invention, the composition includes at least one active agent in a therapeutically effective concentration; and at least one potent solvent in a sufficient amount to substantially solubilize the at least one active agent in the composition. The term "substantially soluble" means that at least 95% of the active agent has been solubilized, i.e., 5% or less of the active agent is present in a solid state. In one or more embodiments, the concentration of the at least one potent solvent is more than about 40% of the at least one solvent of the composition of the present invention; or even more than about 60%.

**[0171]** Non-limiting examples of pairs of active agent and potent solvent include: Betamethasone valerate: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol; Hydrocortisone butyrate: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol; Metronidazole: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in dimethyl isosrbide; Ketoconazole: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol, propylene glycol and dimethyl isosrbide; Mupirocin: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol, hexylene glycol, dimethyl isosorbide, propylene glycol and polyethylene glycol 400 (PEG 400); Meloxicam, a nonsteroidal anti-inflammatory agent: Practically insoluble in mineral oil (<0.001%); soluble in propylene glycol: 0.3 mg/mL; and in PEG 400: 3.7 mg/mL; and Progesterone: Practically insoluble in mineral oil (<0.001%); soluble in PEG 400: 15.3 mg/mL.

**[0172]** A non-limiting exemplary list of solvents that can be considered as potent solvents includes polyethylene glycol, propylene glycol, hexylene glycol, butaneediols and isomers thereof, glycerol, benzyl alcohol, DMSO, ethyl oleate, ethyl caprylate, diisopropyl adipate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, isosorbide derivatives, such as dimethyl isosorbide, glycofurol and ethoxydiglycol (transcutol) and laurocapram .

**[0173]** The use of a potent solvent in a foam composition provides an improved method of delivering poorly soluble therapeutic agents to a target area. It is known that low drug solubility results in poor bioavailability, leading to decreased effectiveness of treatment. Foam compositions of the present invention, for which the solvent includes a potent solvent, increase the levels of the active agent in solution and thus, provide high delivery and improved therapy.

**[0174]** Potent solvents, as defined herein, are usually liquid. Formulations comprising potent solvents and active agents are generally disadvantageous as therapeutics, since their usage involves unwanted dripping and inconvenient method of application; resulting in inadequate dosing. Surprisingly, the foams of the present invention, which are drip-free, provide a superior vehicle for such active agents, enabling convenient usage and accurate effective dosing.

**[0175]** In one or more embodiments of the present invention the present invention the foamable pharmaceutical composition may additionally include a mixture of two or more of the solvents selected from the group of hydrophobic solvents, silicone oils, emollients, polar solvents and potent solvents in an appropriate proportion as would be appreciated to a person skilled in the art.

**[0176]** In one or more embodiments of the present invention, the PPG alkyl ether may act as a potent solvent

**Additional components**

**[0177]** In an embodiment of the present invention, a composition of the present invention includes one or more additional components. Such additional components include but are not limited to anti perspirants, anti-static agents, buffering agents, bulking agents, chelating agents, cleansers, colorants, conditioners, deodorants, diluents, dyes, emollients, fragrances, hair conditioners, humectants, pearlescent aids, perfuming agents, permeation enhancers, pH-adjusting agents, preservatives, protectants, skin penetration enhancers, softeners, solubilizers, sunscreens, sun blocking agents, sunless tanning agents, viscosity modifiers and vitamins. As is known to one skilled in the art, in some instances a specific additional component may have more than one activity, function or effect.

**Propellants**

**[0178]** Suitable propellants include volatile hydrocarbons such as butane, propane, isobutane and fluorocarbon gases, or mixtures thereof.

**[0179]** The propellant makes up about 5-25 wt% of the foamable composition. The propellants are used to generate and administer the foamable composition as a foam. The total composition including propellant, foamable compositions and optional ingredients is referred to as the foamable composition.

**[0180]** Alcohol and organic solvents render foams inflammable. It has been surprisingly discovered that fluorohydrocarbon propellants, other than chloro-fluoro carbons (CMCs), which are non-ozone-depleting propellants, are particularly useful in the production of a non-flammable foamable composition. A test according to European Standard prEN 14851, titled "Aerosol containers - Aerosol foam flammability test" revealed that compositions containing an organic carrier that contains a hydrophobic organic carrier and/or a polar solvent, which are detected as inflammable when a hydrocarbon propellant is used, become non-flammable, while the propellant is an HFC propellant.

**[0181]** Such propellants include, but are not limited to, hydrofluorocarbon (HFC) propellants, which contain no chlorine atoms, and as such, fall completely outside concerns about stratospheric ozone destruction by chlorofluorocarbons or other chlorinated hydrocarbons. Exemplary non-flammable propellants according to this aspect of the invention include propellants made by DuPont under the registered trademark Dymel, such as 1,1,1,2 tetrafluorethane (Dymel 134), and 1,1,1,2,3,3,3 heptafluoropropane (Dymel 227). HFCs possess Ozone Depletion Potential of 0.00 and thus, they are allowed for use as propellant in aerosol products.

**[0182]** Notably, the stability of foamable emulsions including HFC as the propellant can be improved in comparison with the same composition made with a hydrocarbon propellant.

**[0183]** In one or more embodiments foamable compositions comprise a combination of a HFC and a hydrocarbon propellant such as n-butane or mixtures of hydrocarbon propellants such as propane, isobutane and butane.

**MICROEMULSIONS AND NANOEMULSIONS**

**[0184]** Microemulsions and nanoemulsion are monophasic, transparent (or slightly translucent) dispersions of oil and water. Unlike conventional emulsions, microemulsions and nanoemulsion are thermodynamically stable, making them a favorable vehicle for pharmaceutical compositions, which have to maintain stability for long periods of time. They and a method of manufacture are more particularly described in US2006/0233721 which is incorporated herein by way of

reference. As will be appreciated by a man of the art the methodology may be adapted according to the type of carrier composition.

**AGING**

**[0185]** In order to project the potential shelf life and stability of the compositions and their ingredients particularly active or benefit agents the compositions can be subjected to a number of tests, including centrifugation to look for resistance to creaming, phase separation; one or more freeze thaw cycles, standing at room and higher temperatures as an indicator of resistance to aging.

**Composition and Foam Physical Characteristics and Advantages**

**[0186]** A pharmaceutical or cosmetic composition manufactured using the foamable carrier of the present invention is very easy to use. When applied onto the afflicted body surface of mammals, i.e., humans or animals, it is in a foam state, allowing free application without spillage. Upon further application of a mechanical force, e.g., by rubbing the composition onto the body surface, it freely spreads on the surface and is rapidly absorbed.

**[0187]** The foamable composition of the present invention is stable, having an acceptable shelf-life of at least one year, or preferably, at least two years at ambient temperature, as revealed in accelerated stability tests. The foamable compositions according to the present invention are stable. Following accelerated stability studies, they demonstrate desirable texture; they form fine bubble structures that do not break immediately upon contact with a surface, spread easily on the treated area and absorb quickly.

**[0188]** The composition should also be free flowing, to allow it to flow through the aperture of the container, e.g., and aerosol container, and create an acceptable foam.

**[0189]** Foam quality can be graded as follows:

Grade E (excellent): very rich and creamy in appearance, does not show any bubble structure or shows a very fine (small) bubble structure; does not rapidly become dull; upon spreading on the skin, the foam retains the creaminess property and does not appear watery.

Grade G (good): rich and creamy in appearance, very small bubble size, "dulls" more rapidly than an excellent foam, retains creaminess upon spreading on the skin, and does not become watery.

Grade FG (fairly good): a moderate amount of creaminess noticeable, bubble structure is noticeable; upon spreading on the skin the product dulls rapidly and becomes somewhat lower in apparent viscosity.

Grade F (fair): very little creaminess noticeable, larger bubble structure than a "fairly good" foam, upon spreading on the skin it becomes thin in appearance and watery.

Grade P (poor): no creaminess noticeable, large bubble structure, and when spread on the skin it becomes very thin and watery in appearance.

Grade VP (very poor): dry foam, large very dull bubbles, difficult to spread on the skin.

**[0190]** Topically administrable foams are typically of quality grade E or G, when released from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously immediately upon discharge from the container. The finer foam structure looks and feels smoother, thus increasing its usability and appeal.

**[0191]** A further aspect of the foam is breakability. The breakable foam is thermally stable, yet breaks under shear force. Shear-force breakability of the foam is clearly advantageous over thermally induced breakability. Thermally sensitive foams immediately collapse upon exposure to skin temperature and, therefore, cannot be applied on the hand and afterwards delivered to the afflicted area.

**[0192]** Another property of the foam is specific gravity, as measured upon release from the aerosol can. Typically, foams have specific gravity of less than 0.12 g/mL; or less than 0.10 g/mL; or less than 0.08 g/mL, depending on their composition and on the propellant concentration.

**Pharmaceutical composition**

**[0193]** The foamable carrier of the present invention is an ideal vehicle for active pharmaceutical ingredients and active cosmetic ingredients. In the context of the present invention, active pharmaceutical ingredients and active cosmetic ingredients are collectively termed "active agent" or "active agents."

**[0194]** In one or more embodiments, the azelaic acid is the active ingredient. It can be used in the formulation as a suspended solid or in solution, alone or in combination with other active agents. As is known to one skilled in the art, in some instances a specific active agent may have more than one activity, function or effect.

**[0195]** In one embodiment, the azelaic acid is useful as an antibiotic, an antifungal agent, a keratolytic agent, an

inhibitor of the reduction of testosterone to dihydrotestosterone, an inhibitor of the production of sebum in the sebaceous gland, an anti-acne agent, by way of example. Dicarboxylic acids, and azelaic acid in particular, may be used for the treatment of diaper rash, hyperpigmentary drmatoses, acne, presbyderma of aging skin, hyperhydrosis, ischthyosis, and wrinkling of the skin, antitumor agents (for example, in conjunction with vitamins A, E and D), rosacea, a pigmentation disorder, a cell proliferation abnormality a skin infection and a skin inflammation and treatment of corns and callouses due to the anti-keratolytic effects.

**[0196]** In one or more embodiments, the dicarboxylic acid or dicarboxylic ester is used as a solvent for an active agent or as a penetration enhancer for an active agent.

**[0197]** Suitable active agents for use in conjunction with a dicarboxylic acid or a dicarboxylic ester include, but are not limited to, active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, antiyeast agents, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hair growth regulators, hormones, hydroxy acids, immunosuppressants, immunoregulating agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, self tanning agents, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, wound healing agents and wart removers. As is known to one skilled in the art, in some instances a specific active agent may have more than one activity, function or effect.

**[0198]** In one or more embodiments, the formulation may additionally include a steroidal anti-inflammatory agent. A dicarboxylic acid ester may be present in the composition in an amount sufficient to solubilize the steroid. Exemplary steroidal anti-inflammatory agents include, but are not limited to, corticosteroids such as bydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethsone dipropionate, clobetasol valemate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortmate, mepreddisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof. In an embodiment of the present invention, the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the steroid.

**[0199]** In one embodiment, the formulation may additionally include an immunomodulator. A dicarboxylic acid ester may be present in the composition in an amount sufficient to solubilize the immunomodulator. Immunomodulators are chemically or biologically-derived agents that modify the immune response or the functioning of the immune system (as by the stimulation of antibody formation or the inhibition of white blood cell activity). Immunomodulators include, among other options, cyclic peptides, such as cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus (rapamycin), verolimus, laflunimus, laquinimod and imiquimod. Such compounds, delivered in the foam of the present invention, are especially advantageous in skin disorders such as psoriasis, eczema and atopic dermatitis, where the large skin areas are to be treated.

**[0200]** In an embodiment of the present invention, the active agent is selected from a dicarboxylic acid and a dicarboxylic acid ester.

**[0201]** Because of the multiple therapeutic properties of dicarboxylic acids and their respective esters, the combination of such dicarboxylic acids or their respective esters with another active agents can result in a synergistic therapeutic benefit. For example, psoriasis is characterized by a heperkeratinization aspect and an inflammation, and therefore, its treatment can benefit from the combination of a dicarboxylic acid, which is keratolytic and a steroid.

**Fields of Applications**

**[0202]** The foamable carrier of the present invention is suitable for treating any inflicted surface. In one or more embodiments, foamable carrier is suitable for administration to the skin, a body surface, a body cavity or mucosal surface, e.g., the cavity and/or the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum (severally and interchangeably termed herein "target site").

**[0203]** In one embodiment, the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid.

**[0204]** In another embodiment, the disorder is a dermatological disorder that can benefit from the use of a dicarboxylic



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acid or dicarboxylic ester in conjunction with another active agent. The dicarboxylic acid or dicarboxylic ester may benefit by improving the solubility of the active agent or increasing the penetration of the active agent. The dicarboxylic acid or dicarboxylic ester may also provide a synergistic therapeutic effect in combination with the active agent.

**[0205]** By selecting a suitable active agent, or a combination of two or more active agents, the foamable composition of the present invention is useful in treating an animal or a human patient having any one of a variety of dermatological disorders, including dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychial infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, granuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callouses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo.

**[0206]** Likewise, the foamable composition of the present invention is suitable for treating a disorder of a body cavity or mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum. Non limiting examples of such conditions include chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum.

**[0207]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid.

**[0208]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid ester.

**[0209]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by a topical steroid, and the dicarboxylic acid or dicarboxylic ester provides a beneficial effect by increasing the solubility or penetration of the topical steroid.

**[0210]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by an immunomodulator and the dicarboxylic acid or dicarboxylic ester provides a beneficial effect by increasing the solubility or penetration of the topical immunomodulator.

**[0211]** In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by an anti-infective agent, such as an antibacterial agent, and antibiotic, an antifungal agent and an antiviral agent, and the dicarboxylic acid or dicarboxylic ester provides a beneficial effect as an anti-infective agent or by increasing the solubility or penetration of the anti-infective agent.

**[0212]** In an embodiment of the present invention, the disorder is a dermatological disorder, which is common in children. Foam is advantageous in the topical treatment of children, who are sensitive to treatment with a cream or ointment.

**[0213]** In an embodiment of the present invention, the disorder is atopic dermatitis and the active agent is a steroid, further including a dicarboxylic acid (DCA) or DCA ester to stabilize or solubilize the topical steroid.

**[0214]** In an embodiment of the present invention, the disorder is psoriasis and the active agent is a steroid, further including a DCA or DCA ester to stabilize or solubilize the topical steroid.

**[0215]** In an embodiment of the present invention, the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises a steroid and an additional non-steroidal active agent, such as a vitamin D derivative, further including a DCA or DCA ester to stabilize or solubilize the topical steroid and/or non-steroidal active agent.

**[0216]** In an embodiment of the present invention, the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises an immunomodulator, further including a DCA or DCA ester to stabilize or solubilize the immunomodulator.

**[0217]** In an embodiment of the present invention, the composition is useful for the treatment of an infection. In one

or more embodiments, the composition is suitable for the treatment of an infection, selected from the group of a bacterial infection, a fungal infection, a yeast infection, a viral infection and a parasitic infection.

**[0218]** In an embodiment of the present invention, the composition is useful for the treatment of wound, ulcer and burn.

**[0219]** The composition of the present invention is also suitable for administering a hormone to the skin or to a mucosal membrane or to a body cavity, in order to deliver the hormone into the tissue of the target organ, in any disorder that responds to treatment with a hormone.

**[0220]** Other foamable compositions are described in: U.S. Publication No. 05-0232869, published on October 20, 2005, entitled NONSTEROIDAL IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0205086, published on September 22, 2005, entitled RETINOID IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0018937, published on January 26, 2006, entitled STEROID KIT AND FOAMABLE COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0271596, published on December 8, 2005, entitled VASOACTIVE KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0269485, published on November 30, 2006, entitled ANTIBIOTIC KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 07-0020304, published on January 25, 2007, entitled NON-FLAMMABLE INSECTICIDE COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0193789, published on August 31, 2006, entitled FILM FORMING FOAMABLE COMPOSITION; U.S. Patent Application No. 11/732547, filed on April 4, 2007, entitled ANTI-INFECTION AUGMENTATION OF FOAMABLE COMPOSITIONS AND KIT AND USES THEREOF; U.S. Provisional Patent Application No. 60/789186, filed on April 4, 2006, KERATOLYTIC ANTIFUNGAL FOAM; U.S. Provisional Patent Application No. 0/815948, filed on June 23, 2006, entitled FOAMABLE COMPOSITIONS COMPRISING A CALCIUM CHANNEL BLOCKER, A CHOLINERGIC AGENT AND A NITRIC OXIDE DONOR; U.S. Provisional Patent Application No. 60/818634, filed on July 5, 2006, entitled DICARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF; U.S. Provisional Patent Application No. 60/843140, filed on September 8, 2006, entitled FOAMABLE VEHICLE AND VITAMIN PHARMACEUTICAL COMPOSITIONS THEREOF, all of which are incorporated herein by reference in their entirety. More particularly any of the active ingredients; the solvents; the surfactants; foam adjuvants; penetration enhancers; humectants; moisturizers; and other excipients as well as the propellants listed therein can be applied herein and are incorporated by reference.

**[0221]** The following examples further exemplify the azelaic acidfoamable pharmaceutical carriers, pharmaceutical compositions thereof, methods for preparing the same, and therapeutic uses of the compositions. The examples are for the purposes of illustration only and are not intended to be limiting of the invention. Many variations may be carried out by one of ordinary skill in the art and are contemplated within the full scope of the present invention.

## METHODOLOGY

**[0222]** A general procedure for preparing foamable compositions is set out in WO 2004/037225, which is incorporated herein by reference.

### Emulsion Foam

**[0223]**

1. Mix oily phase ingredients and heat to 75°C to melt all ingredients and obtain homogeneous mixture.
2. Mix polymers in water with heating or cooling as appropriate for specific polymer.
3. Add all other water soluble ingredients to water-polymer solution and heat to 75°C.
4. Add slowly internal phase to external phase at 75°C under vigorous mixing and homogenize to obtain fine emulsion. Alternatively the external phase is added slowly to the internal phase.
5. Cool to below 40°C and add sensitive ingredients with mild mixing.
6. Cool to room temperature.

### Waterless Foam

**[0224]**

1. Dissolve the polymers in the main solvent with heating or cooling as appropriate for specific polymer. Add the all other ingredients and heat to 75°C to melt and dissolve the various ingredients.
2. Cool to below 40°C and add sensitive ingredients with mild mixing.
3. Cool to room temperature.

**Oily Waterless Foam**

**[0225]**

1. Mix all ingredients excluding polymers and heat to 75°C to melt and dissolve and obtain homogeneous mixture.
2. Mix well and cool to below 40°C and add the polymers and sensitive ingredients with moderate mixing.
3. Cool to room temperature.

**Oily Foam with phospholipids and/or water**

**[0226]**

1. Swell the phospholipids in the main oily solvent under mixing for at least 20 minutes until uniform suspension is obtained.
2. Add all other ingredients excluding polymers and heat to 75°C to melt and dissolve and obtain homogeneous mixture.
3. Mix well and cool to below 40°C and add the polymers and sensitive ingredients with moderate mixing.
4. Cool to room temperature.
5. In case of polymers dissolved in water or organic solvent, dissolve the polymers in the solvent with heating or cooling as appropriate for specific polymer and add to the oily mixture under vigorous mixing at ~40°C.

Canisters Filling and Crimping

**[0227]** Each aerosol canister is filled with PFF and crimped with valve using vacuum crimping machine.

Pressurizing

Propellant Filling

**[0228]** Pressurizing is carried out using a hydrocarbon gas or gas mixture Canisters are filled and then warmed for 30 sec in a warm bath at 50°C and well shaken immediately thereafter.

Closure Integrity Test.

**[0229]** Each pressurized canister is subjected to bubble and crimping integrity testing by immersing the canister in a 60°C water bath for 2 minutes. Canisters are observed for leakage as determined by the generation of bubbles. Canisters releasing bubbles are rejected.

**TESTS**

**[0230]** By way of non limiting example the objectives of hardness, collapse time and FTC stability tests are briefly set out below as would be appreciated by a person of the art.

Hardness

**[0231]** LFRA100 instrument is used to characterize hardness. A probe is inserted into the test material. The resistance of the material to compression is measured by a calibrated load cell and reported in units of grams on the texture analyzer instrument display. Preferably at least three repeat tests are made. The textural characteristics of a dispensed foam can effect the degree of dermal penetration, efficacy, spreadability and acceptability to the user. The results can also be looked at as an indicator of softness. Note: the foam sample is dispensed into an aluminum sample holder and filled to the top of the holder.

Collapse Time

**[0232]** Collapse time (CT) is examined by dispensing a given quantity of foam and photographing sequentially its appearance with time during incubation at 36°C. It is useful for evaluating foam products, which maintain structural stability at skin temperature for at least 1 min.



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Viscosity

**[0233]** Viscosity is measured with Brookfield LVDV-II + PRO with spindle SC4-25 at ambient temperature and 10, 5 and 1 RPM. Viscosity is usually measured at 10RPM. However, at about the apparent upper limit for the spindle of ~>50,000CP, the viscosity at 1 RPM may be measured, although the figures are of a higher magnitude.

FTC (Freeze Thaw Cycles)

**[0234]** To check the foam appearance under extreme conditions of repeated cycles of cooling, heating, (first cycle) cooling, heating (second cycle) etc., commencing with -100°C (24hours) followed by +400°C (24hours) measuring the appearance and again repeating the cycle for up to three times.

Creaming by centrifugation:

**[0235]**

1. Principle of test
The centrifugation used in this procedure serves as a stress condition simulating the aging of the liquid dispersion under investigation. Under these conditions, the centrifugal force applied facilitates the coalescence of dispersed globules or sedimentation of dispersed solids, resulting in loss of the desired properties of the formulated dispersion.
2. Procedure

2.1. Following preparation of the experimental formulation/s, allow to stand at room temperature for ≥ 24 h.
2.2. Handle pentane in the chemical hood. Add to each experimental formulation in a 20-mL glass vial a quantity of pentane equivalent to the specified quantity of propellant for that formulation, mix and allow formulation to stand for at least 1 h and not more than 24 h.
2.3. Transfer each mixture to 1.5 mL microtubes. Tap each microtube on the table surface to remove entrapped air bubbles.
2.4. Place visually balanced microtubes in the centrifuge rotor and operate the centrifuge at 3,000 rpm for 10 min or at 1,000 rpm for 10 min.

Intra-canister uniformity

**[0236]**

1. Representative product containers are collected, sample test solutions are prepared and the content of the analyte is determined according to standard methods in the art. Variability of content is characterized as percent difference or relative standard deviation, as appropriate, according to the number of samples evaluated.
2. The results ascertain variability or uniformity within a given container in content of analytes (primarily active pharmaceutical ingredients, but also preservatives) taken from different parts of a pressurized canister drug products.
3. Two full canisters were shaken according to product instructions. About 1-3 g of Foam was dispensed from each canister and discarded. Foam sufficient for two replicate sample solution preparations was then dispensed into a glass beaker. This represents the initial sample. A middle portion is then dispensed from each canister being about half the canister contents. This middle dispensed portion may be discarded or collected for testing purposes, as necessary. Foam sufficient for two replicate sample solution preparations was then dispensed into a glass beaker. This represents the final sample. A small amount of formulation remains in the canister. The foam samples were stirred to remove gas / air bubbles. From both the initial and final foam portions from each canister 4 separate sample solutions are prepared and analyzed, 2 from the initial portion and 2 from the final portion. The percent difference is calculated as follows:

$$\frac{\text{Difference between content determined in initial \& final portions}}{\text{Mean of content of initial \& final portions}} \times 100$$

and the intra canister uniformity evaluated from the results.

## STOCK COMPOSITIONS

**[0237]** Non-limiting examples of how stock solutions are made up with and without API. Other stock solutions may be made using the same methodology by simply varying adding or omitting ingredients as would be appreciated by one of the ordinary skills in the art.

## Examples

**[0238]** The invention is described with reference to the following examples. This invention is not limited to these examples and experiments. Many variations will suggest themselves and are within the full intended scope of the claims.

## SUSPENSIONS

Example 1 - Dicarboxylic acid composition

**[0239]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

Part A -Formulation

| Ingredient | %w/w |
|---|---|
| Azelaic Acid | 15.00 |
| Water | 51.90 |
| Caprylic/Capric triglyceride | 10.87 |
| Propylene glycol | 10.87 |
| Dimethyl isosorbide | 5.44 |
| PEG-40 stearate | 2.83 |
| Cetostearyl alcohol | 1.09 |
| Polysorbate 80 | 0.98 |
| Glyceryl stearate | 0.54 |
| Xanthan gum | 0.27 |
| Methylcellulose A4M | 0.11 |
| Benzoic acid | 0.10 |
| NaOH (18% Solution) | to pH=4.5 |
| Total: | 100 |

Notes

**[0240]**

- The composition contains azelaic acid as a benefit agent, which is suitable for treating a skin disorder, selected from acne, rosacea, a pigmentation disorder, a cell proliferation abnormality a skin infection and a skin inflammation.
- The composition contains about 10% capric/caprylic triglyceride to provide emolliency and about 10% propylene glycol and 10% dimethyl isosorbide, to provide (1) enhanced emolliency; (2) improved solubilizing capacity of the azelaic acid; and (3) enhanced skin delivery.
- The compositions contain about 50% water. Therefore, they provide high skin barrier build-up effect.
- The composition can be used as a cream/lotion for topical therapy of a skin diorder.
- In order to create a foamable composition, the composition is filled into an aerosol canister and pressurized using a liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

Part B - 12 month stability test

| Test parameter | | T-0 | T-12 | |
|---|---|---|---|---|
| | | | upright | inverted |
| API* assay by HPLC (%) | % amount of label | 99.3 | 100.5 | 101.7 |
| | % w/w | 14.90 | 15.07 | 15.26 |
| Product content uniformity (Intra canister) of API (%) | | 1.79 | 0.10 | 0.88 |
| *API = active pharmaceutical ingredient | | | | |

**[0241]** The total amount of active agent at T-0 and at T-12 months as a percentage of 100% of ingredient that should be present according to the label and as a percentage in the formulation w/w, respectively was determined. As can be seen, no reduction in API content was observed within the limits of detection and that the content remained uniform. The differences between samples taken from the top of the canisters and from samples taken from the bottom of the canisters were not significant and were well within the acceptable range.

**[0242]** Furthermore, the formulation comprising active ingredient azaleic acid - despite being a suspension and subject to graviational effect - was able to withstand sedimentation and degredation such that it has remained stable and uniformly distributed in the formulation as a suspension over a prolonged period of 12 months, whilst remaining flowable and shakable.

Example 2 - Additional dicarboxylic acid compositions

**[0243]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| Formulation : | AZL018 | AZL03 4 | AZL03 5 | AZL03 6 | AZL03 7 | AZL03 8 | AZL03 9 |
|---|---|---|---|---|---|---|---|
| | %w/w | %w/w | %w/w | %w/w | %w/w | %w/w | %w/w |
| Azelaic Acid | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Caprylic/capric triglyceride | 5.00 | 10.00 | 5.00 | 5.00 | 5.00 | 5.00 | 10.00 |
| Cetostearyl alcohol | 0.90 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Glyceryl stearate | 0.45 | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 |
| Cholesterol | 1.00 | --- | --- | --- | --- | 1.00 | --- |
| Benzoic acid | | 0.20 | --- | 0.20 | 0.20 | 0.20 | --- |
| Benzyl alcohol | 1.00 | --- | 1.00 | --- | --- | --- | 1.00 |
| PEG-40 stearate | | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 |
| Methylcellulose | | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 | 0.10 |
| Hydroxypropyl methylcellulose | 0.10 | --- | --- | --- | --- | --- | --- |
| Xanthan gum | 0.25 | 0.10 | 0.25 | 0.10 | 0.25 | 0.10 | 0.10 |
| Polysorbate 80 | 0.90 | 0.90 | 0.90 | 0.90 | 0.90 | 0.90 | 0.90 |
| EDTA disodium dehydrate | 0.10 | --- | --- | --- | --- | --- | --- |
| PEG-400 | --- | --- | --- | --- | 5.00 | --- | --- |
| Dimethyl isosorbide | 10.00 | --- | --- | 5.00 | --- | --- | 5.00 |
| 50% phosphotidylcholine in propylene glycol | --- | 2.80 | 2.80 | --- | 2.80 | --- | 2.80 |



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(continued)

| Formulation : | AZL018 | AZL03 4 | AZL03 5 | AZL03 6 | AZL03 7 | AZL03 8 | AZL03 9 |
|---|---|---|---|---|---|---|---|
| | %w/w | %w/w | %w/w | %w/w | %w/w | %w/w | %w/w |
| propylene glycol | 6.00 | 5.00 | 10.00 | 10.00 | --- | --- | --- |
| Sodium hydroxide | to pH=4.5 | to pH=4.5 | to pH=5.3 | to pH=4.5 | to pH=4.5 | to pH=4.5 | to pH=5.3 |
| Propellant (butane+ isobutane + propane) | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| Purified water | to 100 | to 100 | to 100 | to 100 | to 100 | to 100 | to 100 |

Example 3 -Compositions with azalaic acid with and without different polymeric agents

**[0244]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | **DCA021** | **DCA023** | **DCA023A** | **DCA026** | **DCA026a** |
|---|---|---|---|---|---|
| Isopropyl myristate | | | | 11.00 | 11.00 |
| MCT oil | | 35.00 | 35.00 | | |
| Azelaic acid | 20.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| Propylene glycol | 30.00 | | | | |
| Steareth 2 | | 8.00 | 8.00 | | |
| Steareth 21 | | 2.00 | 2.00 | | |
| PEG-40 Stearate | | | | 4.00 | 6.00 |
| Polysorbate 80 | 30.00 | | | 1.40 | 2.10 |
| Xanthan gum | 0.30 | | | 0.27 | |
| Methocel A4M | 0.30 | | | 0.11 | |
| Carboxy methyl cellulose | | 0.50 | | | |
| Water purified | 19.40 | 39.50 | 40.00 | 68.22 | 65.90 |
| **Total** | **100.00** | **100.00** | **100.00** | **100.00** | **100.00** |
| Propellant ( propane, isobutene and butane mixture | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| | | | | | |
| **Appearance:** | | | | | |
| foam quality | G-E | G-E | G-E | E | E |
| color | White | White | White | White | White |
| odor | No odor | No odor | No odor | No odor | No odor |
| Microscope | Crystals | Crystals | Crystals | Crystals | Crystals |

**[0245]** Good to excellent foam formulations were prepared with azelaic acid, surfactant, polymeric agent, and either another oil or propylene glycol water (and without any foam adjuvant). Reducing the levels of azelaic acid to lower levels eliminated the appearance of crystals (See below).

**[0246]** Surprisingly, it was possible to prepare good to excellent foam after removal of the polymeric agent. Thus, the presence of a polymeric agent, is surprisingly not essential for foam quality. Nonetheless, polymeric agents may still contribute to and can be significant with respect to foam and active agent stability.



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**IN SOLUTION**

Example 4 - Azalaic acid composition

**[0247]** The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

| | **DCA022** |
|---|---|
| Azelaic acid | 6.00 |
| Propylene glycol | 50.00 |
| Polysorbate 80 | 20.00 |
| Xanthan gum | 0.30 |
| Methocel A4M | 0.30 |
| Water purified | 23.40 |
| **Total** | **100.00** |
| Propellant) propane, isobutene and butane mixture | 8.00 |
| | |
| **Appearance:** | |
| foam quality | G-E |
| Color | White |
| Odor | No odor |
| Microscope | No crystals |

**[0248]** Lower azaleic acid levels provide a soluble composition. No solids or precipitates are observed. No crystals were observed at the level of microscopic examination. By no crystals means the ingredients dissolve and it is not a suspension.

## Claims

**1.** A pharmaceutical or cosmetic composition comprising:

a. a beneficially or therapeutically effective concentration of azelaic acid;
b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent; and mixtures thereof; and
**characterised in that** the composition further comprises an organic solvent comprising capric/caprylic triglyceride and further comprises at least one polar carrier, selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid;
wherein the polymeric agent is about 0.01 % to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;
wherein the azelaic acid, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and
wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

**2.** The composition of Claim 1, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the azelaic acid, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

**3.** The composition of Claim 1, wherein the surface active agent is selected from the group consisting of a polysorbate,



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polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52, PEG-100 stearate, a polyoxyethylene alkyl ether, polyoxyethylene cetyl ether, brij 38, PEG-2 cetyl ether, brij 56, brij W1, a sucrose ester, a partial ester of sorbitol, sorbitan monolaurate, a monoglyceride, a diglyceride, isoceteth-20, steareth 2, glyceryl monostearate, steareth-21, PEG 40 stearate, sorbitan stearate, laureth 4, sorbitan monooleate, ceteareth 20, steareth 20, ceteth 20, macrogol cetostearyl ether, ceteth 2, PEG-30 dipolyhydroxystearate, sucrose distearate, cetomacrogol ether, cetearyl glucoside, polysorbate 20, methyl glucose sesquistearate, PEG 30 dipolyhydroxystearate, sucrose stearic acid esters, and mixtures thereof.

**4.** The composition of Claim 1, wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester, a sucrose ester, an alkyl polyglycoside or is selected from the group consisting of sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate, sucrose laurate and lauryl diglucoside.

**5.** The composition of Claim 1 wherein the polymeric agent is selected from the group consisting of carbopol 934, pemulen TR2, xanthan gum, carboxy methyl cellulose, locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, quince seed extract, tragacanth gum, guar gum, cationic guars, hydroxypropyl guar gum, starch, an amine-bearing polymer, chitosan, alginic acid, hyaluronic acid, a chemically modified starch, a carboxyvinyl polymer, polyvinylpyrrolidone, polyvinyl alcohol, a polyacrylic acid polymer, a polymethacrylic acid polymer, polyvinyl acetate, a polyvinyl chloride polymer, a polyvinylidene chloride polymer, methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxy propylmethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylhydroxyethylcellulose, a cationic cellulose, aluminum starch octenylsuccinate (ASOS), PEG 1000, PEG 4000, PEG 6000 and PEG 8000.

**6.** The composition of Claim 1 wherein the at least one polar carrier is dimethyl isosorbide or propylene glycol and wherein the stabilizer is methylcellulose or xanthan gum.

**7.** The composition of Claim 2, further containing a foam adjuvant selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain; a fatty acid having 16 or more carbons in their carbon chain; fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; a fatty alcohol having at least one double bond; a fatty acid having at least one double bond; a branched fatty alcohol; a branched fatty acid; and a fatty acid substituted with a hydroxyl group.

**8.** The composition of Claim 1, wherein the concentration of azelaic acid is between 5% and 25%.

**9.** The composition of Claim 1, wherein the pH of the composition is below 5.3.

**10.** The composition of Claim 1, further comprising an additional component selected from the group consisting of a modulating agent, a polar solvent, an anti perspirant, an anti-static agent, a buffering agent, a bulking agent, a chelating agent, a colorant, a conditioner, a deodorant, a diluent, a dye, an emollient, a fragrance, a humectant, an occlusive agent, a penetration enhancer, a perfuming agent, a permeation enhancer, a pH-adjusting agent, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent, and a vitamin.

**11.** The composition of Claim 1, consisting of (% w/w)

| | |
|---|---|
| Azelaic Acid | 15.00 |
| Water | 51.90 |
| Caprylic/Capric triglyceride | 10.87 |
| Propylene glycol | 10.87 |
| Dimethyl isosorbide | 5.44 |
| PEG-40 stearate | 2.83 |
| Cetostearyl alcohol | 1.09 |



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(continued)

| | |
|---|---|
| Polysorbate 80 | 0.98 |
| Glyceryl stearate | 0.54 |
| Xanthan qum | 0.27 |
| Methylcellulose A4M | 0.11 |
| Benzoic acid | 0.10 |
| NaOH (18% Solution) | to pH=4.5 |

12. Use of the composition according to any of Claims 1 to 11 for the preparation of a medicament for use in the treatment of dermatological disorders.

13. Use of the composition according to Claim 11 for the preparation of a medicament for use in the treatment of a skin disorder selected from acne, rosacea, a pigmentation disorder, a cell proliferation abnormality, a skin infection and a skin inflammation.

14. A composition according to any of Claims 1 to 11, for the treatment of a dermatological disorder.

**Patentansprüche**

1. Pharmazeutische oder kosmetische Zusammensetzung, die Folgendes beinhaltet:

   a. eine nützliche oder therapeutisch wirksame Azelainsäurekonzentration;
   b. einen Stabilisator, der aus der Gruppe bestehend aus wenigstens einem Tensid, wenigstens einem polymeren Mittel und Gemischen davon ausgewählt ist; und
   **dadurch gekennzeichnet, dass** die Zusammensetzung ferner ein organisches Lösungsmittel, das Caprin/Capryl-Triglycerid beinhaltet, und ferner wenigstens einen polaren Träger beinhaltet, der aus der Gruppe bestehend aus Dimethylisosorbid, Glycerol, Propylenglykol, Hexylenglykol, Terpen-ol, Oleylalkohol, Milchsäure und Glykolsäure ausgewählt ist;
   wobei das polymere Mittel etwa 0,01 bis etwa 5 Gew.-% ausmacht und aus der Gruppe bestehend aus einem bioadhäsiven Mittel, einem Geliermittel, einem Filmbildungsmittel und einem Phasenänderungsmittel ausgewählt ist;
   wobei die Azelainsäure, der Stabilisator und das Lösungsmittel so gewählt werden, dass eine Zusammensetzung entsteht, die gegenüber Alterung und Phasenabscheidung im Wesentlichen resistent ist und/oder die andere Wirkstoffe im Wesentlichen stabilisieren kann; und
   wobei die Zusammensetzung, wenn sie sich in einem Druckbehälter befindet und ferner ein Treibmittel aus verflüssigtem Kohlenwasserstoffgas in einer Konzentration von etwa 3 bis etwa 25 Gew.-% der Zusammensetzung enthält, im Wesentlichen fließfähig ist und bei Abgabe einen Schaumstoff bereitstellt.

2. Zusammensetzung nach Anspruch 1, wobei die Zusammensetzung in einem Druckbehälter enthalten ist und ferner ein Treibmittel aus verflüssigtem Kohlenwasserstoffgas in einer Konzentration von etwa 3 bis etwa 25 Gew.-% der Zusammensetzung enthält, im Wesentlichen fließfähig ist und bei Abgabe einen Schaumstoff bereitstellt, und wobei die Azelainsäure, der Stabilisator und das Lösungsmittel zum Erzeugen eines zerbrechlichen Schaumstoffs von guter bis ausgezeichneter Qualität ausgewählt werden.

3. Zusammensetzung nach Anspruch 1, wobei das Tensid ausgewählt ist aus der Gruppe bestehend aus Polysorbat, Polyoxyethylen (20) Sorbitanmonostearat, Polyoxyethylen (20) Sorbitanmonooleat, einem Polyoxyethylen-Fettsäureester, Myrj 45, Myrj 49, Myrj 52, PEG-100 Stearat, einem Polyoxyethylenalkylether, Polyoxyethylencetylether, brij 38, PEG-2-Cetylether, brij 56, brij W1, einem Saccharoseester, einem Sorbitolpartialester, Sorbitanmonolaurat, einem Monoglycerid, einem Diglycerid, Isoceteth-20, Steareth 2, Glycerylmonostearat, Steareth-21, PEG-40 Stearat, Sorbitanstearat, Laureth 4, Sorbitanmonooleat, Ceteareth 20, Steareth 20, Ceteth 20, Macrogolcetostearylether, Ceteth 2, PEG-30 Dipolyhydroxystearat, Saccharosedistearat, Cetomacrogolether, Cetearylglucosid, Polysorbat 20, Methylglucosesesquistearat, PEG-30 Dipolyhydroxystearat, Saccharosestearinestersäure und Gemischen davon.



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4. Zusammensetzung nach Anspruch 1, wobei das Tensid ausgewählt ist aus der Gruppe bestehend aus einem nichtethoxylierten Sorbitanester, einem Glycerolfettsäureester, einem Saccharoseester, einem Alkylpolyglykosid, oder ausgewählt ist aus der Gruppe bestehend aus Sorbitanmonopalmitat, Sorbitanmonostearat, Sorbitantristearat, Sorbitanmonooleat, Sorbitantrioleat, Sorbitanmonolaurat, Sorbitansesquioleat, Glycerolmonostearat, Glycerolmonooleat, Saccharosestearat, Saccharosedistearat, Saccharosepalmitat, Saccharoselaurat und Lauryldiglukosid.

5. Zusammensetzung nach Anspruch 1, wobei das polymere Mittel ausgewählt ist aus der Gruppe bestehend aus Carbopol 934, Pemulen TR2, Xanthangummi, Carboxymethylcellulose, Johannisbrotkernmehl, Natriumalginat, Natriumcaseinat, Eieralbumin, Gelatine-Agar, Carrageeningummi, Quittensamenextrakt, Tragantgummi, Guargummi, kationischen Guars, Hydroxypropylguargummi, Stärke, einem amintragenden Polymer, Chitosan, Algininsäure, Hyaluronsäure, einer chemisch modifizierten Stärke, einem Carboxyvinylpolymer, Polyvinylpyrrolidon, Polyvinylalkohol, einem Polyacrylsäurepolymer, einem Polymethacrylsäurepolymer, Polyvinylacetat, einem Polyvinylchloridpolymer, einem Polyvinylidenchloridpolymer, Methylcellulose, Hydroxypropylcellulose, Hydroxyethylcellulose, Hydroxypropylmethylcellulose, Methylhydroxyethylcellulose, Methylhydroxypropylcellulose, Hydroxyethylcarboxymethylcellulose, Carboxymethylcellulose, Carboxymethylhydroxyethylcellulose, einer kationischen Cellulose, Aluminiumstärkeoctenylsuccinat (ASOS), PEG 1000, PEG 4000, PEG 6000 und PEG 8000.

6. Zusammensetzung nach Anspruch 1, wobei der wenigstens eine polare Träger Dimethylisosorbid oder Propylenglykol ist und wobei der Stabilisator Methylcellulose oder Xanthangummi ist.

7. Zusammensetzung nach Anspruch 2, die ferner ein Schaumstoffadjuvans enthält, das ausgewählt ist aus der Gruppe bestehend aus einem Fettalkohol mit 15 oder mehr Kohlenstoffatomen in der Kohlenstoffkette; einer Fettsäure mit 16 oder mehr Kohlenstoffen in der Kohlenstoffkette; Fettalkoholen, abgeleitet von Bienenwachs und mit einem Gemisch von Alkoholen, von denen eine Mehrzahl wenigstens 20 Kohlenstoffatome in der Kohlenstoffkette haben; einem Fettalkohol mit wenigstens einer Doppelbindung; einer Fettsäure mit wenigstens einer Doppelbindung; einem verzweigten Fettalkohol; einer verzweigten Fettsäure; und einer durch eine Hydroxylgruppe substituierten Fettsäure.

8. Zusammensetzung nach Anspruch 1, wobei die Azelainsäurekonzentration zwischen 5 % und 25 % liegt.

9. Zusammensetzung nach Anspruch 1, wobei der pH-Wert der Zusammensetzung unter 5,3 liegt.

10. Zusammensetzung nach Anspruch 1, die ferner eine zusätzliche Komponente beinhaltet, die ausgewählt ist aus der Gruppe bestehend aus einem Modulierungsmittel, einem polaren Lösungsmittel, einem Antitranspirant, einem antistatischen Mittel, einem Puffermittel, einem Füllstoff, einem Chelatierungsmittel, einem Farbstoff, einem Konditionierer, einem Deodorant, einem Verdünnungsmittel, einem Farbstoff, einem Weichmacher, einem Duftstoff, einem Befeuchtungsmittel, einem Okklusionsmittel, einem Penetrationsverbesserer, einem Parfümiermittel, einem Permeationsverbesserer, einem pH-Einstellmittel, einem Konservierungsmittel, einem Hautpenetrationsverbesserer, einem Sonnenschutzmittel, einem Sonnenblockiermittel, einem sonnenlosen Bräunungsmittel und einem Vitamin.

11. Zusammensetzung nach Anspruch 1, bestehend aus (Gew.-%):

| | |
|---|---|
| Azelainsäure | 15,00 |
| Wasser | 51,90 |
| Caprin/Capryl-Triglycerid | 10,87 |
| Propylenglykol | 10,87 |
| Dimethylisosorbid | 5,44 |
| PEG-40 Stearat | 2,83 |
| Cetostearylalkohol | 1,09 |
| Polysorbat 80 | 0,98 |
| Glycerylstearat | 0,54 |
| Xanthangummi | 0,27 |
| Methylcellulose A4M | 0,11 |

(fortgesetzt)

| | |
|---|---|
| Benzoesäure | 0,10 |
| NaOH (18%ige Lösung) | bis pH=4,5 |

**12.** Verwendung der Zusammensetzung nach einem der Ansprüche 1 bis 11 für die Herstellung eines Medikaments zur Verwendung bei der Behandlung von dermatologischen Störungen.

**13.** Verwendung der Zusammensetzung nach Anspruch 11 für die Herstellung eines Medikaments zur Verwendung bei der Behandlung einer Hautstörung, die aus Akne, Rosacea, einer Pigmentierungsstörung, einer Zellproliferationsanomalität, einer Hautinfektion und einer Hautentzündung ausgewählt ist.

**14.** Zusammensetzung nach einem der Ansprüche 1 bis 11 zur Behandlung einer dermatologischen Störung.

**Revendications**

**1.** Composition pharmaceutique ou cosmétique comprenant :

a. une concentration efficace en termes bénéfiques ou thérapeutiques d'acide azélaïque ;
b. un stabilisant sélectionné à partir du groupe constitué d'au moins un agent tensioactif ; d'au moins un agent polymère ; et leurs mélanges ; et
**caractérisée en ce que** la composition comprend en outre un solvant organique comprenant un triglycéride caprique/caprylique et comprend en outre au moins un support polaire, sélectionné à partir du groupe constitué d'isosorbide de diméthyle, de glycérol, de propylène glycol, d'hexylène glycol, de terpénol, d'alcool oléylique, d'acide lactique et d'acide glycolique ;
où l'agent polymère représente environ 0,01 % à environ 5 % en poids et est sélectionné à partir du groupe constitué d'un agent bioadhésif, d'un agent gélifiant, d'un agent filmogène et d'un agent de changement de phase ;
où l'acide azélaïque, le stabilisant et le solvant sont sélectionnés afin de fournir une composition qui est substantiellement résistante au vieillissement et à la séparation de phases et/ou peut substantiellement stabiliser d'autres principes actifs ; et
où si la composition est contenue dans un contenant sous pression et comprend en outre un gaz propulseur hydrocarboné liquéfié à une concentration d'environ 3 % à environ 25 % en poids de la composition totale, elle est substantiellement liquide et fournit une mousse lors de la libération.

**2.** Composition selon la revendication 1, où la composition est contenue dans un contenant sous pression et comprend en outre un gaz propulseur hydrocarboné liquéfié à une concentration d'environ 3 % à environ 25 % en poids de la composition totale, est substantiellement liquide et fournit une mousse lors de la libération, et où l'acide azélaïque, le stabilisant et le solvant sont sélectionnés afin de générer une mousse cassante de bonne ou d'excellente qualité.

**3.** Composition selon la revendication 1, où l'agent tensioactif est sélectionné à partir du groupe constitué d'un polysorbate, de monostéarate polyoxyéthylénique (20) de sorbitanne, de mono-oléate polyoxyéthylénique (20) de sorbitanne, d'un ester d'acide gras polyoxyéthylénique, de Myrj 45, de Myrj 49, de Myrj 52, de stéarate de PEG-100, d'un éther d'alkyle polyoxyéthylénique, d'éther cétylique polyoxyéthylénique, de brij 38, d'éther cétylique de PEG-2, de brij 56, de brij W1, d'un ester de saccharose, d'un ester partiel de sorbitol, de monolaurate de sorbitanne, d'un monoglycéride, d'un diglycéride, d'isoceteth-20, de stéareth 2, de monostéarate de glycéryle, de stéareth-21, de stéarate de PEG 40, de stéarate de sorbitanne, de laureth 4, de mono-oléate de sorbitanne, de céteareth 20, de stéareth 20, de céteth 20, d'éther cétostéarylique de macrogol, de céteth 2, de dipolyhydroxystéarate de PEG 30, de distéarate de saccharose, d'éther de cétomacrogol, de glucoside de cétéaryle, de polysorbate 20, de sesquistéarate de méthyl glucose, de dipolyhydroxystéarate de PEG 30, d'esters d'acide stéarique de saccharose, et leurs mélanges.

**4.** Composition selon la revendication 1, où l'agent tensioactif est sélectionné à partir du groupe constitué d'un ester non-éthoxylé de sorbitanne, d'un ester d'acide gras de glycérol, d'un ester de saccharose, d'un polyglycoside d'alkyle ou est sélectionné à partir du groupe constitué de monopalmitate de sorbitanne, de monostéarate de sorbitanne, de tristéarate de sorbitanne, de mono-oléate de sorbitanne, de trioléate de sorbitanne, de monolaurate de sorbitanne,



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de sesquioléate de sorbitanne, de monostéarate de glycérol, de mono-oléate de glycérol, de stéarate de saccharose, de distéarate de saccharose, de palmitate de saccharose, de laurate de saccharose et de diglucoside de lauryl.

**5.** Composition selon la revendication 1, où l'agent polymère est sélectionné à partir du groupe constitué de carbopol 934, de pemulen TR2, de gomme xanthane, de carboxyméthylcellulose, de gomme de caroube, d'alginate de sodium, de caséinate de sodium, d'albumine d'oeuf, de gélose à la gélatine, de gomme de carraghénine, d'extrait de graine de coing, de gomme adragante, de gomme de guar, de guars cationiques, de gomme de guar d'hydroxypropyle, d'amidon, d'un polymère porteur d'amine, de chitosane, d'acide alginique, d'acide hyaluronique, d'un amidon chimiquement modifié, d'un polymère carboxyvinylique, de polyvinylpyrrolidone, d'alcool polyvinylique, d'un polymère d'acide polyacrylique, d'un polymère d'acide polyméthacrylique, d'acétate de polyvinyle, d'un polymère de chlorure polyvinylique, d'un polymère de chlorure de polyvinylidène, de méthylcellulose, d'hydroxypropylcellulose, d'hydroxyéthylcellulose, d'hydroxypropylméthylcellulose, de méthylhydroxyéthylcellulose, de méthylhydroxypropylcellulose, d'hydroxyéthylcarboxyméthylcellulose, de carboxyméthylcellulose, de carboxyméthylhydroxyéthylcellulose, d'une cellulose cationique, d'octénylsuccinate d'amidon aluminium (ASOS), de PEG 1000, de PEG 4000, de PEG 6000 et de PEG 8000.

**6.** Composition selon la revendication 1, où l'au moins un support polaire est de l'isosorbide de diméthyle ou du propylèneglycol et où le stabilisant est de la méthylcellulose ou de la gomme xanthane.

**7.** Composition selon la revendication 2, contenant en outre un adjuvant de mousse sélectionné à partir du groupe constitué d'un alcool gras ayant 15 carbones ou plus dans sa chaîne carbonée ; d'un acide gras ayant 16 carbones ou plus dans sa chaîne carbonée ; d'alcools gras, dérivés de la cire d'abeille et incluant un mélange d'alcools, dont une majorité ont au moins 20 atomes de carbone dans leur chaîne carbonée ; d'un alcool gras ayant au moins une double liaison ; d'un acide gras ayant au moins une double liaison ; d'un alcool gras ramifié ; d'un acide gras ramifié ; et d'un acide gras substitué par un groupe hydroxyle.

**8.** Composition selon la revendication 1, où la concentration d'acide azélaïque est comprise entre 5 % et 25 %.

**9.** Composition selon la revendication 1, où le pH de la composition est inférieur à 5,3.

**10.** Composition selon la revendication 1, comprenant en outre un composant supplémentaire sélectionné à partir du groupe constitué d'un agent de modulation, d'un solvant polaire, d'un anti-transpirant, d'un agent antistatique, d'un agent tampon, d'un agent gonflant, d'un agent chélatant, d'un colorant, d'un conditionneur, d'un déodorant, d'un diluant, d'une matière colorante, d'un émollient, d'un parfum, d'un humectant, d'un agent occlusif, d'un activateur de pénétration, d'un agent parfumant, d'un agent augmentant la pénétration, d'un agent d'ajustement du pH, d'un conservateur, d'un activateur de pénétration cutanée, d'un écran solaire, d'un agent de blocage solaire, d'un agent de bronzage sans soleil, et d'une vitamine.

**11.** Composition selon la revendication 1, constituée des composants suivants (% M/M) :

| | |
|---|---|
| Acide azélaïque | 15,00 |
| Eau | 51,90 |
| Triglycéride caprylique/caprique | 10,87 |
| Propylèneglycol | 10,87 |
| Isosorbide de diméthyle | 5,44 |
| Stéarate de PEG-40 | 2,83 |
| Alcool cétostéarylique | 1,09 |
| Polysorbate 80 | 0,98 |
| Stéarate de glycéryle | 0,54 |
| Gomme xanthane | 0,27 |
| Méthylcellulose A4M | 0.11 |



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(suite)

| | |
|---|---|
| Acide benzoïque | 0,10 |
| NaOH (solution à 18 %) | vers un pH = 4,5 |

**12.** Utilisation de la composition selon l'une quelconque des revendications 1 à 11 pour la préparation d'un médicament destiné à être utilisé dans le traitement de troubles dermatologiques.

**13.** Utilisation de la composition selon la revendication 11 pour la préparation d'un médicament destiné à être utilisé dans le traitement d'une maladie de la peau sélectionnée parmi l'acné, la rosacée, un trouble de la pigmentation, une anomalie de la prolifération cellulaire, une infection de la peau et une inflammation de la peau.

**14.** Composition selon l'une quelconque des revendications 1 à 11 pour le traitement d'un trouble dermatologique.

## REFERENCES CITED IN THE DESCRIPTION

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1 563 638

# PATENT SPECIFICATION (11) 1 563 638

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(31) Convention Application No. 75903
(32) Filed 29 Sept. 1976 in
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(44) Complete Specification published 26 March 1980
(51) INT CL³ C07J 7/00 A61K 31/57//C07J 71/00
(52) Index at acceptance
C2U 2 4A1B 4A2A 4B2B 4C10A 4C4A 4C5 4D1 4N16A 4N1 4N6B 4N6Y 4N9 6A1 6B 8A1

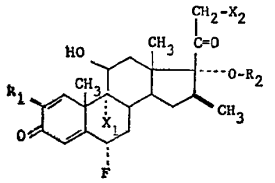
(19)




## (54) 21-HALOGENOPREGNANE COMPOUNDS

(71) We, CIBA-GEIGY AG, a Swiss body corporate, of Basle, Switzerland, do hereby delcare 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 invention relates to the manufacture of new polyhalogenated steroids, especially 9α,21 - dihalogeno - 11β,17α - dihydroxy - 6α - fluoro - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione compounds of the formula




(I)

in which $X_1$ represents chlorine or fluorine, $X_2$ represents bromine or chlorine, $R_1$ represents hydrogen or chlorine and $R_2$ represents the acyl radical Ac of a carboxylic acid, or salts of such compounds having salt-forming properties, as well as to the new compounds themselves or salts of such compounds having salt-forming properties and also to pharmaceutical compositions which contain the new compounds, and the use thereof.

Carbon-containing compounds and radicals designated throughout this specification as "lower" contain not more than 7 carbon atoms.

An acyl group Ac is preferably derived from the carboxylic acids customary in steroid chemistry, for example those containing up to and including 18 carbon atoms, and is in particular derived from corresponding aliphatic cycloaliphatic, cycloaliphatic-aliphatic, aromatic or araliphatic carboxylic acids. The radical Ac is, in particular, lower alkanoyl, such as lower alkanoyl which is substituted or unsubstituted, for example by free or etherified or esterified hydroxy, such as lower alkoxy, for example methoxy or ethoxy, or phenoxy, or halogen, for example chlorine, or carboxyl, i.e. a straight-chain or branched lower alkanoyl, for example acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, 2-ethyl-butyryl, 2,2- or 3,3-dimethylbutyryl, hexanoyl or heptanoyl, or hydroxy-lower alkanoyl, for example 3-hydroxypropionyl, phenoxy-lower alkanoyl, for example phenoxyacetyl, halogeno-lower alkanoyl, for example chloro-acetyl, or carboxy-lower alkanoyl, for example 3-carboxypropionyl or 4-carboxy-butyryl, alkenoyl, for example undecylenoyl, cycloalkyl-lower alkanoyl, for example cyclopentylpropionyl or cyclohexylacetyl, substituted or unsubstituted benzoyl, for example benzoyl, or substituted or unsubstituted phenyl-lower alkanoyl or phenyl-lower alkenoyl, for example phenylacetyl.

Salts of compounds of the formula I having salt-forming groups are those of such compounds which contain corresponding groups, which are optionally in the form of a salt, in an acyl radical Ac, above all the corresponding pharmaceutically useful non-toxic salts which are usually water-soluble. Compounds of the formula I having salt-forming properties are, in particular, those in which $R_2$ represents carboxy-lower alkanoyl radical Ac. Such compounds can in particular be in the form of a metal salt, for example in the form of an alkali metal salt, such as a sodium salt or potassium salt. The sodium salt of a compound of the formula I in which $R_2$ represents 3-carboxypropionyl is particularly preferred.

The compounds of the present invention have valuable pharmacological properties. Thus they are distinguished by a pronounced anti-antiflammatory action, whilst having a reduced systemic action. Accordingly, for example, when applied locally in the raw cotton wool granuloma test on rats, inhibition of the inflammatory



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processes can be observed in the dosage range between about 0.001 and about 0.10 mg per cotton wool pellet. The first indications of a systemic action, however, are only apparent at, or even above, the upper limit of this dosage range, namely in the decrease in weight of the thymus at a dose above 0.03 mg per cotton wool pellet of the adrenals at a dose above 0.1 mg per cotton wool pellet, and of the entire body only at a dose of 1 mg per cotton wool pellet. On topical administration (rat's ear test of Tonelli), $ED_{50}$ is approx. 10 to 30 mcg/ml.

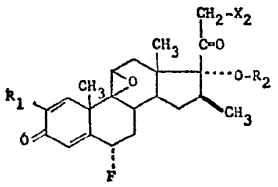
On account of these biological properties, the new compounds can be used in all indications for which glucocorticoid steroids with anti-inflammatory properties are suitable. In particular, they are suitable for use as anti-inflammatory glucocorticoids for topical application, for example for the treatment of inflammatory dermatoses, such as eczemas, or dermatides, or dermatoses which are partially corticoid-resistant, for example psoriasis. They can also be used as useful intermediate products for obtaining other useful substances, especially other pharmacologically active steroids.

The invention preferably relates to those compounds of the formula I in which $X_1$ represents fluorine or chlorine, $X_2$ represents chlorine, $R_1$ represents hydrogen and $R_2$ represents lower alkanoyl, for example propionyl.

The invention relates above all to compounds of the formula I in which $X_1$ represents fluorine or chlorine, $X_2$ represents chlorine, $R_1$ represents chlorine and $R_2$ represents lower alkanoyl, for example propionyl.

The invention above all relates most particularly to the compounds of the formula I mentioned in the examples.

The compounds according to the invention of the formula I can be manufactured in a manner which is known per se, for example by treating a compound of the formula



(II)

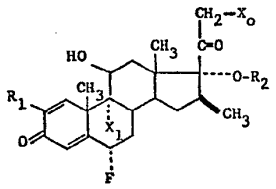
with a hydrogen halide of the formula $H—X_1$ (III) and, if desired converting a compound of the formula I, which is obtainable according to the process and has salt-forming properties, into a salt, and/or converting a salt, which is obtainable according to the process, of a salt-forming compound of the formula I into the free compound of the formula I or into another salt.

Cleavage of the 9β,11β-oxide group in a starting material of the formula II by treatment with a hydrogen halide of the formula III, that is to say with hydrogen chloride or hydrogen fluoride, is carried out in a manner which is known per se, advantageously using an anhydrous hydrogen halide, optionally in the presence of an inert solvent, such as chloroform, tetrahydrofurane or, in particular, dimethylformamide, or also hydrogen fluoride in aqueous solution.

In place of the hydrogen halide of the formula III, it is also possible to use an agent which releases hydrogen fluoride or hydrogen chloride, such as the salt of such an acid with a tertiary organic base, for example pyridine, or, especially if hydrogen fluoride is used, a similar suitable addition compound. A particularly advantageous process is described in U.S. Patent 3,211,758, wherein hydrogen fluoride is used in the form of an adduct with a carbamic acid derivative or thiocarbamic acid derivative, especially with urea.

The starting materials of the formula II can be obtained in a manner which is known per se, for example by eliminating water from a 6α - fluoro - 11β - hydroxy - 16β - methyl - 2 - $R_1$ - 17α - $OR_2$ - 21 - $X_2$ - pregna - 1,4 - diene - 3,20 - dione compound, for example by treatment with a suitable acid chloride, such as phosphorus oxychloride or methanesulphonyl chloride, in the presence of a base, for example pyridine, adding hypobromous acid (which, for example, is used in the form of N-bromoacetamide or N-bromosuccinimide) onto the 9,11-double bond of the 6α - fluoro - 16β - methyl - 2 - $R_1$ - 17α - $OR_2$ - 21 - $X_2$ - pregna - 1,4,9(11) - triene - 3,20 - dione compound which is thus obtainable and eliminating hydrogen bromide from the corresponding 9α, 11β-bromohydrin compound by treatment with a base, for example an alkali metal carbonate or alkali metal hydroxide, for example potassium carbonate or potassium hydroxide, with formation of the desired starting material of the formula II. In the above intermediate products, $R_1$, $R_2$ and $X_2$ have the abovementioned meanings.

The new compounds of the formula I can also be obtained by converting the group $X_0$ in a compound of the general formula



(IV)



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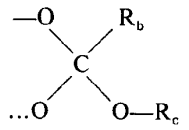
in which $X_0$ represents a group which can be converted into a halogen atom $X_2$, into a halogen atom $X_2$ and, if desired, carrying out the additional process steps.

A group $X_0$ which can be converted into a halogen atom $X_2$ is the group —O—$R_a$, in which $R_a$ represents the acyl radical of an organic sulphonic acid. The replacement of the sulphonyloxy group —O—$R_a$ by the halogen atom $X_2$ is effected in a manner which is known per se. The acyl radical $R_a$ of an organic sulphonic acid is, in particular, the acyl radical of an aliphatic or carboxylic, optionally unsaturated sulphonic acid or of an aromatic sulphonic acid. Such acids are, inter alia, unsubstituted or substituted, for example halogenated, lower alkanesulphonic acids, cycloalkanesulphonic acids, in which the cycloalkyl radical can be monocyclic or polycyclic, or benzenesulphonic acids which are unsubstituted or substituted by lower alkyl, for example methyl, lower alkoxy, for example methoxy, halogen, for example chlorine or bromine, and/or nitro. Typical examples of such acids are trifluoromethanesulphonic acid, (+) - camphor - 10 - sulphonic acid, 4 - bromobenzenesulphonic acid and 3 - nitrobenzenesulphonic acid and especially p-toluenesulphonic acid and, in particular, methanesulphonic acid.

The substitution reaction is usually carried out by treating the starting material with an alkali metal halide of the formula M—$X_2$ (V), in which M represents an alkali metal, in the presence of an aprotic organic solvent which has a dielectric constant of 29 or higher. An alkali metal M which can be used is, preferably, lithium. Aprotic organic solvents which can be used are, in particular, di-lower alkyl sulphoxides, for example dimethyl sulphoxide, N,N-di-lower alkylamides of lower aliphatic carboxylic acids, for example N,N-dimethylformamide or N,N-dimethylacetamide, lower alkanenitriles or lower alkenenitriles, for example acetonitrile, hexa-lower alkylphosphoramides, for example hexamethylphosphortriamide, or, above all when using starting materials of the formula IV in which $R_2$ represents hydrogen, also ketones, especially aliphatic or cycloaliphatic ketones containing up to and including 10 carbon atoms such as corresponding alkanones, for example acetone, 2-butanone, 2- or 3-pentanone, 2-hexanone or 4-decanone, or cycloalkanones containing up to and including 8 ring carbon atoms, for example cyclopentanone or cyclohexanone, or mixtures of such solvents.

The reaction is appropriately carried out between room temperature and the boiling point of the reaction mixture and is effected with at least one equivalent of the alkali metal halide of the formula V.

A further group $X_0$ which can be converted into a halogen atom $X_2$ is hydroxyl and also a radical which, together with —O—$R_2$, forms an etherified hydroxymethylenedioxy group of the formula



(IVa)

in which $R_b$ represents hydrogen or an organic radical, especially an aliphatic hydrocarbon radical, such as lower alkyl, for example methyl or ethyl, and $R_c$ forms an organic radical, especially an aliphatic hydrocarbon radical, such as lower alkyl, for example methyl or ethyl.

The replacement of a hydroxyl group $X_0$ by halogen $X_2$ and also of the group of the formula IVa by $X_2$ in the 21-position with a simultaneous formation of an esterified hydroxyl in the 17$\alpha$-position of the formula —O—CO—$R_b$ can be carried out in a manner which is known per se, for example by treatment with a phosphine, such as a tri-lower alkylphosphine, or preferably triphenylphosphine, and a carbon tetrahalide, preferably carbon tetrachloride, and also bromotrichloromethane. The reaction is preferably carried out in a dipolar aprotic medium, for example in the presence of a corresponding solvent of the amide type, such as dimethyl formamide, dimethylacetamide, 1 - methyl - 2 - pyrrolidone or hexamethylphosphortriamide, with cooling or warming, for example in a temperature range between about 10°C and about 125°C and, if necessary, in a closed vessel and/or in an inert gas atmosphere.

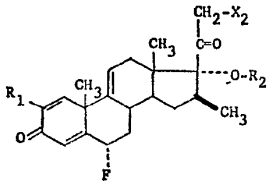
The starting materials of the formula IV are known or can be manufactured in a manner which is known per se, for example compounds of the formula IV, in which $X_0$ represents organic sulphonyloxy, can be manufactured by converting the 21-hydroxyl group in a 6$\alpha$ - fluoro - 11$\beta$,21 - dihydroxy - 16$\beta$ - methyl - 2 - $R_1$ - 9$\alpha$ - $X_1$ - 17$\alpha$ - $OR_2$ - pregna - 1,4 - diene - 3,20 - dione compound into the desired organic sulphonyloxy group —$OR_a$ by treatment with a reactive derivative of an organic sulphonic acid of the formula $R_a$—OH(VI), especially with a corresponding sulphonic acid chloride of the formula $R_a$—Cl (VIa), in the presence of a base, for example pyridine; and compounds of the formula IV in which $X_0$ and —O—$R_2$ together form a group of the formula IVa can be manufactured by treating a 6$\alpha$ -



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fluoro - 11β, 17α,21 - trihydroxy - 16β - methyl - 2 - $R_1$ - 9α - $X_1$ - pregna - 1,4 - diene - 3,20 - dione compound with a suitable orthocarboxylic acid ester, for example triethyl orthoformate or triethyl orthopropionate, in the presence of a strong acid, for example p-toluenesulphonic acid, and advantageously with removal of the alcohol which is set free, for example by azeotropic distillation.

The new compounds of the formula I in which $X_1$ represents chlorine can also be obtained by adding hypochlorous acid onto the 9,11-double bond of a compound of the formula



(VII)

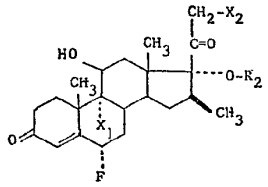
and, if desired, carrying out the additional process steps.

According to the above reaction, the elements of hypochlorous acid are added onto the 9,11-double bond of the starting materials of the formula VII in a manner which is known per se. The reaction is carried out, for example, with aqueous hypochlorous acid, or a hypochlorous acid donor, such as a N-chlorocarboxylic acid amide or imide (cf. U.S. Patent Specification 3,057,886), can be used. The reaction is carried out in an inert solvent, such as a tertiary alcohol, for example tert. butanol, an ether, for example diethyl ether, methyl isopropyl ether, dioxane or tetrahydrofurane, or a ketone, for example acetone, in the presence of water and optionally of a strong acid.

The addition of hypochlorous acid to the 9,11-double bond of the starting material of the formula VII can also be carried out in a non-aqueous medium. A particularly advantageous embodiment of this modification is the use of lower alkyl hypochlorites, above all tert.-butyl hypochlorite, in an inert, water-immiscible solvent, for example a nitro-hydrocarbon, usually in the presence of perchloric acid (cf. German Patent Specification 2,011,559).

The starting materials of the formula VII can be manufactured in a manner which is known per se, for example by eliminating water from a 6α - fluoro - 11β - hydroxy - 16β - methyl - 2 - $R_1$ - 17α - $OR_2$ - 21 - $X_2$ - pregna - 1,4 - diene - 3,20 - dione compound, for example by treatment with a suitable acid chloride, such as phorphorus oxychloride or methanesulphonyl chloride, in the presence of a base, for example pyridine.

The new compounds of the formula I in which $R_1$ represents hydrogen can also be obtained by introducing the 1,2-double bond into a compound of the formula



(VIII)

and, if desired, carrying out the additional measures.

The introduction of the 1,2-double bond can be carried out by dehydrogenation, for example by treatment with a suitable dehydrogenating quinone, such as 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone.

The 1,2-dehydrogenation of starting materials of the formula VIII can also be effected by treatment with selenium dioxide or microbiologically, for example with suitable microorganisms, such as *Corynebacterium simplex* or *Septomyxa affinis*.

The starting materials of the formula VIII have valuable pharmaceutical properties analogous to those of end products of the formula I and can also be used in the same way as these latter. The compounds of the formula VIII, in which $X_1$, $X_2$ and $R_2$ have the above meanings, also form an object of the present invention. They are obtained by means of the process described above, starting in each case from 1,2-saturated, 2-unsubstituted compounds of the type of formula II, IV or VII, and carrying out the corresponding reaction. Thus they can be obtained for example by converting the 21-hydroxyl group of a 6α - fluoro - 11β,21 - dihydroxy - 16β - methyl - 9α - $X_1$ - 17α - $OR_2$ - pregn - 4 - ene - 3,20 - dione compound (i.e. a compound of the formula IV type) for example by treatment with a suitable sulphonic acid derivative, such as methanesulphonyl chloride, into a 21-organic sulphonyloxy group, and treating the intermediate with a lithium halide, for example lithium chloride.

A compound of the formula I which is obtainable according to the process can be converted into another compound of the formula I in a manner which is known per se.

Thus, for example, in a compound of the formula I in which $R_1$ represents hydrogen, the latter can be replaced by chlorine. For this purpose it is possible to add one molecule of chlorine onto the 1,2-double bond in such a compound and to split off one mole of hydrogen chloride from the intermediate 1,2 - dichlor - pregn - 4 -



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ene - 3,20 - dione. The addition of chlorine to the 1,2-double bond can be effected by treatment with elementary chlorine or with a mixture of two different chlorine-containing compounds, one of which releases positive chlorine and the other releases negative chlorine.

The treatment with elementary chlorine can be carried out in an inert organic solvent, for example an ether, such as dioxane or tetrahydrofurane, a halogenated hydrocarbon, for example methylene chloride, or a carboxylic acid, especially a lower aliphatic carboxylic acid, such as acetic acid or propionic acid, or a derivative thereof, such as an acid amide, for example dimethylformamide, or a nitrile, such as a lower alkaenitrile, for example acetonitrile. Advantageously, it is also possible to use mixtures of such solvents, especially mixtures of an ether, such as dioxane, with one of the lower alkanecarboxylic acids mentioned. The chlorination is usually carried out using the stoichiometric amount of chlorine at low temperature, say between −50°C and +30°C, for example at between −20°C and +10°C, and with the exclusion of light.

In a particularly preferred embodiment, the compound of the formula I in which $R_1$ represents hydrogen, is dissolved in one of the above solvents, for example dioxane, and treated with a solution of chlorine in a lower aliphatic carboxylic acid, for example propionic acid, and this solution is then left to stand, for example at the indicated temperature.

In a mixture of two different chlorinating agents, reagents which can set free positive chlorine are chlorinated acid amides or acid imides, such as chlorosuccinimide or chloroacetamide, and reagents which yield negative chlorine are, for example, hydrogen chloride and also alkali metal chlorides.

The elimination of hydrogen chloride from the intermediate 1,2 - dichloro - pregn - 4 - ene - 3,20 - dione is advantageously effected by treatment with a base. Examples of suitable bases are tertiary organic nitrogen bases, such as lower aliphatic amines, for example a tri-lower alkylamine, such as triethylamine, hetero-aromatic bases, for example pyridine or collidine, or mixed aliphatic-aromatic bases, such as N,N-di-lower alkyl-aniline, for example N,N-dimethylaniline. The reaction is preferably carried out with an excess of the base, which at the same time can be used as solvent. However, it is also possible to use inorganic bases, such as, in particular, the alkali metal salts or alkaline earth metal salts which are also used for hydrolysis of the 11β-trifluoroacetate described below, for example potassium acetate or bicarbonate or sodium acetate or bicarbonate, in aqueous-alcoholic solution, as well as the corresponding hydroxides. The dehydrochlorination is preferably carried out in a temperature range between about 20°C and about 100°C. Advantageously, those agents and reaction conditions are chosen which have no influence on the other functional groups, especially those in the 17-position and/or 21-position.

Before adding chlorine onto the 1,2-double bond in a compound of the formula I, in which $R_1$ represents hydrogen, the 11β-hydroxyl group is advantageously protected, for example by esterification, preferably in the form of a trifluoroacetoxy group, a compound of the formula I in which $R_1$ represents hydrogen being reacted in a manner which is known per se with a suitable reactive derivative of an acid, for example with trifluoroacetyl chloride or trifluoroacetic anhydride. It is known that the trifluoroacetyl group can be split off easily by solvolysis, for example by hydrolysis or alcoholysis, for example by treatment with alkali metal hydroxides, carbonates, bicarbonates or acetates or alkaline earth metal hydroxides, carbonates, bicarbonates or acetates, in a suitable medium, for example an alcoholic, such as methanolic, or aqueous-alcoholic medium. A particular method of carrying out the solvolysis of the 11-trifluoroacetoxy group is described in German Patent Specification 1,593,519. This procedure can be used mainly because it leaves intact any esterified hydroxyl group which may be present in the 17α-position and consists in treating the 11β-trifluoroacetoxy compound, in a lower alkanol, with the salt of an acid which has a pKa value in the range of from about 2.3 to about 7.3, for example with an alkali metal azide, for example sodium azide or potassium azide, or an alkali metal formate, for example sodium formate or potassium formate. If appropriate, this salt can also be used only in catalytic amounts. Furthermore, the 11β-trifluoroacetyl group can also be removed by treatment with other bases, for example with amines and especially with hetero-aromatic bases, such as pyridine or collidine. Finally, the cleavage of the trifluoroacetoxy group by treatment with silica gel according to the process described in German Offenlegungsschrift 2,144,405 is also possible.

Liberation of the 11β-hydroxyl group from the protected form can be effected immediately after the addition of chlorine to the 1,2-double bond or at the same time as the dehydrochlorination by means of a base, but if desired, it can also be effected only subsequently to this step as a separate operation.



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Compounds of the formula I which are obtainable according to the process and have salt-forming properties, that is to say which contain an acyl group $R_2$ which is suitable for forming a salt, can be converted into their salts in a manner which is known per se. Accordingly those compounds in which $R_2$ represents a carboxy-lower alkanoyl radical can be converted into their salts by treatment with a suitable base, such as a metal hydroxide, carbonate or bicarbonate, especially an alkali metal hydroxide, carbonate or bicarbonate, such as sodium hydroxide, carbonate or bicarbonate or potassium hydroxide, carbonate or bicarbonate (the equivalent amount of the base preferably being used), usually in an aqueous or aqueous-alcoholic medium.

Conversely, a salt, which is obtainable according to the process, of a compound of the formula with salt-forming properties can be converted into the free compound, the corresponding salt with a base, for example, by treatment with an acid, such as an inorganic acid (for example by acidifying a solution of the salt in an aqueous or aqueous-organic medium to a pH value of about 1—2).

The starting materials used in the above process steps are preferably those which result in the compounds described above as being particularly preferred.

The present invention also relates to pharmaceutical compositions which contain, as active ingredient, a compound according to the invention of the formula I, or a salt of such a compound with salt-forming properties, and to a process for the manufacture of such pharmaceutical compositions.

Suitable pharmaceutical compositions are in particular those for topical application, such as creams, ointments, pastes, foams, tinctures and solutions, which contain from about 0.005% to about 0.1% of the active compound, and also compositions for oral administration, for example tablets, coated tablets and capsules, and those for parenteral administration.

Creams are oil-in-water emulsions which contain more than 50% of water. Fatty alcohols are chiefly used as oleaginous base, for example lauryl, cetyl or stearyl alcohol, fatty acids, for example palmitic or stearic acid, liquid to solid waxes, for example isopropyl myristate, wool wax or bees-wax, and/or hydrocarbons, for example petroleum jelly (petrolatum) or paraffin oil. Suitable emulsifiers are surface-active substances with primarily hydrophilic properties, such as corresponding non-ionic emulsifiers, for example fatty acid esters of polyalcohols or ethylene oxide adducts thereof, such as polyglycerol fatty acid esters or polyoxyethylene sorbitan fatty acid esters (Tweens—Registered Trade Mark); polyoxyethylene fatty alcohol ethers or esters, or corresponding ionic emulsifiers, such as alkali metal salts of fatty alcohol sulphates, for example sodium lauryl sulphate, sodium cetyl sulphate or sodium stearyl sulphate, which are customarily used in the presence of fatty alcohol, for example cetyl alcohol or stearyl alcohol. Additives to the water phase include agents which reduce water loss through evaporation, for example polyalcohols, such as glycerol, sorbitol, propylene glycol and/or polyethylene glycols, as well as preservatives, perfumes etc.

Ointments are water-in-oil emulsions which contain up to 70%, preferably however approx. 20% to about 50%, of water or aqueous phase. The oleaginous phase comprises chiefly hydrocarbons, for example petroleum jelly, paraffin oil and/or hard paraffins, which contain preferably hydroxy compounds suitable for improving the water-absorption, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool wax alcohols, or wool wax. Emulsifiers are corresponding lipophilic substances, such as sorbitan fatty acid esters (Spans—Registered Trade Mark), for example sorbitan oleate and/or sorbitan isostearate. Additives to the water phase include humectants, such as polyalcohols, for example glycerol, propylene glycol, sorbitol and/or polyethylene glycol, and preservatives, perfumes etc.

Greasy ointments are anhydrous and contain as base in particular hydrocarbons, for example paraffin, petroleum jelly and/or liquid paraffins, furthermore natural or partially synthetic fat, for example coconut fatty acid triglycerides, or preferably hardened oils, for example hydrated ground nut or castor oil, and also fatty acid partial esters of glycerol, for example glycerol mono- and distearate, and, for example, the fatty alcohols, emulsifiers and/or additives for increasing the water-absorption mentioned in connection with the ointments.

Pastes are creams and ointments containing powdered ingredients which absorb secretions, such as metal oxides, for example titanium oxide or zinc oxide, and talc and/or aluminium silicates whose purpose it is to bind moisture or secretion present.

Foams are administered from pressurised dispensers and are liquid oil-in-water emulsions in aerosol form, with halogenated hydrocarbons, such as chlorofluoro-lower alkanes, for example dichlorodifluoromethane and dichlorotetrafluoroethane being used as propellants. For the oleaginous phase there are used,



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inter alia, hydrocarbons, for example paraffin oil, fatty alcohols, for example cetyl alcohol, fatty acid esters, for example isopropyl myristate, and/or other waxes. As emulsifiers there are used, inter alia, mixtures of those emulsifiers with primarily hydrophilic properties, such as polyoxyethylene sorbitan fatty acid esters (Tweens—Registered Trade Mark), and those with primarily lipophilic properties, such as sorbitan fatty acid esters (Spans—Registered Trade Mark). In addition, the conventional additives are used, such as preservatives etc.

Tinctures and solutions generally have an aqueous ethanolic base to which are added, inter alia, polyalcohols, for example glycerol, glycols, and/or polyethylene glycol, as humectants for reducing water loss, and fat-restoring substances such as fatty acid esters with lower polyethylene glycols, i.e. lipophilic substances which are soluble in the aqueous mixture as substitute for fatty substances which are taken from the skin with the ethanol, and, if necessary, other assistants and additives.

The pharmaceutical compositions for topical application are obtained in known manner, for example by dissolving or suspending the active substance in the base or in a part thereof, if necessary. When processing the active substance in the form of a solution, it is usually dissolved in one of the two phases before the emulsification, and when processing the active substance in the form of a suspension, it is mixed with a part of the base before the emulsification and than added to the remainder of the formulation.

In addition to the pharmaceutical compositions which can be applied topically, other suitable preparations are those for enteral, for example oral, and parenteral administration to warm-blooded animals and which contain the active substance as sole ingredient or together with a pharmaceutically acceptable carrier. These pharmaceutical compositions contain about 0.01% to about 10% of active substance and are in dosage unit form, such as coated tablets, tablets, capsules, suppositories or ampoules. They are obtained in known manner, for example by conventional mixing, granulating, coating, dissolving or lyophilising methods.

The dosage of active substance depends on the species of warm-blooded animal, the age, and the individual condition as well as on the mode of application.

The new compounds the formula I and the salts of such compounds with salt-forming properties are useful in medicine, preferably for treating inflammations, chiefly an anti-inflammatory glucocorticoids for local application, normally in the form of pharmaceutical compositions, especially in the form of pharmaceutical compositions for topical application.

The following Examples describe the invention in more detail, without in any way restricting the scope thereof.

Example 1

230 mg of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone (DDQ) are added to a solution of 228 mg of 21 - chloro - 6$\alpha$, 9$\alpha$ - difluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate in 11.4 ml of dioxane, which is then refluxed for 20 hours in a nitrogen atmosphere. The reaction mixture is concentrated in a water jet vacuum and the amorphous residue is chromatographed on 100 times its weight of silica gel (stepped column). The fractions eluted with a 99:1 mixture of methylene chloride/methanol yield the pure 21 - chloro - 6$\alpha$,9$\alpha$ - difluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate which melts at 220°—221°C after recrystallisation from methylene chloride/ether.

The 17-monopropionate used as starting material is prepared as follows:

A suspension of 1 g of 21 - chloro - 9$\beta$,11$\beta$ - epoxy - 17$\alpha$ - hydroxy - 16$\beta$ - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate in 5.4 ml of dioxane and 1.4 ml of triethyl orthoformate is treated with 0.9 ml of a solution consisting of 277 mg of p-toluenesulphonic acid, 2.7 ml of dioxane and 0.55 ml of ethyl alcohol and stirred for 90 minutes at room temperature. After addition of 3.8 ml of pyridine, the reaction mixture is diluted with ethyl acetate, washed 3 times with a saturated solution of sodium chloride, dried and concentrated in a water jet vacuum. The crude 3 - ethyl - enol ether (3 - ethoxy - 21 - chloro - 9$\beta$,11$\beta$ - epoxy - 17$\alpha$ - hydroxy - 16$\beta$ - methyl - pregna - 3,5 - dien - 20 - one - 17 - propionate) is dissolved in a mixture of 50 ml of tetrahydrofurane and 10 ml of water and the solution is treated for 40 minutes at room temperature with gaseous perchloroyl fluoride. After nitrogen has subsequently been introduced over the course of 10 minutes, the reaction solution is diluted with ethyl acetate, washed successively with 10% potassium iodide solution, 10% sodium thiosulphate solution and 3 times with a saturated solution of sodium chloride, then dried and concentrated in a water jet vacuum. The crude product is chromatographed on 100 times its weight of silica gel (stepped column).

The column is eluted with a 90:10 mixture of toluene/ethyl acetate. Recrystallisation from methylene chloride/ether of the



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fractions obtained yields 21 - chloro - 6α - fluoro - 9β,11β - epoxy - 17α - hydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate which melts at 174—177°C.

14.5 ml of a reagent prepared by mixing 10 g of urea with 13.25 g of anhydrous liquid hydrogen fluoride are poured over 720 mg of the above compound in a plastic vessel. The reaction mixture is stirred for 3 hours with ice cooling, then poured onto 55 ml of an ice-cold saturated solution of ammonia, weakly acidified with acetic acid and extracted twice with chloroform. The organic phases are combined, washed with the ice-cold sodium hydroxide solution, dried and concentrated in a water jet vacuum. The crude product is chromatographed on 100 times its weight of silica gel (stepped column). The column is eluted with 90:10 mixture of toluene/ethyl acetate. Recrystallisation from methylene chloride/ether of the fractions obtained yields 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate which melts at 212°—213°C.

Example 2

A solution of 3.7 g of 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methylpregna - 1,4 - diene - 3,20 - dione - 17-propionate in 30 ml of dioxane is treated with 1.85 ml of a solution which is prepared by introeucing 7.7 g of chlorine gas into 100 ml of propionic acid. The reaction mixture is allowed to stand for 5 days at 3—4°C. It is then diluted with chloroform, washed successively with a 10% potassium iodide solution, a 10% sodium thiosulphate solution, dilute sodium hydroxide solution and water, dried, and concentrated in a water jet vacuum. The crude 1ξ2ξ - 21 - trichloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methylpregn - 4 - ene - 3,20 - dione - 17 - propionate is dissolved in methylene chloride to remove HCl and filtered through a column of 37 g of basic alumina (activity 2). The eluted solution is concentrated and recrystallised from methylene chloride to yield 2,21 - dichloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methylpregna - 1,4 - diene - 3,20 - dione - 17 - propionate which melts at 202°—204°C.

Example 3

A solution of 350 mg of 9α,21 - dichloro - 6α - fluoro - 11β,17 - dihydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate and 525 mg of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone in 17.5 ml of dioxane is refluxed for 20 hours in an atmosphere of nitrogen. The cooled mixture is filtered and the filtrate is evaporated. The residue is dissolved in methylene chloride and filtered through 15 times its weight of neutral alumina (activity 2). The filtrate is concentrated and purified by preparative thin-layer chromatography (on silica gel, 3 developings by a 9:1 mixture of toluene/methanol as eluant). The desired zone is localised by ultra-violet light having a wavelength of 254 nm, eluted from the adsorbent with ethyl acetate and recrystallised from methylene chloride/ether, affording the desired 9α,21 - dichloro - 6α - fluoro - 11β,17 - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate which melts, with decomposition, at 212°—213°C.

The starting steroid is obtained as follows:

Hydrogen chloride gas is introduced at 0°C in the course of 30 minutes into a solution of 400 mg of 21 - chloro - 6α - fluoro - 9β,11 - epoxy - 17 - hydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dionepropionate in 20 ml of chloroform. The mixture is allowed to stand for a further 30 minutes at 0°C, diluted with chloroform, washed with an ice-cold saturated sodium hydrocarbonate solution, dried and concentrated in vacuo. The crude 9α,21 - dichloro - 6α - fluoro - 11β,17 - dihydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate can be used without purification for the dehydrogenation reaction.

Example 4

Hydrogen chloride gas is introduced at 0°C in the course of 30 minutes into a solution of 2.8 g of 21 - chloro - 6α - fluoro - 9β,11 - epoxy - 17 - hydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dionepropionate in 140 ml of chloroform. The mixture is allowed to stand for a further 30 minutes at 0°C, diluted with chloroform, washed with an ice-cold saturated sodium hydrocarbonate solution, dried and evaporated in vacuo. The crude product is chromatographed on 100 times its weight of silica gel (stepped column). The desired product is eluted with a 99:1 mixture of toluene/methanol. Crystallisation from methylene chloride/ether yields 9α,21 - dichloro - 6α - fluoro - 11β,17 - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate which melts, with decomposition, at 212°—213°C and is identical with the product of Example 3.

The starting steroid is obtained as follows:

A mixture of 3 g of 21 - chloro - 16α - fluoro - 9β,11 - epoxy - 17 - hydroxy - 16β - methyl - pregn - 4 - ene - 3,20 - dionepropionate and 3 g of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone in 150 ml of dioxane is refluxed for 20 hours in an



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atmosphere of nitrogen. The cooled mixture is filtered, and the filtrate concentrated.

The residue is dissolved in methylene chloride and filtered through 15 times its weight of neutral alumina (activity II). The filtrate is concentrated, affording the crude 21 - chloro - 6α - fluoro - 9β,11 - epoxy - 17 - hydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dionepropionate which can be treated with hydrogen chloride without further purification.

Example 5

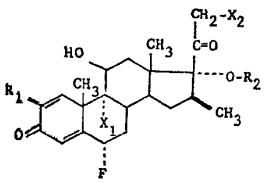
An ointment containing 0.1% of 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate can be prepared as follows:

| Composition | % |
|---|---|
| 21 - chloro - 6α,9α - difluoro - 11β,17α - dihydroxy - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate | 0.1 |
| white petroleum jelly | 45.0 |
| liquid paraffin | 19.6 |
| cetyl alcohol | 5.0 |
| bees-wax | 5.0 |
| sorbitane sesquioleate | 5.0 |
| p-hydroxybenzoic acid ester | 0.2 |
| perfume | 0.1 |
| water | 20.0 |

The fatty substances and emulsifiers are melted together. The preservative is dissolved in water and the solution is emulsified into the fatty melt at elevated temperature. After cooling, a suspension of the active compound in part of the fatty melt is incorporated into the emulsion and the perfume is then added.

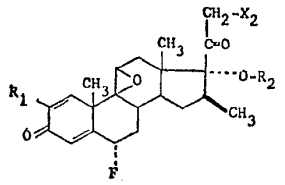
WHAT WE CLAIM IS:—

1. A process for the manufacture of a 9α,21 - dihalogeno - 11β,17α - dihydroxy - 6α - fluoro - 16β - methyl - pregna - 1,4 - diene - 3,20 - dione compound of the formula



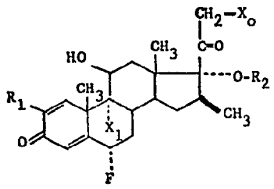
(I)

in which $X_1$ represents chlorine or fluorine, $X_2$ represents bromine or chlorine, $R_1$ represents hydrogen or chlorine and $R_2$ represents the acyl radial Ac of a carboxylic acid, or a salt of such a compound with salt-forming properties, which process comprises (a) treating a compound of the formula



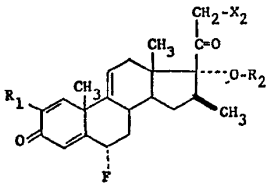
(II)

with a hydrogen halide of the formula H—$X_1$, (III) or with an agent which donates the hydrogen halide HX, or (b) converting the group $X_0$ in a compound of the general formula



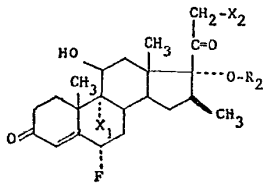
(IV)

in which $X_0$ represents a group which can be converted into a halogen atom $X_2$, into a halogen atom $X_2$, or (c) in order to obtain a compound of the formula I in which $X_1$ represents chlorine adding hypochlorous acid onto the 9,11-double bond of a compound of the formula



(VII)

or (d) in order to obtain a compound of the formula I in which $R_1$ is hydrogen, introducing the 1,2-double bond into a compound of the formula



(VIII)

and, if desired, converting a compound of the formula I, which is obtainable according to the process and has salt-forming properties, into a salt, and/or converting a salt, which is obtainable according to the process, of a salt-forming compound of the formula I into the free compound of the formula I or into another salt.

2. A process according to process variant (b) of Claim 1 wherein the sulphonyloxy group —O—$R_a$ is replaced by chlorine in a compound of the formula IV, in which $X_0$ means the group —O—$R_a$, in which $R_a$

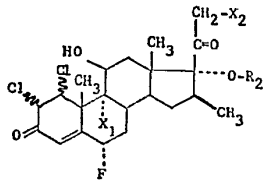


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represents the acyl radical of an organic sulphonic acid.

3. A process according to process variant (c) of Claim 1, wherein a compound of the formula VII is treated with hypochlorous acid or a hypochlorous acid donor.

4. A process for the production of a compound of the formula I, in which $R_1$ is chlorine, wherein chlorine is added onto the 1,2-double bond of a compound of formula I, in which $R_1$ represents hydrogen and hydrogen chloride is split off from the resulting intermediate of the formula



in which $R_2$ represents the acyl radical Ac of a carboxylic acid, $X_1$ represents chlorine or fluorine and $X_2$ represents bromine or chlorine, and in which process the 11-hydroxyl group is, if necessary, in a temporarily protected form, in which case the protective group is removed at any desired stage.

5. A process according to Claim 4, wherein the reaction is carried out while temporarily protecting the 11$\beta$-hydroxyl group by conversion into the trifluoroacetate.

6. A process according to any one of Claims 1 to 3 for the manufacture of a compound of the formula I in which $X_1$ represents fluorine or chlorine, $X_2$ represents chlorine, $R_1$ represents hydrogen and $R_2$ represents lower alkanoyl.

7. A process according to any one of Claims 1 to 5 for the manufacture of a compound of the formula I in which $X_1$ represents fluorine or chlorine, $X_2$ represents bromine or chlorine, and $R_1$ represents chlorine.

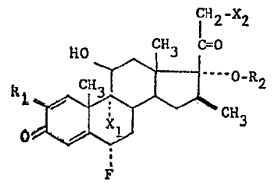
8. A process according to any one of Claims 1 to 5 for the manufacture of a compound of the formula I in which $X_1$ represents fluorine or chlorine, $X_2$ represents chlorine, $R_1$ represents hydrogen or chlorine and $R_2$ represents lower alkanoyl of 2 to 5 carbon atoms.

9. A process according to any one of Claims 1 to 5 for the manufacture of 2,21 - dichloro - 6$\alpha$,9$\alpha$ - difluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

10. A process according to any one of Claims 1 to 3 for the manufacture of 9$\alpha$,21 - dichloro - 6$\alpha$ - fluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

11. A process according to any one of Claims 1 to 3 for the manufacture of 21 - chloro - 6$\alpha$,9$\alpha$ - difluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

12. 9$\alpha$,21 - dihalogeno - 11$\beta$,17$\alpha$ - dihydroxy - 6$\alpha$ - fluoro - 16$\beta$ - methyl - pregna - 1,4 - diene - 3,20 - dione compounds of the formula



(I)

wherein $X_1$ represents chlorine or fluorine, $X_2$ represents bromine or chlorine, $R_1$ represents hydrogen or chlorine and $R_2$ represents the acyl radical Ac of a carboxylic acid, and 2-unsubstituted 1,2-dihydro derivatives thereof.

13. A compound of the formula I according to Claim 12 wherein $X_1$ represents fluorine, $X_2$ represents chlorine, $R_1$ represents hydrogen and $R_2$ represents lower alkanoyl, and 1,2-dihydro derivatives thereof.

14. A compound of the formula I according to Claim 12, wherein $X_1$ represents chlorine or fluorine, each of $X_2$ and $R_1$ represents chlorine and $R_2$ represents lower alkanoyl.

15. A compound according to either of Claims 13 or 14, wherein lower alkanoyl contains 2 to 5 carbon atoms.

16. 2,21 - dichloro - 6$\alpha$,9$\alpha$ - difluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

17. 21 - chloro - 6$\alpha$,9$\alpha$ - difluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

18. 21 - chloro - 6$\alpha$,9$\alpha$ - difluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methyl - pregn - 4 - ene - 3,20 - dione - 17 - propionate.

19. 9$\alpha$,21 - dichloro - 6$\alpha$ - fluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methyl - pregna - 1,4 - diene - 3,20 - dione - 17 - propionate.

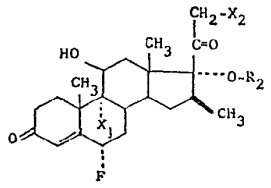
20. 9$\alpha$,21 - dichloro - 6$\alpha$ - fluoro - 11$\beta$,17$\alpha$ - dihydroxy - 16$\beta$ - methylpregn - 4 - ene - 3,20 - dione - 17 - propionate.

21. A pharmaceutical composition which contains at least one of the compounds described in Claims 16 to 24 and at least one pharmaceutical carrier.

22. A process for the manufacture of 9$\alpha$,21 - dihalogeno - 11$\beta$,17$\alpha$ - dihydroxy - 6$\alpha$ - fluoro - 16$\beta$ - methyl - pregn - 4 - ene - 3,20 - dione compounds of the formula

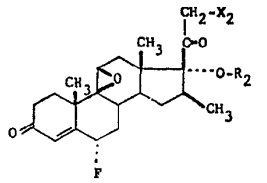


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(VIII)

wherein $X_1$ represents chlorine or fluorine, $X_2$ represents bromine or chlorine, and $R_2$ represents the acyl radical Ac of a carboxylic acid, which process comprises a treating a compound of the formula

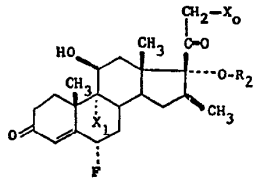


(IIA)

with a hydrogen halide of the formula

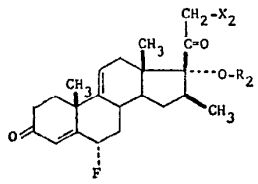
$$H—X_1 \qquad (III)$$

in which $X_1$ represents chlorine or fluorine, or with a corresponding donor of $H—X_1$, or (b) in a compound of the general formula



(IVA)

in which $X_0$ represents a group which can be converted into the halogen atom $X_2$, converting the group $X_0$ into the halogen atom $X_2$, or (c) in order to obtain a compound of the formula VIII, in which $X_1$ represents chlorine, adding hypochlorous acid onto the 9,11-double bond of a compound of the formula



(VIIA)

23. A process according to process variant (b) of Claim 22 wherein a compound of the formula VIA, in which $X_0$ is the group $—O—R_a$, in which $R_a$ is the acyl of an organic sulphonic acid, the group $—O—R_a$ is replaced by chlorine.

24. A process according to process variant (c) of Claim 22, wherein a compound of the formula VIIA is treated with hypochlorous acid or a donor thereof.

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GB 1464388
GB 1045041
GB 887872
US 4082881A
US 4048309A
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(54) **Corticosteroid stick formulations**

(57) Anti-inflammatory formulations, in the form of a stick, comprise a corticosteroid, one or more oleaginous solvents in which the steroid is dissolved, one or more waxes to impart body and stiffness, and an anti-microbial compound to prevent growth and spread of bacteria on the stick from one application area to another, the anti-microbial being present in an amount of 1 to 25% by weight of the composition.

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SPECIFICATION

**Corticosteroid stick formulations**

The present invention relates to corticosteroid formulations which are used as anti-flammatory agents in the form of a stick.

More specifically, the present invention provides a steroid stick composition comprising (an effective amount of) a corticosteroid, one or more oleaginous solvents in which said corticosteroid is fully dissolved, one or more waxes to impart body and stiffness, and an anti-microbial compound to prevent growth and spread of bacteria on the stick from one application area to another, said anti-microbial compound being present in an amount of about 1 to about 25% by weight of said composition.

Topical corticosteroid formulations are extensively employed in the treatment of skin disorders, such as dermatitis. To be therapeutically effective, the active ingredient should be in a molecular dispersion to facilitate desired percutaneous absorption which is particularly important in achieving a therapeutic response for the management of psoriasis.

Conventional dosage forms such as ointment, creams, lotions and the like, used to apply potent steroid to the skin require the patient to use his fingers. Such exposure of the fingers to the steroid could be undesirable. Moreover, a large percentage of dermatoses patients are senile or institutionalized, and many of the require a second party to apply the steroid to affected areas.

A particularly convenient formulation which overcomes the above difficulties is the stick. Use of a stick formulation does not expose fingers to potent steroids and thus may also eliminate possible eye contamination, is ideal for second party application, may be indexed directly to the affected site, covers larger areas with relative ease, and all without accumulation of waste.

Various steroid formulations in the form of a stick are disclosed in U.S. Patents Nos. 4,048,309 and 4,082,881.

It has been found that during application, the stick comes in direct contact with diseased skin and may pick up some microbes. In order to prevent the growth and spread of such microbes, it has been suggested to employ in stick formulations preservatives normally useful in cream or lotions, such as the parabens, chlorocresol, benzoic acid, and chlorobutanol. Unfortunately, however, these cream or lotion preservatives have been found to be virtually ineffective in stick formulations.

In accordance with the present invention, to prevent the growth of these microbes on the stick surface and also to eliminate their spread from one area of application to another, an anti-microbial compound which is effective in stick formulations, even in the presence of oleaginous solvents, is included.

The stick formulation of the present invention comprises two systems, namely, (a) oleaginous solvents to dissolve corticosteroids, and (b) waxes to provide body and stiffness to the formulation, together with an anti-microbial compound which will be effective in sticks which are primarily oleaginous, and optionally liquid softeners or emollients, antioxidants, and/or opacifying agents.

Surprisingly and unexpectedly, it has been found that propylene glycol and 1,3-butylene glycol which are immiscible with oleaginous solvents are particularly effective in the stick formulations of the invention for preventing growth and spread of microbes.

Unlike most of the conventional topical products in which corticosteroids are in solid dispersion, corticosteroids in stick formulations are solubilized assuring maximal possible bio-availability. Solvents suitable for use herein have to be miscible among themselves and with the waxes at the concentration employed so as to prevent separation and syneresis.

The amount of solvent employed preferably should be just sufficient to dissolve all the corticosteroid used in the formulation, that is, ideally, the concentration of dissolved steroid should result in a saturated solution. Should the solution be oversaturated, some of the steroid will undesirably crystallize out. If the solution is undersaturated, the extra solvent will increase the affinity of the base (waxes) for the steroid and will therefore slow the steroid release rate.

In addition, the solvents employed herein should have low intrinsic viscosity, so that after wax matrices are broken down during application, the solvent can readily penetrate the skin. For this reason, where castor oil or mineral oil is employed, these solvents preferably are diluted with dibutyl sebacate or diisopropyl sebacate to reduce their intrinsic viscosities.

Accordingly, as will be seen hereinafter, in order to achieve the necessary saturated solution, while employing a solvent having low intrinsic viscosity, a co-solvent may be employed with the major oleaginous solvent for the steroid. The steroid component will usually be less soluble in the co-solvent and in this manner a solvent system is fashioned which is of low intrinsic viscosity and produces the properly balanced saturated solution. Examples of oleaginous solvents which may be employed herein include, but are not limited to, castor oil, mineral oil, isostearyl alcohol, isopropyl palmitate, isopropyl myristate, dibutyl sebacate, diisopropyl sebacate and mixtures thereof depending upon the solubility of the steroid of choice in the solvent and the intrinsic viscosity of the solvent. Thus, for example, castor oil is a good oleaginous solvent for halcinonide; to complete the solvent system, the castor oil will be balanced with isostearyl alcohol, which is not as good a solvent for halcinonide as is castor oil. In this manner, a solvent mixture which has a desirable solubility, for example, 100 mg halcinonide in 60 gm of the solvent mixture, is achieved. When such a steroid-solvent mixture is formulated with waxes and an anti-microbial compound



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into a stick of 100 gm, a 0.1% halcinonide product is formed.

Other useful mixtures are isostearyl alcohol and dibutyl or diisopropyl sebacate, and castor oil and dibutyl or diisopropyl sebacate which are miscible with all waxes at desired concentrations. However, castor oil and mineral oil are immiscible and thus this combination should be avoided.

Generally, the mixture of oleaginous solvents will be employed in an amount within the range of from about 45 to 85% by weight, and preferably from about 50 to about 80% by weight of the stick formulation. In particularly preferred embodiments depending upon the steroid to be present, isostearyl alcohol is employed in a weight ratio to castor oil within the range of from about 3:1 to about 0.8:1 and preferably from about 2.5:1 to about 1:1, isostearyl alcohol is employed in a weight ratio to dibutyl sebacate within the range of from about 0.5:1 to about 2:1 and preferably from about 0.8:1 to about 1.5:1, and castor oil is employed in a weight ratio to dibutyl sebacate within the range of from about 0.5:1 to 1.5:1 and preferably from about 0.8:1 to about 1.2:1.

The selection of waxes for use herein is important to optimize the stick formulation. Thus, in preferred embodiments, waxes of a wide range of melting point are used to avoid a grainy appearance in the stick. It is also preferable that waxes have minimal solubility in oleaginous solvents so that gel structure will form readily and intrinsic viscosity will not increase substantially. Waxes having some emulsifying activity, such as glyceryl monostearate reduce interfacial tension between moist skin and the oleaginous solvent and are used for this reason. Examples of other waxes suitable for use herein include high melting waxes, such as carnauba wax, white wax, ozokerite, beeswax, candelilla wax, cetyl alcohol, petrolatum, mineral oil thickened with polyethylene as disclosed in U.S. Patents Nos. 2,627,938, 2,628,187, 2,628,205 and 3,733,403, and various mixtures thereof.

The waxes will normally be present in an amount within the range of from about 10 to about 40% and preferably from about 15 to about 30% by weight of the stick formulation.

The anti-microbial compounds employed in the stick formulations of the invention may be present in an amount within the range of from about 1 to about 25% and preferably from about 2 to 10% by weight, and optimally from about 3 to about 8% by weight of the entire stick formulation. Examples of anti-microbial agents suitable for use herein include propylene glycol, 1,3-butylene glycol, and mixtures thereof. Propylene glycol or 1,3-butylene glycol present in the stick formulation of the invention at a concentration of 1-3% or higher kills bacteria, while at a concentration of 6% or higher kills 99.9% of the bacteria originally present on the stick. The glycols not only serve as anti-microbial agents but also as a penetration enhancer.

The fact that the above anti-microbial agents can be effectively included in the stick formulations of the invention is indeed surprising inasmuch as these anti-microbial agents are generally immiscible with the oleaginous materials necessary in the stick formulations. However, it has been found that where the amounts of anti-microbial agent specified above are employed, the anti-microbial agent remains homogeneously dispersed (and not dissolved) in the stick without separating therefrom.

The active steroid ingredient employed in the formulations of the invention will preferably comprise a steroid which will be present in an amount of from about 0.001 to about 3% by weight, and preferably from about 0.025 to about 0.2% based on the total weight of the composition, depending upon the type of steroid employed and its solubility in the oleaginous solvent vehicle.

Exemplary of the steroids contemplated are the acetonide derivations of steroids of the pregnane series described in United States Patents Nos. 3,048,581 and 3,937,720. Included within the steroids described by the former patent are triamcinolone acetonide and halcinonide. In addition, the stick formulation of the invention may include steroids disclosed in U.S. Patents Nos. 3,976,637, 3,979,417, 3,994,935, 4,018,757, 4,116,978, 4,018,774, 4,091,036, 4,094,840, 4,133,811, 4,146,538, 4,160,772 and 4,164,504. It is emphasized that these steroids are meant to be exemplary only and it is not meant to limit this invention to use with any particular steroid or group of topically active anti-inflammatory steroids.

The steroid stick formulation of the invention may also optionally include an opacifying agent, such as titanium dioxide, serving as indicator for homogeneity of dispersion, in an amount within the range of from about 0.2 to about 1% and preferably from about 0.3 to about 0.8% by weight based on the entire formulation. An anti-oxidant may also optionally be included in an amount within the range of from about 0.005 to about 0.1% and preferably from about 0.01 to about 0.03% by weight based on the entire formulation.



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Examples of preferred steroid stick formulations in accordance with the present invention include, but are not limited to, the following:

*Halcinonide Stick, 0.025%*

| | *Ranges* |
|---|---|
| Halcinonide, micronized | 0.020-0.03 gm. |
| Isostearyl alcohol | 30-45 gm. |
| Castor oil | 15-35 gm. |
| Propylene glycol or 1,3-butylene glycol | 6-25 gm. |
| White wax | 2-6 gm. |
| Ozokerite | 3-7 gm |
| Candelilla wax | 1-3 gm |
| Carnauba wax | 2-4 gm. |
| Glyceryl stearate | 2-4 gm. |
| Cetyl alcohol | 5-9 gm. |

*Holcinonide Stick, 0.1%*

| | |
|---|---|
| Halcinonide, micronized | 0.09-0.11 gm. |
| Isostearyl alcohol | 30-45 gm. |
| Castor oil | 15-35 gm. |
| Propylene glycol or 1,3-butylene glycol | 6-25 gm. |
| White wax | 2-6gm. |
| Ozokerite | 3-7 gm. |
| Candelilla wax | 1-3 gm. |
| Carnauba wax | 2-4 gm. |
| Glyceryl stearate | 2-4 gm. |
| Cetyl alcohol | 5-9 gm. |

*Kenalog Stick, 0.025%*

| | *Ranges* |
|---|---|
| Triamcinolone acetonide, micronized | 0.02-0.03 gm. |
| Isostearyl alcohol | 30-45 gm. |
| Castor oil | 15-35 gm. |
| Propylene glycol or 1,3-butylene glycol | 6-25 gm. |
| White wax | 2-6 gm. |
| Ozokerite | 3-7 gm. |
| Candelilla wax | 1-3 gm. |
| Carnauba wax | 2-4 gm. |
| Glyceryl stearate | 2-4 gm. |
| Cetyl alcohol | 5-9 gm. |

*Kenalog Stick, 0.1%*

| | |
|---|---|
| Triamcinolone acetonide, micronized | 0.09-0.11 gm. |
| Isostearyl alcohol | 30-45 gm. |
| Castor oil | 15-35 gm. |
| Propylene glycol or 1,3-butylene glyclo | 6-25 gm. |
| White wax | 2-6 gm. |
| Ozokerite | 3-7 gm. |
| Candelilla wax | 1-3 gm. |
| Carnauba wax | 2-4 gm. |
| Glyceryl stearate | 2-4 gm. |
| Cetyl alcohol | 5-9 gm. |



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*Other Steroid Stick Formulations Containing 0.1% Steroid A or B*

*A* 21-(Acetyloxy)-9-fluoro-1′, 2′, 3′,4′-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]-naphthalene-3,20-dione

or

*B* 21-Chloro-9-fluoro-1′, 2′, 3′, 4′-tetrahydro-11β-hydroxypregna-1,4-dieno[16α, 17-b]-naphthalene-3,20-dione

| | *Steroid Stick A* | *Steroid Stick B* |
|---|---|---|
| Isostearyl alcohol | 30-40 gm | --- |
| Castor oil | --- | 30-40 gm |
| Dibutyl sebacate | 30-40 gm | 30-40 gm |
| Propylene glycol or 1,3-butylene glycol | 5-10 gm | 5-10 gm |
| White wax | 1-5 gm | 1-5 gm |
| Ozokerite | 2-6 gm | 2-6 gm |
| Candelilla wax | 1-5 gm | 1-5 gm |
| Carnauba wax | 4-6 gm | 4-6 gm |
| Glyceryl stearate | 3-5 gm | 3-5 gm |
| Cetyl alcohol | 1-8 gm | 1-8 gm |
| Steroid A | 0.09-0.11 gm | --- |
| Steroid B | --- | 0.09-0.11 gm |

The following Examples represent preferred embodiments of the present invention.

*Examples 1 to 11*

A series of lipophilic sticks having formulations as shown in the following table are prepared as described below.

The steroid is dissolved in the oleaginous solvents, that is, isostearyl alchol, castor oil, and dibutyl sebacate, where employed, with gentle heat not over 90°C. A molten mixture of the remaining ingredients is added to the above solution at 90°C. The mixture is poured into a mold and chilled to solidify the mixture to a stick.

*Parts by Weight*

| Example No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Isostearyl alcohol | 35 | 38 | 39 | 35 | 38 | 39 | 37 | 37 | 33 | -- | -- |
| Castor oil | 18 | 27 | 32 | 18 | 12 | 32 | -- | -- | -- | 37 | 37 |
| Propylene glycol | 24 | 12 | 6 | -- | -- | -- | 6 | -- | -- | 6 | -- |
| Butylene glycol | -- | -- | -- | 24 | 12 | 6 | -- | 6 | 6 | -- | 6 |
| Dibutyl sebacate | -- | -- | -- | -- | -- | -- | 37 | 37 | 33 | 37 | 37 |
| White wax, Ozokerite, Candelilla wax, Glyceryl stearate, Cetyl alcohol | 23 | 23 | 23 | 23 | 23 | 23 | 20 | 20 | 28 | 22 | 20 |
| Halcinonide | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | -- | -- | -- | -- | -- |
| Steroid A | -- | -- | -- | -- | -- | -- | 0.1 | 0.1 | 0.1 | -- | -- |
| Steroid B | -- | -- | -- | -- | -- | -- | -- | -- | -- | 0.1 | 0.1 |

Steroid A - 21-(Acetyloxy)-9-fluoro-1′,2′,3′,4′-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17--b]naphthalene-3,20-dione

Steroid B - 21-Chloro-9-fluoro-1′,2′,3′,4′-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione

The above lipophilic sticks in accordance with the invention contain the steroid component fully dissolved in the form of a saturated solution in each of the mixtures of oleaginous solvents shown, which solvent mixtures have low intrinsic viscosities. The above sticks are found to be therapeutically effective while the anti-microbial compounds present, namely, propylene glycol or 1,3-butylene glycol, are found to prevent the growth and spread of bacteria on the stick from one application area to another.



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CLAIMS

1. A steroid stick composition comprising a corticosteroid, one or more oleaginous solvents in which said corticosteroid is fully dissolved, one or more waxes to impart body and stiffness, and an anti-microbial compound to prevent growth and spread of bacteria on the stick from one application area to another, said anti-microbial compound being present in an amount of about 1 to about 25% by weight of said composition.

2. The composition as defined in claim 1 wherein said one or more oleaginous solvents are present in an amount of about 45 to about 85% by weight of said composition.

3. The composition as defined in claim 1 or 2 wherein said one or more oleaginous solvents comprise isostearyl alcohol, mineral oil, castor oil, dibutyl sebacate, diisopropyl sebacate or a mixture thereof.

4. The composition as defined in claim 1, 2 or 3 wherein said corticosteroid is halcinonide, triamcinolone acetonide, 21-(acetyloxy)-9-fluoro 1', 2', 3', 4'-tetrahydro-11β-hydroxypregna-1,4-dieno-[16α,17-b]-naphthalene-3,20-dione or 21-chloro-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]-naphthalene-3,20-dione.

5. The composition as defined in claim 1, 2, 3 or 4 wherein said anti-microbial compound is propylene glycol or 1,3-butylene glycol.

6. The composition as defined in any one of the preceding claims wherein said anti-microbial compound is present in an amount of about 2 to about 10% by weight of said composition.

7. The composition as defined in any one of the preceding claims wherein said anti-microbial compound is present in an amount of about 3 to about 8% by weight of said composition.

8. The composition as defined in any one of the preceding claims wherein said corticosteroid is present in an amount of about 0.005 to about 0.6% by weight of said composition.

9. The composition as defined in any one of the preceding claims wherein said one or more waxes are present in an amount of about 10 to about 40% by weight of the composition.

10. The composition as defined in any one of the preceding claims wherein said one or more waxes are white wax, ozokerite, candelilla wax, carnauba wax, glyceryl stearate, cetyl alcohol or a mixture thereof.

11. The composition as defined in any one of the preceding claims wherein said corticosteroid is halcinonide and said oleaginous solvent comprises a mixture of isostearyl alcohol and castor oil.

12. The composition as defined in any one of claims 1 to 10 wherein said corticosteroid is triamcinolone acetonide and said oleaginous solvent comprises a mixture of castor oil and dibutyl sebacate.

13. The composition as defined in any one of claims 1 to 10 wherein said corticosteroid is 21 (acetyloxy)-9-fluoro-1', 2', 3', 4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione and said oleaginous solvent comprises a mixture of isostearyl alcohol and dibutyl sebacate.

14. The composition as defined in any one of claims 1 to 10 wherein said corticosteroid is 21-chloro-9-fluoro-1', 2', 3', 4'-tetrahydro-11β-hydroxypregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione and said oleaginous solvent comprises a mixture of castor oil and dibutyl sebacate.

15. A method of treating dermatitis, which comprises administering topically an effective amount of a composition as defined in any one of the preceding claims.

16. The composition as defined in claim 1 substantially as described in any of the Examples.

17. The composition as defined in any one of claims 1 - 14 and 16 for use as an anti-inflammatory agent.

18. The composition as defined in any one of claims 1 - 14, 16 and 17, when in the form of a stick.

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# (54) Topical corticosteroid preparation

(57) Anti-inflammatory preparations comprise a monoglyceride of a $C_6$—$C_{10}$ fatty acid and a corticosteroid. The steroid may be betamethasone, alclometasone, hydrocortisone, prednisolone, triamcinolone, fluocinonide, fluocinolone, dexamethasone, diflucostolone or beclometasone; the monoglyceride can be glycerol monohexanoate, monooctanoate or monodecanoate.

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SPECIFICATION

**Topical corticosteroid preparation**

This invention relates to a topical corticosteroid preparation for treating inflammation. More particularly, it relates to a new anti-inflammatory preparation which may be, for example, in the form of an ointment, gel, emulsion or cream. Specifically, it relates to a topical corticosteroid preparation which comprises a monoglyceride of a $C_6$—$C_{10}$ medium-chain fatty acid together with the active ingredient.

In topical preparations of corticosteroids it has been an accepted notion that manifestation of the therapeutic efficacy of the active ingredient mainly depends upon factors such as for example, the state of mixing of the active ingredient in the base, e.g. dispersed or dissolved, the proportion, the affinity of the mixed composition to the skin, and the absorption of the active ingredient through the skin. These factors are linked in a complex manner and, accordingly, the design of preparation forms is not a simple matter.

In general, the active ingredient should be dissolved rather than dispersed in the base to achieve good results. Excessive enhancement of solubility, however, adversely affects the release of the active ingredient from the base and lessens the therapeutic effect. Thus, selection of the base ingredients must be performed very carefully bearing in mind the above factors and the proportions must be chosen to produce a preparation with high therapeutic efficacy. Additionally, the simpler the preparation procedure the better.

This invention is based upon the discovery that a topical preparation intensifying the efficacy of anti-inflammatory corticosteroids with high safety and stability and good feel when applied to the skin may be produced by using a monoglyceride of a $C_6$—$C_{10}$ medium-chain fatty acid. Such glycerides balance the dispersion or solubility of the active ingredient in the base against the release of active ingredient to the skin even when other adjuvants are present.

In addition, it was discovered that such preparations brought out a remarkable improvement with respect to reduction in skin irritation and also have excellent physical stability.

Accordingly, the present invention provides a topical corticosteroid preparation which comprises a monoglyceride of $C_6$—$C_{10}$ fatty acid, especially a saturated fatty acid, together with an active corticosteroid ingredient.

The topical preparations of the present invention preferably contain 0.01—2.00 weight percent (abbreviated as wt.% hereinafter) of a corticosteroid and 0.5—20 wt.% of the monoglyceride as indispensable ingredients and may also contain any one or more of the following pharmacologically acceptable adjuvants:—

a. 1—15 wt.% of a primary, secondary or tertiary $C_2$—$C_6$ alcohol;
b. 1—10 wt% of a polyethylene glycol having a mean molecular weight of about 200—4000;
c. 1—90 wt.% of oily substance;
d. 0.5—15 wt.% of nonionic surfactant; and/or
e. water.

Additionally, the preparation may contain a suitable amount of, for example, a stabilizing agent and/or a solubilizing agent.

Examples of the active ingredient include betamethasone valerate, betamethasone dipropionate, alclometasone dipropionate, hydrocortisone acetate, dextamethasone, prednisolone, diflucortolone valerate, triamcinolone, acetonide, fluocinonide, fluocinolone acetonide and beclometasone dipropionate; preferably, betamethasone valerate, betamethasone dipropionate, alclometasone dipropionate, dextamethasone, triamcinolone acetonide, fluocinonide or fluocinolone acetonide; most preferably, betamethasone valerate, betamethasone diproprionate or alclometasone dipropionate. An ordinary effective amount of the active ingredient as used in topical drugs is employed in the preparation e.g. about 0.01—2.00 wt.%, preferably 0.05—1.0 wt.%. Some antibiotics may also be used with the corticosteroid as further active ingredients.

Examples of the monoglycerides are monoglycerides of $C_6$—$C_{10}$ straight chain fatty acids, especially $C_6$—$C_{10}$ saturated fatty acids, e.g. glycerol monohexanoate, glycerol monooctanoate or glycerol monodecanoate. They may be used alone or in combination. The proportion employed in the present preparations is usually about 0.5—20 wt.%, preferably 2—15 wt.%. This proportion should be chosen depending upon the solubility of the active ingredient, a low proportion being enough for corticosteroids having high solubility in the monoglyceride, such as betamethasone valerate or betamethasone dipropionate, but a high proportion being necessary for corticosteroids having poor solubility such as hydrocortisone acetate or alclometasone dipropionate. The proportion should be also chosen in accordance with the kind and amount of the other ingredients.

Amongst other pharmacologically acceptable adjuvants which may be used in the invention are $C_2$—$C_6$ primary, secondary or tertiary alcohols, including straight- or branched-chain alcohols, e.g. ethanol, isopropanol, ethylene glycol, propylene glycol, triethylene glycol, 1,3-butanediol, 1,5-pentandiol, 1,6-hexanediol, glycerol or 1,2,6-hexanetriol. Such alcohols may be contained in the preparations in a proportion of about 1—15 wt.% preferably about 5—10 wt.%.

Other possible adjuvants are polyethylene glycols having a mean molecular weight of about 200 to 4000, e.g. polyethylene glycol, 200, 300, 400, 600, 1000, 1500, 1540 or 4000. They may be



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employed in a proportion of about 1—10 wt.% preferably about 2—5 wt.% based upon the final preparation. Polyethylene glycols are usually used in combination with alcohols as noted above since polyethylene glycols alone do not sufficiently manifest the efficacy of the active ingredient. Although this combination is well known in the field of ointments, caution should generally be exercised not to use mixtures of polyethylene glycols and alcohols in amounts exceeding that required to dissolve the active ingredient, otherwise so-called syneresis of the ointment results. Addition of monoglycerides used in the invention in certain proportions prevents such syneresis and improves the stability and efficacy of the resulting preparations.

Other pharmacologically acceptable ingredients which may be employed are oily substances. They are used for the purpose of adjusting the solubility of the active ingredient and the viscosity of the preparation and for improving the feel for application. Examples of oily substances include liquid higher alcohols (e.g. 2-hexyldecanol or 2-octyldecanol), solid higher alcohols (e.g. cetyl alcohol or stearyl alcohol), higher fatty acids (e.g. palmitic acid or stearic acid), esters (e.g. isopropyl myristate, 2-octyldodecyl myristate, diethyl sebacate or diisopropyl adipate), liquid, semi-solid or solid hydrocarbons (e.g. squaline, liquid paraffin, various kinds of paraffins, vaseline, microcrystalline wax or ceresin), waxes (e.g. beeswax, spermaceti or carnauba wax), triglycerides or natural fatty acids (e.g. castor oil or olive oil), synthetic triglycerides, diglycerides, and monoglycerides of higher fatty acids.

The oily substances are generally used in a proportion of about 1—90 wt.% of the preparation, the choice and combination ratio of such oily substances as well as their proportion with respect to the whole preparation weight being dependent upon the corticosteroid to be used, the preparation form and nature of the monoglyceride to be used and its proportion. The proportion used may be, for example, about 5—90 wt.% for an ointment, and it is usually about 1—50 wt.%, preferably 2—35 wt.%, for an emulsion or a cream.

Surfactants may also serve as adjuvants. Surfactants are useful for forming a desired dosage form and for obtaining fine and homogeneous dispersions, emulsions and miscellaneous prepartions. There may be selected from non-ionic surfactants causing little irritation to the skin. Examples of non-ionic surfactants include sorbitan fatty acid esters, sorbitol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene alkyl ethers, polyoxyethylene hydrogenated castor oil derivatives, and polyoxyethylene polyoxypropylene alkyl ethers. Practical examples of surfactants are sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesquistearate, polyoxyethylene sorbitan monolaurate, polyoxyethylene, mono-palmitate, polyoxyethylene sorbitan mono-stearate, polyoxyethylene sorbitan tri-stearate, polyoxyethylene sorbitan mono-oleate, polyoxyethylene sorbitan tri-oleate, polyoxyethylene sorbitol mono-laurate, polyoxyethylene sorbitol hexa-stearate, polyoxyethylene sorbitol tetra-oleate, polyoxyethylene lauryl ester, polyoxyethylene stearyl ester, polyoxyethylene oleyl ester, polyoxyethylene lauryl ether, polyoxyethylene cetyl ether, polyoxyethylene stearyl ether, polyoxyethylene oleyl ether, polyoxyethylene hexadecyl ether, propylene glycol mono-stearate, and polyoxypropylene polyoxyethylene cetyl ether. They may be used alone or as mixtures in the proportion of about 0.5—15 wt.%, preferably about 1—10 wt.%, of the preparation.

Other ingredients such as, for example, stabilizing agents including anti-oxidants, chelating agents, antiseptics, or buffer agents, may be used in a suitable amount if necessary or desired.

Solubilizing agents (e.g. crotamiton and benzyl alcohol) may also be used, if necessary.

Practical embodiments of the present invention are given below, the ingredients having been abbreviated as follows:

monoglyceride = monoglyceride of a $C_6$—$C_{10}$ medium-chain fatty acid;
alcohol = primary, secondary or tertiary $C_2$—$C_6$ alcohol;
polyethylene glycol = polyethylene glycol having a mean molecular weight of 200—4000;
surfactant = non-ionic surfactant

(1) Ointment 1

| | |
|---|---|
| Corticosteroid | 0.01—2.00 wt.% |
| Monoglyceride | 1—20 wt.% |
| Surfactant | 0.5—5 wt.% |
| Oily substance | the balance |

(2) Ointment 2

| | |
|---|---|
| Corticosteroid | 0.01—2.00 wt.% |
| Monoglyceride | 1—15 wt.% |



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| | |
|---|---|
| Alcohol | 1—15 wt.% |
| Surfactant | 0.5—5 wt.% |
| Oily substance | the balance |

(3) Ointment 3

| | |
|---|---|
| Corticosteroid | 0.01—2.00 wt.% |
| Monoglyceride | 1—15 wt.% |
| Polyethylene glycol | 1—10 wt.% |
| Surfactant | 0.5—5 wt.% |
| Oily substance | the balance |

(4) Ointment 4

| | |
|---|---|
| Corticosteroid | 0.01—2.00 wt.% |
| Monoglyceride | 1—15 wt.% |
| Alcohol and polyethylene glycol | 1—10 wt.% |
| Surfactant | 0.5—5 wt.% |
| Oily substance | the balance |

(5) Cream 1

| | |
|---|---|
| Corticosteroid | 0.01—2.00 wt.% |
| Monoglyceride | 1—20 wt.% |
| Surfactant | 0.5—15 wt.% |
| Oily substance | 2—35 wt.% |
| Water | the balance |

(6) Cream 2

| | |
|---|---|
| Corticosteroid | 0.01—2.00 wt.% |
| Monoglyceride | 1—20 wt.% |
| Alcohol | 1—15 wt.% |
| Surfactant | 0.5—15 wt.% |
| Oily substance | 2—35 wt.% |
| Water | the balance |

(7) Cream 3

| | |
|---|---|
| Corticosteroid | 0.01—2.00 wt.% |



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| | |
|---|---|
| Monoglyceride | 1—20 wt.% |
| Polyethylene glycol | 1—10 wt.% |
| Surfactant | 0.5—15 wt.% |
| Oily substance | 2—35 wt.% |
| Water | the balance |

(8) Cream 4

| | |
|---|---|
| Corticosteroid | 0.01—2.00 wt.% |
| Monoglyceride | 1—20 wt.% |
| Alcohol and polyethylene glycol | 1—10 wt.% |
| Surfactant | 0.5—15 wt.% |
| Oily substance | 2—35 wt.% |
| Water | the balance |

The above preparations are only examples and certainly do not limit the broad scope of the present invention. The above preparations may also contain, for example, a stabilizing agent or a solubilizing agent as noted above.

The topical preparations of this invention may be prepared by the usual methods for preparing topical preparations. Thus, the active ingredient may be dissolved in the monoglyceride which may be mixed with the above-mentioned alcohols, polyethylene glycol and/or a part of the oily substance, if any, beforehand. The solution or mixture may then be subjected to, for example, heating, mixing with other adjuvants, dispersing or emulsifying according to the desired dosage form, followed by cooling to room temperature. Furthermore, the required amount of stabilizing agent may be added, if desired.

The efficacy and safety of the present preparations were evaluated by vasoconstrictor assay and skin irritation tests, respectively.

Efficacy and safety evaluation

1. Efficacy by vasoconstrictor assay (Enclosed method)

A fixed amount of each preparation disclosed in the working Examples and References is applied to a commercially available adhesive test tape. The test tapes are applied on a test site on the forearm and the back of the healthy human subject and kept there for 4 hours. After removal of the test tapes, the blanching (intensity of vasoconstriction) of the test spot to which the test tape was applied is observed two and four hours later. The results are shown in Tables 1 and 2.

The figures in the Tables are relative values for the blanching intensity of the spot calculated on the basis that the intensity of the spot to which the reference preparation is applied is taken as 100. The value is proportional to the extent of vasoconstriction.

2. Safety evaluation by closed patch test (Skin irritation test)

A fixed amount of each preparation (including the active ingredient, corticosteroid) in the working Examples and References is placed on a commercially available patch (Finn chamber (Trademark), Taisho Seiyaku Co.m & Ltd.). The test tapes are applied to test sites on the back of healthy human subjects and maintained there for 48 hours. The test tapes are removed and the reddish marks at the test spots (irritation to the skin) are observed after 0.5 hour and 24 hours. The scores for both classes of observed spots are assessed and the results are shown in Tables 1 and 2.

The figures in the Tables represent relative values calculated on the basis that the intensity that the reddish irritation mark for the reference preparation is taken as 100. The value is proportional to the extent of skin irritation and inversely proportional to the safety rating.



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TABLE 1

(Ointment)

| Test Preparation | | Efficacy (Vasoconstriction) | | Safety (Irritation) |
|---|---|---|---|---|
| Example No. | Reference | 2nd Hour | 4th Hour | |
| 1 – 1 | A | 130 | 120 | 98 |
| 1 – 1 | B | 147 | 129 | 105 |
| 1 – 2 | C | 210 | 180 | 100 |
| 1 – 3 | D | 150 | 175 | 101 |
| 1 – 3 | E | 162 | 160 | 103 |
| 1 – 4 | F | 161 | 218 | 100 |
| 1 – 5 | G | 208 | 140 | 38 |
| 1 – 6 | H | 312 | 206 | 62 |

TABLE 2

(Cream)

| Test Preparation | | Efficacy (Vasoconstriction) | | Safety (Irritation) |
|---|---|---|---|---|
| Example No. | Reference | 2nd Hour | 4th Hour | |
| 2 – 1 | I | 275 | 255 | 114 |
| | J | 172 | 221 | 58 |
| 2 – 2 | I | 293 | 231 | 46 |
| | K | 185 | 207 | 64 |
| | L | 227 | 214 | 102 |
| 2 – 3 | I | 191 | 168 | 35 |
| 2 – 4 | M | 144 | 121 | 85 |
| | N | 149 | 118 | 101 |
| 2 – 5 | M | 127 | 108 | 40 |
| | N | 152 | 110 | 87 |
| 2 – 6 | O | 161 | 135 | 67 |



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As noted in Tables 1 and 2, the preparations of the working Examples are superior to the corresponding Reference preparations. Thus, the present invention enables the provision of preparations having high efficacy and safety.

The following Examples are intended to illustrate the invention. The proportions in Tables 3-1, 3-2, 4-1, 4-2 and 4-3 are weight percentages.

EXAMPLE 1 (Ointment)

Ointments are prepared as follows:

White vaseline is melted at 70—80°C, other ingredients are added thereto and mixed homogeneously, and the resultant mixture is cooled to room temperature to give the preparations of Tables 3-1 and 3-2.

EXAMPLE 2 (Cream)

Creams are prepared as follows:

All ingredients except for water are mixed and heated, stirred and blended at 70—80°C. A fixed amount of purified water is added thereto. The mixture is stirred and emulsified and cooled to room temperature to give the preparations of Tables 4-1, 4-2 and 4-3.



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TABLE 3–1

| Ingredient | Example No. | | | Reference | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1–1 | 1–2 | 1–3 | A | B | C | D | E |
| Betamethasone Dipropionate | 0.064 | 0.06 | 0.05 | 0.064 | 0.064 | 0.06 | 0.05 | 0.05 |
| Betamethasone Valerate | | | | | | | | |
| Alclometasone Dipropionate | | | | | | | | |
| Glycerol Monohexanoate | 5.0 | 10.0 | 10.0 | | | | | |
| Glycerol Monooctanoate | | | | | | | | |
| Glycerol Monodecanoate | | | | | | | | |
| Glycerol Monostearate | | | | | 10.0 | | | 10.0 |
| Sorbitan Monostearate | 2.0 | 2.0 | 2.0 | | | | | |
| Sorbitan Tristearate | | | | | | | | |
| Propyleneglycol Monostearate | | | | | | | | |
| Diisopropyl Adipate | 5.0 | 2.0 | | | | | | |
| Paraffin Wax | | | | 10.0 | | 10.0 | 10.0 | |
| Liquid Paraffin | | | | | | | | |
| White Vaseline | 87.936 | 85.94 | 87.95 | 89.936 | 89.936 | 89.94 | 89.95 | 89.95 |



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TABLE 3–2

| Ingredient | Example No. | | | Reference | | |
|---|---|---|---|---|---|---|
| | 1–4 | 1–5 | 1–6 | F | G | H |
| Bethamethasone Valerate | | | 0.12 | | | 0.12 |
| Alclometasone Dipropionate | | 0.05 | | | 0.05 | |
| Dexamethasone | 0.1 | | | 0.1 | | |
| Glycerol Monohexanoate | 5.0 | | 5.0 | | | |
| Glycerol Monodecanoate | | 10.0 | | | | |
| Propylene Glycol | | 3.0 | 4.0 | | 10.0 | 10.0 |
| Polyethylene Glycol 300 | | | 2.0 | | | 5.0 |
| Polyethylene Glycol 400 | 2.0 | | | | | |
| Sorbitan Sesquistearate | 2.0 | | | | | |
| Sorbitan Monooleate | | 2.0 | | | 2.0 | |
| Polyethylene Glycol Mono-stearate | | | 2.0 | | | 2.0 |
| Diethyl Sebacate | 3.0 | | | | | |
| White Beeswax | | 3.0 | 3.0 | | 3.0 | 2.0 |
| Plastibase (50W)* | | | | 99.9 | | |
| White Vaseline | 87.9 | 81.95 | 84.88 | | 84.95 | 80.88 |

*(Trademark) a mixed base of polyethylene with liquid paraffin (Squilb & Sons Co., Ltd.)



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TABLE 4–1

| Ingredient | Example No. | | | Reference | | | |
|---|---|---|---|---|---|---|---|
| | 2–1 | 2–2 | 2–3 | I | J | K | L |
| Alclometasone Dipropionate | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| Glycerol Monohexanoate | 12.0 | | | | | | |
| Glycerol Monooctanoate | | 6.0 | | | | | |
| Glycerol Monodecanoate | | | 14.0 | | | | |
| Glycerol Monostearate | | | | | | | 6.0 |
| Propylene Glycol | | | | 20.0 | | | |
| Polyoxyethylene (20) Cetyl Ether | 5.0 | | | 3.0 | | | |
| Polyoxyethylene (30) Stearyl Ester | | | 6.0 | | | | 5.0 |
| Polyoxyethylene Sorbitan Mono-Stearate | | 5.0 | | | 5.0 | 5.0 | |
| Crotamiton | | | 1.8 | | | | |
| Diisopropyl Adipate | 5.0 | | 4.0 | | 10.0 | | |
| Diethyl sebacate | | 10.0 | | | | 10.0 | |
| Cetyl Alcohol | 10.0 | 8.0 | 10.0 | 8.0 | 10.0 | 10.0 | 8.0 |
| Liquid Paraffin | | | | 5.0 | | | 10.0 |
| White Beeswax | 5.0 | | | 5.0 | 5.0 | 5.0 | |
| White Vaseline | | 10.0 | 10.0 | 7.0 | | | 10.0 |
| Purified Water | 63.0 | 61.0 | 54.0 | 52.0 | 70.0 | 70.0 | 60.95 |



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TABLE 4–2

| Ingredient | Example No. | | Reference | |
|---|---|---|---|---|
| | 2–4 | 2–5 | M | N |
| Betamethasone Dipropionate | 0.064 | 0.064 | 0.064 | 0.064 |
| Glycerol Monooctanoate | 3.5 | 2.5 | | |
| Glycerol Monodecanoate | 1.5 | | | |
| Glycerol Monostearate | | | | 5.0 |
| Polyoxyethylene (20) Cetyl Ether | 4.0 | | 2.0 | 4.0 |
| Sorbitan Monooleate | | 0.5 | | |
| Polyoxyethylene Sorbitan Mono-oleate | | 1.5 | | |
| 2-Octyldodecanol | | 3.0 | | |
| 2-Octyldodecanol Myristate | 10.0 | | | 10.0 |
| Cetyl Alcohol | 7.0 | 2.0 | 8.0 | 7.0 |
| Liquid Paraffin | | | 6.0 | |
| White Vaseline | 10.0 | | 15.0 | 10.0 |
| Purified Water | 64.0 | 90.0 | 69.0 | 63.936 |



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TABLE 4–3

| Ingredient | Example No. | | | Reference |
|---|---|---|---|---|
| | 2–6 | 2–7 | 2–8 | 0 |
| Betamethasone Valerate | 0.12 | | | 0.12 |
| Dexamethasone | | 0.1 | | |
| Prednisolone | | | 1.0 | |
| Glycerol Monooctanoate | | 4.0 | 16.0 | |
| Glycerol Monodecanoate | 8.0 | 1.0 | | |
| Polyoxyethylene (20) Cetyl Ether | | 4.0 | | 2.0 |
| Polyoxyethylene (30) Stearyl Ester | 4.5 | | | |
| Sorbitan Sesquistearate | 1.0 | | | |
| Polyoxyethylene Sorbitan Mono-stearate | | | 5.0 | |
| Crotamiton | | | 1.8 | |
| Diethyl Sebacate | | 2.0 | | |
| 2-Octyldodecyl Myristate | | 8.0 | | |
| Cetyl Alcohol | 10.0 | 8.0 | 10.0 | 8.0 |
| Liquid Paraffin | 7.5 | | | 6.0 |
| White Vaseline | 10.0 | 12.0 | 10.0 | 15.0 |
| Purified Water | 59.0 | 61.0 | 56.0 | 69.0 |



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CLAIMS

1. A topical cortisteroid preparation which comprises a monoglyceride of a $C_6$—$C_{10}$ fatty acid together with an active corticosteroid.

2. A preparation as claimed in claim 1 containing 0.01—2.00 weight percent of a corticosteroid.

3. A preparation as claimed in claim 1 or claim 2 containing 0.5—20.0 weight percent of the monoglyceride.

4. A preparation as claimed in claim 3 containing 1—15 weight percent of the monoglyceride.

5. A preparation as claimed in any one of claims 1 to 4 also containing one or more of the following:

a. 1—15 weight percent of a primary, secondary or tertiary $C_2$—$C_6$ alcohol;

b. 1—10 weight percent of a polyethylene glycol having a mean molecular weight of 200 to 4000.

c. 1—90 weight percent of an oily substance;

d. 0.5—15 weight percent of a non-ionic surfactant; and/or

e. water.

6. A preparation as claimed in claim 5 which contains 0.5—5 weight percent of surfactant and oily substance.

7. A preparation as claimed in claim 5 which contains 0.5—15 weight percent of surfactant and 2—35 weight percent of oily substance and water.

8. A preparation as claimed in claim 6 or claim 7 which also contains 1—15 wt. percent of an alcohol.

9. A preparation as claimed in claim 6 or claim 7 which also contains 1—10 wt. percent of an polyethylene glycol.

10. A preparation as claimed in claim 6 which also contains 1—10 wt. percent of an alcohol and a polyethylene glycol.

11. A preparation as claimed in any one of claims 1 to 10 also containing a solubilizing agent.

12. A preparation as claimed in any one of claims 1 to 11 also containing a stabilizing agent.

13. A preparation as claimed in any one of claims 1 to 12, wherein the corticosteroid is betamethasone valerate, betamethasone dipropionate, alclometasone diproprionate, dexamethasone, triamcinolone acetonide, fluocinonide or fluocinolone acetonide.

14. A preparation as claimed in any one of claims 1 to 12, wherein the corticosteroid is betamethasone valerate, betamethasone dipropionate or alclometasone dipropionate.

15. A preparation as claimed in any one of claims 1 to 14, wherein the monoglyceride is glycerol monohexanoate, glycerol monoocatanoate or glycerol monodecanoate.

16. A preparation as claimed in claim 1 and substantially as hereinbefore described.

17. A preparation as claimed in claim 1 and substantially as hereinbefore described under the headings Ointment 1, 2, 3 or 4 or Cream 1, 2, 3 or 4 or in any one of the individual runs of Example 1 or of Example 2.

18. A process for improving the activity of a topical corticosteroid preparation, which process comprises including a monoglyceride of a $C_6$—$C_{10}$ fatty acid in the preparation.

19. A process as claimed in claim 18 and further defined by the specific feature of any one or more of claims 2 to 15.

20. A process as claimed in claim 18 and substantially as hereinbefore described.

21. A monoglyceride of a $C_6$—$C_{10}$ medium-chain fatty acid intended for use in a preparation as claimed in claim 1 or in a process as claimed in claim 18.

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最終頁に続く

(54)【発明の名称】被膜形成型の副腎皮質ステロイド薬含有外用製剤

(57)【要約】
【課題】従来、副腎皮質ステロイド剤の閉鎖密封療法はその有効性より副作用が深刻となっていた。一方、閉鎖密封療法は製剤的にはべた付き、衣服への付着、物理的要因による製剤の目減りなどがない利点もある。そこで課題としては、閉鎖密封療法ではないが、べた付き、衣服への付着、物理的要因による製剤の目減りなどがなく、皮膚患部への保護性が高い副腎皮質ステロイド剤含有の外用製剤を提供することにある。
【解決手段】エマルション型接着剤成分又はラテックス型接着剤成分とその分散媒としての水を含むことを特徴とすることより閉鎖密封療法ではない被膜形成型の副腎皮質ステロイド薬含有外用製剤を提供することができ、本課題を解決した。



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【特許請求の範囲】
【請求項１】
エマルション型接着剤成分又はラテックス型接着剤成分とその分散媒としての水を含むことを特徴とする被膜形成型の副腎皮質ステロイド薬含有外用製剤。
【請求項２】
前記エマルション型接着成分又はラテックス型接着成分として、酢酸ビニル樹脂系、酢酸ビニル・アクリル共重合樹脂系、アクリル共重合樹脂系、酢酸ビニル・パーサチック酸ビニル共重合樹脂系、アクリル・スチレン共重合樹脂系、エチレン・酢酸ビニル共重合樹脂系、天然ゴム系、合成ゴム系、ウレタン系の何れかの接着成分から選ばれた一つ以上のものを用いることを特徴とする請求項１に記載の被膜形成型の副腎皮質ステロイド薬含有外用製剤。
【請求項３】
前記エマルション型接着成分又はラテックス型接着成分として、酢酸ビニル樹脂系を用いることを特徴とする請求項１に記載の被膜形成型の副腎皮質ステロイド薬含有外用製剤。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】
本発明は副腎皮質ステロイド剤を含有した外用製剤に関するものである。さらに詳しくは、閉鎖密封療法ではないことを特徴とする被膜形成外用製剤に関するものである。
【０００２】
【従来の技術】
副腎皮質ステロイド外用剤は皮膚病変の場合内服あるいは注射投与よりは、全身的な副作用が比較的少ないということで、繁用されてきた。
【０００３】
それら副腎皮質ホルモン外用剤の単純塗布では十分な効果の見られない皮膚疾患の治療法として密封閉鎖療法がある。密封閉鎖療法とはｏｃｃｌｕｓｉｖｅ ｄｒｅｓｓｉｎｇ ｔｈｅｒａｐｙ略してＯＤＴのことで外用剤を病変部に塗擦した上を、病変部よりやや大きめのプラスチックフィルムで覆い、周囲を絆創膏で固定する療法である。基剤から角層中に移動した物質は、物質の濃度差に従って角層内に拡散する。この角層内の物質の移動は、角層中の水分量が増加すると速くなる。ＯＤＴは角層中の水分量を１０・３０％も増加させるので、単純塗擦法に比べてステロイドの吸収は、１０倍も経皮吸収が増加する。
【０００４】
角質層は普通の状態では約１０％の水分を含有している。角質層の主成分であるケラチンは水を吸収する性質があり、密封包帯で周囲の湿度を１００％にすると、角質層の厚さは約　３倍になる。これは分子レベルで、ケラチン分子の周りに水が結合し、ケラチン分子間の距離が長くなり、副腎皮質ステロイド剤が角質層へ移行し、さらに角質層に貯留したものが真皮へ移行しやすくなり、経皮吸収量は上昇する。１９６０年代、この閉鎖密封療法が流行したが，最近は副腎皮質ステロイド剤の力価が高くなるにつれ，それらを用いてこの方法を行うと，その有効性よりも副作用の方が深刻になってきた。その副作用としては皮膚萎縮，毛細血管拡張などの局所的副作用を起こしやすく、広範囲な病巣に用いた場合には全身的な副作用も起こりやすく、また治療作業の煩雑さもあり現在ではあまり用いられることの少ない療法となっている。そのためこの療法の禁忌としては、ビラン、潰瘍などの湿潤性病変，急性炎症性病変、発育期の子供は全身的影響を生じやすいので乳幼児、学童への適応、また、老人は皮膚からの吸収が活発なので，老人への適応などがある。また、毛のう炎，セツなどの細菌性感染症を誘発したり、悪化させたり、汗が貯留して汗疹を発生させたり、毛細血管拡張，皮膚萎縮を生じやすい。さらには患部を覆うプラスチックフィルム、バンソウコウの接触は皮膚炎を生じ、夏には蒸れて悪臭を生じることさえある。
【０００５】
一方、副腎皮質ステロイド剤の製剤としては軟膏およびクリームが一般的であるが、それ


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らの製剤ではべた付き、衣服への付着、そういった衣服への付着のような物理的要因による製剤の目減りなどの問題がある。その問題を解決する方法として塗布後にプラスチックフィルムで被覆したり、プラスター剤、パップ剤などの貼付剤を用いる方法がある。このような方法であると、皮膚患部への保護性が高くなる利点もある。しかしそれらの方法、剤型は閉鎖密封療法にほかならず、前述の問題があった。

【０００６】

プラスター剤のなかでもエマルジョン法で作成したものは比較的水分を透過させることが知られているがそれも十分ではなく、問題の解決までは至っていなかった。

【０００７】

【発明が解決しようとする課題】

上記のような状況から、べた付き、衣服への付着、物理的要因による製剤の目減りなどがなく、皮膚患部への保護性が高く、また閉鎖密封療法ではないすなわち、非ＯＤＴである副腎皮質ステロイド剤含有の外用製剤の登場が望まれていた。そこで本発明の解決課題は、そのような外用製剤を提供することにある。

【０００８】

斯かる目的を解決するために本発明者らは、水分散性接着成分を使用した被膜形成型の軟膏により皮膚上に形成した被膜の水蒸気の透過について鋭意検討したところ、その外用製剤が非ＯＤＴ外用製剤であることを発見し、またその被膜形成型外用剤がべた付き、衣服への付着および物理的要因による製剤の目減りなどがなく、皮膚患部への保護性も高いことから本課題を解決するに至った。

【０００９】

また、エマルジョン法によるプラスター剤は乾燥固化後、熟成期間を経たものであって、本発明の被膜形成型外用剤はその熟成期間がないのでエマルジョン法によるプラスター剤より水分透過性が高いことが確認された

【００１０】

【課題を解決するための手段】

本発明の製剤持続残存性外用製剤はエマルション型接着剤成分又はラテックス型接着剤成分とその分散媒としての水および副腎皮質ステロイド剤を含むことを特徴とする。

【００１１】

上記エマルジョン型接着成分又はラテックス型接着成分としては酢酸ビニル樹脂系、酢酸ビニル・アクリル共重合樹脂系、アクリル共重合樹脂系、酢酸ビニル・パーサチック酸ビニル共重合樹脂系、アクリル・スチレン共重合樹脂系、エチレン・酢酸ビニル共重合樹脂系、天然ゴム系、合成ゴム系、ウレタン系の何れかの接着成分から選ばれた一つ以上のものを用いることが好ましく、中でも酢酸ビニル樹脂系が特に好ましい。

【００１２】

【発明の実施の形態】

本発明の外用製剤の特徴は、被膜形成型外用剤であり、非ＯＤＴであることにある。すなわち、製剤の皮膚への塗布時において本発明の外用製剤はエマルション型接着剤成分又はラテックス型接着剤成分が水中で分散した状態の軟膏状または液状で、その後、皮膚上で製剤中の水分が蒸散することにより、固化し強固な被膜形成し、べた付き、衣服への付着および物理的要因による製剤の目減りなどがなく、皮膚患部への保護性も高く、なおかつ非ＯＤＴであることにある。

【００１３】

以下に、本発明の実施形態及びその効果について説明する。

本発明の外用製剤は本発明に係るエマルション型接着剤成分又はラテックス型接着剤成分は通常接着剤として用いられる高分子のうち、その微粒子が分散媒である水に分散する状態が可能な接着剤成分であれば特に限定はされないが、例えば酢酸ビニル樹脂系、酢酸ビニル・アクリル共重合樹脂系、アクリル共重合樹脂系、酢酸ビニル・パーサチック酸ビニル共重合樹脂系、アクリル・スチレン共重合樹脂系、エチレン・酢酸ビニル共重合樹脂系、天然ゴム系、合成ゴム系、ウレタン系を挙げることができ、これらより一種または二種



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以上を選択して使用することが好ましい。特に、固化、被膜形成後、製剤のべたつきが少ないことから、酢酸ビニル樹脂系はより好ましい。

【００１４】

ここでエマルション接着剤とは接着剤成分のモノマーを水中で乳化重合させたものをいい、ラテックス型接着剤とは接着剤の微粒子を水中に分散したものをいう。どちらの接着剤成分を使用しても分散媒として水を使用しているため安全性が高く、また、水洗いによって皮膚より除去しやすい場合が多く、外用に適している。溶剤を使用して接着剤成分を溶解したものを使用し、外用後に溶剤の気散とともに固化し被膜化する方法も考えられるが、それは安全性が低く、皮膚より除去しづらい場合が多いので、外用に適さない。すなわち、本発明の外用製剤はエマルション型接着剤成分又はラテックス型接着剤成分とその分散媒としての水を含むことを、言い換えると接着剤成分の水分散組成物であることを特徴とすることにより、強固な被膜性、安全性、利便性に非常に優れる。

【００１５】

エマルション型接着剤成分又はラテックス型接着剤成分の配合量としては重量％で１０％以上、８０％以下が好ましく、１０％未満であると水分蒸発後固化しづらく、固化したとしても固化までに時間がかかり好ましくなく、８０％を超えると水に分散不可能となるので好ましくない。

【００１６】

本発明に係る水分含量としては２０％以上、９０％以下が好ましく、２０％未満であると水に分散不可能となるので好ましくなく、９０％を超えると固化までに時間がかかり好ましくない。

【００１７】

本発明の係る副腎皮質ステロイド薬としては外用に使用される副腎皮質ステロイド薬であれば、特に限定はされない。

本発明の外用製剤の剤型としては本外用剤の主旨から比較的可塑性を持つ剤型であれば特に限定されないが、たとえばエアロゾル剤、軟膏剤、クリーム剤、ローション剤などが挙げられる。

【００１８】

本発明の外用製剤は必要に応じて、水分蒸散促進剤を配合することができる。水分蒸散促進剤を配合することにより、本外用製剤の固化被膜形成までの時間を調整することができる。水分蒸散促進剤としてはエタノールやイソプロパノールなどが挙げられる。

【００１９】

本発明の外用製剤は必要に応じて接着剤成分けん濁分散の安定化剤として界面活性剤を配合することができる。界面活性剤としてはポリビニルアルコール、ポリソルベート類、ショ糖脂肪酸エステル、ポリグリセリン脂肪酸エステルなどが挙げられる。

【００２０】

本発明の外用製剤は必要に応じて、可塑剤を配合することができる。可塑剤を配合することにより、本外用製剤は固化被膜形成後の製剤の物理的性能を調整することができる。可塑剤としてはミリスチン酸イソプロピル、セバシン酸ジエチルなどのエステル類やマクロゴール、脂肪酸、脂肪酸グリセリル、アルコール類などが挙げられる。

【００２１】

本発明の外用剤には，必要に応じて，賦形剤、着色剤、香料、滑沢剤、結合剤、乳化剤、増粘剤、湿潤剤、安定剤、保存剤、溶剤、溶解補助剤、緩衝剤、ｐＨ調整剤などを通常の配合量で配合できる。

【００２２】

【実施例】

次に、実施例および試験例を示し、本発明を更に詳しく説明するが、これらは本発明を何ら限定するものではない。なお、本実施例および比較例における配合量の値は、全て質量％である。

【００２３】



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【実施例】
表１の処方で被膜形成型クリーム状製剤を調製した。
すなわち、吉草酸ベタメタゾン、防腐剤をセバシン酸ジエチルとマクロゴールに溶解し、ポリ酢酸ビニルエマルジョン水溶液と精製水を加え一様になるまでかくはん混合し、被膜形成型クリーム剤を作成した。
【００２４】
【表１】

| | |
|---|---|
| 吉草酸ベタメタゾン | 0.12 |
| セバシン酸ジエチル | 6 |
| マクロゴール | 4 |
| ポリ酢酸ビニルエマルジョン水溶液 | 80 |
| 防腐剤 | 適量 |
| 精製水 | 残余 |

【００２５】
【比較例】
表２の処方で、溶媒法を用いてプラスター剤を調整した。
すなわち、溶媒にトルエンを用いて、ブチルヒドロキシトルエン、スチレン・イソプレン・スチレンブロック共重合体、脂環族飽和炭化水素樹脂、ポリブテン、流動パラフィン、セバシン酸ジエチル、マクロゴールを溶解混合し、次いでプラスチックフィルムに均一な厚みで塗工し、８０℃で２０分乾燥し、ポリエステル布と膏体面を会わせラミネートし所望の大きさに切断して、プラスター剤を作成した。このときプラスター剤の膏体の厚みを５０マイクロメータに調整した。
【００２６】
【表２】
比較例処方

| | |
|---|---|
| マクロゴール | 4 |
| セバシン酸ジエチル | 6 |
| ブチルヒドロキシトルエン | 1 |
| ポリブテン | 5 |
| 脂環族飽和炭化水素樹脂 | 45 |
| スチレン-イソプレン-スチレンブロック共重合体 | 25 |
| 流動パラフィン | 14 |

【００２７】
【試験例１】水分透過度試験
実施例の被膜形成型クリーム状製剤をプラスチックフィルムに乾燥後の被膜の厚みが５０マイクロメータになるよう調整して塗工し、乾燥し、被膜形成直後のものをサンプル１とし、被膜形成後室温で７日間放置したものをサンプル２とした。また、サランラップをサンプル３、比較例のプラスター剤をサンプル４とした。直径３ｃｍの口の開いた筒状の瓶に精製水を１０ｇ入れ、瓶の口を作成しておいたサンプルにて覆い被せ密閉し３２℃においた。１時間後、３時間後、６時間後、１２時間後、２４時間後重量測定を行い水の減量を測定した。試験はそれぞれのサンプルごとにｎ＝３でおこなった。
その結果を図１に示す。
【００２８】
図１の結果より、通常ＯＤＴ療法とされているサランラップ、プラスター剤はほとんど水の透過がみられなかった。サンプル１に比べサンプル２の水透過性が低かったのはサンプ


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ル２が被膜形成後７日間放置したため樹脂の熟成が進み、水の透過性が低くなったためと考えられる。すなわち、エマルジョン法によるプラスター剤は基剤の熟成の影響で本発明の外用剤に比べ水の透過性が低くなると考えられる。

【００２９】

【試験例２】

実施例の被膜形成型クリーム製剤、比較例のプラスター剤、サランラップを被験者６人の前腕中央部に塗布、被膜形成または貼付し、その部分の皮膚相対水分量を経時的にコルネオメーター（ＣＭ８２５ＰＣ、Ｃｏｕｒａｇｅ＋Ｋｈａｚａｋａ Ｅｌｅｃｔｒｏｎｉｃ ＧｍｂＨ）を用い測定した。測定は初期、１，３，６時間後に行った。また、対象として未処置も同時に試験した。

その結果を図２に示す。

【００３０】

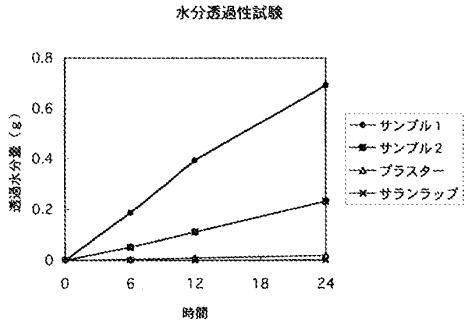
本発明の外用製剤は塗布時の皮膚水分量が変化しないことから、十分な通気性を有した非ＯＤＴ製剤であることが明らかとなった。

【図面の簡単な説明】

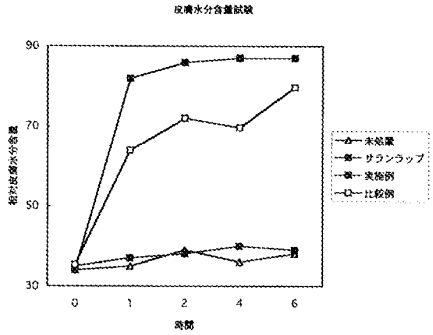
【図１】水分透過度試験について示したもので、Ｙ軸は初期からのそれぞれの水の減量を水の透過量として表し、Ｘ軸は経過時間を表す。

【図２】皮膚水分含量試験について示したもので、Ｘ軸は経過時間、Ｙ軸は相対皮膚水分含量を表す。

【図１】




【図２】






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フロントページの続き

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4C076BB31
4C076CC04
4C076EE04A
4C076EE07A
4C076EE09A
4C076EE22A
4C076FF67
4C086AA01
4C086AA02
4C086DA10
4C086MA03
4C086MA05
4C086MA28
4C086MA63
4C086NA06
4C086ZB11

Overview Close

(57) [Overview]

PROBLEM TO BE SOLVED: To obtain an external preparation containing an adrenocorticosteroid medicine, which is not used for an occlusive dressing technique, has no greasiness, no adhesion to clothing, no loss in weight of a preparation by a physical factor and high protection of the affected part of the skin.

SOLUTION: The coating film-forming type external preparation containing an adrenocorticosteroid medicine not useful for an occlusive dressing technique comprises an emulsion type adhesive component or a latex type adhesive component and water as its dispersion medium.

Scope of Claims Close

[Patent Claims]

[Claim 1]

This preparation contains an emulsion-type adhesive component or a latex type adhesive component and water as a dispersion medium.

[Claim 2]

As the emulsion type adhesive component or the latex type adhesive component, a vinyl acetate resin system, a vinyl acetate / acrylic copolymer resin system, an acrylic copolymer resin system, and a vinyl acetate / perfluoroacid vinyl acetate copolymer resin system are used. The composition according to claim 1, wherein one or more of an acrylic styrene copolymer resin system, an ethylene vinyl acetate copolymer resin system, a natural rubber system, a synthetic rubber system and a urethane system is used.

[Claim 3]

The preparation of claim 1, wherein the adhesive component or latex type adhesive component is a vinyl acetate resin system.

Detailed Description Close





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[Detailed description of the invention]

[0001]

[Technical field of invention]

The present invention relates to an external preparation containing a corticosteroid. More part icularly, the present invention relates to an external preparation for coating which is characteri zed in that it is not a closed sealing therapy.

[0002]

[Prior art]

Corticosteroids have been widely used because of their relatively low systemic side effects co mpared to oral or injectable administration in the case of skin lesions.

[0003]

There is a seal closing therapy as a cure for skin disease with which effect sufficient in simple application of these adenocoriticotropic hormone external preparations is not seen. In the cas e of the sealed closure therapy, an ODT is used for a short occlusive dressing therapy, and a medical treatment is performed in which a plastic film is rubbed with a plastic film which is sli ghtly larger than a lesion portion and is fixed to the lesion portion. Substances transferred fro m the base into the horny layer diffuse into the horny layer according to the concentration diff erence of the material. The migration of material within the stratum corneum increases as the water content in the stratum corneum increases. Since ODT increases the water content in th e horny layer by as much as 10 · 30%, the absorption of steroids is increased by 10 times as much as compared with the simple rubbing method.

[0004]

The stratum corneum normally contains about 10% moisture. Keratin, which is a major comp onent of the stratum corneum, has the property of absorbing water, and when the surroundin g humidity is 100% with a sealing bandage, the thickness of the stratum corneum is about 3 t imes. This is because, at the molecular level, water binds around the keratin molecules, the di stance between the keratin molecules becomes long, the corticosteroid migrates to the stratu m corneum, and further, those stored in the stratum corneum easily migrate into the dermis, and thus the transdermal absorption amount increases. In the 1960 s, this closed sealing ther apy has been popular, but recently, as the potency of corticosteroids increases, the efficacy of this method has become more severe than their effectiveness. As a side effect thereof, a local side effect such as skin atrophy and the like is liable to occur, and when used for a wide range of lesions, systemic side effects tend to occur, and a complicated treatment is also involved, a nd thus, a therapy which is rarely used at present is hardly used. Thus, as contraindications of this treatment, there are wet lesions such as a bilane and an ulcer, acute inflammatory lesion s, an adaptation to an infant, an adaptation to an infant, and an adaptation to an elderly pers on because an elderly person is actively absorbed from the skin. In addition, it is liable to indu ce bacterial infections such as folliculitis, sex, or the like, aggravate or aggravate sweat, cause sweat rash, or cause capillary expansion or skin atrophy. Furthermore, contact of the plastic fi

lm covering the affected part with the bungy sushi causes dermatitis, and in summer, it is swe aty and may be unpleasant.

[0005]

On the other hand, as a preparation of an adrenocorticosteroid, an ointment and a cream are generally used.

These formulations suffer from problems such as stickiness, adhesion to garments, and loss of formulation due to physical factors such as adhesion to such garments. As a method of solvin g the problem, there is a method of coating with a plastic film after coating or a method of usi ng a plaster such as a plaster or a poultice. This method has an advantage in that the protecti ve property against the affected portion of the skin becomes high. However, these methods a nd dosage forms are not other than closed sealing therapy, and have the aforementioned prob lems.

[0006]

Among the plaster agents, those prepared by an emulsion method have been known to be rel atively permeable to moisture, but they have not yet been used for 10 minutes but have not r eached the solution of the problem.

[0007]

[Problem to be solved by the invention]

In view of the above circumstances, it has been desired to develop an external preparation co ntaining an adrenocorticosteroid, which has no stickiness, adhesion to clothes, loss of eye loss of the preparation due to physical factors, and the like, has high protection against the affecte d part of the skin, and is not a closed sealing therapy, I. e., a non-ODT. It is therefore an obje ct of the present invention to provide such an external preparation.

[0008]

In order to solve such a problem, the present inventors have intensively studied the permeati on of water vapor of a coating formed on the skin by using a film-forming type ointment using a water-dispersible adhesive component. It has been found that the preparation for external u se is a preparation for external use of a non-ODT, and that the preparation for external use of a film has a high protection against an affected part of a skin and a high protective property a gainst an affected part of a skin, without causing a stickiness, etc., of a preparation due to sti ckiness, adhesion to clothes and physical factors.

[0009]

It was also confirmed that the plaster agent according to the present invention has a higher w ater permeability than a plaster agent according to an emulsion method because a plaster age nt according to an emulsion method has been dried and solidified, and after a ripening period, a film forming type external preparation of the present invention has no aging period.

[0010]

[Means for solving the problem]

The sustained retention external preparation of the present invention comprises an emulsion type adhesive component or a latex type adhesive component and water and a corticosteroid as a dispersion medium thereof.

[0011]

As the emulsion-type adhesive component or the latex-type adhesive component, a vinyl acetate resin system, a vinyl acetate / acrylic copolymer resin system, an acrylic copolymer resin system, and a vinyl acetate / pertic acid vinyl acetate copolymer resin system are used. It is preferable to use one or more of acrylic styrene copolymer resin system, ethylene vinyl acetate copolymer resin system, natural rubber system, synthetic rubber system and urethane system, and particularly preferred is vinyl acetate resin system.

[0012]

[Embodiment of invention]

A characteristic of an external preparation of the present invention is a film-forming type external preparation, which is a non-ODT. In other words, when applied to the skin of a formulation, an external preparation for external use of the present invention is an ointment or a liquid in which an emulsion-type adhesive component or a latex-type adhesive component is dispersed in water. Thereafter, the moisture in the formulation is evaporated on the skin, so that it solidifies to form a firm film, and there is no loss of the preparation due to stickiness, adhesion to clothes and physical factors, and the protective property against the affected part of the skin is high, and it is not ODT.

[0013]

Hereinafter, embodiments of the present invention and effects thereof will be described.

There is no particular limitation on the preparation for external use of the present invention, as long as the emulsion type adhesive component or latex type adhesive component according to the present invention is an adhesive component which can be dispersed in water in which the fine particles are a dispersion medium, among the polymers which are usually used as an adhesive. For example, a vinyl acetate resin system, a vinyl acetate / acrylic copolymer resin system, an acrylic copolymer resin system, a vinyl acetate / pertic acid vinyl acetate copolymer resin system, an acrylic / styrene copolymer resin system, an ethylene / vinyl acetate copolymer resin system, a natural rubber system, a synthetic rubber system and a urethane system can be given, and one kind or 2 kinds of them can be used.

It is preferable to select and use the above. In particular, a vinyl acetate resin system is more preferred because of its low tackiness after solidification and film formation.

[0014]

Here, an emulsion adhesive refers to a product obtained by emulsion-polymerizing a monomer of an adhesive component in water, and a latex adhesive refers to a product obtained by dispersing fine particles of an adhesive in water. Since water is used as a dispersion medium when any of the adhesive components is used, it is highly safe, and is often easily removed from t

he skin by washing with water, and is suitable for external use. A method of using a solvent in which an adhesive component is dissolved, and a method of solidifying and forming a film together with the evaporation of a solvent after an external application is conceivable, but it is not suitable for external use since it is low in safety and is often difficult to be removed from the skin. In other words, the preparation for external use of the present invention is characterized in that it contains an emulsion-type adhesive component or a latex type adhesive component and water as a dispersion medium thereof, in other words, is characterized in that it is an aqueous dispersion composition of an adhesive component, so that it is very excellent in a strong coating property, safety, and convenience.

[0015]

The amount of the emulsion-type adhesive component or latex type adhesive component to be blended is preferably 10% or more and 80% or less by weight, and if it is less than 10%, it is difficult to solidify after evaporation, and even if solidified, it takes a long time to solidify, and if it is more than 80%, it is not preferable because it cannot be dispersed in water.

[0016]

The moisture content of the present invention is preferably not more than 20% and not more than 90%, and is not preferably less than 20%, so that it is not preferable, and if it exceeds 90%, it takes a long time to solidify.

[0017]

The corticosteroid of the present invention is not particularly limited as long as it is a corticosteroid used for external use.

The dosage form of the external preparation for external use of the present invention is not particularly limited as long as it is a dosage form having relatively plasticity from the spirit of the external preparation, and includes, for example, an aerosol, an ointment, a cream, a lotion, and the like.

[0018]

The preparation for external use of the present invention may be blended with a water evaporation promoting agent if necessary. By blending the moisture evaporation promoting agent, it is possible to adjust the time until the solidified film formation of the preparation for external use. Examples of the moisture evaporation accelerator include ethanol and Isopropanol.

[0019]

If necessary, a surfactant may be added to the external preparation for the external preparation of the present invention as a stabilizer for the dispersion of the adhesive component. Examples of the surfactant include polyvinyl alcohol, polysorbates, sucrose fatty acid esters, and polyglycerin fatty acid esters.

[0020]

If necessary, a plasticizer may be incorporated into the external preparation of the present invention. By incorporating a plasticizer, the topical formulation can adjust the physical performance of the formulation after the solidified film is formed. Examples of the plasticizer include es

ters such as isopropyl myristate and diethyl sebacate, macrogol, fatty acids, fatty acid glycery l, and alcohols.

[0021]

As the external preparation of the present invention, if necessary, an excipient, a coloring age nt, a flavor, a lubricant, a binder, an emulsifier, a thickener, a wetting agent, a stabilizer, a pre servative, a solvent, a solubilizing aid, a buffer, a pH adjuster, and the like may be blended in a usual blending amount.

[0022]

[Examples]

Next, the present invention will be described in more detail with reference to Examples and Te st Examples, which do not limit the present invention in any way. In addition, all of the blendi ng amounts in the present examples and Comparative examples are% by mass.

[0023]

[Examples]

A film-forming cream formulation was prepared with the formulation of Table 1.

Namely, betamethasone valerate, a preservative was dissolved in diethyl sebacate and macro gol, and a polyvinyl acetate emulsion aqueous solution and purified water were added thereto and stirred and mixed until uniform to prepare a film-forming type cream.

[0024]

[Table 1]

| | |
|---|---|
| 吉草酸ベタメタゾン | 0.12 |
| セバシン酸ジエチル | 6 |
| マクロゴール | 4 |
| ポリ酢酸ビニルエマルジョン水溶液 | 80 |
| 防腐剤 | 適量 |
| 精製水 | 残余 |

[0025]

[Comparative example]

In the formulation of Table 2, a plaster was prepared using a solvent method.

In other words, toluene is used as a solvent, and butyl hydroxytoluene, a styrene / isoprene s tyrene block copolymer, an alicyclic saturated hydrocarbon resin, polybutene, a Liquid Paraffi n, and diethyl sebacate are used. The macrogol was dissolved and mixed, then applied to a pl



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astic film with a uniform thickness, dried at 80 ° C. for 20 minutes, and then laminated with a polyester cloth and a plaster surface to form a desired size. At this time, the thickness of the plaster of the plaster was adjusted to 50 micrometers.

[0026]

[Table 2]

比較例処方

| | |
|---|---|
| マクロゴール | 4 |
| セバシン酸ジエチル | 6 |
| ブチルヒドロキシトルエン | 1 |
| ポリブテン | 5 |
| 脂環族飽和炭化水素樹脂 | 45 |
| スチレン-イソプレン-スチレンブロック共重合体 | 25 |
| 流動パラフィン | 14 |

[0027]

[The example 1 of an examination] Moisture transmittance examination

A film forming type creamy preparation of Example was coated on a plastic film so that the thickness of the dried film became 50 micrometers, dried, and a film immediately after the film formation was used as a sample 1, and the film was left at room temperature for 7 days after the film formation, to obtain a sample 2. Further, a sample 3 was used as the Saran wrap and a sample 4 as the comparative example. 10 g of purified water was placed in a 3 cm diameter open cylindrical bottle, and the bottle was covered with a sample having a mouth of a bottle, covered with a sample, and then sealed at 32 ° C. After 1 hour, 3 hours, 6 hours, 12 hours, and 24 hours after the measurement, the weight loss of water was measured. Tests were performed at = 3 for each sample.

The results are shown in FIG. 1.

[0028]

From the results shown in FIG. 1, it was found that almost no water permeation of water was observed in the Saran wrap and plaster, which were normally ODT therapy. Sample 1 has lower water permeability than Sample 2.

This is considered to be due to the fact that, since the stick 2 was left for 7 days after the film

formation, aging of the resin proceeded and the water permeability decreased. In other words, it is considered that the plaster agent according to the emulsion method has lower water permeability than the external preparation of the present invention due to the effect of ripening of the base.

[0029]

[The example 2 of an examination]

The film forming type cream preparation, the plaster of the comparative example, and the Saran wrap were applied to the central portion of the forearm of 6 subjects, and the coating film formation or the coating was applied, and the relative moisture content of the portion was measured with a corneometer (CM 825 P C,Courage+Khazaka Electronic GmbH) over time. Measurements were initially made 1,3,6 hours later. Also, untreated and simultaneously tested were tested.

The results are shown in FIG. 2.

[0030]

Since the external preparation for external use of the present invention does not change the water content of skin at the time of application, it is clear that the preparation is a non-ODT preparation having sufficient air permeability.

[Brief Description of the Drawings]

[Fig. 1]As shown for the moisture permeation test, the Y-axis represents the weight loss of water from the beginning as the water permeation amount, and the X-axis represents the elapsed time.

[Fig. 2]As shown for skin moisture content test, the X-axis represents elapsed time and the Y-axis represents relative skin moisture content.

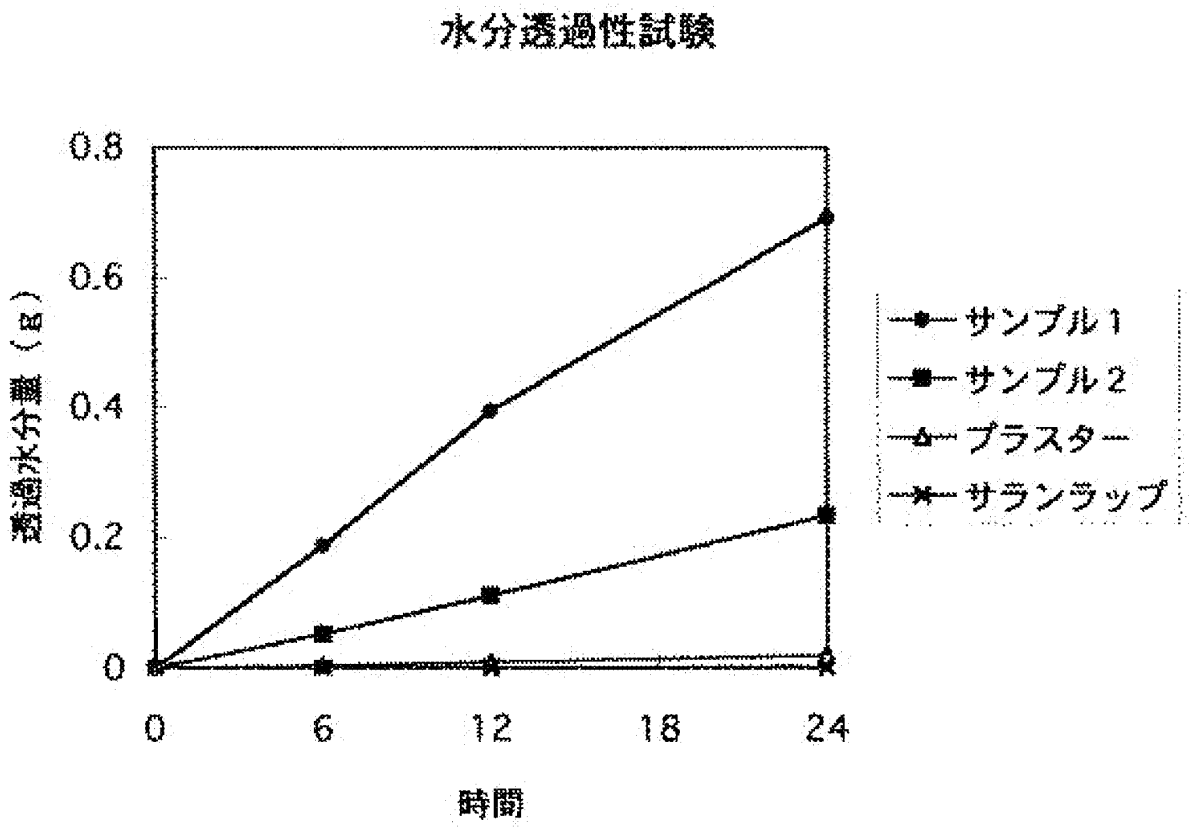
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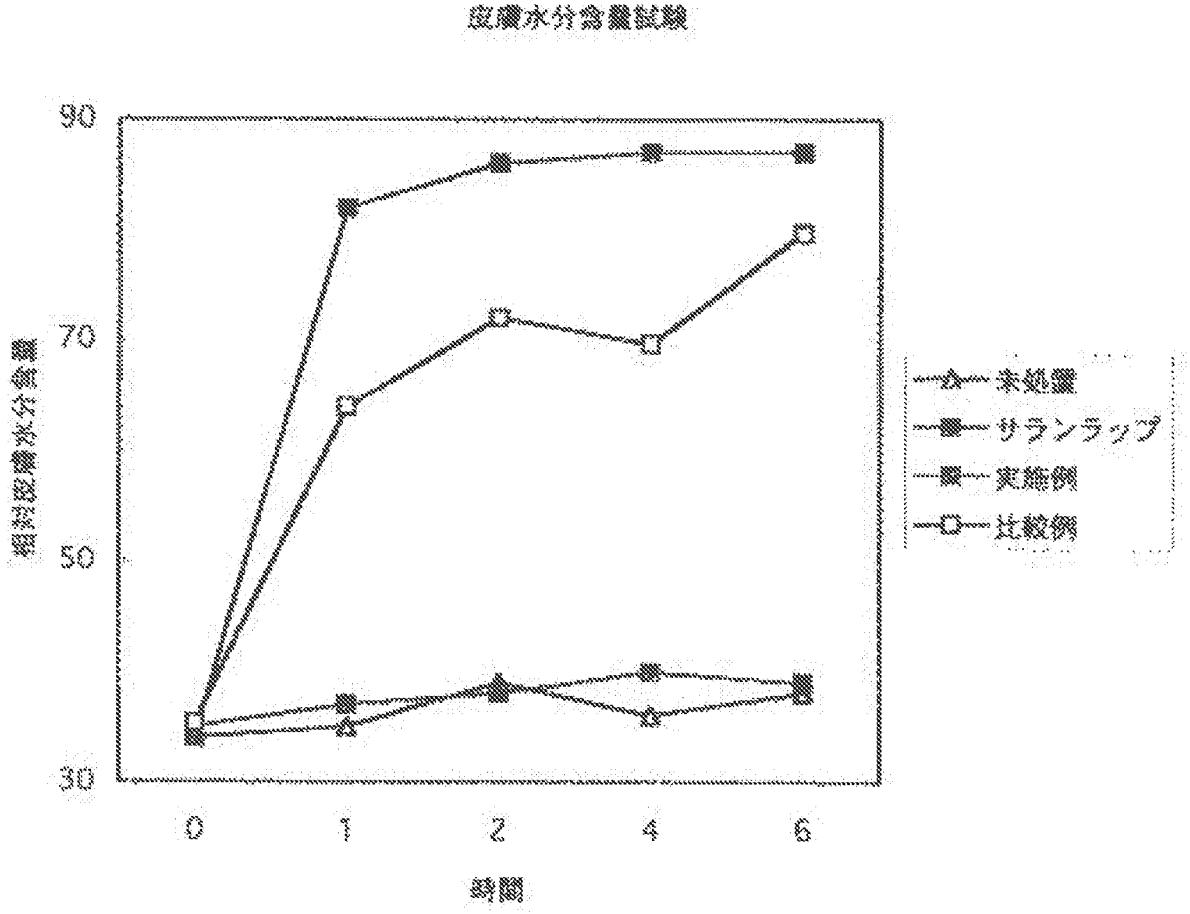


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[FIG.1]


水分透過性試験
0.8
0.6
0.4
0.2
0
透過水分量（g）
0
6
12
18
24
時間
サンプル１
サンプル２
プラスター
サランラップ

[FIG.2]




Drawings Open



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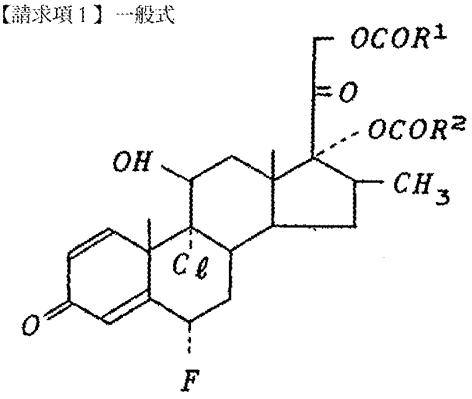
審査官　佐伯　とも子

(54)【発明の名称】　ステロイドクリーム製剤

1

【特許請求の範囲】

【請求項１】一般式




〔式中、R¹はメチル基又はエチル基を示し、R²は炭素数

2

１～４のアルキル基又はフェニル基を示す。〕

で表わされるステロイド類0.01～0.5重量％、アジピン酸ジイソプロピル、セバシン酸ジエチル及びトリアセチンから選ばれた１種又は２種以上の溶解剤２～40重量％、プロピレングリコール及び／又は1,3－ブチレングリコール２～30重量％、界面活性剤0.5～15重量％、高級パラフィン系炭化水素２～50重量％、精製水30～85重量％を含有し、ほぼ飽和状態に溶解した上記ステロイドを不連続相として乳化含有させたことを特徴とするステロイドクリーム製剤。

【請求項２】ステロイド類0.01～0.2重量％、アジピン酸ジイソプロピル、セバシン酸ジエチル及びトリアセチンから選ばれた１種又は２種以上の溶解剤２～20重量％、プロピレングリコール及び／又は1,3－ブチレングリコール５～20重量％、界面活性剤0.5～10重量％、高



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級パラフィン系炭化水素4～40重量%、精製水40～80重量%を含有する特許請求の範囲第1項に記載のステロイドクリーム製剤。

【発明の詳細な説明】

産業上の利用分野

本発明は、薬物放出性及び経皮吸収性に優れ、皮膚刺激性が少く、しかも、薬物の結晶析出がない安定な水中油型ステロイドクリーム製剤に関する。

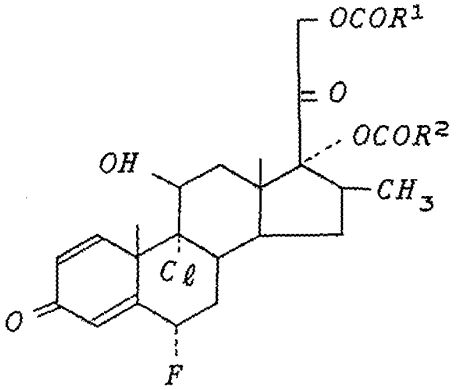
従来の技術とその問題点

ステロイド類は、公知の如く優れた抗炎症作用を有し、主に、油性軟膏製剤、クリーム製剤等の形態で広く使用されている。これらのうちステロイドクリーム製剤としては、一般に、複数の油相成分を、複数の水相成分中に或いはその逆に乳化し、更に、半固形の安定な系とするために、油性軟膏製剤よりも多量の界面活性剤を添加したものが使用されている。本発明者は、優れた抗炎症作用を有し、副作用が殆んどない外用高脂溶性ステロイドである6α－フルオロ－9α－クロロ－16β－メチルプレドニゾロン17,21－ジエステル類（特公昭61-45970号）を主薬として使用し、従来技術に従ってクリーム製剤を得ることを試みた。しかし、得られたクリーム製剤は、1）薬剤放出性が低い、2）経皮吸収性が不充分である、3）皮膚刺激性がある、4）薬物の結晶析出が起る等の問題点が生じ、上記ステロイドの優れた効果を充分発揮させ得ないことが判明した。

問題点を解決するための手段

本発明の目的は、主薬として上記高脂溶性ステロイド類を含み、高い薬剤放出性を有し、経皮吸収性に優れ、皮膚刺激性が少なく、且つ薬物の結晶析出が起らず、上記ステロイドの効果を充分に発揮させ得るステロイドクリーム製剤を提供することにある。

即ち本発明は、一般式




（1）

〔式中、$R^1$はメチル基又はエチル基を示し、$R^2$は炭素数1～4のアルキル基又はフェニル基を示す。〕

で表わされるステロイド類0.01～0.5重量%、アジピン酸ジイソプロピル、セバシン酸ジエチル及びトリアセチンから選ばれた1種又は2種以上の溶解剤2～40重量%、プロピレングリコール及び／又は1,3－ブチレングリコール2～30重量%、界面活性剤0.5～15重量%、高級パラフィン系炭化水素2～50重量%、精製水30～85重量%を含有し、ほぼ飽和状態に溶解した上記ステロイドを不連続相として乳化含有させたことを特徴とするステロイドクリーム製剤に係る。

本発明は、製剤処方において、薬物親和性の高い基剤成分を必要最少量とすると薬物は放出され易くなり、更に薬物を飽和溶解状態とし、加えて薬物の連続相中における拡散性を高める物質を添加した場合には、放出性は最大となるという新規な知見に基づいて完成されたものであり、a）主薬である上記一般式（1）で表わされるステロイド類、b）製剤中において前記ステロイド類をほぼ飽和状態に溶解するための溶解剤、c）精製水（連続相）中でのステロイドの拡散性を高めるためのプロピレングリコール及び／又は1,3－ブチレングリコール、d）連続相である精製水中に、ステロイドを溶解剤にほぼ飽和状態で溶解した溶液を、不連続相として微粒化分散させるための界面活性剤、e）製剤に皮膚保護作用、皮膚粘滑作用等を付与するための高級パラフィン系炭化水素並びにf）精製水を夫々特定量含むことを必須とする。即ち、本発明クリーム製剤は、連続相である精製水中に、ステロイドをほぼ飽和状態に溶解した溶解剤を含む不連続相を、界面活性剤で微粒化分散した系から成っている。本来ステロイドの溶解性を殆んど有さない連続相（精製水）に、プロピレングリコール及び／又は1,3－ブチレングリコールを添加することによって、同相中における薬物拡散性が増加し、高い薬物放出性、優れた皮膚移行性等が付与された、薬物の結晶析出が起らない本発明製剤が提供される。しかも、本発明製剤では、適量の高級パラフィン系炭化水素を含んでいるため、皮膚刺激性が少ない。更に、該製剤を皮膚に適用した場合には、水分揮散による組成変化が生じ、皮膚上で、連続相であるプロピレングリコール及び／又は1,3－ブチレングリコール水溶液が濃縮されるにともなって、薬物の拡散性が増加し、薬物の経皮吸収性のより一層の向上が認められるのである。



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ステロイド類としては、上記一般式（１）で表わされる公知のステロイド類が使用できる。その具体例としては、例えば、６α－フルオロ－９α－クロロ－16β－メチルプレドニゾロン17,21－ジアセテート、６α－フルオロ－９α－クロロ－16β－メチルプレドニゾロン17,21－ジプロピオネート、６α－フルオロ－９α－クロロ－16β－メチルプレドニゾロン17－バレレート,21－アセテート、６α－フルオロ－９α－クロロ－16β－メチルプレドニゾロン17－プロピオネート,21－アセテート、６α－フルオロ－９α－クロロ－16β－メチルプレドニゾロン17－ベンゾエート,21－アセテート等を挙げることができる。ステロイドの配合量は、使用するステロイドの薬理活性強度に応じ、通常製剤全量の0.01～0.5重量％程度、好ましくは0.01～0.2重量％程度、より好ましくは0.02～0.1重量％程度とすればよい。

溶解剤としては、アジピン酸ジイソプロピル、セバシン酸ジエチル及びトリアセチンから選ばれた１種又は２種以上を使用できる。その配合量は、ステロイドの溶解剤以外の不連続相成分に対する溶解性及びステロイドをほぼ飽和状態とすることを考慮すると、製剤全量の２～40重量％程度、好ましくは２～20重量％程度、より好ましくは３～20重量％程度とすればよい。

プロピレングリコール及び1,3－ブチレングリコールは、薬物の放出性及び経皮吸収性を向上させる。プロピレングリコール及び／又は1,3－ブチレングリコールの配合量は、製剤全量の２～30重量％程度、好ましくは５～20重量％程度、より好ましくは５～15重量％程度とすればよい。２重量％未満では、薬物の連続相中における拡散性が不充分となり、薬理試験において十分な効果を示し得ず、一方30重量％を越えると、薬物の基剤親和性が高くなりすぎ、放出性が低下するとともに、皮膚刺激性を示す可能性が高くなり好ましくない。

界面活性剤としては、水中油型クリーム製剤の調製に利用される公知のものが何れも使用できるが、なかでも、非イオン性界面活性剤が皮膚への安全性の面から好ましい。その具体例としては、例えば、ポリオキシエチレンアルキルエーテル、ポリオキシエチレンアルキルフェニルエーテル、ポリオキシエチレンポリオキシプロピレンセチルエーテル、テトラオレイン酸ポリオキシエチレンソルビット、トリオレイン酸ポリオキシエチレンソルビタン、ポリオキシエチレンヒマシ油、ポリオキシエチレン硬化ヒマシ油、ポリオキシエチレンソルビットミツロウ、ショ糖脂肪酸エステル、ポリグリセリン脂肪酸エステル、ポリオキシエチレンラノリン、ポリオキシエチレンラノリンアルコール、ポリオキシエチレンステアリン酸アミド、レシチン、モノ脂肪酸ポリオキシエチレンソルビタン、モノ脂肪酸ポリエチレングリコール、モノ脂肪酸グリセリン、モノ脂肪酸プロピレングリコール、モノ脂肪酸ソルビタン若しくはこれらの混合物等を挙げることができる。また、イオン性界面活性剤としては、例えば、ラウリル硫酸ナトリウム、セチル硫酸ナトリウム、ポリオキシエチレンアルキルエーテルリン酸等の陰イオン性界面活性剤等を挙げることができる。本発明では、上記非イオン性界面活性剤と陰イオン性界面活性剤とを併用することもできる。界面活性剤の配合量は、製剤に充分な乳化安定性が付与される必要最少量とすればよく、通常製剤全量の0.5～15重量％程度、好ましくは0.5～10重量％程度、より好ましくは３～10重量％程度とすればよい。

高級パラフィン系炭化水素は、非極性物質であるため、薬物に対する親和性を殆ど有さず、薬物放出性に影響を与えない基剤成分であり、しかも、製剤に皮膚保護作用、皮膚粘滑作用等を付与する。高級パラフィン系炭化水素としては、炭素数16～40程度の公知のパラフィン系炭化水素が何れも使用でき、例えば、軟質流動パラフィン、流動パラフィン、白色ワセリン、パラフィン、ミクロクリスタリンワックス、セレシン等を挙げることができる。高級パラフィン系炭化水素の配合量は、製剤全量の２～50重量％程度、好ましくは４～40重量％程度、より好ましくは10～30重量％程度とすればよい。２重量％未満では、前述の基剤効果が望めず、また好ましい製剤物性や安定な乳化状態を付与することが困難となる。一方50重量％を越えると、薬物を不連続相に飽和溶解することが困難となり、また油性が強くなりすぎて使用感が悪くなる。

精製水の量は、通常製剤全量の30～85重量％程度、好ましくは40～80重量％程度、より好ましくは40～70重量％程度とすればよい。

本発明クリーム製剤には、必要に応じて、通常のクリーム製剤に使用される公知の添加剤を添加してもよい。添加剤としては、例えば、製剤中での薬物の安定性を高めるpH調整剤、製剤の外観・性状改良剤、防腐剤、増粘或いは乳化安定化剤等を挙げることができる。pH調整剤としては公知のものが何れも使用でき、例えば、クエン酸、乳酸、リン酸等を挙げることができる。その配合量は、製剤のpHが4.0～6.5程度、好ましくは4.5～6.0程度となるようにすればよい。また、製剤の外観・性状を良くするために、例えば、ステアリルアルコール、セチルアルコール等の高級アルコール、鯨ロウ、ミツロウ等のロウ類等を添加してもよく、その配合量は、製剤全量の５重量％以下程度とすればよい。防腐剤としては、例えば、メチルパラベン、エチルパラベン、ブチルパラベン等のパラオキシ安息香酸アルキルエステル類等を挙げることができる。その製剤全量の配合量は、0.01～0.3重量％程度とすればよい。増粘或いは乳化安定化剤としては、例えば、メチルセルロース、エチルセルロース、ヒドロキシプロピルセルロース、ポリビニルアルコール、ポリビニルピロリドン、アルギン酸ナトリウム、デンプン等の水溶性高分子化合物、トラガカントゴム、アラビアゴム等のガム質等を挙げることができる。その配合量



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は、製剤全量の５重量％未満程度でよい。
本発明クリーム製剤は、上記各成分の所定量を、公知の方法によって混合して製造される。例えば、まず、ステロイドを、溶解剤、油溶性成分（高級パラフィン系炭化水素、パラオキシ安息香酸エステル、高級アルコール、ロウ類等）及び界面活性剤の混合物に加えて加温溶解し、油相とする。この際、ステロイドを予め溶解剤に溶解した後、これにその他の成分を添加して溶解すると製造の作業性が良好である。次いで、精製水に、水溶性成分（多価アルコール、パラオキシ安息香酸エステル、pH調整剤等）を加えて加温溶解し、水相とする。上記油相に、加温下撹拌しながら上記水相を徐々に加えて乳化し、更に撹拌しながら冷却することによって、本発明クリーム製剤を製造することができる。本発明クリーム製剤には、更に必要に応じて、抗ヒスタミン剤、鎮痛剤、抗生物質等を配合してもよい。

発明の効果

本発明クリーム製剤は、薬物と親和性の高い基剤成分を必要最少量とし、主薬ステロイドを飽和溶解状態で含有させ、並びに連続相中での薬物拡散性を高めることにより、極めて優れたステロイド放出性並びに経皮吸収性を有し、高い治療効果を発揮する。しかも、皮膚刺激性が少なく、薬物の結晶析出が起らない。

実施例

以下に実施例（本発明クリーム製剤の製剤例）及び本発明製剤の有用性を示す薬理試験を挙げ、本発明をより一層明瞭なものとする。
尚、各実施例において、精製水は、イオン交換樹脂によって精製した水を使用し、粘度はDVL－３型回転粘度計（No.4ローター,3rpm.,25℃，東京計器（株）製）によって、またpHはニードル型のpH電極を使用して、日立－堀場Ｆ－７型pHメーター〔（株）堀場製作所製〕によって測定した値である。

実施例1:6α－フルオロ－９α－クロロ－16β－メチルプレドニゾロン17,21－ジアセテートクリーム

| | |
|---|---|
| ６α－フルオロ－９α－クロロ－16β－メチルプレドニゾロン17,21－ジアセテート | 0.05g |
| アジピン酸ジイソプロピル | 10.0〃 |
| 1,3－ブチレングリコール | 10.0〃 |
| 白色ワセリン | 20.0g |
| サラシミツロウ | 1.0〃 |
| セタノール | 3.0〃 |
| モノステアリン酸グリセリン | 4.0〃 |
| モノステアリン酸ソルビタン | 2.0〃 |
| ステアリン酸ポリオキシル40 | 1.0〃 |
| プロピルパラベン | 0.1〃 |
| メチルパラベン | 0.1〃 |
| クエン酸 | 0.015〃 |
| 精製水 | 残部 |
| 計 | 100.0g |

６α－フルオロ－９α－クロロ－16β－メチルプレドニゾロン17,21－ジアセテートを、アジピン酸ジイソプロピルに加えて加温溶解し、これに、白色ワセリン、サラシミツロウ、セタノール、モノステアリン酸グリセリン、モノステアリン酸ソルビタン、ステアリン酸ポリオキシル及びプロピルパラベンの混合物を加えて加温溶解し、油相とした。別に、1,3－ブチレングリコール、メチルパラベン及びクエン酸を精製水に加えて加温溶解し、水相とした。次いで、加温下に撹拌しながら、水相を油相に徐々に加えて乳化し、更に撹拌しながら冷却して本発明クリーム製剤を得た。（粘度:140.5パスカル秒,pH:5.20）

実施例２

アジピン酸ジイソプロピルに代えてトリアセチンを、並びに1,3－ブチレングリコールに代えてプロピレングリコールを使用し（配合量は同じ）、更に、モノステアリン酸ソルビタンの配合量を1.0g及びステアリン酸ポリオキシルの配合量を2.0gとする以外は、実施例１と同様にして本発明クリーム製剤を得た。
（粘度:67.5パルカス秒,pH:5.33）

実施例３

アジピン酸ジイソプロピル10gに代えてセバシン酸ジエチル5.0g及びトリアセチン1.0gを使用し、1,3－ブチレングリコールに代えてプロピレングリコールを使用する（配合量は同じ）以外は、実施例１と同様にして本発明クリーム製剤を得た。（粘度:89.2パスカル秒,pH5.25）

薬理試験Ｉ

下記第１表に示す組成を有する本発明クリーム製剤（Ａ）及び比較のためのクリーム製剤（B,C,D,E）、並びに市販のステロイドクリーム製剤を使用し、外用ステロイドの作用の１つである血管収縮作用について試験した。ヒト血管収縮作用試験は、臨床効果を非常に良く反映するものであり、外用ステロイドの効力検定法として最も重要視されている。

1.クリーム製剤A,B,C,D及びＥの調製

下記第１表に示す組成（重量％）を有するクリーム製剤（A,B,C,D,E）を、前記実施例と同様にして調製した。
尚、製剤Ｂは、溶解剤としてプロピレングリコールを使用した。従って、製剤Ｂでは、プロピレングリコールは油相成分となる。得られた各製剤の粘度及びpHを第２表に示す。


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第　1　表

| 成分＼処方 | | A | B | C | D | E |
|---|---|---|---|---|---|---|
| 油相成分 | 6α－フルオロ－9α－クロロ－16β－メチルプレドニゾロン17，21－ジアセテート | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| | アジピン酸ジイソプロピル | 10.0 | — | 10.0 | 10.0 | 10.0 |
| | 白色ワセリン | 20.0 | 20.0 | 20.0 | — | 20.0 |
| | 流動パラフィン | — | 10.0 | — | — | — |
| | ミリスチン酸イソプロピル | — | — | — | 20.0 | — |
| | サラシミツロウ | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| | セタノール | 3.0 | 3.0 | 3.0 | 6.0 | 3.0 |
| | モノステアリン酸グリセリン | 4.0 | 4.0 | 4.0 | 4.0 | 4.0 |
| | モノステアリン酸ソルビタン | 2.0 | 4.0 | 6.0 | 2.0 | 4.0 |
| | ステアリン酸ポリオキシル40 | 1.0 | 2.0 | 3.0 | 4.0 | 2.0 |
| | プロピルパラベン | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| 水相成分 | メチルパラベン | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| | プロピレングリコール | 10.0 | (10.0) | 10.0 | 10.0 | — |
| | クエン酸 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 |
| | 精製水 | 残部 | 残部 | 残部 | 残部 | 残部 |

第　2　表

| | 粘度(パスカル秒) | pH |
|---|---|---|
| A | 137.7 | 5.18 |
| B | 110.2 | 5.25 |
| C | 160.7 | 5.24 |
| D | 147.9 | 5.15 |
| E | 134.0 | 5.21 |

2.市販のステロイドクリーム製剤

市販のステロイドクリーム製剤として、ジフロラゾンジアセテートを主成分とするクリーム製剤〔商品名：ジフラールクリーム，山之内製薬（株）製，以下クリーム製剤FCとする〕、吉草酸ベタメサゾンを主成分とするクリーム製剤〔商品名：リンデロンＶクリーム，塩野義製薬（株）製，以下クリーム製剤RCとする〕及びプロピオン酸ベクロメタゾンを主成分とするクリーム製剤〔商品名：プロパデルムクリーム，協和醗酵（株）製，以下クリーム製剤PCとする〕を使用した。

3.被験者

皮膚疾患のない30～43才の健康な成人男子志願者10名を被験者とした。

4.試験手順

まず、被験者毎に、上記８種の試験試料の全てをアトランダムに割りつけた。次いで、内径15㎜の穴の開いた絆創膏を被験者の上背部に貼付し、その穴部に、試験試料約50㎎を塗布し、１時間放置した。判定は、貼付した絆創膏及び試験試料を除去した後、2,4,6および８時間経過後に行なった。

5.判定方法

血管収縮作用による皮膚の蒼白化現象の度合を、次の基準で判定した。

０点…反応なし

１点…微弱な蒼白現象

２点…明らかな蒼白現象

３点…顕著な蒼白現象

尚、本試験は、二重盲検法に準じて実施した。

6.試験結果

結果を第３表（各試験試料の平均得点）に示す。

第　3　表

| 検体 | 2時間 | 4時間 | 6時間 | 8時間 |
|---|---|---|---|---|
| A | 0.6 | 1.9 | 2.4 | 2.7 |
| B | 0.3 | 0.8 | 1.4 | 1.7 |
| C | 0.4 | 1.6 | 1.8 | 2.0 |
| D | 0.3 | 0.6 | 1.0 | 1.2 |
| E | 0.4 | 1.7 | 1.9 | 2.2 |
| FC | 0.3 | 0.6 | 1.1 | 1.5 |
| RC | 0.7 | 1.5 | 1.9 | 1.9 |
| PC | 0.3 | 0.3 | 0.3 | 0.5 |

以上の結果から、本発明クリーム製剤が、非常に優れた血管収縮作用を示すことが明らかである。従って、本発明クリーム製剤が、優れた薬物放出性及び経皮吸収性を有し、高い薬理効果を発揮することが実証された。また、使用中に被験者に全く炎症等の副作用は生じることがなく、皮膚刺激性が少ないことが分った。しかも、薬物の結晶析出は起らなかった。



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Bibliography Close

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A61K 31/57 7431-4C

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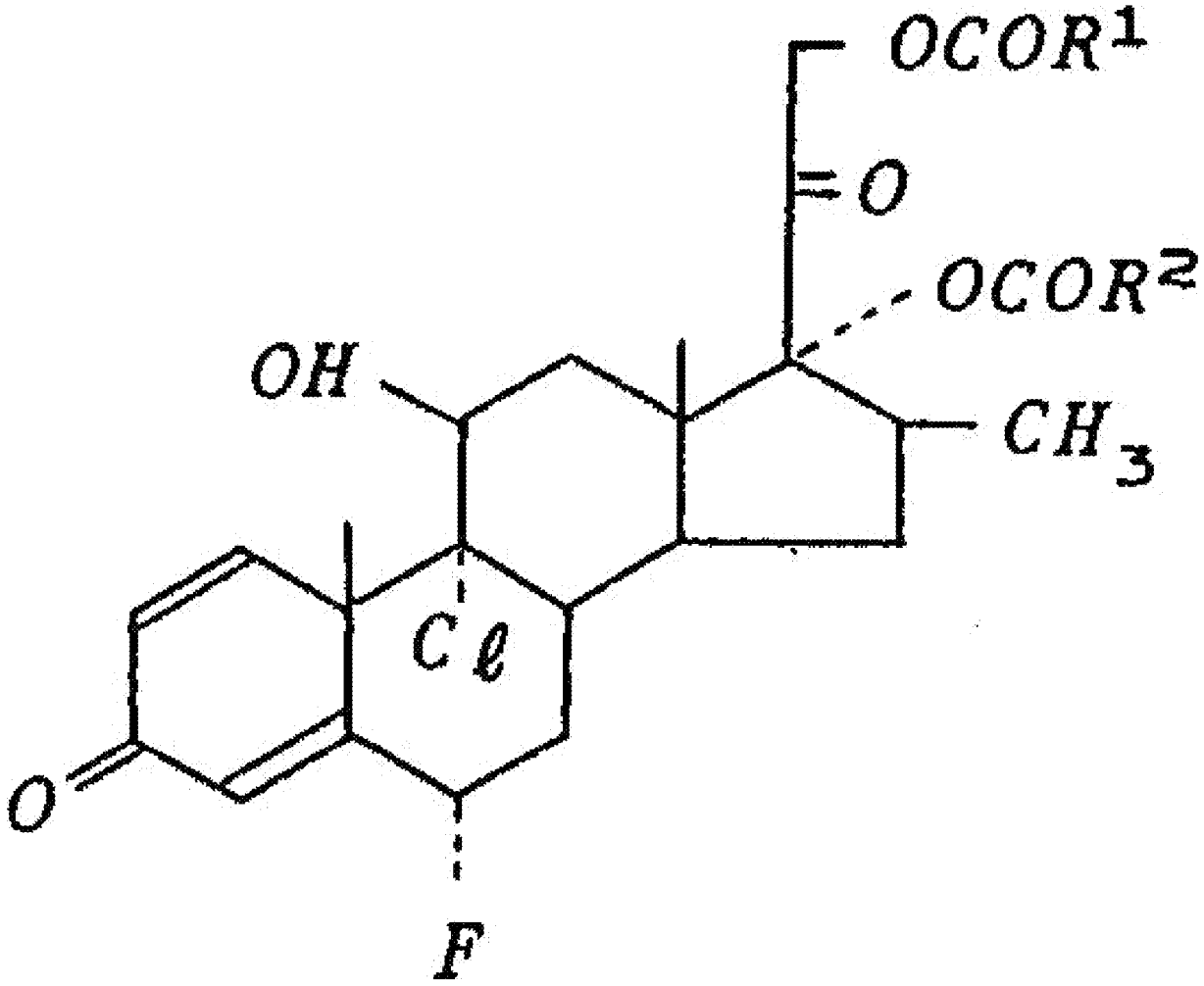
[Name] SAEGUSA, Eiji (and 2 others)

[Examiner] SAIKI, Tomoko

Scope of Claims Close

[Patent Claims]

[Claim 1] General formula




R1 shows a methyl group or an ethyl group among [type, and R2 is a carbon number.

The alkyl group or phenyl group of 1-4 is shown. ]
1 type or 2 type or more of resolvents [ 2 to 40 % by weight of ] which came out and were ch osen from 0.01 to 0.5 % by weight of steroids expressed, adipic acid diisopropyl, diethyl seba cate, and a triacetin, and propylene glycol -- and/or 1,3-butylene glycol2-30 % by weight, Th is steroid cream preparation contains 0.5 to 15 wt.% of a surfactant, 2 to 50 wt.% of a high p araffinic hydrocarbon, 30 to 85 wt.% of purified water, and the above steroids dissolved in a n early saturated state as a discontinuous phase.
[Claim 2] 0.01 to 0.2 wt.% of steroids, 2 to 20 wt.% of 1 or 2 or more kinds of solubilizing ag ents selected from diisopropyl adipate, diethyl sebacate, and thoria cetin, Propylene Glycol an d / or 1,3-butylene glycol 5 to 20 wt.%, surfactant 0.5 to 10 wt.%, and high high ;

A steroid cream formulation according to claim 4, comprising from about 40% by weight to ab out 40% by weight of purified water and from about 80% by weight of purified water.

Detailed Description Close

[Detailed description of the invention]

Field of industrial application

The present invention relates to a stable oil-in-water steroid cream preparation which is excellent in drug release and percutaneous absorbability, has low skin irritation, and is free from crystal precipitation of a drug.

BACKGROUND of the Invention

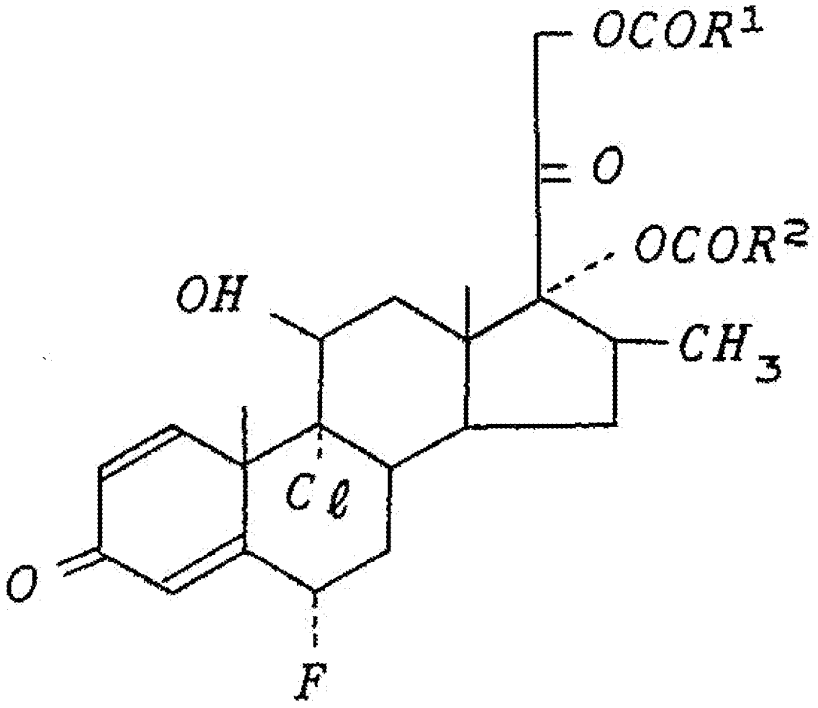
Steroids have an excellent anti-inflammatory effect as well known in the art, and are widely used mainly in the form of an oily preparation, a cream preparation, etc. *. Among these, a steroid cream preparation is generally used in which a plurality of oil phase components are emulsified in a plurality of aqueous phase components or vice versa, and a larger amount of surfactant is added than an oily ointment preparation in order to form a semisolid stable system. Anti-*** which was excellent in the inventor

It had business, and side effects used the 6alpha-fluoro-9alpha-chloro-16beta-methylprednisolone 17,21-diester (JP S 61 - 45970B) which is external use quantity lipophilicity steroid which is not as for *** as a chief remedy, and tried to obtain cream preparation according to a prior art. However, it has been found that the obtained cream preparation has problems such as 1) low drug release property, 2) insufficient percutaneous absorbability, 3) skin irritation, 4) crystal precipitation of the drug, and that the excellent effect of the steroid cannot be sufficiently exhibited.

The means for solving a problem

It is an object of the present invention to provide a steroid cream preparation which contains the above high fat-soluble steroids as a main agent, has high drug releasing property, is excellent in percutaneous absorbability, has little skin irritation, does not cause crystal precipitation of a drug, and can sufficiently exhibit the effect of the steroid.

That is, the present invention is a general formula.




( 1 )

In the formula, R 1 represents a methyl group or an ethyl group, and R 2 represents an alkyl group having 1 to 4 carbon atoms or a phenyl group.

1 type or 2 type or more of resolvents [ 2 to 40 % by weight of ] which came out and were ch osen from 0.01 to 0.5 % by weight of steroids expressed, adipic acid diisopropyl, diethyl seba cate, and a triacetin, and propylene glycol -- and/or 1,3-butylene glycol2-30 % by weight, Th is steroid cream preparation contains 0.5 to 15 wt.% of a surfactant, 2 to 50 wt.% of a high p araffinic hydrocarbon, 30 to 85 wt.% of purified water, and the above steroids dissolved in a s ubstantially saturated state.

The present invention has been completed on the basis of a novel finding that, in a pharmace utical formulation, a drug is easily released when a base component having high drug affinity i s used, and a releasing property is maximized when the drug is added in a saturated dissolve d state and in addition, a diffusion property in a continuous phase of a drug is increased. A) a steroid of the general formula (1) which is a main agent, b) a solubilizing agent for dissolving the steroids in a substantially saturated state in the preparation, and c) a Propylene Glycol an d / or a 1,3-butylene glycol for increasing the diffusibility of the steroid in the purified water (continuous phase).

D) It is essential to contain a solution of a steroid dissolved in a purified water which is a conti nuous phase in almost saturated state, a surfactant for finely dispersing the steroid as a disco ntinuous phase, a high paraffinic hydrocarbon for imparting a skin protective effect, a skin mu cilage, and the like to the preparation, and f) a purified water. In other words, the cream prep aration of the present invention comprises a system in which a discontinuous phase containin



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g a solubilizer in which a steroid is dissolved in a substantially saturated state is dispersed in a purified water as a continuous phase by a surfactant. By adding a Propylene Glycol and / or a 1,3-butylene glycol to a continuous phase (purified water) having almost no solubility of a steroid, it is possible to provide a drug of the present invention in which drug diffusibility in an in-phase phase is increased, a high drug release property, an excellent skin transfer property and the like are imparted, and a drug is not precipitated. In addition, since the preparation of the present invention contains an appropriate amount of high paraffinic hydrocarbons, it has low skin irritation. Furthermore, when the formulation is applied to the skin, a change in composition due to moisture evaporation occurs, and as the Propylene Glycol and / or aqueous 1,3-butylene glycol of the continuous phase is concentrated on the skin, the diffusivity of the drug increases, and further improvement of the transdermal absorption of the drug is recognized.

As the steroids, known steroids represented by the above general formula (1) can be used. As specific examples thereof, 6 α - fluoro- 9 α - chloro - 16 β - methylprednisolone 17,21 - diacetate, 6 α - fluoro - 9 α - chloro - 16 β - methylprednisolone 17,21 - dipropionate 6. alpha. - Fluoro - 9. alpha. - chloro - 16. beta. - methylprednisolone 17 - valerate, 21 - acetate. Mention may be made of 6 α - fluoro - 9 α - chloro - 16 β - methylprednisolone 17 - propionate, 21 - acetate, 6 α - fluoro - 9 α - chloro - 16 β - methylprednisolone 17 - benzoate, 21 - acetate, and the like. The amount of the steroid to be added may be about 0.01 to about 0.5% by weight, preferably about 0.01 to about 0.2% by weight, and more preferably about 0.02 to about 0.1% by weight, based on the pharmacologically active strength of the steroid used.
As the solubilizing agent, 1 or 2 or more of diisopropyl adipate, diethyl sebacate and thoria cetin may be used. In view of solubility of a steroid in a discontinuous phase component other than a solubilizing agent and a substantially saturated state of a steroid, the amount of the compound added may be about 2 to 40% by weight, preferably about 2 to 20% by weight, and more preferably about 3 to 20% by weight of the total amount of the formulation.
Propylene Glycol and 1,3-butylene glycol enhance drug release and transdermal absorption. The amount of Propylene Glycol and / or 1,3-butylene glycol to be blended may be about 2 to 30% by weight, preferably about 5 to 20% by weight, and more preferably about 5 to 15% by weight of the total amount of the formulation. If it is less than 2% by weight, the diffusibility in the continuous phase of the drug becomes insufficient, and it is not possible to exhibit a sufficient effect in the pharmacological test, whereas if it exceeds 30% by weight, the affinity of the drug for the drug becomes too high and the release property is lowered, and it is not preferable, which is not preferable.
As a surfactant, any known one used for preparing an oil-in-water type cream preparation can be used, and among them, a nonionic surfactant is preferred from the viewpoint of safety to skin. As the example, it is polyoxyethylene alkyl ether, for example Polyoxyethylene alkyl phenyl ether, polyoxyethylene polyoxypropylene cetyl ether, tetraoleic acid polyoxyethylene sorbitol, triolein acid polyoxyethylene sorbitan, Polyoxyethylene castor oil, polyoxyethylene hydroge



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nated castor oil, polyoxyethylene sorbitol yellow bees wax, Sucrose fatty acid ester, polyglycer yl fatty acid ester, polyoxyethylene lanolin, polyoxyethylene lanolin alcohol, polyoxyethylene o ctadecanamide, Examples of the lecithin, the monofatty acid polyoxyethylene sorbitan, the m onofatty acid polyethylene glycol, the monofatty acid Glycerin, the monofatty acid Propylene Glycol, the monofatty acid sorbitan, and the * include mixtures thereof. As an ionic surfactan t, it is an example.

Examples thereof include anionic surfactant such as sodium lauryl sulfate, sodium cetyl sulfat e, and polyoxyethylene alkyl ether phosphoric acid. In the present invention, the nonionic surf actant and the anionic surfactant may be used in combination. The amount of the surfactant t o be incorporated may be a minimum amount required to impart sufficient emulsification stabi lity to the formulation, and may be about 0.5 to 15% by weight, preferably about 0.5 to 10% by weight, and more preferably about 3 to 10% by weight of the total amount of the formulati on.

Since a high paraffinic hydrocarbon is a non-polar substance, it has little affinity for a drug, ha s no influence on drug releasability, and imparts a skin protective action, a skin soothing actio n, and the like to a preparation. As a higher paraffinic hydrocarbon, any known paraffinic hydr ocarbon having about 16 to 40 carbon atoms can be used, and examples thereof include a sof t Liquid Paraffin, a Liquid Paraffin, a White Petrolatum, a paraffin, a microcrystalline wax, and a ceresin. The blending amount of the high paraffinic hydrocarbon may be about 2 to about 5 0% by weight, preferably about 4 to about 40% by weight, and more preferably about 10 to a bout 30% by weight of the total amount of the formulation. If the amount is less than 2% by weight, the above-mentioned base effect cannot be expected, and it is difficult to impart a fav orable formulation property and a stable emulsified state. On the other hand, when the amou nt is more than 50% by weight, it becomes difficult to dissolve the drug into the discontinuous phase, and the oily property becomes too strong, resulting in poor feeling of use.

The amount of purified water may be about 30 to 85% by weight, preferably about 40 to 80% by weight, and more preferably about 40 to 70% by weight of the total amount of the prepara tion.

To the cream preparation of the present invention, known additives used in an ordinary cream preparation may be added if necessary. As the additive, for example, a pH adjuster which enh ances the stability of the drug in the formulation, an agent which improves the appearance an d the quality of the formulation, an antiseptic agent, a thickening or emulsifying stabilizer, and the like can be mentioned. Any known pH adjusting agent may be used, and examples thereof include citric acid, lactic acid, and phosphoric acid. The blending amount may be set so that th e pH of the formulation is about 4.0 to 6.5, preferably about 4.5 to 6.0. Further, in order to im prove the appearance and quality of the preparation, higher alcohols such as Stearyl Alcohol a nd cetyl alcohol, and waxes such as spermaceta and beeswax may be added, and the blendin g amount thereof may be about 5% by weight or less of the total amount of the formulation.

Examples of the preservative include alkyl p-hydroxybenzoate such as methylparaben, ethylparaben, and butylparaben. The total amount of the formulation may be about 0.01 to about 0.3% by weight. Examples of the thickening or emulsifying stabilizer include water-soluble polymer compounds such as methylcellulose, ethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, Sodium Alginate, and starches ; and gums such as tragacanth, Acacia, and the like. The compounding amount

It may be less than 5% by weight of the total amount of the formulation.

The cream preparation of the present invention is prepared by mixing a predetermined amount of each of the above components by a known method. For example, first, a steroid is added to a mixture of a solubilizing agent, an oil-soluble component (higher paraffinic hydrocarbon, a higher paraffinic hydrocarbon, a higher alcohol, a higher alcohol, a wax, and the like) and a surfactant is heated and dissolved into an oily phase. In this case, when the steroid is dissolved in a solubilizing agent in advance and the other components are added to the solution and dissolved, the workability of the preparation is improved. Then, water soluble components (polyhydric alcohol, paraoxybenzoic acid ester, pH adjusting agent, etc.) are added to purified water to be dissolved in water to form an aqueous phase. The cream preparation of the present invention can be produced by gradually adding the above aqueous phase to the oil phase while stirring it with stirring, emulsifying it, and cooling it with stirring. The cream preparation of the present invention may further contain, if necessary, an antihistamine, an analgesic, an antibiotic, etc.

EFFECT OF THE INVENTION

The cream preparation of the present invention has a very excellent steroid releasing property and percutaneous absorbability and exhibits a high therapeutic effect by adding a base component having high affinity for a drug to a minimum amount, containing a main drug steroid in a saturated dissolved state, and enhancing the drug diffusibility in a continuous phase. In addition, there is little skin irritation and crystal precipitation of the drug does not occur.

EXAMPLE

The pharmacological test which shows the usefulness of an Example (example of pharmaceutical preparation of present invention cream preparation) and present invention pharmaceutical preparation is listed to below, and let the present invention be a still clearer thing.

In each of the examples, water purified by an ion exchange resin is used as the purified water, and the viscosity is DVL - 3 type rotary viscometer (No. 4 rotor, 3 rpm, 25 ° C., manufactured by Tokyo Meter Co., Ltd.). Furthermore, the pH is a value measured by using a needle-shaped pH electrode using a Hitachi - Horiba type F - 7 pH meter (manufactured by Horiba, Ltd.).

Example 1:6 α - Fluoro - 9 α - Chloro 16.

β methylprednisolone 17 21

**********

6alpha-fluoro-9alpha-chloro- 16

| | |
|---|---|
| β-methylprednisolone17,21 | |
| Diacetate | 0.05g |
| Adipic acid diisopropyl- | 10.0 〃 |
| 1,3-butylene glycol | 10.0 |
| White vaseline | 20.0g |
| White beeswax | 1.0 〃 |
| Cetanol | 3.0 |
| Glyceryl Monostearate | 4.0 |
| Mono Stearic Acid sorbitan | 2.0 |
| Stearic Acid polyoxyl 40 | 1.0 |
| | |
| Propylparaben | 0.1 〃 |
| Methylparaben | 0.1 〃 |
| 0.015 citrate | |
| Purified water | |
| Total | 100.0g |

6. alpha. - Fluoro- 9. alpha. - chloro - 16. beta. - methylprednisolone 17,21 - diacetate In addition to diisopropyl adipate, the mixture was dissolved in warm water, and a mixture of White Petrolatum, bleached beeswax, Cetanol, Glyceryl Monostearate, mono Stearic Acid sorbitan, Stearic Acid polyoxyl and propyl paraben was added thereto, and the mixture was heated and dissolved to obtain an oil phase. Separately, 1,3-butylene glycol, methyl paraben and citric acid were added to purified water and dissolved in water to prepare an aqueous phase. Then, while stirring under warming, the aqueous phase was gradually added to the oil phase, emulsified, and cooled with stirring to obtain a cream preparation of the present invention. (Viscosity : 140.5 Pascal seconds, pH : 5.20).

Example 2

In place of diisopropyl adipate, a triazin cetin is used, and a Propylene Glycol is used instead of a 1,3-butylene glycol. Further, a creamy preparation of the present invention was obtained in the same manner as in Example 1, except that 1.0 g of monoglycerol sorbitan and 2.0 g of Stearic Acid polyoxyl were added to the Stearic Acid.

(viscosity: -- 67.5 PAL dregs -- a second -- pH -- : -- 5.33)

Example 3

A creamy preparation of the present invention was obtained in the same manner as in Example 1 except that 5.0 g of diethyl sebacate and 1.0 g of thoria cetin were used instead of 10 g of diisopropyl adipate, and Propylene Glycol was used instead of the 1,3-butylene glycol. (Viscosity : 89.2 Pascal seconds, pH 5.25).

Pharmacological Test I

A cream formulation (A) of the invention having the composition shown in Table 1 below and a cream formulation (B, C, D,) for comparison and a commercially available steroid cream for

mulation were used to test for the vasoconstrictive action which is one of the action of extern al steroids. Human vasoconstriction effects are very well reflective of clinical efficacy and are most important as an efficacy assay for external steroids.

Preparation of cream formulations A, B, C, D and ; 1.

Cream formulations (A, B, C, D,) having the composition shown in Table 1 below (% by weigh t) were prepared in the same way as in the previous Examples. In Preparation B, Propylene Gl ycol was used as a solubilizer. Thus, in Formulation B, Propylene Glycol becomes an oil phase i ngredient. The viscosity and pH of each formulation obtained are shown in Table 2.

第 1 表

| 成分＼処方 | | A | B | C | D | E |
|---|---|---|---|---|---|---|
| 油相成分 | 6α－フルオロ－9α－クロロ－16β－メチルプレドニゾロン17，21－ジアセテート | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| | アジピン酸ジイソプロピル | 10.0 | － | 10.0 | 10.0 | 10.0 |
| | 白色ワセリン | 20.0 | 20.0 | 20.0 | － | 20.0 |
| | 流動パラフィン | － | 10.0 | － | － | － |
| | ミリスチン酸イソプロピル | － | － | － | 20.0 | － |
| | サラシミツロウ | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| | セタノール | 3.0 | 3.0 | 3.0 | 6.0 | 3.0 |
| | モノステアリン酸グリセリン | 4.0 | 4.0 | 4.0 | 4.0 | 4.0 |
| | モノステアリン酸ソルビタン | 2.0 | 4.0 | 6.0 | 2.0 | 4.0 |
| | ステアリン酸ポリオキシル40 | 1.0 | 2.0 | 3.0 | 4.0 | 2.0 |
| | プロピルパラベン | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| 水相成分 | メチルパラベン | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| | プロピレングリコール | 10.0 | (10.0) | 10.0 | 10.0 | － |
| | クエン酸 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 |
| | 精製水 | 残部 | 残部 | 残部 | 残部 | 残部 |

第 2 表

| | 粘度(パスカル秒) | pH |
|---|---|---|
| A | 137.7 | 5.18 |
| B | 110.2 | 5.25 |
| C | 160.7 | 5.24 |
| D | 147.9 | 5.15 |
| E | 134.0 | 5.21 |

2. commercial steroid cream formulations

As a commercially available steroid cream preparation, a cream preparation based on diflorioz one diacetate (trade name : Diflal Cream, manufactured by Yamanouchi Pharmaceutical Co., L td., hereinafter referred to as "cream preparation FC"), and betamethasone valerate are com mercially available. A cream preparation [trade name : Rinderon V cream, manufactured by S hiichi Seiyaku Co., Ltd., hereinafter referred to as "cream Preparation RC") and a cream prepa ration based on beclomethasone propionate (trade name : Propaderm Cream, manufactured b y Kyowa Hakko, hereinafter referred to as "cream preparation PC") were used.

3. Test Subject

10 healthy adult male volunteers of 30 to 43 years of age without skin disease were used as s ubjects.

4. Testing Procedure

First, all of the 8 test samples were randomly assigned for each subject. Next, a perforated ba ndage having an inner diameter of 15 was affixed to the upper back of the subject, and about 50 mg of test sample was applied to the hole and left for 1 hours. The determination was mad e at 2,4,6 and 8 hours after removal of the attached bandage and test sample.

5. Evaluation Method

The degree of whitening of the skin by vasoconstriction was determined on the basis of the fol lowing criteria :.

Point O.

1 points.

Two points -- Clear pale phenomenon

3.

Note that this test was carried out according to a double-blind method.

6. Test Result

Results are shown in Table 3 (average score of each test sample).



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第 3 表

| 検体 | 2時間 | 4時間 | 6時間 | 8時間 |
|---|---|---|---|---|
| A | 0.6 | 1.9 | 2.4 | 2.7 |
| B | 0.3 | 0.8 | 1.4 | 1.7 |
| C | 0.4 | 1.6 | 1.8 | 2.0 |
| D | 0.3 | 0.6 | 1.0 | 1.2 |
| E | 0.4 | 1.7 | 1.9 | 2.2 |
| FC | 0.3 | 0.6 | 1.1 | 1.5 |
| RC | 0.7 | 1.5 | 1.9 | 1.9 |
| PC | 0.3 | 0.3 | 0.3 | 0.5 |

From the above results, it is clear that the cream preparation of the present invention exhibits a very excellent vasoconstriction effect. Accordingly, it has been demonstrated that the cream preparation of the present invention has excellent drug release and percutaneous absorption a nd exhibits a high pharmacological effect. In addition, it has been found that no side effects s uch as inflammation or the like occur in the subject during use, and the skin irritation is small. Moreover, no crystal precipitation of the drug occurred.



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| | |
|---|---|
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## (54)STEROID CREAM PREPARATION

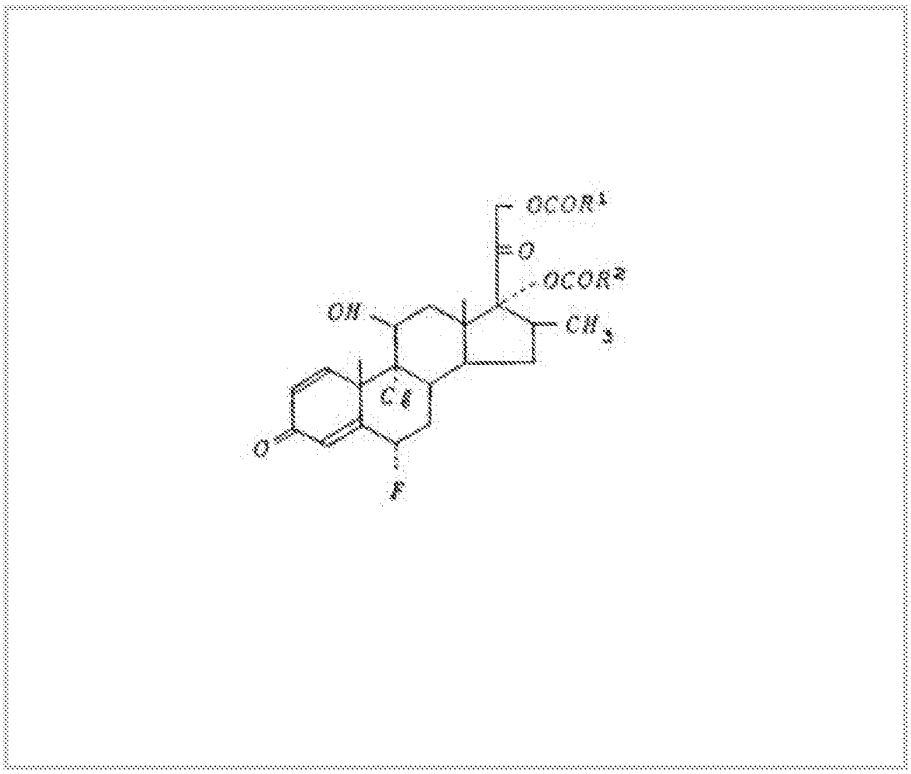
**(57)Abstract**

PURPOSE: To obtain the titled anti-inflammatory compound having high drug- releasing property and transcutaneous absorbability, giving little irritation to skin and resistant to crystallization of drug component, by using specific amounts of highly fat-soluble steroids, diisopropyl adipate, diethyl sebacate, etc., as essential components.

CONSTITUTION: The objective preparation contains (A) 0.01W0.5wt.% steroids of formula (R1 is methyl or ethyl; R2 is 1W4C alkyl or phenyl), (B) 2W40wt.% dissolution assistant selected from diisopropyl adipate, diethyl sebacate and triacetin, (C) 2W30wt.% propylene glycol and/or 1,3-butylene glycol, (D) 0.5W15wt.% surfactant, (E) 2W50wt.% higher paraffinic hydrocarbon and (F) 30W85wt.% refined water. The preparation is produced by dissolving the compound of formula in nearly saturated state and including the compound in the form of emulsion particles constituting a discontinuous phase.



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OCOR1
O
OCOR2
OH
CH3
O
F

⑲日本国特許庁（JP）　⑪特許出願公開

⑫公開特許公報（A）　昭63－255228

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⑬公開　昭和63年(1988)10月21日

審査請求　未請求　発明の数 1　（全8頁）

⑭発明の名称　ステロイドクリーム製剤

⑳特　願　昭62－91142

㉒出　願　昭62(1987)4月14日

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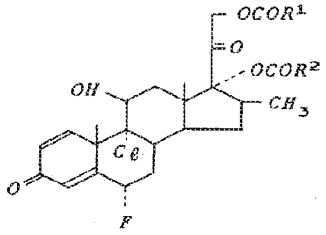
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明　細　書

発明の名称　ステロイドクリーム製剤

特許請求の範囲

① 一般式




（式中、$R^1$はメチル基又はエチル基を示し、$R^2$は炭素数1～4のアルキル基又はフェニル基を示す。）

で表わされるステロイド類0．01～0．5重量％、アジピン酸ジイソプロピル、セバシン酸ジエチル及びトリアセチンから選ばれた1種又は2種以上の溶解剤2～40重量％、プロピレングリコール及び／又は1，3－ブチレングリコール2～30重量％、界面活性剤0．5～15重量％、高級パラフィン系炭化水素2～50重量％、精製水30～85重量％を含有し、ほぼ飽和状態に溶解した上記ステロイドを不連続相として乳化含有させたことを特徴とするステロイドクリーム製剤。

② ステロイド類0．01～0．2重量％、アジピン酸ジイソプロピル、セバシン酸ジエチル、及びトリアセチンから選ばれた1種又は2種以上の溶解剤2～20重量％、プロピレングリコール及び／又は1，3－ブチレングリコール5～20重量％、界面活性剤0．5～10重量％、高級パラフィン系炭化水素4～40重量％、精製水40～80重量％を含有する特許請求の範囲第1項に記載のステロイドクリーム製剤。

発明の詳細な説明

産業上の利用分野



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本発明は、薬物放出性及び経皮吸収性に優れ、皮膚刺激性が少く、しかも、薬物の結晶析出がない安定な水中油型ステロイドクリーム製剤に関する。

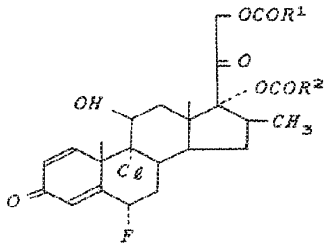
従来の技術とその問題点

ステロイド類は、公知の如く優れた抗炎症作用を有し、主に、油性軟膏製剤、クリーム製剤等の形態で広く使用されている。これらのうちステロイドクリーム製剤としては、一般に、複数の油相成分を、複数の水相成分中に或いはその逆に乳化し、更に、半固形の安定な系とするために、油性軟膏製剤よりも多量の界面活性剤を添加したものが使用されている。本発明者は、優れた抗炎症作用を有し、副作用が殆んどない外用高脂溶性ステロイドである6α－フルオロ－9α－クロロ－16β－メチルプレドニゾロン17，21－ジエステル類（特公昭61－45970号）を主薬として使用し、従来技術に従ってクリーム製剤を得ることを試みた。しかし、得られたクリーム製剤は、1）薬剤放出性が低い、2）経皮吸収性が不充分である、3）皮膚刺激性がある、4）薬物の結晶析出が起る等の問題点が生じ、上記ステロイドの優れた効果を充分発揮させ得ないことが判明した。

問題点を解決するための手段

本発明の目的は、主薬として上記高脂溶性ステロイド類を含み、高い薬剤放出性を有し、経皮吸収性に優れ、皮膚刺激性が少なく、且つ薬物の結晶析出が起らず、上記ステロイドの効果を充分に発揮させ得るステロイドクリーム製剤を提供することにある。

即ち本発明は、一般式



（1）

（式中、$R^1$はメチル基又はエチル基を示し、$R^2$は炭素数1～4のアルキル基又はフェニル基を示す。）

で表わされるステロイド類0.01～0.5重量%、アジピン酸ジイソプロピル、セバシン酸ジエチル、及びトリアセチンから選ばれた1種又は2種以上の溶解剤2～40重量%、プロピレングリコール及び／又は1，3－ブチレングリコール2～30重量%、界面活性剤0.5～15重量%、高級パラフィン系炭化水素2～50重量%、精製水30～85重量%を含有し、ほぼ飽和状態に溶解した上記ステロイドを不連続相として乳化含有させたことを特徴とするステロイドクリーム製剤に係る。

本発明は、製剤処方において、薬物親和性の高い基剤成分を必要最少量とすると薬物は放出され易くなり、更に薬物を飽和溶解状態とし、加えて薬物の連続相中における拡散性を高める物質を添加した場合には、放出性は最大となるという新規な知見に基づいて完成されたものであり、a）主薬である上記一般式（1）で表わされるステロイド類、b）製剤中において前記ステロイド類をほぼ飽和状態に溶解するための溶解剤、c）精製水（連続相）中でのステロイドの拡散性を高めるためのプロピレングリコール及び／又は1，3－ブチレングリコール、d）連続相である精製水中に、ステロイドを溶解剤にほぼ飽和状態で溶解した溶液を、不連続相として微粒化分散させるための界面活性剤、e）製剤に皮膚保護作用、皮膚粘滑作





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用等を付与するための高級パラフィン系炭化水素並びに f）精製水を夫々特定量含むことを必須とする。即ち、本発明クリーム製剤は、連続相である精製水中に、ステロイドをほぼ飽和状態に溶解した溶解剤を含む不連続相を、界面活性剤で微粒化分散した系から成っている。本来ステロイドの溶解性を殆んど有さない連続相（精製水）に、プロピレングリコール及び／又は１，３－ブチレングリコールを添加することによって、同相中における薬物拡散性が増加し、高い薬物放出性、優れた皮膚移行性等が付与された、薬物の結晶析出が起らない本発明製剤が提供される。しかも、本発明製剤では、適量の高級パラフィン系炭化水素を含んでいるため、皮膚刺激性が少ない。更に、該製剤を皮膚に適用した場合には、水分揮散による組成変化が生じ、皮膚上で、連続相であるプロピレングリコール及び／又は１，３－ブチレングリコール水溶液が濃縮されるにともなって、薬物の拡散性が増加し、薬物の経皮吸収性のより一層の向上が認められるのである。

ステロイド類としては、上記一般式（１）で表わされる公知のステロイド類が使用できる。その具体例としては、例えば、６α－フルオロ－９α－クロロ－１６β－メチルプレドニゾロン１７，２１－ジアセテート、６α－フルオロ－９α－クロロ－１６β－メチルプレドニゾロン１７，２１－ジプロピオネート、６α－フルオロ－９α－クロロ－１６β－メチルプレドニゾロン１７－バレレート，２１－アセテート、６α－フルオロ－９α－クロロ－１６β－メチルプレドニゾロン１７－プロピオネート，２１－アセテート、６α－フルオロ－９α－クロロ－１６β－メチルプレドニゾロン１７－ベンゾエート，２１－アセテート等を挙げることができる。ステロイドの配合量は、使用するステロイドの薬理活性強度に応じ、通常製剤全量の０．０１～０．５重量％程度，好ましくは０．０１～０．２重量％程度、より好ましくは０．０２～０．１重量％程度とすればよい。

溶解剤としては、アジピン酸ジイソプロピル、セバシン酸ジエチル及びトリアセチンから選ばれた１種又は２種以上を使用できる。その配合量は、ステロイドの溶解剤以外の不連続相成分に対する溶解性及びステロイドをほぼ飽和状態とすることを考慮すると、製剤全量の２～４０重量％程度、好ましくは２～２０重量％程度、より好ましくは３～２０重量％程度とすればよい。

プロピレングリコール及び１，３－ブチレングリコールは、薬物の放出性及び経皮吸収性を向上させる。プロピレングリコール及び／又は１，３－ブチレングリコールの配合量は、製剤全量の２～３０重量％程度、好ましくは５～２０重量％程度、より好ましくは５～１５重量％程度とすればよい。２重量％未満では、薬物の連続相中における拡散性が不充分となり、薬理試験において十分な効果を示し得ず、一方３０重量％を超えると、薬物の基剤親和性が高くなりすぎ、放出性が低下するとともに、皮膚刺激性を示す可能性が高くなり好ましくない。

界面活性剤としては、水中油型クリーム製剤の調製に利用される公知のものが何れも使用できるが、なかでも、非イオン界面活性剤が皮膚への安全性の面から好ましい。その具体例としては、例えば、ポリオキシエチレンアルキルエーテル、ポリオキシエチレンアルキルフェニルエーテル、ポリオキシエチレンポリオキシプロピレンセチルエーテル、テトラオレイン酸ポリオキシエチレンソルビット、トリオレイン酸ポリオキシエチレンソルビタン、ポリオキシエチレンヒマシ油、ポリオキシエチレン硬化ヒマシ油、ポリオキシエチレンソルビットミツロウ、ショ糖脂肪酸エステル、ポリグリセリン脂肪酸エステル、ポリオキシエチレンラノリン、ポリオキシエチレンラノリンアルコ





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ール、ポリオキシエチレンステアリン酸アミド、レシチン、モノ脂肪酸ポリオキシエチレンソルビタン、モノ脂肪酸ポリエチレングリコール、モノ脂肪酸グリセリン、モノ脂肪酸プロピレングリコール、モノ脂肪酸ソルビタン若しくはこれらの混合物等を挙げることができる。また、イオン性界面活性剤としては、例えば、ラウリル硫酸ナトリウム、セチル硫酸ナトリウム、ポリオキシエチレンアルキルエーテルリン酸等の陰イオン界面活性剤等を挙げることができる。本発明では、上記非イオン性界面活性剤と陰イオン界面活性剤とを併用することもできる。界面活性剤の配合量は、製剤に充分な乳化安定性が付与される必要最少量とすればよく、通常製剤全量の０．５～１５重量％程度、好ましくは０．５～１０重量％程度、より好ましくは３～１０重量％程度とすればよい。

高級パラフィン系炭化水素は、非極性物質であるため、薬物に対する親和性を殆んど有さず、薬物放出性に影響を与えない基剤成分であり、しかも、製剤に皮膚保護作用、皮膚粘滑作用等を付与する。高級パラフィン系炭化水素としては、炭素数１６～４０程度の公知のパラフィン系炭化水素が何れも使用でき、例えば、軽質流動パラフィン、流動パラフィン、白色ワセリン、パラフィン、ミクロクリスタリンワックス、セレシン等を挙げることができる。高級パラフィン系炭化水素の配合量は、製剤全量の２～５０重量％程度、好ましくは４～４０重量％程度、より好ましくは１０～３０重量％程度とすればよい。２重量％未満では、前述の基剤効果が望めず、また好ましい製剤物性や安定な乳化状態を付与することが困難となる。一方５０重量％を越えると、薬物を不連続相に飽和溶解することが困難となり、また油性が強くなりすぎて使用感が悪くなる。

精製水の量は、通常製剤全量の３０～８５重量％程度、好ましくは４０～８０重量％程度、より好ましくは４０～７０重量％程度とすればよい。

本発明クリーム製剤には、必要に応じて、通常のクリーム製剤に使用される公知の添加剤を添加してもよい。添加剤としては、例えば、製剤中での薬物の安定性を高めるｐＨ調整剤、製剤の外観・性状改良剤、防腐剤、増粘或いは乳化安定化剤等を挙げることができる。ｐＨ調整剤としては公知のものが何れも使用でき、例えば、クエン酸、乳酸、リン酸等を挙げることができる。その配合量は、製剤のｐＨが４．０～６．５程度、好ましくは４．５～６．０程度となるようにすればよい。また、製剤の外観・性状を良くするために、例えば、ステアリルアルコール、セチルアルコール等の高級アルコール、鯨ロウ、ミツロウ等のロウ類等を添加してもよく、その配合量は、製剤全量の５重量％以下程度とすればよい。防腐剤としては、例えば、メチルパラベン、エチルパラベン、ブチルパラベン等のパラオキシ安息香酸アルキルエステル類等を挙げることができる。その製剤全量の配合量は、０．０１～０．３重量％程度とすればよい。増粘或いは乳化安定化剤としては、例えば、メチルセルロース、エチルセルロース、ヒドロキシプロピルセルロース、ポリビニルアルコール、ポリビニルピロリドン、アルギン酸ナトリウム、デンプン等の水溶性高分子化合物、トラガカントゴム、アラビアゴム等のガム質等を挙げることができる。その配合量は、製剤全量の５重量％未満程度でよい。

本発明クリーム製剤は、上記各成分の所定量を、公知の方法によって混合して製造される。例えば、まず、ステロイドを、溶解剤、油溶性成分（高級パラフィン系炭化水素、パラオキシ安息香酸エステル、高級アルコール、ロウ類等）及び界面活性剤の混合物に加えて加温溶解し、油相とする。この際、ステロイドを予め溶解剤に溶解した後、これにその他の成分を添加して溶解すると製造の作





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薬性が良好である。次いで、精製水に、水溶性成分（多価アルコール、パラオキシ安息香酸エステル、ｐＨ調整剤等）を加えて加温溶解し、水相とする。上記油相に、加温下撹拌しながら上記水相を徐々に加えて乳化し、更に撹拌しながら冷却することによって、本発明クリーム製剤を製造することができる。本発明クリーム製剤には、更に必要に応じて、抗ヒスタミン剤、鎮痛剤、抗生物質等を配合してもよい。

## 発明の効果

本発明クリーム製剤は、薬物と親和性の高い基剤成分を必要最少量とし、主薬ステロイドを飽和溶解状態で含有させ、並びに連続相中での薬物拡散性を高めることにより、極めて優れたステロイド放出性並びに経皮吸収性を有し、高い治療効果を発揮する。しかも、皮膚刺激性が少なく、薬物の結晶析出が起らない。

## 実施例

| | |
|---|---|
| 白色ワセリン | ２０．０ｇ |
| サラシミツロウ | １．０〃 |
| セタノール | ３．０〃 |
| モノステアリン酸グリセリン | ４．０〃 |
| モノステアリン酸ソルビタン | ２．０〃 |
| ステアリン酸ポリオキシル40 | １．０〃 |
| プロピルパラベン | ０．１〃 |
| メチルパラベン | ０．１〃 |
| クエン酸 | ０．０１５〃 |
| 精製水 | 残部 |
| 計 | １００．０ｇ |

６α－フルオロ－９α－クロロ－１６β－メチルプレドニゾロン１７，２１－ジアセテートを、アジピン酸ジイソプロピルに加えて加温溶解し、これに、白色ワセリン、サラシミツロウ、セタノール、モノステアリン酸グリセリン、モノステアリン酸ソルビタン、ステアリン酸ポリオキシル及びプロピルパラベンの混合物を加えて加温溶解し、油相とした。別に、１，３－ブチレングリコール、メチルパラベン及びクエン酸を精製水に加えて加温溶解し、水相とした。次いで、加温下に撹拌しながら、水相を油相に徐々に加えて乳化し、更に撹拌しながら冷却して本発明クリーム製剤を得た。（粘度：１４０．５パスカル秒，ｐＨ：５．２０）

実施例２

アジピン酸ジイソプロピルに代えてトリアセチンを、並びに１，３－ブチレングリコールに代えてプロピレングリコールを使用し（配合量は同じ）、更に、モノステアリン酸ソルビタンの配合量を１．０ｇ及びステアリン酸ポリオキシルの配合量を２．０ｇとする以外は、実施例１と同様にして本発明クリーム製剤を得た。

（粘度：６７．５パスカル秒，ｐＨ：５．３３）

実施例３

アジピン酸ジイソプロピル１０ｇに代えてセバシン酸ジエチル５．０ｇ及びクロタミトン１．０

以下に実施例（本発明クリーム製剤の製剤例）及び本発明製剤の有用性を示す薬理試験を挙げ、本発明をより一層明瞭なものとする。

尚、各実施例において、精製水は、イオン交換樹脂によって精製した水を使用し、粘度はＤＶＬ－３型回転粘度計（Ｎｏ４ローター，３ｒｐｍ．，２５℃，東京計器㈱製）によって、またｐＨはニードル型のｐＨ電極を使用して、日立－堀場Ｆ－７型ｐＨメーター（㈱堀場製作所製）によって測定した値である。

実施例１：６α－フルオロ－９α－クロロ－１６β－メチルプレドニゾロン１７，２１－ジアセテートクリーム

| | |
|---|---|
| ６α－フルオロ－９α－クロロ－１６β－メチルプレドニゾロン１７，２１－ジアセテート | ０．０５ｇ |
| アジピン酸ジイソプロピル | １０．０〃 |
| １，３－ブチレングリコール | １０．０〃 |





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gを使用し、1，3－ブチレングリコールに代えてプロピレングリコールを使用する（配合量は同じ）以外は、実施例1と同様にして本発明クリーム製剤を得た。（粘度：89．2パスカル秒，pH：5．25）

薬理試験I

下記第1表に示す組成を有する本発明クリーム製剤（A）及び比較のためのクリーム製剤（B，C，D，E），並びに市販のステロイドクリーム製剤を使用し、外用ステロイドの作用の1つである血管収縮作用について試験した。ヒト血管収縮作用試験は、臨床効果を非常に良く反映するものであり、外用ステロイドの抗力検定法として最も重要視されている。

1．クリーム製剤A，B，C，D及びEの調製

下記第1表に示す組成（重量%）を有するクリーム製剤（A，B，C，D，E）を，前記実施例と同様にして調製した。尚、製剤Bは、溶解剤としてプロピレングリコールを使用した。従って、製剤Bでは、プロピレングリコールは油相成分となる。得られた各製剤の粘度及びpHを第2表に示す。

第　1　表

| 成分＼製方 | | A | B | C | D | E |
|---|---|---|---|---|---|---|
| 油相成分 | 6α－フルオロ－9α－クロロ－11β，21－ジヒドロキシ－16α－メチルプレグナ－1，4－ジエン－3，20－ジオン－17，21－ジアセテート | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| | アラビン酸シイソプロピル | 10.0 | － | 10.0 | 10.0 | 10.0 |
| | 白色ワセリン | 20.0 | 20.00 | 20.0 | － | 20.0 |
| | 流動パラフィン | － | 10.0 | － | － | － |
| | ミリスチン酸イソプロピル | － | － | － | 20.00 | － |
| | サラシミツロウ | 1.0 | 1.0 | 1.00 | 1.00 | 1.00 |
| | セタノール | 3.00 | 3.00 | 3.00 | 6.00 | 3.00 |
| | モノステアリン酸グリセリン | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 |
| | モノステアリン酸ソルビタン | 2.00 | 4.00 | 6.00 | 2.00 | 4.00 |
| | ステアリン酸ポリオキシル40 | 1.0 | 2.00 | 3.00 | 4.00 | 2.01 |
| | プロピルパラベン | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| 水相成分 | メチルパラベン | 0.1 | (0.1) | 0.1 | 0.1 | 0.1 |
| | プロピレングリコール | 10.0 | (10.0) | 10.0 | 10.0 | － |
| | クエン酸 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 |
| | 精製水 | 残部 | 残部 | 残部 | 残部 | 残部 |

第　2　表

| | 粘度（パスカル秒） | pH |
|---|---|---|
| A | 137．7 | 5．18 |
| B | 110．2 | 5．25 |
| C | 160．7 | 5．24 |
| D | 147．9 | 5．15 |
| E | 134．0 | 5．21 |

2．市販のステロイドクリーム製剤

市販のステロイドクリーム製剤として、ジフロラゾンジアセテートを主成分とするクリーム製剤〔商品名：ジフラールクリーム，山之内製薬㈱製，以下クリーム製剤FCとする〕、吉草酸ベタメサゾンを主成分とするクリーム製剤〔商品名：リンデロンVクリーム，塩野義製薬㈱製，以下クリーム製剤RCとする〕及びプロピオン酸ベクロメタ





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ゾンを主成分とするクリーム製剤（商品名：プロパデルムクリーム，協和醗酵㈱製，以下クリーム製剤ＰＣとする）を使用した。

３．被験者

皮膚疾患のない３０～４３才の健康な成人男子志願者１０名を被験者とした。

４．試験手順

まず、被験者毎に、上記８種の試験試料の全てをアトランダムに割りつけた。次いで、内径１５㎜の穴の開いた絆創膏を被験者の上背部に貼付し、その穴部に、試験試料約５０㎎を塗布し、１時間放置した。判定は、貼付した絆創膏及び試験試料を除去した後，２，４，６および８時間経過後に行なった。

５．判定方法

血管収縮作用による皮膚の蒼白化現象の度合を、次の基準で判定した。

０点…反応なし

１点…微弱な蒼白現象

２点…明らかな蒼白現象

３点…顕著な蒼白現象

尚、本試験は、二重盲検法に準じて実施した。

６．試験結果

結果を第３表（各試験試料の平均得点）に示す。

第　３　表

| 検体 | ２時間 | ４時間 | ６時間 | ８時間 |
|---|---|---|---|---|
| A | ０．６ | １．９ | ２．４ | ２．７ |
| B | ０．３ | ０．８ | １．４ | １．７ |
| C | ０．４ | １．６ | １．８ | ２．０ |
| D | ０．３ | ０．６ | １．０ | １．２ |
| E | ０．４ | １．７ | １．９ | ２．２ |
| ＦＣ | ０．３ | ０．６ | １．１ | １．５ |
| ＲＣ | ０．７ | １．５ | １．９ | １．９ |
| ＰＣ | ０．３ | ０．３ | ０．３ | ０．５ |

以上の結果から、本発明クリーム製剤が、非常に優れた血管収縮作用を示すことが明らかである。従って、本発明クリーム製剤が、優れた薬物放出性及び経皮吸収性を有し、高い薬理効果を発揮することが実証された。また、使用中に被験者に全く炎症等の副作用は生じることがなく、皮膚刺激性が少ないことが分った。しかも、薬物の結晶析出は起らなかった。

（以　上）

代理人　弁理士　三　枝　英　二

手続補正書（自発）

昭和６２年５月１８日

特許庁長官　黒　田　明　雄　殿

１　事件の表示

昭和６２年特許願第９１１４２号

２　発明の名称

ステロイドクリーム製剤

３　補正をする者

事件との関係　特許出願人

株式会社　大塚製薬工場

４　代　理　人

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(6521)　弁理士　三　枝　英　二

５　補正命令の日付

自　発

６　補正の対象

明細書中「特許請求の範囲」の項及び「発明の詳細な説明」の項

７補正の内容

別紙版付の通り





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補正の内容

1　明細書中「特許請求の範囲」の項の記載を別紙の通り訂正する。

2　明細書第５頁下から第７～６行に「セバシン酸ジエチル、」とあるを「セバシン酸ジエチル」と訂正する。

3　明細書第１０頁第７行に「非イオン界面活性剤」とあるを「非イオン性界面活性剤」と訂正する。

4　明細書第１１頁第９行及び第１１行に「陰イオン界面活性剤」とあるを「陰イオン性界面活性剤」と訂正する。

5　明細書第１８頁第１５行に「ｐＨ：５．３３）」とあるを以下の通り訂正する。

「ｐＨ：５．３３）

実施例３

アジピン酸ジイソプロピル１０ｇに代えてセバシン酸ジエチル５．０ｇ及びトリアセチン１．０ｇを使用し、１，３－ブチレングリコールに代えてプロピレングリコールを使用する（配合量は同じ）以外は、実施例１と同様にして本発明クリーム製剤を得た。（粘度：８９．２パスカル秒，ｐＨ５．２５）」

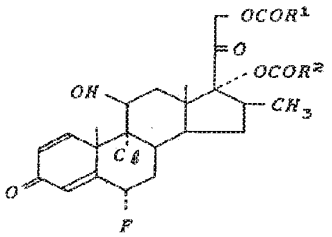
6　明細書第１８頁第１６行～第１９頁第５行に「実施例３……ｐＨ５．２５）」とあるを削除する。

7　明細書第１９頁第１３行に「抗力」とあるを「効力」と訂正する。

（以　上）

特許請求の範囲

①　一般式




（式中、$R^1$はメチル基又はエチル基を示し、$R^2$は炭素数１～４のアルキル基又はフェニル基を示す。）

で表わされるステロイド類０．０１～０．５重量％、アジピン酸ジイソプロピル、セバシン酸ジエチル及びトリアセチンから選ばれた１種又は２種以上の溶解剤２～４０重量％、プロピレングリコール及び／又は１，３－ブチレングリコール２～３０重量％、界面活性剤０．５～１５重量％、高級パラフィン系炭化水素２～５０重量％、精製水３０～８５重量％を含有し、ほぼ飽和状態に溶解した上記ステロイドを不連続相として乳化含有させたことを特徴とするステロイドクリーム製剤。

②　ステロイド類０．０１～０．２重量％、アジピン酸ジイソプロピル、セバシン酸ジエチル及びトリアセチンから選ばれた１種又は２種以上の溶解剤２～２０重量％、プロピレングリコール及び／又は１，３－ブチレングリコール５～２０重量％、界面活性剤０．５～１０重量％、高級パラフィン系炭化水素４～４０重量％、精製水４０～８０重量％を含有する特許請求の範囲第１項に記載のステロイドクリーム製剤。





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(54) Title: TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS

(57) Abstract

The present invention provides a method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a corticosteroid. This invention is especially useful for treating psoriasis.



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# TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS

## CROSS REFERENCE TO RELATED APPLICATIONS

This patent application claims priority from Provisional Patent Application 60/03915 filed on February 20, 1997.

## BACKGROUND OF THE INVENTION

### 1. FIELD OF THE INVENTION

This invention relates to pharmaceutical compositions for application to the skin and to a method for the treatment of proliferating skin diseases. The composition may be applied topically. The treatment can be either therapeutic or prophylactic.

### 2. DESCRIPTION OF RELATED ART

Proliferative skin diseases are widespread throughout the world and afflict millions of humans and their domesticated animals. This invention provides a method for treatment of such diseases. As used hereinafter in this specification and in the claims, the expression "proliferative skin diseases" means benign and malignant proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation. Such diseases include: psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun-induced keratosis, non-malignant



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keratosis, acne, and seborrhic dermatitis in humans and atopic dermatitis in domesticated animals.

Heretofore, proliferative skin diseases have been generally accepted by mankind as an ongoing evil having degrees of severity variable with inherited skin traits and external factors but always have been recognized as unsightly, painful, morbid diseases. Over the history of mankind innumerable medicines and treatments have been proposed, tried and used with varying degrees of success.

Treatments which are prescribed and used for the treatment of proliferative skin diseases include the following:

(1) topical applications, e.g. coal tar derivatives, 5-fluorouracil, vitamin A acid, glucocorticoids in high dosage, bath oils and non-specific emollient creams and ointments;

(2) systemic administration, e.g. glucocorticoids and classic anti-cancer agents, for example, methothrexate, hydroxyurea, azaribine, cyclophosphamide; and

(3) physical modalities, e.g. ultra violet light, x-radiation, and, in severe cases, surgery.

While these treatments provide, in certain cases some remission of the original symptoms, each treatment suffers some defect, for example, temporary and incomplete mitigation of symptoms, rapid re-occurrence of the disease when mitigation is terminated, serious and sometimes irreversible damage (atrophy) resulting from the topical application for extended times of glucocorticoids, acute bone marrow suppression, cirrhosis of the liver resulting from the protracted use of methothrexate which may lead to death of the patient, and the causation of cancer by the application of anti-cancer drugs, x-radiation, or ultra violet rays.



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Recently, a new compound has been approved by the Food and Drug Administration for the treatment of psoriasis and acne. Tazarotene. Tazarotene is available as Tazorac® 0.1% and Tazorac® 0.05% topical gel from Allergan, Inc. of Irvine, California.

## BRIEF SUMMARY OF THE INVENTION

The present invention relates to a method of treating psoriasis in humans with tazarotene, preferably a gel comprising 0.1%, tazarotene by weight, and a corticosteroid, preferably a cream. The tazarotene gel may be administered once daily in the evening and the corticosteroid cream may be administered to the subject once daily in the morning, or the gel and cream may be administered on alternate days. The tazarotene gel is disclosed in U.S. patent Application Serial no. 623,184, which is entitled "Stable Gel Formulation for Topical Treatment of Skin Conditions", which was filed on March 28, 1996, in the name of Prakash Charu and is hereby incorporated by reference in its entirety.

In one aspect of the invention, the corticosteroid may be Synalar® cream (0.01% fluocinolone acetonide), Elocon® cream (0.1% mometasone furoate) or Lidex® cream (0.05% fluocinonide), i.e. a low-potency, mid-potency and high-potency corticosteroid, respectively.

In another aspect of the invention, the corticosteroid may be fluocinonide 0.05% ointment, Lidex®, a high potency steroid, mometasone fuoate 0.1% ointment, Elocon®, a high potency steroid, diflorasone diacetate 0.05% ointment, Maxiflor®, a high potency steroid, fluticasone propionate 0.005% ointment, Cultivate®, a mid-potency steroid, betamethasone dipropionate 0.05% cream, Diprosone®, a mid-potency steroid, diflorasone diacetate 0.05% cream, Maxiflor®, a mid-



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potency steroid, clobetasol propionate 0.05% ointment, Temovate®, a super-potency steroid, betamethasone valerate 0.1% lotion, Valisone®, a mid-potency steroid.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph comparing the reduction in plaque elevation over a 12 week treatment period with tazarotene in combination with placebo, high-potency corticosteroid, mid-potency corticosteroid and low-potency corticosteroid.

Figure 2 shows the treatment success with the combination therapies of Figure 1.

## DETAILED DESCRIPTION OF THE INVENTION

In accordance with this invention it has been found that proliferative skin diseases are alleviated, that is, the symptoms of the disease are noticeably improved or become undetectable, by the treatment of the afflicted patient, or animal, with the pharmaceutical compounds described in detail, hereinbelow.

For the purposes of this specification and the claims, a proliferative skin disease is alleviated when there is a noticeable decrease in the thickness of a lesion to palpation, with or without residual redness, or residual slightly dilated blood vessels or residual hyper- or hypo-pigmentation. For purposes of this invention and the claims hereof, psoriasis is alleviated when a scale-free psoriasis lesion is noticeably decreased in thickness, or noticeably but incompletely cleared or completely cleared.



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The compositions utilized in the method of this invention may be applied topically.

The term "topical" as employed herein relates to the use of the active ingredient incorporated in a suitable pharmaceutical carrier, and applied at the site of the disease for exertion of local action. Accordingly, such topical compositions include those pharmaceutical forms in which the compound is applied externally by direct contact with the skin surface to be treated. Conventional pharmaceutical forms for this purpose include ointments, lotions, pastes, jellies, sprays, aerosols, bath oils and the like. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases, e.g., petroleum, lanolin, polyethylene glycols, as well as mixtures thereof. Topical application with occlusion of an area larger than the medicated area may produce improved results relative to non-occluded topical applications.

The percentage by w/w of the active ingredient, i.e. the corticosteroid herein utilized ranges from about 0.001% to about 1% of the pharmaceutical preparation, preferably from about 0.005% to about 0.1%, by weight.

The percentage by w/w of the active ingredient, i.e. tazarotene herein utilized ranges from about 0.01% to about 15% of the pharmaceutical preparation, preferably from about 0.1% to about 2% and in these preparations the aforesaid pharmaceutical carrier for topical application constitutes a major amount of the said preparation.

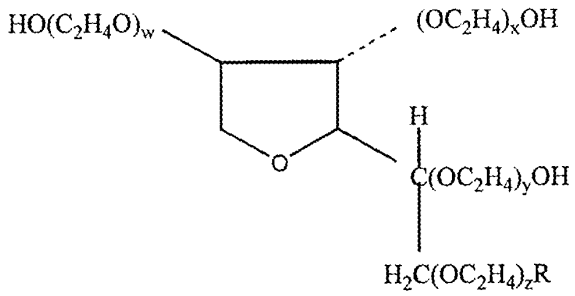
Preferably tazarotene is utilized as a stable gel formulation for topical treatment of skin conditions in humans, said stable gel formulation comprising: Ethyl-6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate in a plurality of nonaqueous vehicles for both solubilizing tazarotene and forming a gel therewith, said nonaqueous vehicles enabling topical application of the gel to a skin condition, said plurality of vehicles each



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being present in amounts, and in combination, to control release of tazarotene from the gel to the skin conditions. In the tazarotene formulation the vehicles are present in amounts selected to produce maximum release of the active agent, i.e. tazarotene, from the gel when all the vehicles are present therein. Preferably the formulation comprises three vehicles and more preferably the formulation comprises three vehicles which are used to both solubilize the active agent and form a gel.

The formulation preferably comprises the three vehicles, e.g. Polysorbate 40, Poloxamer 407 and Hexylene glycol. Polysorbate 40 is




wherein the Sum of w, x, y, and z is 20 and R is $(C_{15}H_{31})COO$ and Poloxamer 407 is $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$ having the following properties.



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USAN for Poloxamers

| Poloxamer | Physical Form | Average Molecular Weight | Average Values a | b | BASF Corp. Brand Name |
|---|---|---|---|---|---|
| | | | | | Pluronic |
| 124 | Liquid | 2090 to 2360 | 12 | 20 | L 44 |
| 188 | Solid | 7680 to 9510 | 80 | 27 | F 68 |
| 237 | Solid | 6840 to 8830 | 64 | 37 | F 87 |
| 338 | Solid | 12700 to 17400 | 141 | 44 | F 108 |
| 407 | Solid | 9840 to 14600 | 101 | 56 | F 127 |

More preferably, tazarotene is utilized as a stable gel formulation for topical treatment of psoriasis comprising an effective amount of Ethyl-6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate in a pharmaceutical carrier comprising:

(a) water;
(b) edetate disodium;
(c) ascorbic acid;
(d) Carbomer 934P;
(e) Poloxamer 407;
(f) polyethylene glycol;
(g) Polysorbate 40;
(h) hexylene glycol;
(i) butylated hydroxytoluene;
(j) butylated hydroxyanisole;



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(k) benzyl alcohol; and

(l) tromethamine.

The tazarotene formulation may comprise Polysorbate 40 in an amount up to about 0.4% by weight, Poloxamer 407 in an amount up to about 0.4% by weight, and hexylene glycol in an amount up to about 2% by weight or more preferably Polysorbate 40, in an amount of about 0.32% by weight, Poloxamer 407 in an amount of about 0.18% by weight, and hexylene glycol in an amount of about 2% by weight.

Most preferably, the tazarotene formulation comprises:

| INGREDIENT | FUNCTION | CONCENTRATION %W/W |
|---|---|---|
| tazarotene | Drug | 0.1 |
| purified water | Excipient | 49.25 |
| Edetate Disodium | Stabilizer | 0.05 |
| Ascorbic acid | Stabilizer | 0.05 |
| Carbomer 934P[1] | Thickening agent | 1.25 |
| Poloxamer 407 | Surfactant | 0.2 |
| PEG-400 | Co-solvent | 45.0 |
| Polysorbate 40 | Surfactant | 0.2 |
| Hexylene glycol | Co-solvent | 2.0 |
| Butylated hydroxytoluene | Stabilizer | 0.05 |
| Butylated hydroxyanisole | Stabilizer | 0.05 |
| Benzyl alcohol | Preservative | 1.0 |
| Triethanolamine/ Tromethamine | Neutralizer | 0.8 |

[1]Carbomer 934P [1975]. NF. The viscosity of a neutralized 0.5 percent aqueous dispersion of Carbomer 934P is between 29,400 and 39,400 centiposes. (1) Polymer of 2-propenoic acid, cross-linked with allyl ethers of sucrose or pentaerythritol; (2) Polymer of acrylic acid, cross-linked with allyl ethers of sucrose or pentaerythritol. Molecular weight is approximately 3,000,000.



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The tazarotene formulation and the corticosteroid formulation, each, will be applied, topically, in an amount to achieve the maximum effect on alleviating the proliferative skin disease symptoms without causing an adverse reaction. Selection of such an amount of either formulation is well within the skill of the art.

Preferably, the tazarotene formulation is utilized to provide from about 0.5 to about 5 mg of tazarotene per $cm^2$ of affected skin, more preferably from about 1 to about 3 $mg/cm^2$, e.g. 2 $mg/cm^2$.

The method of this invention also employs a corticosteroid. The expression "corticosteroid" refers to a naturally occurring product of the adrenal cortex, or a synthetic analog thereof possessing anti-inflammatory activity and minimal or no mineralocorticoid activity or sex steroid activity. The corticosteroids include glucocorticoids. Of the natural glucocorticoids, one may use for example, hydrocortisone or the synthetic glucocorticoids such as methyl prednisolone acetate (Prednisone) or triamcinolone for topical therapy. The corticosteroids are preferably employed in amounts of from 0.5 to 5 mg per $cm^2$ of affected skin, more preferably from about 1 to 3 $mg/cm^2$, e.g. 2 $mg/cm^2$.

The treatment period may be 12 weeks with a 4 week follow-up period. The subjects are evaluated for plaque elevation, scaling and erythema with a successful treatment defined as about 50% improvement or better. During the treatment period, tazarotene in combination with the mid- or high-potency corticosteroid produced significantly better results than treatment with tazarotene in combination with placebo in reducing plaque elevation, scaling, erythema and overall severity. During the 4 week post-treatment period, the results with tazarotene plus mid- or high-potency corticosteroid were equal to or better than tazarotene plus placebo or tazarotene plus low-potency corticosteroid.

The most common adverse events resulting from the treatment were burning, pruritus and erythema; however there was a lower incidence of such adverse events in patients treated with tazarotene plus the medium- or high-potency corticosteroid.



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Thus, treating psoriasis in humans with a combination of tazarotene and a mid-potency or high-potency corticosteroid is more effective than a combination of tazarotene and low-potency or placebo and results in a lower incidence of adverse events such as burning pruritis and erythema.

The invention is further illustrated by the following examples which are illustrative of various aspects of the invention, and are not intended as limiting the scope of the invention as defined by the appended claims.

## EXAMPLE 1

The study reported here utilizes a combination regimen that alternates between tazarotene 0.1% gel and a corticosteroid or placebo cream every evening. The aim of the study was to determine whether such alternating therapy may offer clinical benefits by maximizing the therapeutic benefits of both drugs, while also minimizing corticosteroid use and thus reducing the potential for adverse corticosteroid-induced effects.

This study was a multicenter, investigator-masked, parallel-group study, enrolling 398 patients with stable plaque psoriasis. Topical applications of tazarotene 0.1% gel, were administered every other evening, and one of the following creams administered on alternate evenings): placebo; low-potency corticosteroid (hydrocortisone acetate 1%); medium-potency corticosteroid (alclometasone dipropionate 0.05%); or high-potency corticosteroid (betamethasone valerate 0.1%).

The study required a 12-week treatment period plus a 4-week follow-up phase. The patient demographics included 388 patients (231 male and 157 female) with evaluable data, mean age of 46.7 years (range: 21-88 years) and a mean duration of psoriasis of 17.39 years.

All treatment groups achieved clinically significant reductions in plaque elevation at all treatment and post-treatment visits, with the tazarotene/high-potency combination taz/high group achieving consistently greater reductions than



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the other treatments throughout the study. At week 4, these reductions were significantly greater than those in all the other treatment groups. The taz/high also achieved clinically significant reductions in plaque elevation more rapidly than the other treatments, i.e. in two weeks compared with four weeks in all the other groups. (See the results set forth in Figure 1.)

Treatment success was defined as a moderate, marked, almost clear or completely cleared response ($\geq$ 50% global clinical improvement). All tazarotene/corticosteroid treatment groups achieved treatment success rates of > 50% within 4 weeks. However, the taz/high combination achieved significantly greater treatment success rates than the tazarotene/placebo (taz/plac) and tazarotene/medium-potency corticosteroid (taz/med) combinations throughout the 12-week treatment period. Peak treatment success rates ranged from 56% (for patients treated with taz/plac at Week 8) to 77% (for taz/high at Week 8).

During the 4-week follow-up period, all groups retained $\geq$ 60% global clinical improvements in psoriasis, with treatment success rates ranging from 60% (for taz/med) to 75% (for taz/high) at study Week 16. These improvements were statistically and clinically significant compared with the pretreatment levels and there were no significant differences between the groups at the end of the follow-up period. (See Figure 2.)

Week 12, the probability of patients being considered a treatment success at any study visit was 77% in the taz/high group. In the other groups the treatment success was 56 to 61%.

The taz/high combination also achieved initial treatment success significantly faster than any of the other combinations. The median time to treatment success was 2 weeks in the taz/high group, compared with 4 weeks in each of the other groups.

All treatment groups achieved clinically significant reductions in scaling during the treatment period, and the taz/high combination was consistently the most efficacious treatment throughout the 12-week treatment period. The reductions in



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scaling achieved in all groups by the end of the treatment period were generally maintained during the 4-week follow up period.

All treatment groups achieved statistically significant reductions in erythema during the treatment period and, once again, the taz/high combination was the most efficacious treatment. During the follow-up period, all groups retained significant reductions in erythema compared with baseline levels, and these reductions were clinically significant in the taz/high, taz/med, and taz/plac groups.

The overall incidence of adverse events that were possibly, probably or definitely treatment-related decreased with increased corticosteroid potency, falling from 42% in the taz/plac group, to 36%, 32% and 31% in the tazarotene/low-potency corticosteroid (taz/low), taz/med, and taz/high groups, respectively. (See Table II, below.)

**Table II.** Overall incidence of adverse events

| | Patients (%) | | | |
|---|---|---|---|---|
| | Taz/plac | Taz/low | Taz/med | Taz/high |
| Pruritus | 15 | 19 | 16 | 8 |
| Erythema | 12 | 7 | 6 | 6 |
| Irritation | 8 | 9 | 5 | 4 |
| Burning | 6 | 4 | 4 | 8 |

In view of the above Example, the following conclusions may be drawn. Alternate-day treatment with tazarotene 0.1% gel and the high potency corticosteroid cream was consistently more effective than the other three regimens in reducing plaque elevation, scaling and erythema. Patients in the tazarotene plus high-potency corticosteroid group also achieved significantly higher treatment



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success rates (≥ 50% global clinical improvement, and achieved treatment success faster, than patients in the other groups. Treatment-related adverse events comprised mainly mild to moderate local irritation including pruritus, erythema and burning skin. The incidence of treatment-related adverse events decreased as the potency of the corticosteroid cream used increased.

EXAMPLE 2

The study of Example 1 is substantially repeated with fluocinolone acetonide 0.01% cream (low-potency), mometasone furoate 0.1% cream (mid-potency) and fluocinonide 0.05% cream (high-potency) used as the corticosteroids. In this study tazarotene 0.1% gel in combination with a mid-potency or high-potency corticosteroid, when compared with tazarotene plus placebo cream, was associated with significantly higher treatment success rates, significantly greater reductions in scaling, erythema, and overall lesional severity, with a decreased incidence of adverse events. The corticosteroids are Synalar® cream, Elocon® cream and Lidex® cream, respectively.

While particular embodiments of the invention have been described, it will be understood of course that the invention is not limited thereto since many obvious modifications can be made and it is intended to include within this invention any such modifications as will fall within the scope of the appended claims.

Having now described the invention, I claim.



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1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a corticosteroid.

2. The method of claim 1 wherein said corticosteroid is selected from the group consisting of fluocinolone acetonide, mometasone furoate, fluocinonide, diflorasone diacetate, fluticasone propionate, betamethasone dipropionate, clobetasol propionate, betamethasone valerate.

3. The method of claim 1 wherein tazarotene is applied as a 0.1% gel.

4. The method of claim 1 wherein said corticosteroid is a mid- or high-potency corticosteroid.

5. The method of claim 4 wherein said corticosteroid is selected from the group consisting of mometasone furoate and fluocinolone acetonide.

6. A method for treating psoriasis in a human subject by topically applying to the psoriatic skin of said subject an effective amount of tazarotene and an effective amount of a corticosteroid.

7. The method of claim 6 wherein tazarotene is applied as a 0.1% gel.

8. The method of claim 7 wherein said corticosteriod is a cream.

9. The method of claim 8 wherein said corticosteroid is a mid- or high-potency corticosteroid.



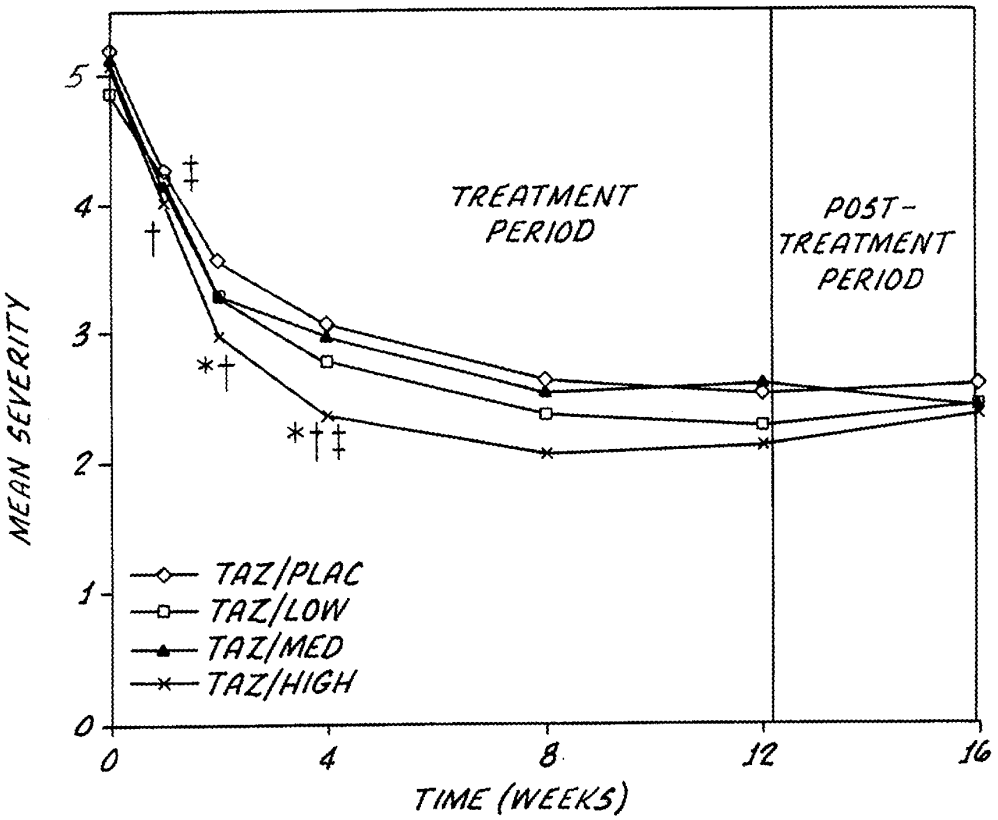
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10. The method of claim 9 wherein said corticosteroid is selected from the group consisting of mometasone furoate and fluocinolone.

11. The method of claim 6 wherein tazarotene is administered once daily in the evening and the corticosteroid is administered once daily in the morning.



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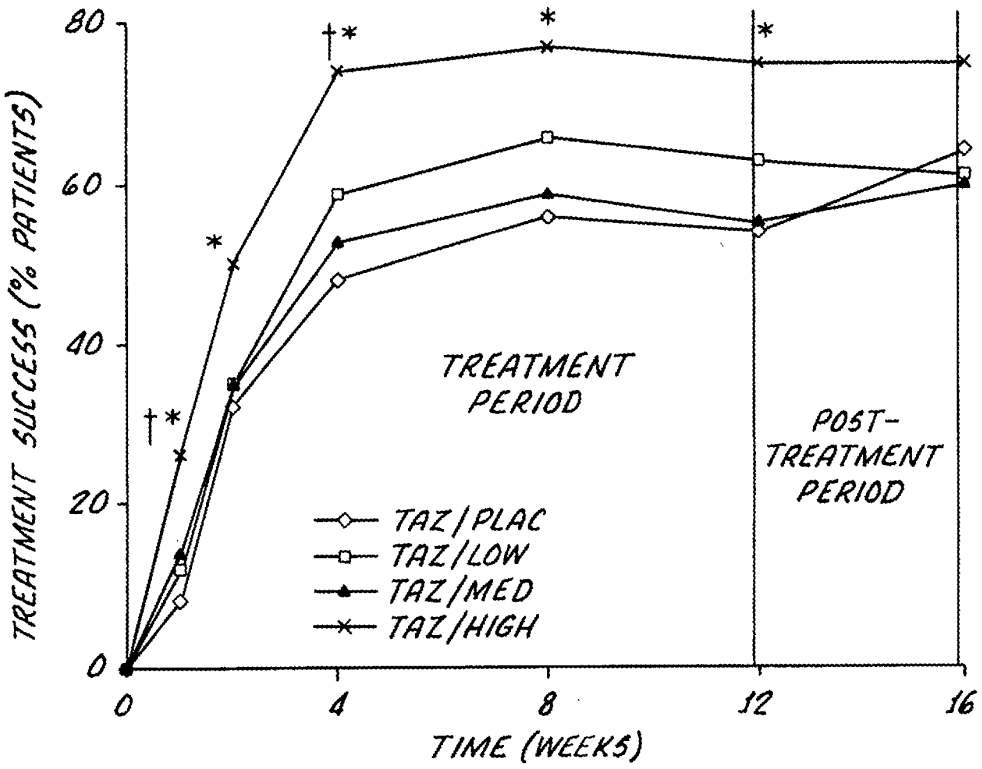



*P < 0.05 VS TAZ/PLAC;
†P < 0.05 VS TAZ/LOW;
‡P < 0.05 VS TAZ/MED.

FIG. 1.



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*P < 0.05 VS TAZ/PLAC AND TAZ/MED
†P < 0.05 VS TAZ/LOW

FIG. 2.



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# INTERNATIONAL SEARCH REPORT

Intern ..onal Application No
PCT/US 98/03355

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57 //(A61K31/57,31:44)

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

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | BIOLOGICAL ABSTRACTS, vol. 10, Philadelphia, PA, US; abstract no. 981998, SCHWARTZ E ET AL: "In vivo prevention of corticosteroid-induced skin atrophy by tretinoin in the hairless mouse is accompanied by modulation of collagen, glycosaminoglycans, and fibronectin" XP002067726 see abstract & JOURNAL OF INVESTIGATIVE DERMATOLOGY, 102 (2). 1994. 241-246., --- -/-- | 1-11 |

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 11 June 1998 | 01. 07. 1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Leherte, C |

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# INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/US 98/03355

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | BIOLOGICAL ABSTRACTS, vol. 31,<br>Philadelphia, PA, US;<br>abstract no. 16902,<br>VAN DER RHEE H J ET AL: "COMBINED TREATMENT OF PSORIASIS WITH A NEW AROMATIC RETINOID TIGASON IN LOW DOSAGE ORALLY AND TRIAMCINOLONE ACETONIDE CREAM TOPICALLY A DOUBLE-BLIND TRIAL"<br>XP002067727<br>see abstract<br>& BR J DERMATOL, 102 (2). 1980. 203-212., | 1-11 |

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# INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/US 98/03355

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)



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(54) Title: TOPICAL FORMULATION OF THE OIL–IN–WATER TYPE, COMPRISING GALACTOLIPID MATERIAL AS EMULSIFIER, WITH A PROLONGED EFFECT OF AN INCORPORATED ACTIVE SUBSTANCE

(57) Abstract

The invention relates to the use of a topical formulation of the oil–in–water type comprising an oily material, an aqueous phase and an emulsifier, wherein the emulsifier is a galactolipid material, as a carrier for providing a prolonged effect of an incorporated active substance. New topical formulations are also described.



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TOPICAL FORMULATION OF THE OIL-IN-WATER TYPE, COMPRISING GALACTOLIPID MATERIAL AS EMULSIFIER, WITH A PROLONGED EFFECT OF AN INCORPORATED ACTIVE SUBSTANCE

The present invention refers to a topical formulation of the oil-in-water emulsion type, in which a variety of pharmaceutical or cosmetic compounds can be incorporated, and which after application on the skin gives a prolonged local effect of the incorporated compound.

BACKGROUND OF THE INVENTION

Dermatological formulations for topical administration, such as creams, lotions, ointments and gels, are used in pharmacy, medicine and cosmetics for curative and prophylac- tic treatment of different conditions. It is in general desirable that said formulation brings about a prolonged effect.

There are different areas where there is a continuous need of an improved, that is long lasting, topical treatment as exemplified below.

- People with very dry skin such as atopic dry skin and people who frequently are exposed to water and soap and thus often develop dry skin conditions need to apply a protective cream or ointment to their skin. Examples of people frequently exposed to water and soap are doctors and nurses who must wash their hands and face before examining patients, workers who are handling paints and grease and often need to use strong detergents to clean their hands, and, most common of all, home workers. For these and other categories of people having dry skin conditions a cream or lotion with an extended effect on skin smoothing and moisturising would be preferred.

- The use of hydrocortisone and other steroidal creams is very common in the treatment of local inflammatory conditions in the skin. The systemic absorption of the steroid potentially gives unwanted side-effects. A cream with a sustained release of the active steroid could increase the local effect and decrease the systemic absorption, a very much preferred therapeutic situation, especially in small children.

- The treatment of Athlete's foot or other fungal



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infections with topical antifungal or of many skin infec- tions with antibiotics or antivirals requires twice or three times daily applications of the cream or gel to be effective. A once-daily formulation would certainly improve compliance, effectiveness, as well as comfort during treatment.

- The treatment of any other skin condition, including psoriasis, eczemas, other inflammatory disorders, cancers, precancerous conditions, ageing, wrinkling, ultraviolet radiation damage and any other condition which may respond to a topically applied therapeutic agent.

Preferred topical formulations are creams and lotions, that is typically oil-in-water emulsions which spread readily on the skin, leave no detectable residue and adhere to the treated area without being tacky. Said emulsions normally consist of an oil phase, an aqueous phase and an emulsifier. Ointments, which mainly comprises an oil phase, are greasy and form a greasy film on the skin preventing moisture loss. Gels which might be liposomal preparations do not contain any oil. Topical preparations of the oil-in-water emulsion type are generally more appreciated by the user from a cosmetic point of view, but have not previously been claimed to give any extended effect of incorporated substances of dermatological or cosmetological interest. From a dermatological standpoint oil-in-water emulsion type formulations are often preferred, particularly if the number of ingredients can be reduced to a minimum.

PRIOR ART

Highly structured vehicles, such as inversed hexagonal and cubic liquid crystals, may exhibit sustained-release properties, either by binding the water or by stiffening the amphiphilic film within the formulation, see Osborne, D.W., et al. in Drugs and the Pharmaceutical Sciences, Swarbrick J.(ed.), Vol. 42 (1990), pp. 374-379. Drug formulations containing liposomes for topical use may give a sustained local effect of the incorporated compound, see Korting, H.C., et al. in J. Am. Acad. Dermatol., Vol. 25 (1991), pp. 1068-1071. The topical drug



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delivery systems described are, however, far more complicated lipid preparations than a topical cream of the oil-in-water emulsion type. For reasons of stability of topical liposomal systems, most authors have proposed a gel base. Gel formulations are, however, more likely to produce side effects than cream or ointment preparations.

WO 95/03784, Insite Vision Inc., discloses a cross-linked polymeric medicament delivery system containing an interactive agent associated with the polymer, which is said to slow release of medicament out of the system. The system can be used in dermal formulations but is particularly useful as topical ophthalmic delivery systems. This invention does not relate to any slow release effects of the cream, but on polymeric systems included in the cream. The slow release effects in this system can be ascribed to the polymeric system.

Topical creams of the oil-in-water emulsion type have not previously been reported as having potential sustained release properties. However, there is a need for topical sustained release formulations, such as oil-in-water emulsions, which are uncomplicated with respect to compositional design as well as manufacturing. Furthermore, less complicated formulations have a major advantage in that they are less likely to cause irritant or hypersensitivity reactions and hence to be more acceptable as skin care preparations for therapeutic or cosmetic use.

WO 95/20943, Karlshamns LipidTeknik AB, discloses an oil-in-water emulsion comprising 0.01-50 % by weight of a galactolipid material as an emulsifier. Said emulsion is said to be useful as a carrier for active substances in a pharmaceutical composition but also in nutritional, cosmetic, food and agricultural products. The emulsions do not exhibit any unpleasant odour or taste and are stable towards oxidation. There is, however, nothing stated about an optional sustained effect.

## DESCRIPTION OF THE INVENTION

The present invention relates to an oil-in-water



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emulsion for topical application to the skin comprising an emulsifier, an oil phase, and an aqueous phase, into which cosmetic or pharmaceutical substances can be incorporated for the local treatment of various skin conditions and disorders.

It has surprisingly been found that a topical cream or lotion of the oil-in-water emulsion type, in which a galactolipid material is used as the emulsifier, and into which a variety of pharmaceutical or cosmetic compounds can be incorporated, after application on the skin gives a sustained local effect of the incorporated compound.

The present invention refers to a topical formulation of the oil-in-water emulsion type, in which a variety of pharmaceutical or cosmetic compounds can be incorporated, comprising an oily material, an emulsifier being a glycolipid based material, and an aqueous phase, and which after application on the skin gives a sustained local effect of the incorporated compound.

According to another aspect the invention refers to the use of a topical formulation of the oil-in-water type comprising an oily material, an aqueous phase and an emulsifier, wherein the emulsifier is a galactolipid material, as a carrier for providing a prolonged effect of an incorporated active substance.

Especially the invention refers to the use of a topical formulation, which can be a cream or a lotion, comprising 0.1-50 % by weight oily material, preferably 1-40 %, and 0.5-20 % by weight emulsifier.

No particular limitation is imposed on the oily material, that is the non-polar lipid material, of the formulation. Examples are vegetable oils, animal oils, fatty acids, synthetic oils, mineral oils, natural and synthetic glycerides, sterol esters, fatty alcohols, and other substances, including lipophilic drugs, obvious to a person skilled in the art, which can be emulsified using a polar lipid emulsifier.

Preferred oily materials to be emulsified are any fatty acid or a derivative thereof, such as vegetable oils of all



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types, such as oils from the seeds and beans of soybean, sunflower, rapeseed (canola), palm, corn, evening primrose, borage, groundnut, sesame, and similar.

There are also synthetic or semi-synthetic glycerides, propanediol derivatives, cholesteryl esters, other esters and other appropriate lipid materials. Another oily material for the emulsion is a medium-chain triacylglycerol (MCT) oil.

There are also many lipids such as free fatty acids, mono-, di- and triacylglycerols, phospholipids, cholesterol esters and lipids and oils of many other types which have therapeutic actions in themselves, such as tea tree oil, and which may be advantageously formulated in the form of a topical cream or optionally lotion. In this case the therapeutically active substance is the oily material, which can also have other bioactive properties.

The emulsifier according to the invention should be a glycolipid, preferably a galactolipid based material. Galactolipids can be defined as glycosylglycerides based on galactose and are well known constituents of plant cell membranes. The most important classes of these contain one to four sugars linked glycosidically to diacylglycerol. The two most abundant classes contain one and two galactose units, respectively, and are commonly known as mono- and digalactosyldiacylglycerol, MGDG and DGDG. Galactolipids, primarily DGDG and DGDG-rich materials, have been investigated and found to be a surface active material of interest in industrial application such as food, cosmetics, and pharmaceutical applications.

Synthetic diglycosyldiacylglycerols based on galactose, optionally in combination with other monosaccharide units, such as glucose, semi-synthetic, and natural glycosylglycerides, isolated from any source, can be used in accordance with the invention.

An intrinsic beneficial feature of the galactolipids is the galactose units comprising the polar head group in each lipid molecule, which may sterically stabilise the emulsion droplets in an emulsion. The galactose groups may also interact strongly



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with water and other polar substances, such as a water-soluble drug or a excipient, added to the emulsion.

WO 95/20943 describes the use of DGDG-rich material, a galactolipid material, as an emulsifier in oil-in-water emulsions. Said galactolipid material was prepared from cereals by extraction of the lipids with ethanol and a subsequent purification on a chromatographic column to pure DGDG or a DGDG-rich fraction of polar lipids. The galactolipid emulsifier consists of at least 50 % digalactosyldiacylglycerols and a remainder of other polar lipids and can be used as the galactolipid emulsifier of the invention, preferably in an amount of 1.0-5.0 % by weight. The galactolipid material for instance consists of 70-80 % DGDG and 20-30 % other polar lipids.

According to a preferred embodiment of the invention the galactolipid emulsifier consists of 50-70 % digalactosyldiacyl-glycerols and 30-50 % other polar lipids. This material is manufactured by Scotia LipidTeknik AB, Stockholm, as CPL®-Galactolipid (registered trade mark owned by Scotia Holdings plc). A preferred topical formulation of the invention comprises CPL®-Galactolipid as the galactolipid material.

WO 97/11141 describes a method for producing a fractionated vegetable oil which is characterised in containing 10-90 % by weight of polar lipids, preferably 20-75 %, and a remainder of non-polar lipids. Said fractionated vegetable oil can also be used as the galactolipid emulsifier of the invention, preferably in an amount of 2.0-10.0 % by weight. The fractionated vegetable oil preferably contains more than 5 % by weight, preferably more than 20 %, glycolipids and preferably more than 3 % by weight, preferably more than 15 %, DGDG.

According to a preferred embodiment of the invention the galactolipid material consists of 40-60 % polar lipids and a remainder of non-polar lipids. A fractionated oat oil of this composition consisting of a wide range of polar and amphiphilic lipids in a continuous triglyceride phase is manufactured by Scotia LipidTeknik AB, Stockholm, as Galactolec™. A preferred



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topical formulation comprises Galactolec™ as the galactolipid material.

The galactolipid based emulsifier is a safe and non-toxic material for human and veterinary use. It is also an environmentally friendly material.

Topical formulations, such as creams and lotions, are prepared by using a polar lipid emulsifier either as the sole emulsifier or in combination with other amphiphilic compounds, that is co-surfactants. The formulation may also comprise optional additives known in the art for improving different aspects of the composition, such as thickening agents, preservatives, antioxidants, fragrance and the like.

The creams according to the invention are characterised by having excellent cosmetic properties. Furthermore, they contain a minimum number of ingredients, without any stabilising ingredients known to give irritation or sensitisation of the skin. Despite the low numbers of ingredients the creams are extremely stable, with shelf lives of several years.

The active substances can be either water soluble or oil soluble or amphiphilic, and can be any type of pharmaceutical or cosmetological ingredient suitable for topical preparations, such as moisturising agents, e.g. glycerol, propylene glycol, urea, vitamins, e.g. retinol and tocopheryl esters, anti-inflammatories, e.g. glucocorticosteroids such as hydrocortisone, hydrocortisone butyrate, chlobetasol, triamcinolone, fluticasone, momethasone and betamethasone, antibiotics, e.g. erythromycin, antivirals, e.g. acyclovir, antifungals, e.g. miconazole, antiseptics, e.g. cetrimide, agents for treating acne, e.g. tretinoin, benzylperoxide, psoriasis, e.g. dithranol and calcipotriol, senile pruritus, dry skin and wrinkles, cancer and pre-cancerous conditions, such as active keratosis, and UV protecting agents to be included in suntan creams and lotions.

Topical creams according to the invention are prepared by conventional methods. For example, a cream with 20 % by weight



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