(Carrer et al., Effect of propylene glycol on the skin penetration of drugs. Arch Dermatol Res 312, 337–352 (2020), https://doi.org/10.1007/s00403-019-02017-5, McGowan MA et al., Propylene Glycol in Contact Dermatitis: A Systematic Review. Dermatitis, 2018; 29(1):6-12, doi: 10.1097/DER.0000000000000307). Additionally, it is known to be an excellent solvent for other adjuvants or other ingredients and to be an excellent emulsifier. However, cases have been reported in which patients with atopic dermatitis show allergic reactions to propylene glycol and it is known to be irritating to the eyes. Furthermore, it is a diol and may undergo unwanted side reactions, due to its nucleophilic nature. Such reactions are known for example with sorbitol or glycerol in the presence of cetirizine, which is well known as an anti-allergic compound.

Propylene glycol is commonly used as a solvent of hydrophilic compounds. For example, parabens are only slightly soluble in water. In the preparation of an aqueous pharmaceutical formulation or a formulation comprising an aqueous component, parabens must be solved in a solvent, such as propylene glycol, suitable to introduce the parabens in the aqueous phase.

5-aminolevulinic acid (also termed herein "ALA" or "5-ALA") is a small biogenic amino acid with a molecular weight (as HCl salt) of 167.59 g/mol and is very hydrophilic, i.e. readily soluble in water with octanol-water partition coefficient (logP) of around -3. ALA is used in Photodynamic Therapy (PDT) as a prodrug to drive the synthesis of protoporphyrin IX in diseased tissue, which is subsequently illuminated with light of appropriate wavelengths to induce the photodynamic effect.

Known formulations of ALA for topical use on the skin, are instable in aqueous solutions (see Reinhold, Future Oncology, 2017 Nov;13(27):2413-2428, doi: 10.2217/fon-2017-0247). So far, the nanoemulsion put to use with ALA contained 10% active ingredient and was formulated as a gel. The previous gel formulation showed stability up to 36 months at refrigerated temperatures (2-8°C) but was susceptible to higher temperatures (standard room temperature and above). Exposure to higher temperatures was tolerated in the range of few weeks without risking pharmaceutical quality for human use.

Summary

A first aspect of the disclosure relates to a formulation comprising (a) a nanoemulsion comprising: (i) at least one aqueous component; (ii) a carrier component comprising: (1) at least one lipophilic component, (2) at least one surfactant, and (3) at least one alcohol; and (b) an active agent comprising a carboxylic acid group, or a derivative, or salt of a carboxylic acid group, wherein the formulation comprises less than 1% w/w of propylene glycol or no propylene glycol.

Another example of the disclosure relates to the formulation of the first aspect for use in a method of treatment and/or prevention of a dermatological disease or condition.

Another example of the disclosure relates to a method for the preparation of the formulation as described herein, comprising the following steps: (a) mixing the at least one lipophilic component, the at least one surfactant, and the at least one alcohol having at least three carbon atoms, and (b) contacting the mixture obtained in step (a) with an aqueous component, under conditions allowing formation of a nanoemulsion, wherein the active agent is added under conditions allowing interactions of the active agent with the surface of the nanovesicles when dissolved in the aqueous phase.

In another aspect, the present disclosure relates to the formulation as disclosed herein for use in therapy. In yet another aspect, the present disclosure relates to a use of the formulation as disclosed herein in the manufacture of a medicament for treating and/or preventing of a dermatological disease or condition.

Detailed description

Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in “A multilingual glossary of biotechnological terms: (IUPAC Recommendations)”, Leuenberger, H.G.W, Nagel, B. and Kölbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland).

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturers' specifications, instructions etc.), whether supra or infra, is hereby incorporated by reference in its entirety.

In the following, the elements of the present invention will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and preferred embodiments should not be construed to limit the present invention to only the explicitly described embodiments. This description should be understood to support and encompass embodiments, which combine the explicitly described embodiments with any number of the disclosed and/or preferred elements. Furthermore, any permutations and combinations of all described elements in this application should be considered disclosed by the description of the present application unless the context indicates otherwise.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, are to be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion

Claims

1. A formulation comprising
   (a) a nanoemulsion comprising:
      (i) at least one aqueous component;
      (ii) a carrier component comprising:
         (1) at least one lipophilic component,
         (2) at least one surfactant, and
         (3) at least one alcohol; and
   (b) an active agent comprising a carboxylic acid group, or a derivative, or salt of a carboxylic acid group,

   wherein the formulation comprises less than 1% w/w of propylene glycol or no propylene glycol.

2. The formulation of claim 1, wherein the formulation comprises less than or equal to 0.9% w/w of propylene glycol or no propylene glycol.

3. The formulation of any one of the preceding claims, wherein the formulation comprises essentially no propylene glycol.

4. The formulation of any one of the preceding claims, wherein the formulation comprises no propylene glycol.

5. The formulation of any of the preceding claims, wherein the formulation comprises no, essentially no, less than 1%, or less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms.

6. The formulation of any one of the preceding claims, wherein the formulation comprises no, essentially no, less than 1%, or less than or equal to 0.99%, 0.95%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of a polyol having 2 to 12 carbon atoms.

7. The formulation of any one of the preceding claims, wherein the at least one alcohol comprises at least three carbon atoms, preferably 3, 4 or 5 carbon atoms, more preferably the at least one alcohol is selected from the group consisting of 1-propanol and 2-propanol and mixtures thereof.

8. The formulation of any one of the preceding claims, wherein the at least one lipophilic component is selected from triglycerides and mixtures thereof, preferably wherein the at least one lipophilic component is a caprylic and/or a capric triglyceride or a mixture thereof.

9. The formulation of any one of the preceding claims, wherein the at least one surfactant is selected from the group consisting of a phospholipid, a lysophospholipid, a ceramide and/or a mixture thereof, and/or the at least one surfactant is a polyoxyethylene-type surfactant.

10. The formulation of any one of the preceding claims, comprising a total aqueous component in an amount of 50% to 99% (w/w), preferably from 70% to 95% (w/w), more preferably from 75% to 95% (w/w), even more preferably from 80% to 90% (w/w).

11. The formulation of any one of the preceding claims, comprising

(a) the at least one lipophilic component in an amount from 0.1% to 30% (w/w), preferably from 0.25% to 15% (w/w), preferably from 0.25% to 10% (w/w), and more preferably from 2% to 10% (w/w) or 3% to 8% (w/w); and/or

(b) the at least one alcohol in an amount from 0.1% to 10% (w/w), preferably from 0.5% to 5% (w/w), more preferably from 1% to 5% (w/w) and even more preferably from 1% to 3%,

based on the total weight of the nanoemulsion (a).

12. The formulation of any one of the preceding claims, wherein the active agent is a hydrophilic active agent.

13. The formulation of any one of the preceding claims, wherein the active agent is a photosensitizer or a metabolic precursor thereof.

14. The formulation of any one of the preceding claims, wherein the active agent is 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof.

15. The formulation of any one of the preceding claims, wherein the active agent is present in an amount of from 0.1% to 25% (w/w), based on the total weight of the formulation.

16. The formulation of any one of the preceding claims, wherein the nanoemulsion comprises nanovesicles, wherein the nanovesicles have a size of less than or equal to 500 nm, preferably less than or equal to 200 nm, more preferably in the range of 5 nm to 200 nm when

a) stored for one month, two months, three months, six months, twelve months or at least one month, at least two months, at least three months, at least six months or at least twelve months at 2-25°C; and/or

b) stored for one month, two months, three months, six months, twelve months, eighteen months, twenty-four months, thirty months, thirty-six months or at least one month, at least two months, at least three months, at least six months or at least twelve months, at least eighteen months, at least twenty-four months, at least thirty months or at least thirty-six months at 2-8°C.

17. The formulation of any one of the preceding claims, characterized by a polydispersity index of less than or equal to 0.4 when

a) stored for one month, two months, three months, six months, twelve months or at least one month, at least two months, at least three months, at least six months or at least twelve months at 2-25°C; and/or

b) stored for one month, two months, three months, six months, twelve months, eighteen months, twenty-four months, thirty months, thirty-six months or at least one month, at least two months, at least three months, at least six months or at least twelve months, at least eighteen months, at least twenty-four months, at least thirty months or at least thirty-six months at 2-8°C.

18. The formulation of any one of the preceding claims, comprising at least one gelling agent, preferably wherein the gelling agent is selected from the group consisting of poloxamer, xanthan, bentonite, sodium carboxymethylcellulose, hydroxymethyl cellulose, carbomer, hydroxypropyl cellulose, gellan gum, guar gum, pectin, poly(ethylene)oxide, polycarbophil, alginate, tragacanth, povidone, gelatin, and mixtures thereof, more preferably wherein the gelling agent is selected from poloxamer, xanthan and mixtures thereof.

19. The formulation of any one of the preceding claims, which is essentially free of parabens.

20. The formulation of any one of the preceding claims, for use in therapy.

21. Use of the formulation of any one of the preceding claims in the manufacture of a medicament for treating and/or preventing of a dermatological disease or condition.