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IPR2026-00396
Sun Pharmaceutical Industries, Inc. et al. v. Biofrontera, Inc.
Sun's Exhibit 1003
EX1003, Page 1

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Montserrat FOGUET	Nonprovisional Application Number (if known):	
Title of Invention:	NANOEMULSION WITHOUT PROPYLENE GLYCOL		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /James H. Velema/	Date 2023-12-08
Name (Print/Typed) James H. Velema, Esq.	Practitioner Registration Number 56,130

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of _____ forms are submitted.

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
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NANOEMULSION WITHOUT PROPYLENE GLYCOL

Related Applications

This application claims priority to International Patent Application No. PCT/EP2023/059291, filed April 6, 2023, the entire disclosure of which is hereby incorporated herein by reference.

Description

The present invention relates to a composition for topical use comprising an oil in water nanoemulsion and an active ingredient, wherein the composition is essentially free of propylene glycol. The formulation shows less impurities and side products of the active ingredient over time and therefore ensures a higher quality standard and an improved shelf-life.

Background of the invention

Dispersions are colloidal systems, which include micelles, liposomes, virosomes, emulsions and micro-, nanoemulsions, suspensions and polymer solutions. Emulsions or micro emulsions can be oil in water, water in oil or middle phased dispersions, often dispersed with surfactants as emulsifiers. Nanoemulsions are a subgroup of the emulsions that contain very fine oil in water dispersions. Nanoemulsions are highly homogeneous, transparent, and slightly opalescent dispersions (or emulsions) of oil and water. The dispersed droplets (liquid) or vesicles in such emulsions are composed of a lipid core surrounded by at least one surfactant or emulsifier monolayer. Nanoemulsions are characterized by a mean particle or vesicle size of less than 200 nm, often less than 100 nm and a narrow monodisperse particle or vesicle size distribution.

Nanoemulsions are thermodynamically more stable than conventional emulsions, making them a favorable vehicle for pharmaceutical compositions, which have to maintain stability for long periods of time. Nanoemulsions can be in a metastable state and the structure depends often of the manufacturing process, making them a fragile system and complicated to formulate to a pharmaceutical composition with a long shelf-life under different storage conditions. If destabilized they can become heterogeneous, milky and/or exhibit phase separation. However, they can provide useful applications in skin care in that they may exhibit good textural and sensual properties due to the very fine droplet or globule size.

Nanoemulsions are generally manufactured by mechanical fragmentation of an oily phase in an aqueous phase in the presence of a surfactant. The very small size of the oily globules is often obtained by virtue of at least one pass through a high-pressure homogenizer or a sonicator.

Formulations comprising nanoemulsions as vehicles for the delivery of active ingredients often contain adjuvants, such as organic molecules or solvents, e.g., propylene glycol. Propylene glycol is known to have advantageous properties, such as penetration enhancing or preservative effects (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 of the invention

A first aspect of the invention 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 aspect of the invention 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 aspect of the invention 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.

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 of any other integer or step or group of integer or step. As used in this specification and the appended claims, the singular forms “a”, “an”, and “the” include plural referents, unless the content clearly dictates otherwise.

Formulating a topical pharmaceutical gel composition is a highly complex process, which needs to take account of different aspects, such as pH, solubility, polymorphism, applicability, and overall stability of the pharmaceutical composition. Additionally, one must consider the benefits and constraints of the active pharmaceutical ingredient (API), excipients, the interaction of all components and the manufacturing process. In oil in water nanoemulsion formulations, there are two different phases, which may need to be stabilized and compliant with patients: one is the hydrophobic carrier component, which is usually the carrier and needs to stabilize and release the API and the other one the aqueous component. All these aspects lead to complex formulations with a large number of ingredients. However, the more ingredients a composition has, the more problems/pitfalls may arise during formulation, such as undesired side reactions/interactions of ingredients or higher impurity profiles. Additionally, patients may have allergic reactions or skin irritations to various components after application on the skin. Therefore, a pharmaceutical composition should only have the necessary ingredients and omit as many adjuvants and/or excipients as possible. One very popular class of excipients in cosmetics, pharmaceutical or food products are polyols, in particular propylene glycol. It may be used as a solvent, humectant, preservative agent or emulsion stabilizer. One rather attractive property in topical pharmaceuticals is its ability to enhance penetration of active ingredients.

The prior art fails to teach a pharmaceutical composition comprising a nanoemulsion composition containing an active agent comprising a carboxylic acid group or a derivative, or pharmaceutically acceptable salt of a carboxylic acid group, being free of propylene glycol.

In the context of the present specification, the term “propylene glycol” refers to propane-1,2-diol (also known as 1,2-propanediol, α-propylene glycol, 1,2-dihydroxypropane, methyl ethyl glycol or methylethylene glycol).

As described above, nanoemulsions tend to coalesce under certain circumstances, such as exposure to extreme temperature differences, leading to bigger droplet sizes and harm the nanoemulsion quality.

These aspects make it clear that design and formulation of a composition with a high penetration and improved impurity profile is highly desirable.

The examples of the present invention demonstrate that the omission of propylene glycol in a pharmaceutical formulation comprising an active agent, in particular an hydrophilic active agent

and/or an active agent comprising a carboxylic acid group or a derivative, or pharmaceutically acceptable salt of a carboxylic acid shows a better impurity profile without restricting the penetration properties of the topical pharmaceutical composition compared to a pharmaceutical formulation comprising propylene glycol. Surprisingly, the penetration of the vehicles is improved by the omission of propylene glycol, which is a non-obvious discovery for a person skilled in the art.

The terms “active agent” and “active ingredient” are used interchangeably herein. As used herein, “active agent”, includes an active pharmaceutical agent (herein also termed “pharmaceutical active agent” or “active pharmaceutical ingredient”, “API”) and an active cosmetic agent (herein also termed “cosmetic active agent”). As used herein, an active pharmaceutical agent is defined as the chemical, biological, mineral or any other entity or component responsible for the therapeutic (pharmacological, physiological, physical, etc.) effects in a product. As used herein, an active cosmetic agent is defined as the chemical, biological, mineral or any other entity or component responsible for the cosmetic effects in a product. The active agent may be a plant extract. The active agent may be present as a pharmaceutically acceptable salt. The active agent may be present as a cosmetically acceptable salt.

In the following specification, unless specifically mentioned otherwise, the term “active agent comprising a carboxylic acid group” also refers to active agents comprising a derivative of a carboxylic acid group, or a salt of a carboxylic acid group.

Preferably, the active agent comprising a carboxylic acid group is a hydrophilic active agent. It is preferred that the hydrophilic active agent has a logP value equal to or lower than 1, lower than 0.5, lower than 0.4, lower than 0.3, lower than 0.2, lower than 0.1 or a negative lg P value, wherein P is the octanol-water partition-coefficient.

In the context of the present specification, the term “derivative of a carboxylic acid group” refers to a carboxylic acid group that has formed a chemical compound by reacting with another chemical moiety, in particular a carboxylic acid group that has formed an ester by reacting with a hydroxy group.

Without wishing to be bound by theory, active agents comprising a carboxylic acid group may undergo nucleophilic reactions to form undesired products, such as esters, with propylene glycol. In instances where the active agent comprises a derivative of carboxylic acid group in the form of an ester, the active agent may still undergo nucleophilic reactions to form undesired products, such as esters, with propylene glycol, e.g. via transesterification. Omission of propylene glycol may thus lead to less undesired side products.

In addition to an extinction of the expected esters formed by 5-ALA and propylene glycol, the examples show that in a 5-ALA gel formulation of the invention, being free of propylene glycol, a previously detected impurity with m/z of 246 was surprisingly greatly reduced. This reduction is a

meaningful improvement in view of prior art formulations: Firstly, this impurity poses the highest probability for "out-of-specification" results during stability testing. Secondly, the amount of this impurity increases at higher temperatures and after longer storage. A reduction of this impurity, as observed in the formulation of the invention, being free of propylene glycol, improves stability under stressed conditions and allows for longer storage. Additionally, the unknown impurities may be harmful for patients, since it is impossible to predict their metabolism and long-term influence on the human body.

Furthermore, functional in vitro tests described in the Examples revealed that omission of propylene glycol does not impair the drug release and skin penetration qualities of the formulation at any rate. Improved penetration results of ALA were achieved with the formulation of the invention without propylene glycol compared to comparative formulation with propylene glycol. The formulation without propylene glycol has non-inferior penetration properties compared to the formulation containing propylene glycol. This finding is surprising, as propylene glycol is a well-known and highly effective penetration enhancer used in topical pharmaceutical formulations.

In an in-vitro release assay, the formulation of the invention, being free of propylene glycol, released more 5-ALA than the comparative formulation comprising propylene glycol. This finding is surprising since the addition of polyols, in particular glycerol or propylene glycol, which does not evaporate upon application, is expected to improve adhesion and thus improves drug release.

The formulations of the invention comprise two phases:

(I) an aqueous phase or aqueous component,

(II) a lipid carrier phase.

A first aspect of the invention 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.

In preferred embodiments, the formulation is a pharmaceutical formulation.

In some embodiments, the formulation is a lotion, a spray, a foam, an emulsion, a nanoemulsion, a gel or a cream. In some embodiments, the formulation is a lotion. In the context of the present specification, a lotion is a low-viscosity topical preparation intended for application to the skin. A

lotion has a lower viscosity than a cream or a gel due to its higher water content. In some embodiments, the lotion has a viscosity of ≤ 8 Pa s (pascal-second), ≤ 6 Pa s, ≤ 5 Pa s, ≤ 4 Pa s, ≤ 3 Pa s, ≤ 1.0 Pa s, or ≤ 0.5 Pa s.

The skilled person is aware of suitable methods for determining the viscosity. Preferably, the viscosity is determined as described in the examples section.

In preferred embodiments, the formulation is for topical use.

In preferred embodiments of the formulations described in the present invention, the aqueous component comprises an aqueous phase or forms an aqueous phase. Preferably, the active agent is dissolved in the aqueous phase.

In preferred embodiments of the formulations described in the present invention, the carrier component comprises or consists of nanovesicles. Preferably, the active agent is capable to interact with the surface of the nanovesicles.

The active agent may be present as a salt. Examples in which the active agent is present as a salt are e.g. 5-aminolevulinic acid HCl, and 5-aminolevulinic acid phosphate.

In even more preferred embodiments of the formulations described in the present invention, the active agent is dissolved in the aqueous phase and is capable to interact with the surface of the nanovesicles. The active agent preferably comprises a carboxylic acid group, a derivative of a carboxylic acid group, or pharmaceutically acceptable salt of a carboxylic acid group.

Examples in which the active agent comprises a derivative of a carboxylic acid group are e.g. esters of 5-aminolevulinic acid such as methyl δ-aminolevulinate (MAL), and hexyl δ-aminolevulinate (HAL).

Examples in which the active agent comprises a pharmaceutically acceptable salt of a derivative of a carboxylic acid group are e.g. methyl δ-aminolevulinate hydrochloride, hexyl δ-aminolevulinate hydrochloride.

In all embodiments described herein, the salt of a carboxylic acid group is preferably a pharmaceutically acceptable salt of a carboxylic acid group. As used herein “capable to interact with the surface of the nanovesicles” includes non-covalently binding of the active agent to the nanovesicles, in particular to the surface of the nanovesicles. For example, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 70%, at least 80%, or at least 90%, of the total amount of active agent interacts with the surface of the nanovesicles, the balance being dissolved in the aqueous phase.

In the context of the present specification, the expression "the formulation comprises less than or equal to 0.9% w/w of propylene glycol" is meant to include embodiments in which the formulation comprises essentially no propylene glycol.

In preferred embodiments, the formulation comprises essentially no propylene glycol.

As used herein, the expressions "essentially free of compound X", "does essentially not comprise compound X", or "comprises essentially no compound X" with respect to a formulation are interchangeable. In particular, these expressions specify that the formulation is either free of compound X or comprises less than 0.1% (w/w), less than 0.08% (w/w), less than 0.07% (w/w), less than 0.06% (w/w), less than 0.05% (w/w), less than 0.04% (w/w), less than 0.03% (w/w), less than 0.02% (w/w), or less than 0.01% (w/w) of compound X based on the total weight of the formulation.

As used herein, the expression "the composition comprises less than X% of compound X", is meant to include embodiments in which the composition is free of compound X.

The formulation may comprise 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 propylene glycol or no propylene glycol.

In particular, the formulation may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of propylene glycol.

More particular, the formulation may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of propylene glycol.

Most particular, the formulation may comprise less than or equal to 0.3% or 0.1% w/w of propylene glycol.

In preferred embodiments, the formulation comprises no propylene glycol.

In addition to comprising no propylene glycol or only small amounts of propylene glycol as defined above, it is preferred that 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 3 carbon atoms (i.e., having not more than 3). Preferably, 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 4, 2 to 5, 2 to 6, 2 to 7, 2 to 8, 2 to 9 or 2 to 10 carbon atoms (i.e., having not more than 4, 5, 6, 7, 8, 9, or 10 carbon atoms, respectively). More preferably, 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 4, 2 to 5, 2 to 6, 2 to 7, 2 to 8, 2 to 9, 2 to 10, 2 to 11 or 2 to 12 carbon atoms (i.e., having not more than 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms, respectively). More preferably, 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 15, 2 to 20, 2 to 25 or 2 to 30 carbon atoms (i.e., having not more than 15, 20, 25 or 30 carbon atoms, respectively). Even more preferably, 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 15, 2 to 20, 2 to 25 or 2 to 30 carbon atoms (i.e., having not more than 15, 20, 25 or 30 carbon atoms, respectively). Even more preferably, 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.

"Non-cyclic polyol" in the context of the present specifications means that the polyol does not comprise any cyclic hydrocarbon moieties, in particular no cyclic sugar moieties. The non-cyclic polyol may be linear or branched. The non-cyclic polyol may be a diol, a triol or may comprise more than three OH groups.

In preferred embodiments, the formulation of the invention comprises no, essentially no or less than 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 a molecular weight of less than 100 g/mol, less than 200 g/mol, less than 300 g/mol, less than 400 g/mol, less than 500 g/mol, less than 600 g/mol, less than 700 g/mol, less than 800 g/mol, less than 900 g/mol, or less than 1000 g/mol.

The formulation of the present invention may be essentially free of glycerin.

The formulation of the present invention may be essentially free of diglycerin.

The formulation of the present invention may be essentially free of polyglycerin.

The formulation of the present invention may be essentially free of diethylene glycol.

The formulation of the present invention may be essentially free of dipropylene glycol.

The formulation of the present invention may be essentially free of butylene glycol.

The formulation of the present invention may be essentially free of pentylene glycol.

The formulation of the present invention may be essentially free of hexylene glycol.

The formulation of the present invention may be essentially free of 1,3-propanediol.

The formulation of the present invention may be essentially free of 1,5-pentanediol.

The formulation of the present invention may be essentially free of octane-1,2-diol.

The formulation of the present invention may be essentially free of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups.

The formulation of the present invention may be essentially free of monosaccharides and disaccharides such as sorbitol, mannitol, and mixtures thereof.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of glycerin or no glycerin. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of glycerin. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of glycerin. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of glycerin. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of diglycerin or no diglycerin. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of diglycerin. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of diglycerin. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of diglycerin. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of polyglycerin or no polyglycerin. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of polyglycerin. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of polyglycerin. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of polyglycerin. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of diethylene glycol or no diethylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of diethylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of diethylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of diethylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of dipropylene glycol or no dipropylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of dipropylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of dipropylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of dipropylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of butylene glycol or no butylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of butylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of butylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of butylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of pentylene glycol or no pentylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of pentylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of pentylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of pentylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of hexylene glycol or no hexylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of hexylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of hexylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of hexylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of 1,3-propanediol or no 1,3-propanediol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of 1,3-propanediol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of 1,3-propanediol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of 1,3-propanediol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of 1,5-pentanediol or no 1,5-pentanediol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of 1,5-pentanediol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of 1,5-pentanediol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of 1,5-pentanediol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of octane-1,2-diol or no octane-1,2-diol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of octane-1,2-diol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of octane-1,2-diol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of octane-1,2-diol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups or no polyethyleneglycols. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of monosaccharides and disaccharides such as

sorbitol, mannitol and mixtures thereof or no sugars such as sorbitol, mannitol and mixtures thereof. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of monosaccharides and disaccharides such as sorbitol, mannitol and mixtures thereof. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of monosaccharides and disaccharides such as sorbitol, mannitol and mixtures thereof. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of monosaccharides and disaccharides such as sorbitol, mannitol and mixtures thereof. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may be free of, may be essentially free of, or may comprise less than an indicated amount, such as less than 1%, less than 0.99%, less than 0.95%, less than 0.9%, less than 0.8%, less than 0.7%, less than 0.6%, less than 0.5%. less than 0.4%, less than 0.3%, less than 0.2% or less than 0.1% of one polyol, all polyols or any chosen number of polyols selected from the group consisting of glycerin, diglycerin, polyglycerin, diethylene glycol, propylene glycol, dipropylene glycol, butylene glycol, pentylene glycol, hexylene glycol, 1,3-propanediol, 1,5-pentanediol, octane-1,2-diol, polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups, and monosaccharides or disaccharides such as sorbitol, mannitol and mixtures thereof. The formulation of the present invention may be essentially free of one polyol or any chosen number of polyols selected from the group consisting of glycerin, diglycerin, polyglycerin, diethylene glycol, propylene glycol, dipropylene glycol, butylene glycol, pentylene glycol, hexylene glycol, 1,3-propanediol, 1,5-pentanediol, octane-1,2-diol, polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups, and monosaccharides or disaccharides such as sorbitol, mannitol and mixtures thereof, but may comprise another polyol. The formulation of the present invention may be essentially free of a polyol which is linear or branched, but non-cyclic. The formulation of the present invention may be essentially free of a polyol having a carbon atom number of 2 to 30, more preferably 2 to 20, even more preferably 2 to 10 or 2 to 8, most preferably 2 to 6 or 2 to 3.

The formulation may comprise 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 or no polyol. The polyol may be a polyol as described herein.

The formulation may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of a polyol. The polyol may be a polyol as described herein.

The formulation may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of a polyol. The polyol may be a polyol as described herein.

The formulation may comprise less than or equal to 0.3% or 0.1% w/w of a polyol. The polyol may be a polyol as described herein.

The formulation may comprise no polyol.

The small size of the nanovesicles and their high homogeneity confers on them advantageous properties which distinguish them from conventional emulsions: The nanoemulsions and formulations comprising nanoemulsions of the present invention are transparent. Further, the nanoemulsion and formulations comprising nanoemulsions of the present invention can carry active agents more efficiently and, thus, become increasingly important in the field of medicine and pharmacy.

"Aging" as used herein, refers to alteration, disintegration and/or degradation of the formulation, affecting chemical and physical stability during storage, in particular under stressed conditions. Such physical or chemical changes due to storage may include, but are not limited to Ostwald ripening, flocculation, coalescence and/or breaking, which may lead to a change in vesicle size or polydispersity index. "Aging" as used herein, may include the formation of impurities after storage, for example for 6 months at 25°C or 40°C. Typical impurities of formulations comprising 5-aminolevulinic acid as active agent are 2-hydroxypropyl-δ-aminolevulinate and an impurity characterized by m/z = 246.

The inventors have found that the formulations of the present invention are surprisingly stable and resistant to aging. In particular, the formulations of the present invention comprise fewer impurities than prior art formulations, even after storage, for example for 6 months at 25°C or 40°C.

As used herein, "stressed conditions" for storage are temperatures significantly exceeding room temperature (e.g., 40°C).

As used herein, a "nanovesicle emulsion" or a "nanoemulsion" is a dispersion of oil in water (oil-in-water dispersion, oil-in-water emulsion, O/W emulsion). The nanoemulsion can be monophasic, transparent and/or slightly opalescent. The nanoemulsions of the present invention can be colloidal systems, which include dispersed nanovesicles comprising a lipid core surrounded by at least one surfactant or emulsifier monolayers. The nanoemulsions and the formulations comprising the nanoemulsions of the present invention are characterized by a mean particle or nanovesicle size of less than 500 nm less, than 200 nm, or less than 100 nm. The nanoemulsions and the formulations comprising the nanoemulsions of the present invention has a narrow (homogeneous) nanovesicle size distribution, for example a nanovesicle size distribution characterized by a polydispersity index of less than or equal to 0.4.

As used herein, "nanovesicle", "nano vesicle", "lipid vesicles", "oil droplets", "droplets" and "oil globules" are interchangeable and refer to small oil droplets in an oil in water emulsion. A lipid vesicle of an average size (see above, e.g., below 500, 200, 100 nm) that is compiled of a

monolayer of a surfactant and a lipid core. In the present invention, the nanovesicles can have a size of less than or equal to 500 nm, or less than or equal to 300 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 100 nm.

As used herein, the term “nanoparticle” or “nano particle”, is distinguished form “nanovesicles”, and refers to solid particles, which are not described in this invention. The formulation of the present invention may be a formulation which is essentially free of nanoparticles. “Essentially free of nanoparticles” means, that the formulation comprises less than or equal to 2% by weight, or less than or equal to 1% by weight of, or does not comprise nanoparticles. Nanoparticles are mainly inorganic, solid lipids or polymeric solid particles may have a size of below 100 nm, below 200 nm, or below 500. The size can be determined by the methods as described herein. For example, the formulation may be essentially free of nanoparticles with a diameter of less than 100 nm, as determined by dynamic light scattering.

As used herein, “topical use” of the formulation of the invention describes an application to a particular place on or in the body, in particular the human body. This includes, but is not limited to administration of the formulation to body surfaces such as the skin or mucous membranes. The topical use can be epicutaneous, meaning that the formulation is directly administered to the skin. In particular the topical use is a pharmaceutical use.

As used herein, the “stability” of a formulation comprising nanovesicles, as described herein, includes, but is not limited to the physical and chemical stability. In particular, in the present invention, a formulation is stable if the integrity of the nanovesicles is found to be stable. A measure known to the skilled person to describe integrity of the nanovesicles is the size, as for example determined by dynamic light scattering, as described herein. The nanovesicles produced according to the invention can have a size below 100 nm, preferably below 50 nm, more preferably in the range of 20-30 nm, immediately after manufacture. For example, the formulation as described herein is stable if the nanovesicles in the formulation of the present invention have a size (or diameter) of less than or equal to 500 nm or less than or equal to 300 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 100 nm.

“Stability” can also refer to the absence of processes above described as aging, leading to a loss of pharmaceutical functionality or quality. The composition described in this invention is functional or pharmaceutically functional, as long as the vesicle size is less than or equal to 500 nm or less than or equal to 300 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 100 nm.

Furthermore, “stability” can refer to the stable content of the hydrophilic active compound, in particular 5-ALA. During storage, the content of 5-ALA is, for example, considered stable if at least 70%, at least 80% or at least 90% of the content of the active agent is still present, when stored, for example, at stressed conditions, as described herein.

In a formulation of the invention, the 5-ALA content may be

(i) at least 95% after storage for 3 months at 40°C, and/or

(ii) at least 95% or at least 97% after storage for 3, 6, 9 or 12 months at 25°C, and/or

(iii) at least 95%, at least 97% or at least 99% after storage for 12, 18, 24 or 36 months at 5°C.

As used herein "stability" of the compositions also refers to a low content of impurities to a small amount of impurities. For example, the formulation of the invention is stable if it contains an entity of m/z= 246 in an amount of less than or equal to 1.5%, 1.0% or 0.75% when stored for 6 months at 40°C, or in an amount of less than or equal to 0.5%, 0.4%, 0.3% or 0.2% when stored for 6 months at 25°C.

In the present invention, the formulation can be stable for at least one month, at least 3 months, at least 6 months, at least 9 months, at least 12 months, e.g., at room temperature (e.g., 15-25°C). In particular, the formulation of the invention can be stable for at least one month, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 24 months, or at least 36 months, at 2-8°C, or at about 5°C.

The formulation of the present invention may have a nanovesicle size of less than or equal to 500 nm, or less than or equal to 300 nm, or less than or equal to 200 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 150 nm, when stored for one month at 40°C.

The formulation of the present invention may have a nanovesicle size of less than or equal to 500 nm, or less than or equal to 300 nm, or less than or equal to 200 nm, preferably in the range of 5 nm to 200 nm, when stored for six months at 25°C.

The size or diameter of the nanovesicles as described herein can be expressed as the Z-average (also termed "z-average"). The size distribution of the nanovesicles can be characterized by the polydispersity index. These parameters are well known to the skilled person, and are widely used in the art to characterize particle or vesicles in emulsions, suspensions and/or polymeric solutions.

In the present invention, the size of the nanovesicles (e.g., z-average in nm) and/or the heterogeneity of nanovesicle formulations (characterized by the polydispersity index) can be determined by dynamic light scattering (also referred as Photon Correlation Spectroscopy (PCS) or Quasi-Elastic Light Scattering (QELS)). Dynamic light scattering is well known in the art and well established to determine size of nano or micro particles or vesicles in emulsions, suspensions and/or polymeric solutions with a laser.

In the formulation as described herein, the total aqueous component can present in an amount of 50% to 99% w/w, based on the total weight of the nanoemulsion (a), preferably from 70% to 95% (w/w), and more preferably from 75% to 95% (w/w), or 80% to 95%.

As used herein, "weight per weight", "weight/weight" or "w/w" means the weight concentration or mass concentration of a component in a formulation described herein. The weight or mass of a component is expressed as a percentage of a reference formulation. For example, the weight or mass of a component can be expressed as a percentage of the total weight or mass of the formulation of the invention, or as a percentage of the total weight or mass of the nanoemulsion (a).

The aqueous component can comprise at least one pH buffering agent. Any suitable buffering agent may be used. Suitable buffering agents are known to the skilled person. For example, the at least one pH buffering agent can be selected from the group consisting of citrate, phosphate, acetate and carbonate.

The pH of the aqueous component can be in the range of 2-9. The pH of the aqueous component can also be preferably in the range of 2-6, such as 2, 3, 4, 5 or 6, more preferably in the range of 4-6, such as 4, 5 or 6, or 2-4, such as 2, 3 or 4.

In the formulation as described herein, the at least one lipophilic component can be selected from triglycerides and mixtures thereof.

Preferably, the at least one lipophilic component is a lipid, a synthetic oil, a vegetable oil and/or an animal oil. Suitable lipids according to the present invention are physiologically acceptable lipids such as ceramide, mono-, di- and triacylglycerin (triglycerides). In particular, the at least one lipophilic component is a triglyceride, preferably a triglyceride comprising a C_{8-10} fatty acid, or a mixture thereof. More particular, the at least one lipophilic component is a caprylic and/or capric triglyceride and/or a mixture thereof, particularly preferably Miglyol (such as Miglyol 812, available e.g., from IOI Oleochemical) or Myritol (such as Myritol 318, available e.g., from BASF). Suitable vegetable and animal oils e.g., are sunflower oil, soybean oil, peanut oil, rape oil, fish oil and/or cetaceum.

In the formulation as described herein, the at least one lipophilic component can be present in an amount of from 0.1% to 30% (w/w) based on the total weight of the nanoemulsion (a), preferably from 0.25% to 15% (w/w), preferably from 0.25% to 10% (w/w), and more preferably from 0.5% to 8% (w/w) or 3% to 8% (w/w). Also preferred is the at least one lipophilic component being present in an amount of from 10% to 30% (w/w) based on the total weight of the nanoemulsion (a), more preferably 15-30%, or 10-20%.

In the formulation as described herein, a triglyceride or triglycerides can be present in an amount of from 2% to 10% (w/w), based on the total weight of nanoemulsion(a), preferably from 3% to 8% (w/w).

In the formulation as described herein, the at least one surfactant may be any suitable surfactant known to the skilled person.

Surfactants, also referred as surface active agents or emulsifiers, are well-known in the art and include any agent linking oil and water in the composition to form an emulsion. They lower the surface tension of two liquids and are amphiphilic. In emulsions they are referred as emulsifiers and coat the droplets preventing coalescing. Emulsifiers can be described with the hydrophilic/lipophilic balance (HLB), which expresses their affinity towards water or oil. Low HLB (e.g., HLB=1) refers to lipophilic emulsifiers and high (e.g., HLB=20) to hydrophilic emulsifiers. In general, lipophilic emulsifiers are used for water-in-oil emulsions and hydrophilic emulsifiers for oil-in-water emulsions. Persons skilled in the art will identify which emulsifiers or mixtures of them are suited for the preferred vehicles and purpose of the composition. In certain emulsions, combinations of emulsifiers might be advantageous.

A suitable membrane-forming surfactant is a phospholipid, a lysophospholipid, a ceramide and/or a mixture thereof. Preferably, the phospholipid is lecithin or cephalin from soybeans or hens' eggs. More preferably the at least one surfactant is lecithin, most preferably soy lecithin.

In the formulation as described herein, the phospholipid, the lysophospholipid, the ceramide and/or the mixture thereof can be present in an amount of from 0.1% to 10% (w/w), based on the total weight of nanoemulsion(a), preferably from 0.15% to 5% (w/w), more preferably from 1% to 5% and even more preferably from 0.2% to 3% (w/w).

Preferably, the lecithin has a phosphatidylcholine content of at least 80% by weight, more preferably of at least 90% by weight, and most preferably of at least 94% by weight. The quality of the lecithin, namely its phosphatidylcholine content, plays a crucial role for the size of the vesicles of the nanoemulsion. The higher the phosphatidylcholine content of the lecithin, the smaller is the size of the vesicles of the nanoemulsion.

As O/W emulsion-forming surfactant, anionic, nonionic, cationic and/or amphoteric surfactants are suitable as well as block copolymers. Suitable anionic surfactants are soaps, alkylbenzene sulphonates, alkane sulphonates, alkylsulfates and/or alkyl ether sulfates. Suitable cationic surfactants are quaternary ammonium compounds, preferably having one or two hydrophobic groups (e.g., cetyltrimethylammonium bromide and cetyltrimethylammonium chloride) and/or salts of tong-chain primary amines. A suitable amphoteric surfactant is N-(acylamidoalkyl)betaine, N-alkyl-β-aminopropionate, phosphate-alkyl-ammonium compounds, and/or amine-N-oxide. A suitable copolymer building block, for example, is propylene oxide. In the present invention, a nonionic surfactant is particularly preferred as O/W emulsion-forming surfactant.

In the formulation as described herein, the at least one surfactant can be any a polyoxyethylene-type surfactant. A suitable nonionic surfactant can be selected from the group consisting of fatty alcohol polyglycolether, alkylphenol polyglycolether, alkylpolyglucoside, fatty acid glucamide, fatty acid polyglycolether, ethylen oxide-propylene oxide-block polymer, polyglycerol fatty acid ester, fatty acid alcanolamide and (ethoxylated) sorbitane fatty acid ester (sorbitane). A

particularly preferred ethoxylated sorbitane fatty acid ester is polyoxyethylene sorbitane monooleate, most preferably Polysorbate 80.

The at least one surfactant, such as the polyoxyethylene-type surfactant, can be present in an amount of from 0.1% to 10% (w/w), based on the total weight of the nanoemulsion (a), more preferably from 2% to 10% (w/w), even more preferably from 0.2% to 5% (w/w), and most preferably from 1% to 5% (w/w) or 0.5% to 5% (w/w).

The formulation of the invention can comprise as least one hydrophilic surfactant with an HLB of 9 to 17, more preferably 12-16, particularly polysorbate 80 to form a nanoemulsion.

The at least one surfactant can be a sugar-based surfactant. Sugar-based surfactants are a group of non-ionic surfactants using hydrophilic sugars to which hydrophobic tails are bound. One common substance of this class is n-dodecyl-β-D-maltoside, a member of the maltoside surfactants so named because the sugar unit used is maltose. An example of a pyranoside surfactant is n-octyl-β-D-thioglucopyranoside. This class uses pyranose as the sugar unit. Examples of the glycoside surfactants are octyl glucoside, decyl glucoside, and lauryl glucoside. An example of a polysugar surfactant is digitonin.

Another very important group of sugar-based surfactants are the Tween surfactants, most notable Tween 20 (also termed herein Polysorbate 20) and Tween 80 (also termed herein Polysorbate 80). These surfactants are based on a sorbitan sugar, which is why they are commonly referred to as polysorbate surfactants. Three oligo(ethylene glycol) side groups of varying lengths are bound to the sugar increasing the hydrophilicity of the head group. This structure forms the core of all Tween surfactants. They deviate in the hydrophobic tail, which is a fatty acid coupled via an ester to four oligo(ethylene glycol) tail. In Tween 20 this fatty acid is lauric acid; in Tween 80 it is oleic acid.

In preferred embodiments, the at least one alcohol comprises at least three carbon atoms.

In the formulation as described herein, the at least one alcohol preferably independently has 3-5 (i.e. no more than 5) or 3-4 (i.e. no more than 4) carbon atoms. The at least one alcohol can be at least one monohydric alcohol. Particularly suitable alcohols having 5 carbon atoms are 1-pentanol and/or 4-methyl-2-pentanol. Suitable alcohols having 4 carbon atoms are 1-butyl alcohol, *iso*-butyl alcohol (2-methyl-1-propanol), *tert*-butyl alcohol (2-methyl-2-propanol) and/or *sec*-butyl alcohol (2-butanol). The alcohol is not propylene glycol.

Preferably, the at least one alcohol has 3 carbon atoms, i.e. is selected from the group consisting of 1-propanol or 2-propanol (isopropyl alcohol) and mixtures thereof. A preferred alcohol is 2-propanol.

In the formulation as described herein, the alcohol may present in an amount of from 0.1% to 10% w/w based on the total weight of the nanoemulsion (a), preferably from 1% to 5% (w/w) or 0.5% to 5% (w/w), and more preferably from 1% to 2% (w/w).

The formulation as described herein may comprise a gelling agent. Any suitable gelling agent may be used. Suitable gelling agents and mixtures thereof are known to the skilled person. In the formulation as described herein, the gelling agent may be 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.

It is preferred that the gelling agent is selected from poloxamer, xanthan and/or mixtures thereof.

It is also preferred that the gelling agent is xanthan (xanthan gum).

It is also preferred that the gelling agent is a poloxamer.

Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). Commercially available are Poloxamer 407 and Poloxamer 188. Poloxamer 407 can have an average molecular weight of about 12600 Dalton. Poloxamer 188 can have an average molecular weight of about 8400 Dalton. In the formulation as described herein, a preferred poloxamer is Poloxamer 407.

In the formulation as described herein, the gelling agent may be present in an amount of from 0.1% to 10% (w/w), based on the total weight of the formulation, preferably from 0.25% to 5% (w/w), and more preferably from 0.5% to 4% (w/w) or 1% to 4% (w/w).

The formulation as described herein may comprise a preservative. Any suitable preservative may be used. Suitable preservatives are known to the skilled person. The preservative can be selected from benzoate, citric acid, EDTA, potassium sorbate, vitamin C and/or derivatives and any mixtures thereof, wherein the preservative is preferably sodium benzoate. Suitable aqueous mixtures of sodium benzoate and potassium sorbate are commercially available, for example Euxyl™ K 712 preservative (Ashland).

The preservative can be present in the formulation as described herein in an amount of from 0.01% to 3% (w/w) based on the total weight of the formulation, preferably from 0.2% to 2% (w/w) or 0.1-2% (w/w), and more preferably from 0.2% to 1.5% (w/w).

In particular, the formulation of the present invention is essentially free of parabens, preferably free of parabens. The class of paraben compounds include *p*-hydroxybenzoates and PHB esters (esters of *p*-hydroxybenzoic acid, also known as 4-hydroxybenzoic acid).

Parabens are only slightly soluble in water. In the preparation of an aqueous formulation or a formulation comprising an aqueous component, parabens must be dissolved in a solvent suitable

to introduce the parabens in the aqueous phase. A suitable solvent may be a polyol, in particular propylene glycol (1,2-propanediol). In the present invention, this preparation of a solution of a paraben in propylene glycol is not needed, so the formulation of the present invention can be free of a polyol, and/or a mixture of two or more polyols, such as propylene glycol.

The formulation of the present invention can be essentially free of a polyol and/or a mixture of two or more polyols, and a paraben, preferably free of propylene glycol and a paraben.

The formulation of the present invention may be a gel formulation. As used herein, a "gel" is a two-phase elastic colloidal material, consisting of a dispersed liquid incorporated in the solid phase often constituted by a gelling agent. Suitable gelling agents, such as xanthan, are described herein.

The formulation of the present invention may be provided in a container or dispenser. Suitable dispensers and containers are known to the skilled person. For example, the dispenser may be a squeeze tube, comprising the formulation as described herein. The squeeze tube may contain the gel formulation as described herein. The dispenser may also be a metered dose dispenser or a foam dispenser or spray dispenser.

The container or dispenser may comprise a propellant, wherein the propellant is provided to pressurize the container or dispenser. Any suitable propellant may be used. Suitable propellants and mixtures thereof are known to the skilled person. Preferably, the propellant is selected from propane, isobutane, n-butane and mixtures thereof.

The formulation of the present invention may be prepared as a foamable formulation.

The formulation of the present invention may be prepared as a pressurized formulation, wherein a propellant is provided to pressurize the formulation. Any propellant as described herein can be used.

The formulation of the present invention may be prepared as a pressurized, foamable formulation, wherein a propellant is provided to pressurize the formulation. Any propellant as described herein can be used.

The formulation of the invention may be provided in a foam dispenser, as described herein, The foam dispenser comprises a container, wherein said container comprises the formulation as described herein, and a propellant. The propellant is provided to pressurize the foam dispenser. Any suitable propellant may be used, as described herein. A foam-generating device is mounted on the container. In particular, the formulation is prepared as a foamable formulation.

The invention also provides a foam, comprising the formulation of the present invention, as described herein.

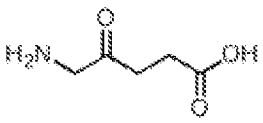
In preferred embodiments, the active agent in the formulation of the invention comprises at least one carboxylic acid group, capable of undergoing esterification reactions. Preferably, the active

agent is a small molecule containing a carboxylic acid group, having a molecular weight of 50 to 1000 g/mol, more preferably a molecular weight of 50 to 900 g/mol, most preferably from 100 to 850 g/mol.

The active agent may be present in an amount of from 0.001% to 50% w/w, based on the total weight of the formulation. In particular, the active agent may be present in an amount of from 0.01% to 30% w/w, based on the total weight of the formulation, or 0.1% to 25% w/w, 0.5% to 25% w/w, 1% to 25% w/w, or 5% to 25% w/w, based on the total weight of the formulation.

In particular the active agent in the formulation of the invention is a hydrophilic compound, which has one carboxylic acid group. The active agent may be a photosensitizer or a metabolic precursor thereof, most preferably **5-aminolevulinic acid (also termed herein "ALA" or "5-ALA"),** a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof. A preferred salt of 5-aminolevulinic acid is 5-aminolevulinic acid hydrochloride. Another preferred salt of 5-aminolevulinic acid is 5-aminolevulinic acid phosphate.

5-Aminolevulinic acid has the following chemical structure:



Molecular Weight: 131,13 g/mol

5-Aminolevulinic acid is a hydrophilic agent, which may interact with the surface of the nanovesicles when dissolved in the aqueous phase.

5-Aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof may be present in an amount of from 0.001% to 50% w/w, based on the total weight of the formulation. In particular, 5-Aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof may be present in an amount of from 0.01% to 30% w/w, based on the total weight of the formulation, or 0.1% to 25% w/w, 0.5% to 25% w/w, 1% to 25% w/w, or 5% to 25% w/w, based on the total weight of the formulation.

In particular, the formulation of the present invention may comprise or consist of:

(a) a nanoemulsion comprising

  (i) an aqueous component, present in an amount of 70% to 95% w/w, based on the total weight of the nanoemulsion (a).

  (ii) nanovesicles, comprising

(1) 1-5% of at least one phospholipid, based on the total weight of the nanoemulsion (a);

(2) 2-10% of at least one polyoxyethylene-type surfactant, based on the total weight of the nanoemulsion (a);

(3) 1-5% C_3 to C_5 alcohol, based on the total weight of the nanoemulsion (a); and

(4) 2-10% triglycerides, based on the total weight of the nanoemulsion (a);

(b) 0.1-20% of an active agent, preferably an active agent comprising a carboxylic acid group, based on the total weight of the formulation; and

(c) 0.1-2% of at least one preservative, based on the total weight of the formulation;

wherein the formulation comprises essentially no propylene glycol, and wherein the formulation preferably has a pH of 2-4. Preferably, the formulation can comprise two surfactants, more preferably soy lecithin and Polysorbate 80.

In this formulation, the at least one phospholipid, the at least one polyoxyethylene-type surfactant, the C_3 to C_5 alcohol, the triglycerides, and the at least one preservative may be independently selected according to the herein-described disclosure.

In particular, the formulation of the present invention may comprise, essentially consist of or consist of:

(a) an emulsion of nanovesicles comprising

(i) an aqueous component, present in an amount of 70% to 95% w/w, based on the total weight of the nanoemulsion (a).

(ii) nanovesicles, comprising

(1) 1-5% of at least one phospholipid, based on the total weight of the nanoemulsion (a);

(2) 2-10% of at least one polyoxyethylene-type surfactant, based on the total weight of the nanoemulsion (a);

(3) 1-5% C_3 to C_5 alcohol, based on the total weight of the nanoemulsion (a); and

(4) 2-10% triglycerides, based on the total weight of the nanoemulsion (a);

(b) 0.1-20% of an active agent, preferably a hydrophilic active agent, preferably a photosensitizer or a metabolic precursor thereof, most preferably 5-aminolevulinic acid hydrochloride, based on the total weight of the formulation;

(c) 0.1-2% of at least one preservative, based on the total weight of the formulation; and

wherein the formulation essentially does not comprise propylene glycol, and wherein the formulation preferably has a pH of 2-4.

Preferably, the formulation can comprise two surfactants, more preferably soy lecithin and Polysorbate 80.

In this formulation, the at least one phospholipid, the at least one polyoxyethylene-type surfactant, the C_3 to C_5 alcohol, the triglycerides, and the at least one preservative may be independently selected according to the herein-described disclosure.

The present invention also relates to a nanovesicle, comprising, essentially consisting of or consisting of

(i) 16-19% w/w of soy lecithin,
(ii) 32-36% w/w of Polysorbate 80,
(iii) 32-36% w/w of caprylic/capric triglycerides, and
(iv) 12-16% w/w of isopropyl alcohol.

A preferred nanovesicle of the invention comprises essentially consists of or consists of

(i) 17% w/w of soy lecithin
(ii) 34% w/w of Polysorbate 80
(iii) 35% w/w of caprylic/capric triglycerides
(iv) 14% w/w of isopropyl alcohol.

The present invention also relates to a nanoemulsion, comprising, essentially consisting of or consisting of

(a) 1.6-3.6% w/w of soy lecithin
(b) 3.3-6.9% w/w of Polysorbate 80
(c) 3.3-7.0% w/w of caprylic/capric triglycerides
(d) 1.3-2.9% w/w of isopropyl alcohol
(e) aqueous phosphate buffer, for example aqueous 5-20 mM phosphate buffer, pH 2-8, preferably pH 2-7, more preferably pH 3-6, ad 100%.

A preferred nanoemulsion of the present invention comprises, essentially consists of or consists of:

(a) 1.7% w/w of soy lecithin
(b) 3.4% w/w of Polysorbate 80
(c) 3.5% w/w of caprylic/capric triglycerides
(d) 1.4% w/w of isopropyl alcohol
(e) aqueous 10 mM phosphate buffer, pH 6, ad 100%.

This formulation is termed herein “BF200”. The BF200 nanoemulsion can be obtained by contacting a mixture of ingredients (a)-(d) in a total amount of 10% w/w and 90% w/w of an aqueous 10 mM phosphate buffer, pH 6, under condition allowing formation of a nanoemulsion, thereby forming the nanoemulsion. An exemplary method for manufacture of the BF200 formulation is described in Example 1.

Another preferred nanoemulsion of the present invention comprises, essentially consists of or consists of:

(a) 2-3% w/w of soy lecithin
(b) 4.5-5.5% w/w of Polysorbate 80
(c) 4.5-5.5% w/w of caprylic/capric triglycerides
(d) 2-3% w/w of isopropyl alcohol
(e) aqueous 10 mM phosphate buffer, pH 6 or less, ad 100%.

This formulation is termed herein "BF215". The BF215 nanoemulsion can be obtained by contacting a mixture of ingredients (a)-(d) in a total amount of 15% w/w and 85% w/w of an aqueous 10 mM phosphate buffer, pH 6, under condition allowing formation of a nanoemulsion, thereby forming the nanoemulsion. An exemplary method for manufacture of the BF215 formulation is described in Example 1.

Yet another preferred nanoemulsion of the present invention comprises, essentially consists of or consists of:

(a) 3-4% w/w of soy lecithin
(b) 6-7% w/w of Polysorbate 80
(c) 6-8% w/w of caprylic/capric triglycerides
(d) 2-4% w/w of isopropyl alcohol
(e) aqueous 10 mM phosphate buffer, pH 6, ad 100%.

This formulation is termed herein "BF220". The BF220 nanoemulsion can be obtained by contacting a mixture of ingredients (a)-(d) in a total amount of 20% w/w and 80% w/w of an aqueous 10 mM phosphate buffer, pH 6, under condition allowing formation of a nanoemulsion, thereby forming the nanoemulsion. An exemplary method for manufacture of the BF220 formulation is described in Example 1.

A preferred formulation of the present invention being essentially free of propylene glycol, comprises, essentially consists of or consists of:

(1) 17.5% w/w of nanoemulsions BF200, as described herein
(2) 2.9% w/w Xanthan,
(3) 0.24% w/w sodium benzoate,
(4) 10% w/w 5-ALA hydrochloride, and
(5) water, ad 100%

This formulation may have a pH of 2-3. Preparation of this formulation is described in Example 3.

An exemplary comparative formulation, not covered by the claims, can comprise, essentially consist of or consist of:

(1) 17.5% w/w nanoemulsions BF200, as described herein
(2) 2.9% w/w Xanthan,
(3) 1% w/w propylene glycol,
(4) 0.24% w/w sodium benzoate,

(5) 10% w/w 5-ALA hydrochloride, and

(6) water, ad 100%

This formulation may have a pH of 2-3. Preparation of this formulation is described in Example 2.

All definitions and embodiments described for the first aspect are also envisioned for all other aspects described herein, where applicable.

Yet another aspect of the present invention relates to the formulations, as described herein, for use in medicine.

Yet another aspect of the present invention relates to the formulations as described herein, for use in a method of treatment and/or prevention of a dermatological disease or condition in a subject.

The treatment and/or prevention of the dermatological disease or condition may also comprise:

(a) topically administering to the subject, a pharmaceutically effective amount of the formulation comprising a photosensitizer or a metabolic precursor thereof, preferably 5-aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof, as described herein, to a diseased or affected area and optionally an area surrounding the diseased or affected area of the skin, and

(b) optionally incubating the pharmaceutically formulation on the skin of the subject with or without occlusion of the area of the skin to which the formulation was administered, the occlusion preferably performed using low density polyethylene or polyurethane film, to enhance deep layer tissue penetration.

The treatment and/or prevention of the dermatological disease or condition may also comprise:

(a) topically administering to the subject, a pharmaceutically effective amount of the formulation comprising a photosensitizer or a metabolic precursor thereof, preferably 5-aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof, as described herein, to a diseased or affected area and optionally an area surrounding the diseased or affected area of the skin, and

(b) optionally incubating the pharmaceutically formulation on the skin of the subject with or without occlusion of the area of the skin to which the formulation was administered, the occlusion preferably performed using low density polyethylene or polyurethane film, to enhance deep layer tissue penetration, and

(c) irradiating the skin area to which the formulation was administered with light.

The light spectrum used for irradiation in step (c) may match the absorption spectrum of a fluorescent porphyrin. For example, the light spectrum may match the absorption peaks of protoporphyrin IX. In particular, the light used for irradiation in step (c) may comprise any visible wavelength in the range of 380 nm to 780 nm, preferably with equal irradiance throughout or irradiance peak(s) at around 410 nm and/or 505 nm and/or 542 nm and/or 575 nm and/or 635

nm. The wavelength spectrum may be essentially free of radiation with a wavelength of less than 380 nm and/or larger than 780 nm. In particular, the light used for irradiation in step (c) may comprise any visible wavelength in the range of 380-440 nm and/or 580-650 nm. The light used for irradiation in step (c) may further be capable to induce red fluorescence of accumulated porphyrins.

The light used in step (c) may be red light, blue light, green light and/or violet light, preferably red light and/or violet light, more preferably wherein (a) the red light results in a radiant exposure of 10-75 J/cm^2, preferably of 25-45 J/cm^2; and/or the violet light results in a radiant exposure of 1-30 J/cm^2, preferably 5 to 15 J/cm^2.

Irradiation in step (c) may be performed with sunlight and/or daylight or with an artificial light source emitting light with a wavelength spectrum and preferably also irradiance similar or identical to sun light. The light with a wavelength spectrum and preferably also irradiance similar or identical to sun light may have a wavelength spectrum of 100 nm to 1000 nm, a wavelength spectrum of 380 nm to 780 nm, preferably with equal irradiance throughout or irradiance peak(s) at around 410 and/or 505 and/or 635 nm, or a wavelength spectrum of 570 nm to 650 nm or 570 nm to 630 nm, and/or a wavelength spectrum of 380 nm to 440 nm. Artificial light may be provided by an LED. A suitable device providing artificial light is described, for example, in US patent No. 11235169 B1 and US patent No. 11219781 B2, the disclosure of which is incorporated herein by reference.

The area surrounding the diseased or affected area of the skin may include a surrounding area not affected, to ensure that the diseased or affected area is adequately treated in the peripheral diseased or affected areas. For example, the area surrounding the diseased or affected area of the skin may include an area of at least about 5 mm width.

The dermatological disease or condition to be treated with the formulation as described herein, may include, but is not limited to, diseases or conditions of the skin, skin appendages or mucosa.

The dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of inflammatory, neoplastic, proliferative, infectious, and/or autoimmune diseases or conditions, and/or the cutaneous manifestation thereof, and/or diseases associated with single lesions or fields of lesions, neoplastic, proliferative and/or inflammatory changes.

The inflammatory dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of dermatitis, contact dermatitis, acne, atopic dermatitis, eczema, pustular dermatitis, seborrheic dermatitis, perioral dermatitis, chronic wound, urticaria, skin ulcer, rosacea, rash, drug eruptions, toxic epidermal necrolysis; erythema multiforme, erythema nodosum, granuloma annulare, and other cutaneous manifestations of inflammation.

The neoplastic and/or proliferative dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of basal cell carcinoma, preferably superficial basal cell carcinoma or nodular basal cell carcinoma; squamous cell carcinoma, preferably Morbus Bowen or invasive squamous cell carcinoma; vulvar intraepithelial neoplasia (VIN); cutaneous T-cell lymphoma; Merkel cell carcinoma; hemangioma; a nodular or subcutaneous cancer disease; field cancerization; non-melanoma skin cancer in organ transplant recipients; and prevention of non-melanoma skin cancer in organ transplant recipients.

The infectious dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of bacterial infections, viral infections, fungal infections, parasitic infections, and combinations thereof.

The autoimmune dermatological disease or condition, or the cutaneous manifestation of the autoimmune condition to be treated with the formulation as described herein, may be selected from the group consisting of psoriasis, pemphigus, systemic lupus erythematodes, lichen planus, morphea, sclerodermia, epidermolysis bullosa, dermatomyositis, graft-versus-host syndrome.

The dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of disorders of sweating, pigmentation disorders including hypopigmentation such as vitiligo, albinism and post inflammatory hypopigmentation and hyperpigmentation such as melasma, reactions to sunlight, such as sunburn, skin ageing, photosensitivity, disorders of hair follicles and sebaceous glands such as hypertrichosis, alopecia, male pattern baldness.

The pharmaceutical as described herein, in particular a pharmaceutical composition comprising a photosensitizer or a metabolic precursor thereof, preferably 5-aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof, as described herein, may be used in a method of photodynamic diagnosis of a neoplastic and/or proliferative dermatological disease or condition, such as benign or malignant neoplasia or precursors thereof; an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation such as acne.

The formulation as described herein, may be used in the treatment of a disease or condition, as described herein, for example neoplastic and/or proliferative dermatological diseases or conditions, such as benign or malignant skin neoplasia or precursors thereof, inflammatory dermatological diseases or conditions such as atopic dermatitis, eczema, psoriasis, rosacea or chronic wounds, and conditions associated with bacterial proliferation such as acne.

Yet another aspect of the present invention is 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 step (b), the conditions allowing formation of the nanoemulsion may include mixing both phases at an appropriate temperature and stirring in a fashion to form nanovesicle. The skilled person knows suitable temperature and stirring conditions. A vesicle size of less than or equal to 500 nm or less than or equal to 300 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 100 nm can be obtained. In particular, the nanoemulsion of the present invention according to step (b) can be prepared without the use of high energy methods, which are well known in the art. High energy method includes high-pressure homogenization, microfluidization, and ultrasonication (Prev Nutr Food Sci. 2019 Sep; 24(3): 225–234).

The method comprises a step of adding the active agent. Preferably, the active agent is a hydrophilic active pharmaceutical ingredient.

A hydrophilic compound, such as an amino acid, preferably a photosensitizer or a metabolic precursor, such as ALA, or/and a pharmaceutically acceptable salt thereof (such as ALA hydrochloride), can be added to the aqueous component before contacting the mixture obtained in step (a) with an aqueous component in step (b), such that the active agent may be non-covalently bound to the nanovesicles (in particular to the nanovesicle surface) in step (b).

A hydrophilic compound, such as an amino acid, preferably a photosensitizer or a metabolic precursor, such as ALA, or/and a pharmaceutically acceptable salt thereof (such as ALA hydrochloride), can also be added to the nanoemulsion obtained in step (b), such that the active agent may be non-covalently bound to the nanovesicles (in particular to the nanovesicle surface).

The method for the preparation the pharmaceutical formulation of the present invention can further comprise:

(i) adding a gelling agent, and/or

(ii) adding a preservative.

Yet another aspect of the present invention is a dispenser product or container product, comprising the formulation as described herein. In the dispenser product or container product, the formulation of the present invention is provided in a container or dispenser. Suitable dispensers and containers are known to the skilled person. For example, the dispenser may be a squeeze tube, comprising the formulation as described herein. The squeeze tube may contain the gel formulation as described herein. The dispenser may also be a metered dose dispenser or a foam dispenser.

The container or foam dispenser may comprise a propellant, wherein the propellant is provided to pressurize the container or foam dispenser. Any suitable propellant may be used. Suitable propellants and mixtures thereof are known to the skilled person. Preferably, the propellant is selected from propane, isobutane, n-butane and mixtures thereof.

The dispenser product may be a foam dispenser product, comprising a foam dispenser, as described herein. The foam dispenser comprises a container, wherein said container comprises the formulation as described herein, and a propellant. The propellant is provided to pressurize the foam dispenser. Any suitable propellant may be used, as described herein. A foam-generating device is mounted on the container. In particular, the formulation is prepared as a foamable formulation.

Yet another aspect of the present invention is the use of the formulation of the present invention, as described herein, for the manufacture of a medicament for the treatment and/or prevention of a dermatological disease or condition in a subject. In particular, the dermatological disease is a dermatological disease or condition as described herein.

Yet another aspect of the present invention is a method of treatment and/or prevention of a dermatological disease or condition in a subject, said method comprising administering to the subject, a pharmaceutically effective amount of the formulation as described herein. In particular, the dermatological disease is a dermatological disease or condition as described herein.

Yet another aspect of the present invention is a method of photodynamic diagnosis of a neoplastic and/or proliferative dermatological disease or condition, such as benign or malignant neoplasia or precursors thereof; an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation such as acne.

ALA (and derivatives) containing drugs drive the synthesis of fluorescent porphyrins that accumulate preferentially in cells/tissues with increased metabolic activity. This can be exploited in the method of photodynamic diagnostics, which can be applied to neoplastic diseases of the skin, such as benign or malignant neoplasia or precursors thereof, inflammatory conditions or conditions associated with bacterial proliferation such as acne. For photodynamic diagnosis, a ALA (or derivative) containing formulation is applied to the skin area to be diagnosed and incubated for an appropriate time (e.g., 1-3 h). Subsequently, blue spectrum light is applied to induce red fluorescence of accumulated porphyrins. The fluorescence can be detected by visual inspection or appropriate technical devices for qualitative or quantitative assessment.

The method of photodynamic diagnoses may comprise:

(i) administering the formulation comprising a photosensitizer or a metabolic precursor, such as 5-aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof, as described herein to the skin area to be diagnosed, under conditions allowing synthesis of fluorescent porphyrins in the cells and/or tissues, and

(ii) irradiating the skin area to which the formulation was administered, under conditions inducing fluorescence of accumulated porphyrins,

wherein increased fluorescence of porphyrins indicates increased metabolic activity, being indicative for a neoplastic and/or proliferative dermatological disease or condition, an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation.

In step (i), the formulation may be incubated on the skin for e.g., 1-3 h.

in step (ii), the skin can be irradiated with light capable to induce red fluorescence of accumulated porphyrins. Suitable irradiation conditions are described herein.

Diagnosis of the neoplastic and/or proliferative dermatological disease or condition, can be performed by detection of increased fluorescence (e.g., compared with healthy tissue and/or skin, e.g., adjacent to the suspected area). Detection of fluorescence can be performed by visual inspection or appropriate technical devices for qualitative or quantitative assessment.

Diagnosis according to the method described herein may be performed for demarcation of tumor borders to assist surgery, to assess treatment efficacy, and/or the assessment of light induced photobleaching for light dosimetry in photodynamic therapy.

An alternative aspect of the invention relates to a formulation as described in the first aspect of the invention, but comprising propylene glycol. The formulation of the alternative aspect may be free of, may be essentially free of, or may comprise less than an indicated amount, such as less than 1%, less than or equal to 0.99%, less than or equal to 0.95%, less than or equal to 0.9%, less than or equal to 0.8%, less than or equal to 0.7%, less than or equal to 0.6%, less than or equal to 0.5%. less than or equal to 0.4%, less than or equal to 0.3%, less than or equal to 0.2% or less than or equal to 0.1% of one polyol, all polyols or any chosen number of polyols selected from the group consisting of glycerin, diglycerin, polyglycerin, diethylene glycol, dipropylene glycol, butylene glycol, pentylene glycol, hexylene glycol, 1,3-propanediol, 1,5-pentanediol, octane-1,2-diol, polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups, and monosaccharides or disaccharides such as sorbitol, mannitol and mixtures thereof. The formulation of the alternative aspect may be essentially free of one polyol or any chosen number of polyols selected from the group consisting of glycerin, diglycerin, polyglycerin, diethylene glycol, dipropylene glycol, butylene glycol, pentylene glycol, hexylene glycol, 1,3-propanediol, 1,5-pentanediol, octane-1,2-diol, polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups, and monosaccharides or disaccharides such as sorbitol, mannitol and mixtures thereof.

The invention also pertains to the following embodiments:

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 embodiment 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 embodiment 1 or 2, preferably 2, wherein the formulation comprises essentially no propylene glycol.

4. The formulation of any one of embodiments 1 to 3, preferably 3, wherein the formulation comprises no propylene glycol.

5. The formulation of any one of embodiments 1 to 4, preferably 4, 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 embodiments 1 to 5, preferably 5, 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 embodiments 1 to 6, 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;

- 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; and/or

- 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.

8. The formulation of any one of embodiments 1 to 7, 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).

9. The formulation of any one of embodiments 1 to 8, 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).

10. The formulation of any one of embodiments 1 to 9, wherein the active agent is a photosensitizer or a metabolic precursor thereof.

11. The formulation of any one of embodiments 1 to 10, wherein the active agent is 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof.

12. The formulation of any one of embodiments 1 to 11, 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.

13. The formulation of any one of embodiments 1 to 12, 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.

14. The formulation of any one of embodiments 1 to 13, 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.

15. The formulation of any one of embodiments 1 to 14, 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.

16. The formulation of any one of embodiments 1 to 15, which is essentially free of parabens.

17. A formulation comprising
    (a) a nanoemulsion comprising:
        (i) at least one aqueous component;
        (ii) a carrier component comprising:
            (4) at least one lipophilic component,
            (5) at least one surfactant, and
            (6) 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 active agent is a photosensitizer or a metabolic precursor thereof;
    wherein the formulation comprises essentially no propylene glycol.

18. The formulation of embodiment 17, wherein the active agent is 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof.

19. A formulation comprising

(a) a nanoemulsion comprising:
(i) at least one aqueous component;
(ii) a carrier component comprising:
(7) at least one lipophilic component,
(8) at least one surfactant, and
(9) at least one alcohol; and
(b) 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,
wherein the formulation comprises less than 1% w/w of propylene glycol or no propylene glycol.

20. A method of treating a dermatological disease or condition, comprising administration of an effective amount of the formulation of embodiment 10 to 12 to a subject in need thereof.

The invention also pertains to the following items:

1. A formulation comprising
(a) a nanoemulsion, said emulsion 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, preferably less than or equal to 0.99%, 0.95% or 0.9% w/w of propylene glycol or no propylene glycol.

2. The formulation of item 1, wherein the formulation comprises essentially no propylene glycol.

3. The formulation of any of the preceding items, 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 3 carbon atoms, preferably 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.

4. The formulation of any of the preceding items, 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 5 carbon atoms, preferably 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.

5. The formulation of any of the preceding items, wherein the at least one alcohol comprises at least three carbon atoms, preferably 3, 4 or 5 carbon atoms.

6. The formulation of any of the preceding items, wherein the active agent is a photosensitizer or a metabolic precursor thereof.

7. The formulation of any of the preceding items, wherein the active agent is present in an amount of from 0.01% to 25% (w/w), preferably 0.1% to 25% (w/w), more preferably 1% to 25% (w/w), based on the total weight of the formulation.

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

9. The formulation of item 8, wherein the 5-aminolevulinic acid, the derivative, the precursor, the metabolite thereof, and/or the pharmaceutically acceptable salt thereof, is present in an amount of from 0.01% to 25% (w/w), preferably 0.1% to 25% (w/w), more preferably 1% to 25% (w/w), based on the total weight of the formulation.

10. The formulation of any one of the items 8 or 9, wherein the formulation comprises an entity characterized by m/z= 246 in an amount of less than or equal to 1.5%, 1.0% or 0.75% when stored for 3 months at 40°C.

11. The formulation of any one of the items 8 to 10, wherein the formulation comprises an entity characterized by m/z= 246 in an amount of less than or equal to 1.5%, 1.0%, 0.5% or 0.2% when stored for 6 months at 25°C.

12. The formulation of any of the preceding items, wherein the formulation is a pharmaceutical formulation.

13. The formulation of any of the preceding items, wherein the formulation is for topical use and/or wherein the formulation is a lotion, a spray, a foam, an emulsion, a nanoemulsion, a gel or a cream.

14. The formulation of any of the preceding items, wherein the active agent is dissolved in the aqueous phase and/or is capable to interact with the surface of the nanovesicles.

15. The formulation of any of the preceding items, wherein the active agent is a hydrophilic active agent

16. The formulation of any one of the preceding items, wherein the nanoemulsion comprises nanovesicles, wherein the nanovesicles have a size of less than or equal to 500 nm, preferably in the range of 5 nm to 200 nm when stored for one month at 40°C.

17. The formulation of any one of the preceding items, wherein the nanoemulsion comprises nanovesicles, wherein the nanovesicles have a size of less than or equal to 500 nm, preferably in the range of 5 nm to 200 nm when stored for six months at 25°C.

18. The formulation of any one of the preceding items, wherein the aqueous component is present in an amount of 50% to 99% w/w, based on the total weight of the nanoemulsion (a), preferably from 70% to 95% (w/w), and more preferably from 80% to 95% (w/w).

19. The formulation of any one of the preceding items, wherein the aqueous component comprises at least one pH buffering agent.

20. The formulation of item 19, wherein the pH buffering agent is selected from the group consisting of citrate, phosphate, acetate and carbonate.

21. The formulation of any one of the preceding items, having a pH of 2-6.

22. The formulation of any one of the preceding items, having a pH of 2-4.

23. The formulation of any one of the preceding items, wherein the at least one lipophilic component is selected from triglycerides and mixtures thereof.

24. The formulation of any one of the preceding items, wherein the at least one lipophilic component comprises a caprylic and/or a capric triglyceride or a mixture thereof.

25. The formulation of any one of the preceding items, wherein the at least one lipophilic component is present in an amount of from 0.1% to 30% (w/w), based on the total weight of the nanoemulsion (a), preferably from 0.25% to 10% (w/w), and more preferably from 0.5% to 8% (w/w) or 3% to 8% (w/w).

26. The formulation of any one of the preceding items, wherein the at least one surfactant comprises (a) a phospholipid, a lysophospholipid, a ceramide and/or a mixture thereof, and/or (b) a polyoxyethylene-type surfactant.

27. The formulation of any one of the preceding items, wherein the at least one surfactant comprises lecithin, preferably soy lecithin.

28. The nanoemulsion of item 27, wherein the lecithin has a phosphatidylcholine content of at least 80% by weight.

29. The formulation of any one of items 26-28, wherein the phospholipid, the lysophospholipid, the ceramide and/or the mixture thereof is present in an amount of from 0.1% to 10% (w/w), based on the total weight of nanoemulsion (a), preferably from 0.15% to 5% (w/w), and more preferably from 0.2% to 3% (w/w).

30. The formulation of any one of the items 26-29, wherein the polyoxyethylene-type surfactant comprises Polysorbate 80.

31. The formulation of any one of items 26-30, wherein the polyoxyethylene-type surfactant is present in an amount of from 0.1% to 10% (w/w), based on the total weight of the nanoemulsion (a), more preferably from 0.2% to 5% (w/w), and most preferably from 0.5% to 5% (w/w).

32. The formulation of any one of the preceding items, wherein at least one alcohol is selected from the group consisting of 1-propanol or 2-propanol and a mixture thereof.

33. The formulation of any one of the preceding items, wherein the at least one alcohol is present in an amount of from 0.1% to 10% (w/w), based on the total weight of the nanoemulsion (a), preferably from 0.5% to 5% (w/w), and more preferably from 1% to 2% (w/w).

34. The formulation of any one of the preceding items, comprising at least one gelling agent.

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

36. The formulation of item 34 or 35, wherein the gelling agent is selected from poloxamer, xanthan and/ or mixtures thereof.

37. The formulation of any one of the preceding items, wherein the gelling agent is present in an amount of from 0.1% to 10% (w/w), based on the total weight of the formulation, preferably from 0.25% to 5% (w/w), and more preferably from 1% to 4% (w/w).

38. The formulation of any one of the preceding items, further comprising at least one preservative.

39. The formulation of item 38, wherein the preservative is benzoate, preferably sodium benzoate.

40. The formulation of item 38 or 39, wherein the preservative is present in an amount of from 0.01% to 3% w/w, based on the total weight of the formulation, preferably from 0.2% to 2% (w/w), and more preferably from 0.2% to 1.5% (w/w).

41. The formulation of any one of the preceding items, which is essentially free of parabens.

42. The formulation of any one of the preceding items, characterized by a polydispersity index of less than or equal to 0.8, wherein the polydispersity index is determined by dynamic light scattering.

43. The formulation of any one of the items 1-42, comprising:

(a) an emulsion of nanovesicles comprising

(i) an aqueous component, present in an amount of 70% to 95% w/w, based on the total weight of the nanoemulsion (a).

(ii) nanovesicles, comprising

(1) 1-5% of at least one phospholipid, based on the total weight of the nanoemulsion (a);

(2) 2-10% of at least one polyoxyethylene-type surfactant, based on the total weight of the nanoemulsion (a);

(3) 1-5% C_3 to C_5 alcohol, based on the total weight of the nanoemulsion (a); and

(4) 2-10% triglycerides, based on the total weight of the nanoemulsion (a);

(b) 0.1-20% of a photosensitizer or a metabolic precursor thereof, preferably 5-aminolevulinic acid hydrochloride, based on the total weight of the formulation;

(c) 0.1-2% of at least one preservative, based on the total weight of the formulation; and

wherein the formulation essentially does not comprise propylene glycol, and wherein the formulation preferably has a pH of 2-4.

44. The formulation of any one of the preceding items, provided in a container, wherein the container further comprises a propellant, and wherein the propellant is provided to pressurize the container and/or to pressurize the formulation in the container.

45. The formulation of any one of the preceding items, for use in medicine.

46. The formulation of any one of the preceding items, for use in a method of treatment and/or prevention of a dermatological disease or condition in a subject.

47. The formulation of any one of the preceding items, for use in a method of treatment and/or prevention of a dermatological disease or condition in a subject, wherein the treatment and/or prevention of the dermatological disease or condition comprises:

(a) topically administering to the subject, a pharmaceutically effective amount of the formulation of any one of the items 1-46, to a diseased or affected area and optionally an area surrounding the diseased or affected area of the skin, and

(b) incubating the pharmaceutically formulation on the skin of the subject with or without occlusion of the area of the skin to which the formulation was administered, the occlusion preferably performed using low density polyethylene or polyurethane film, to enhance deep layer tissue penetration.

48. The formulation for use of item 47, further comprising the step:

(c) irradiating the skin area to which the formulation was administered, with light.

49. The formulation for use of any one of the items 47-48, wherein the area surrounding the diseased or affected area of the skin includes an area of at least about 5 mm width.

50. The formulation for use of any one of the items 46-49, wherein the dermatological disease or condition includes diseases or conditions of the skin, skin appendages or mucosa.

51. The formulation for use of any one of the items 46-50, wherein the dermatological disease or condition is selected from the group consisting of inflammatory, neoplastic, proliferative, infectious, and/or autoimmune diseases or conditions, and/or the cutaneous manifestation thereof, and/or diseases associated with single lesions or fields of lesions, neoplastic, proliferative and/or inflammatory changes.

52. The formulation for use of item 51, wherein the inflammatory dermatological disease or condition is selected from the group consisting of dermatitis, contact dermatitis, acne, atopic dermatitis, eczema, pustular dermatitis, seborrheic dermatitis, perioral dermatitis, chronic wound, urticaria, skin ulcer, rosacea, rash, drug eruptions, toxic epidermal necrolysis;

erythema multiforme, erythema nodosum, granuloma annulare, and other cutaneous manifestations of inflammation.

53. The formulation for use of item 51, wherein the neoplastic and/or proliferative dermatological disease or condition is selected from the group consisting of basal cell carcinoma, preferably superficial basal cell carcinoma or nodular basal cell carcinoma; squamous cell carcinoma, preferably Morbus Bowen or invasive squamous cell carcinoma; vulvar intraepithelial neoplasia (VIN); cutaneous T-cell lymphoma; Merkel cell carcinoma; hemangioma; a nodular or subcutaneous cancer disease; field cancerization; non-melanoma skin cancer in organ transplant recipients; and prevention of non-melanoma skin cancer in organ transplant recipients.

54. The formulation for use of item 51, wherein the infectious dermatological disease or condition is selected from the group consisting of bacterial infections, viral infections, fungal infections, parasitic infections, and combinations thereof.

55. The formulation for use of item 51, wherein the autoimmune dermatological disease or condition, or the cutaneous manifestation of the autoimmune condition is selected from the group consisting of psoriasis, pemphigus, systemic lupus erythematodes, lichen planus, morphea, sclerodermia, epidermolysis bullosa, dermatomyositis, graft-versus-host syndrome.

56. The formulation for use of any one of the items 47-50, wherein the dermatological disease or condition is selected from the group consisting of disorders of sweating, pigmentation disorders including hypopigmentation such as vitiligo, albinism and post inflammatory hypopigmentation and hyperpigmentation such as melasma, reactions to sunlight, such as sunburn, skin ageing, photosensitivity, disorders of hair follicles and sebaceous glands such as hypertrichosis, alopecia, male pattern baldness.

57. The formulation of any one of the preceding items, for use in a method of photodynamic diagnosis of a neoplastic and/or proliferative dermatological disease or condition, such as benign or malignant neoplasia or precursors thereof; an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation such as acne.

58. A method for the preparation the formulation of any one of the items 1-57, 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.

59. The method of item 58, further comprising
    (i) adding a gelling agent, and/or
    (ii) adding a preservative.

60. A dispenser product, comprising the formulation of any one of the items 1-57.

61. A container, comprising the formulation of any one of the items 1-57.

62. Use of the formulation according to any one of the items 1-57, for the manufacture of a medicament for the treatment and/or prevention of a dermatological disease or condition in a subject.

63. A method of treatment and/or prevention of a dermatological disease or condition in a subject, said method comprising administering to the subject, a pharmaceutically effective amount of the formulation of any one of the items 1 to 57.

64. A method of photodynamic diagnosis of a neoplastic and/or proliferative dermatological disease or condition, such as benign or malignant neoplasia or precursors thereof; an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation such as acne, said method comprising

(i) administering the formulation according to any one of the items 1-57 to the skin area to be diagnosed, under conditions allowing synthesis of fluorescent porphyrins in the cells and/or tissues, and

(ii) irradiating the skin area to which the formulation was administered, under conditions inducing fluorescence of accumulated porphyrins,

wherein increased fluorescence of porphyrins indicates increased metabolic activity, being indicative for a neoplastic and/or proliferative dermatological disease or condition, an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation.

The invention also pertains to the following items:

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 item 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 items, wherein the formulation comprises essentially no propylene glycol.

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

5. The formulation of any of the preceding items, 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 items, 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 items, 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 items, 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 items, 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 items, 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 items, 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 items, wherein the active agent is a hydrophilic active agent.

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

14. The formulation of any one of the preceding items, 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 items, 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 items, 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 items, 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 items, 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 items, which is essentially free of parabens.

20. The formulation of any one of the preceding items, for use in medicine, in particular for use in a method of treatment and/or prevention of a dermatological disease or condition.

The present invention is further illustrated by the following figures and Examples.

Figure legends

Figure 1: Content of known impurity (2-hydroxypropyl-δ-aminolevulinate, m/z 190) and m/z 246-impurity in Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) after storage for 6 months at 25°C or 40°C.

Figure 2: Chromatograms of known impurity (2-hydroxypropyl-δ-aminolevulinate; m/z 190) and m/z 246-impurity in Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) after storage for 3 months at 40°C.

Figure 3: Skin penetration of Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) in ex vivo human skin. PpIX: protoporphyrin IX. Error bars indicate standard deviation.

Figure 4: Franz cell (top: scheme, bottom: photograph)

Figure 5: Release of 5-ALA from Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) after 2.5 hours (linear range of Higuchi plot). The values shown are the mean values from the experiment six-fold. The cumulative transport into the acceptor compartment is expresses as µg per cm^2 of membrane area against square root of time.

Examples

Example 1: Preparation of Nanoemulsions BF200, BF215 and BF220

Table 1: Lipophilic content of nanoemulsions used in the Examples

BF200	10% lipophilic content
BF215	15% lipophilic content
BF220	20% lipophilic content

The qualitative and quantitative compositions of the nanoemulsions BF200, BF215 and BF220 are given in **Table 2**.

Table 2: Composition of nanoemulsions BF200, BF215 and BF220

	Ingredient	**Content (% w/w) BF200**	**Content (% w/w) BF215**	**Content (% w/w) BF220**	**Function**	**Quality**
1	Soy lecithin	1.7	2.0-3.0	3.0-4.0	surfactant	>90% phosphadidylcholine, for pharmaceutical use, USP
2	Polysorbate 80 (polyoxyethylene sorbitol monooleate)	3.4	4.5-5.5	6.0-7.0	surfactant	Ph. Eur.
3	Caprylic/capric triglycerides	3.5	4.5-5.5	6.0-8.0	lipid core	Ph. Eur.
4	Isopropyl alcohol	1.4	2.0-3.0	2.0-4.0	solvent	Ph. Eur.
	Content (% w/w) ingredients 1-4	**10.0**	**15.0**	**20.0**		
	10 mM phosphate buffer, pH 6	ad 100.00	ad 100.00	ad 100.00	solvent	Water for injection: Ph. Eur.; Disodium phosphate and sodium hydrogen phosphate: Ph. Eur.

The manufacturing process for the nanoemulsions in a typical batch size consists of the following steps 1-4:

Step 1: Preparation of a 10 mM phosphate buffer (aqueous component)

10 mM phosphate buffer (1000 g), pH 6, was prepared and the phosphate buffer optionally sterilized by filtration through a sterile filter.

Step 2: Preparation of a carrier containing the lipophilic component, the surfactants and the alcohol

Table 3: Carrier component

Ingredient	***Weight (g)***
Soy lecithin	17
Polysorbate 80 (polyoxyethylene sorbitol monooleate)	34
Caprylic/capric triglycerides	35
Isopropyl alcohol	14

Soy lecithin (17 g) was weighed in a suitable vessel, isopropyl alcohol (14 g) was added and the vessel was covered to avoid alcohol evaporation. Soy lecithin was dissolved under continuous stirring with a suitable stirrer at room temperature. Caprylic/capric triglycerides (35 g) and Polysorbate 80 (34 g) were weighed and added to the solution of soy lecithin. The mixture was stirred with a suitable stirrer at room temperature until a homogenous clear solution was obtained. This solution is the carrier phase to be included in the nanoemulsion containing all emulsifiers and lipid components of the nanoemulsion BF200. According to this procedure BF215 and BF220 was prepared by adapting the amount of the components (see Table 2).

In all examples shown herein, nanoemulsion BF200 was used.

Step 3: Manufacturing of the nanoemulsion by mixing the aqueous component from Step 1 and the carrier from Step 2 for a lipid content of 10% (BF200)

Manufacturing of an emulsion by mixing 900 g phosphate buffer (from Step 1) and 100 g carrier (from Step 2). First, the aqueous component comprising the phosphate buffer was heated to approximately 45-60°C in a suitable vessel. Then, the carrier (concentrate) of step 2 was heated to approximately 45-60°C. Subsequently, the carrier was poured to the phosphate buffer under continuous stirring with a propeller mixer resulting in the formation of a stable trombe (or spout) having the maximal possible diameter without causing foaming or sputtering. The resulting nanoemulsion is stirred for 15 min. Finally, the nanoemulsion was cooled down to room temperature.

In nanoemulsion BF215, 850 g phosphate buffer (from Step 1) and 150 g carrier were mixed. In nanoemulsion BF220, 800 g phosphate buffer (from Step 1) and 200 g carrier were mixed.

Step 4: Preparation of the final formulation and primary packaging

Optionally, the nanoemulsion can be sterilized by filtration.

Depending on the purpose of the nanoemulsion, one may add adjuvants and/ or excipients and/or active ingredients (at the appropriate step according to the description) and/or dilute the nanoemulsion with in a way to get a suitable pharmaceutical formulation, e.g., by adding water, a suitable buffer, or an additional aqueous gel base with e.g. poloxamer 407 or xanthan gum.

The pharmaceutical formulations with different nanoemulsions BF200, BF215 and BF220 were filled into a conventional glass container or into a squeeze tube with an appropriate size, respectively.

Example 2: Preparation of gel Formulation 1, containing propylene glycol (comparative example)

Step 1: Preparation of Nanoemulsion

Nanoemulsion BF200 is produced according to Example 1. Sodium benzoate, 5-ALA and propylene glycol were added under stirring to nanoemulsion BF200.

Table 4: Composition of Nanoemulsion, based upon BF200

Component	**Nanoemulsion**	
	per 287.35 mg of emulsion	
BF200		
Soybean Phosphatidylcholine	3.00 mg	
Polysorbate 80	6.00 mg	
Triglycerides, medium chain (Miglyol 812)	6.00 mg	
Isopropyl alcohol	2.50 mg	
Disodium phosphate dihydrate	0.03 mg	
Sodium dihydrogen phosphate dihydrate	0.22 mg	
Purified water	**157.25 mg**	**175.00 mg**
Components added to BF200		
5-aminolevulinic acid hydrochloride	100.000 mg	
Propylene glycol	10.000 mg	
Sodium benzoate	2.35 mg	**112.350 mg**
		287.35 mg

Step 2: Preparation of gel base with Xanthan gum (XT).

A round bottom flask was disinfected with isopropanol. Water was put into the bowl and then Xanthan was spread thereon. The resulting basis gel was filled in an appropriate beaker.

Table 5: Composition of Gel base

Component	Gel base	
	per 712.65 mg of gel base	
Xanthan gum	28.50 mg	4.0%
Purified water	**684.15 mg**	96.0%

Step 3: Preparation of Formulation 1.

28.74% of the nanoemulsion produced in step 1 (including 17.5% of nanoemulsion BF200), and 71.26% of Xanthan gel base produced in step 2 are mixed and homogenized, resulting in Formulation 1.

Table 6: Components of gel Formulation 1 (nanoemulsion BF200, gel base, 5-ALA, propylene glycol), mg per g gel

Component	Formulation 1
	per 1 g of gel
5-aminolevulinic acid hydrochloride	100.000 mg
Xanthan gum	28.50 mg
Soybean Phosphatidylcholine	3.00 mg
Polysorbate 80	6.00 mg
Triglycerides, medium chain (Miglyol 812)	6.00 mg
Isopropyl alcohol	2.50 mg
Disodium phosphate dihydrate	0.03 mg
Sodium dihydrogen phosphate dihydrate	0.22 mg
Propylene glycol	**10.000 mg**
Sodium benzoate	2.350 mg
Purified water	**841.4 mg**

Formulation 1 was filled in a 2 g squeeze tube.

Example 3: Preparation of gel Formulation 2, free of propylene glycol

Step 1: Preparation of Nanoemulsion

Nanoemulsion BF200 is produced according to Example 1. Sodium benzoate and 5-ALA were added under stirring to nanoemulsion BF200. Formulation 2 is free of propylene glycol. In view of Formulation 1, the propylene glycol was replaced by the corresponding amount of xanthan gel base (10 mg/g, 1%).

Table 7: Composition of Nanoemulsion based upon BF200

Component	Nanoemulsion	
	per 277.35 mg of emulsion	
BF200		
Soybean Phosphatidylcholine	3.00 mg	
Polysorbate 80	6.00 mg	

Triglycerides, medium chain (Miglyol 812)	6.00 mg	
Isopropyl alcohol	2.50 mg	
Disodium phosphate dihydrate	0.03 mg	
Sodium dihydrogen phosphate dihydrate	0.22 mg	
Purified water	**157.25 mg**	**175.00 mg**
Components added to BF200		
5-aminolevulinic acid hydrochloride	100.000 mg	
Propylene glycol	0.000 mg	
Sodium benzoate	2.350 mg	**102.350 mg**
		277.35 mg

Step 2: Preparation of gel base with Xanthan gum (XT).

The gel based in produced as described in Step 2 of Example 1.

Table 8: Composition of Gel base

Component	**Gel base**	
	per 722.65 mg of gel base	
Xanthan gum	28.90 mg	4.0%
Purified water	**693.75 mg**	96.0%

Step 3: Preparation of Formulation 2.

27.74% of the nanoemulsion produced in step 1 (including 17.5% of nanoemulsion BF200), and 72.26% of Xanthan gel base produced in step 2 are mixed and homogenized, resulting in Formulation 2.

Table 9: Components of gel Formulation 2 (nanoemulsion BF200, gel base, 5-ALA), mg per g gel

Component	**Formulation 2**
	per 1 g of gel
5-aminolevulinic acid hydrochloride	100.000 mg
Xanthan gum	**28.90 mg**
Soybean Phosphatidylcholine	3.0 mg
Polysorbate 80	6.00 mg
Triglycerides, medium chain (Miglyol 812)	6.00 mg
Isopropyl alcohol	2.5 mg
Disodium phosphate dihydrate	0.03 mg
Sodium dihydrogen phosphate dihydrate	0.22 mg
Propylene glycol	**0.000 mg**
Sodium benzoate	2.350 mg
Purified water	**851.000 mg**

Formulation 2 was filled in a 2 g squeeze tube.

Example 4: Determination of vesicle size and polydispersity index by dynamic light scattering

The size of the nanovesicles, expressed as the z-average size (e.g., in nm), and the homogeneity of nanovesicle formulations, expressed as polydispersity index was determined by dynamic light scattering (sometimes referred as Photon Correlation Spectroscopy (PCS) or Quasi-Elastic Light Scattering (QELS)). The technique is well known in the art and well established to determine size of nano or micro particles or vesicles in emulsions, suspensions or polymeric solutions with a laser. Measurements were conducted with an Zetasizer Nano ZS (Malvern Instruments Ltd, Malvern, Worcestershire, UK). The measurement was performed according to the manufacturer's instructions.

The Zetasizer Nano ZS is instrumented with a 633 nm green laser and optics with a 173°scattering detector angle for size measurement. The device may be operated under vacuum for measurements, but in these cases, vacuum was not applied to the samples for size and homogeneity measurements.

Example 5: Determination of impurity

Qualitative and quantitative analysis of impurities was performed by LC-MS using positive electrospray ionisation (ESI+). The scan change covered degradation products in a range of 100-2000 m/z.

Example 6: Determination of viscosity

Viscosity was measured by rotation (measuring geometry: cone/plate) with a constant shear rate of 90.0 s^{-1} at 20°C.

Example A

Content of impurities in an 5-ALA nanoemulsion gel (compared with a comparative formation containing propylene glycol) after storage for 6 months

Formulation 1 (containing 1% propylene glycol) was prepared as described in Example 2. Formulation 1 (free of propylene glycol) was prepared as described in Example 3.

10-ml glass vials, containing either Formulation 1 or Formulation 2 were stored for six months at 25°C or 40°C.

Impurities were detected with mass spectroscopy, as described in Example 5.

The results are summarized in **Figure 1**. As expected, the ester of 5-ALA and propylene glycol (2-Hydroxypropyl-δ-aminolevulinate) is not present in Formulation 2 (without propylene glycol). An impurity with m/z=246 was found to be present in the comparative Formulation 1 (with propylene glycol) in a mean amount of about 0.3% after storage at 25°C and 1.2% after storage at 40°C. Unexpectedly, the impurity was found to be present in Formulation 2 (without of

propylene glycol) in a mean amount of about 0.15% after storage at 25°C and 0.6% after storage at 40°C.

This behavior is also illustrated in **Figure 2**. Chromatograms of known impurity (2-hydroxypropyl-δ-aminolevulinate; m/z 190) and impurity m/z 246 in Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) after storage for 3 months at 40°C.

Conclusion: A 5-ALA formulation, being free of propylene glycol, is safer / pharmaceutically more tolerable than a comparative 5-ALA formulation, containing propylene glycol.

Example B

Ex-vivo skin penetration study with human eye lid skin

Formulation 1 (with propylene glycol) was prepared as described in Example 2. Formulation 2 (without of propylene glycol) was prepared as described in Example 3.

Objective

- Comparison of skin penetration properties of Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol)
- Assess the amount of protoporphyrin IX (PpIX) in skin biopsy samples in fresh, vital skin samples after drug application.

Experimental set-up

Test material

- Human upper eyelid skin from routine blepharoplastic surgeries (eyelid tightening)
- Formulation 1 with propylene glycol (batch no. 166M, (1) in Figure 3)
- Formulation 2 without propylene glycol (batch no. 111M, (2) in Figure 3)

Methodology

- Incubation of skin explants with formulation for 0, 1, 3 h
- Cryosectioning, extraction of protoporphyrin IX from skin sections
- PpIX extraction from tissues and fluorimetric analysis of PpIX content in lysates

Results

The results are summarized in **Figure 3**.

- Means of n=5 plotted against (incubation) time
- PpIX concentrations increase with incubation time
- Although propylene glycol is a well-known penetration enhancer, equivalent penetration results were achieved with new Formulation 2 without propylene glycol compared to

comparative Formulation 1 with propylene glycol (the formulation without propylene glycol is non-inferior to formulation with propylene glycol).

- Differences between formulations at different time points were not statistically significant (Mann-Whitney's U-test)

Conclusion: A 5-ALA formulation, being free of propylene glycol, which is found to be more stable that a comparative 5-ALA formulation, containing propylene glycol (Example 1), provides equivalent penetration efficacy.

Example C

In vitro release test of 5-aminolevulinic acid from Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol)

Formulation 1 (with propylene glycol) was prepared as described in Example 2 (Batch 166M). Formulation 2 (without propylene glycol) was prepared as described in Example 3 (Batch 110M).

Objective

- Method development and evaluation of in vitro release (acc. to SUPAC-SS guideline (FDA, SUPAC, 1997)) of ALA from gel formulations (GMP GLP)

Experimental set-up

Test material

- Synthetic membranes (nylon, 0.20 µm)
- IVRT (in vitro release test) with so-called "Franz diffusion cell", **Figure 4**
- Formulation 1 with propylene glycol (comparative gel)
- Formulation 2 without propylene glycol

Methodology

- Analytical method for quantification of ALA: HPLC-MS/MS

Drug application, sampling and analysis

- Application of 300 mg ALA nanoemulsion to nylon membrane (0.20 µm)
- Incubation at 32 +-1 °C and sampling at t= 20, 40, 60, 90, 120, and 150 min
- n = 6 for each formulation (with/without propylene glycol) → 12 Franz cells
- HPLC-MS/MS for quantification of ALA in receptor compartiment

Results

The results are described in **Figure 5**:

- Higuchi plot (Takeru Higuchi 1961: "Rate of release of medicaments from ointment bases containing drugs in suspension" (DOI: 10.1002/jps.2600501018), cumulative transport of 5-ALA (in µg cm^{-2}), against square root of time (in $h^{-0.5}$).
- Transported amount is higher for Formulation 2 without propylene glycol
- The standard deviations two curves overlap completely.
- There is no significant difference between the two tested formulations

Statistical comparison of the slopes of the release curve:

Table 10:

Formulation 1	**Formulation 2**	**Limits of the 90% confidence interval**		
with propylene glycol	without propylene glycol	Lower Limit 8th value (0.75)	Upper-limit 29th value (1.33)	Significant difference
Batch 166M K27033 Test Item A	Batch 110M K27080 Test Item B	0.816	1.036	No

- There is no significant difference between the two tested formulations.
- The formulation without propylene glycol is to be considered at least as good as the formulation with propylene glycol in terms of drug release.

Conclusion: A 5-ALA gel formulation, being free of propylene glycol, which is found to be more stable that a comparative 5-ALA formulation, containing propylene glycol (Example 1), provides an equivalent in vitro release profile.

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	12/08/2023 12:07:49 PM Z ET	748419: BFR9-002

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Leslie Roberts
PATENT CENTER #	63542163	AUTHORIZED BY	James Velema
CUSTOMER #	12779	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Montserrat FOGUET

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 7127	E2023B8C08137727	Leslie Roberts

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
120600	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	140.00	1	140.00
1817	REQUEST FOR PRIORITIZED EXAMINATION	4200.00	1	4200.00
1111	UTILITY PATENT APPL. SEARCH FEE	700.00	1	700.00
1011	BASIC FILING FEE - UTILITY (PAPER FILING ALSO REQUIRES NON-	320.00	1	320.00

	ELECTRONIC FILING FEE UNDER 1.16(T))			
1051	SURCHARGE- LATE FILING FEE, SEARCH FEE, EXAMINATION FEE, INVENTOR'S OATH OR DECLARATION, OR APPLICATION FILED WITHOUT AT LEAST ONE CLAIM OR BY REFERENCE	160.00	1	160.00
1311	PATENT APPL. EXAMINATION FEE	800.00	1	800.00
			TOTAL AMOUNT:	**$6,320.00**

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If a new application is being filed and the application includes the necessary components for 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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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

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CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	James Velema

Documents

TOTAL DOCUMENTS: 6

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
748419_BFR9-002_ADS.pdf		8	Application Data Sheet	2174 KB
748419_BFR9-002_Patent_Application.pdf		60	-	379 KB
748419_BFR9-002_Patent_Application-SPEC.pdf	(1-55)	55	Specification	347 KB
748419_BFR9-002_Patent_Application-CLM.pdf	(56-59)	4	Claims	104 KB
748419_BFR9-	(60-60)	1	Abstract	115 KB

002_Patent_Application-ABST.pdf			
748419_BFR9-002_Figures.pdf	6	Drawings-other than black and white line drawings	4486 KB
748419_BFR9-002_Track_1_Request.pdf	2	Track One Request	120 KB

Digest

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New Applications Under 35 U.S.C. 111

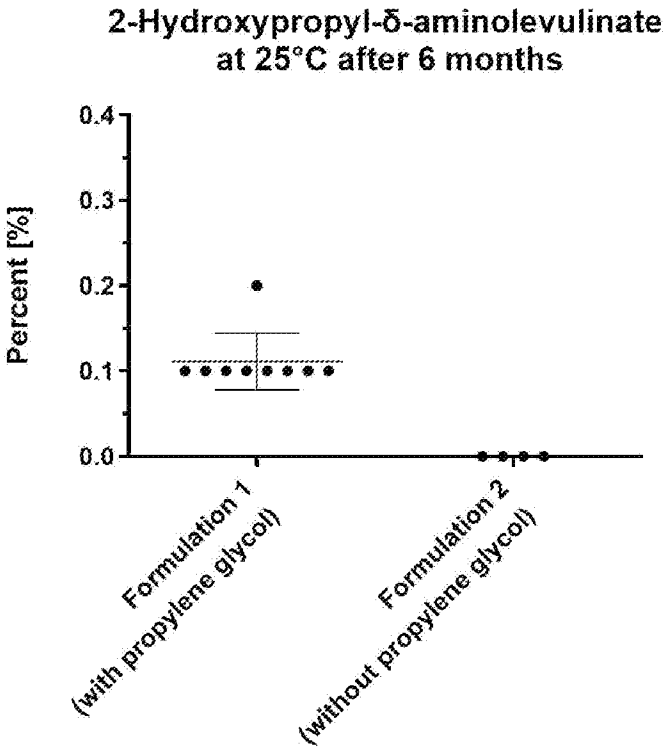
If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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New International Application Filed with the USPTO as a Receiving Office

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2-Hydroxypropyl-δ-aminolevulinate
at 25°C after 6 months
Percent [%]
0.4
0.3
0.2
0.1
0.0
Formulation 1
(with propylene glycol)
Formulation 2
(without propylene glycol)

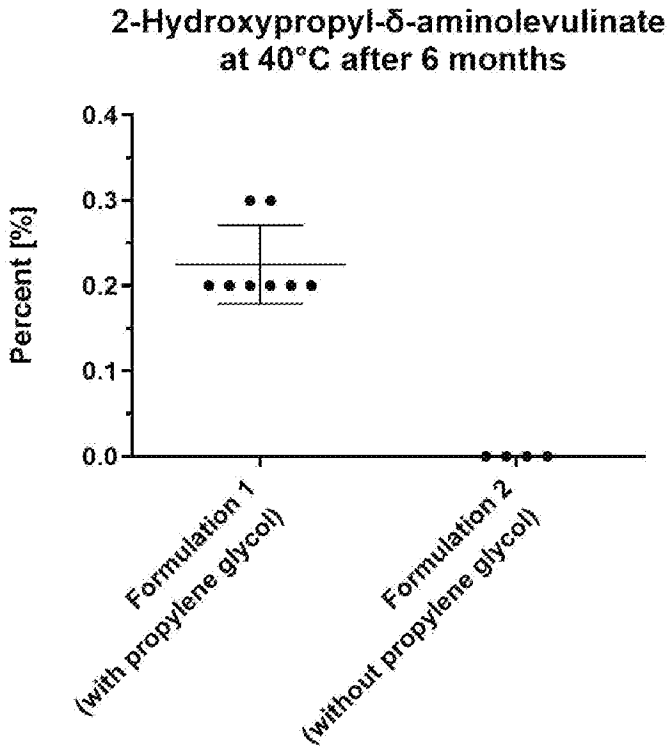

2-Hydroxypropyl-δ-aminolevulinate
at 40°C after 6 months
Percent [%]
0.4
0.3
0.2
0.1
0.0
Formulation 1
(with propylene glycol)
Formulation 2
(without propylene glycol)

Figure 1

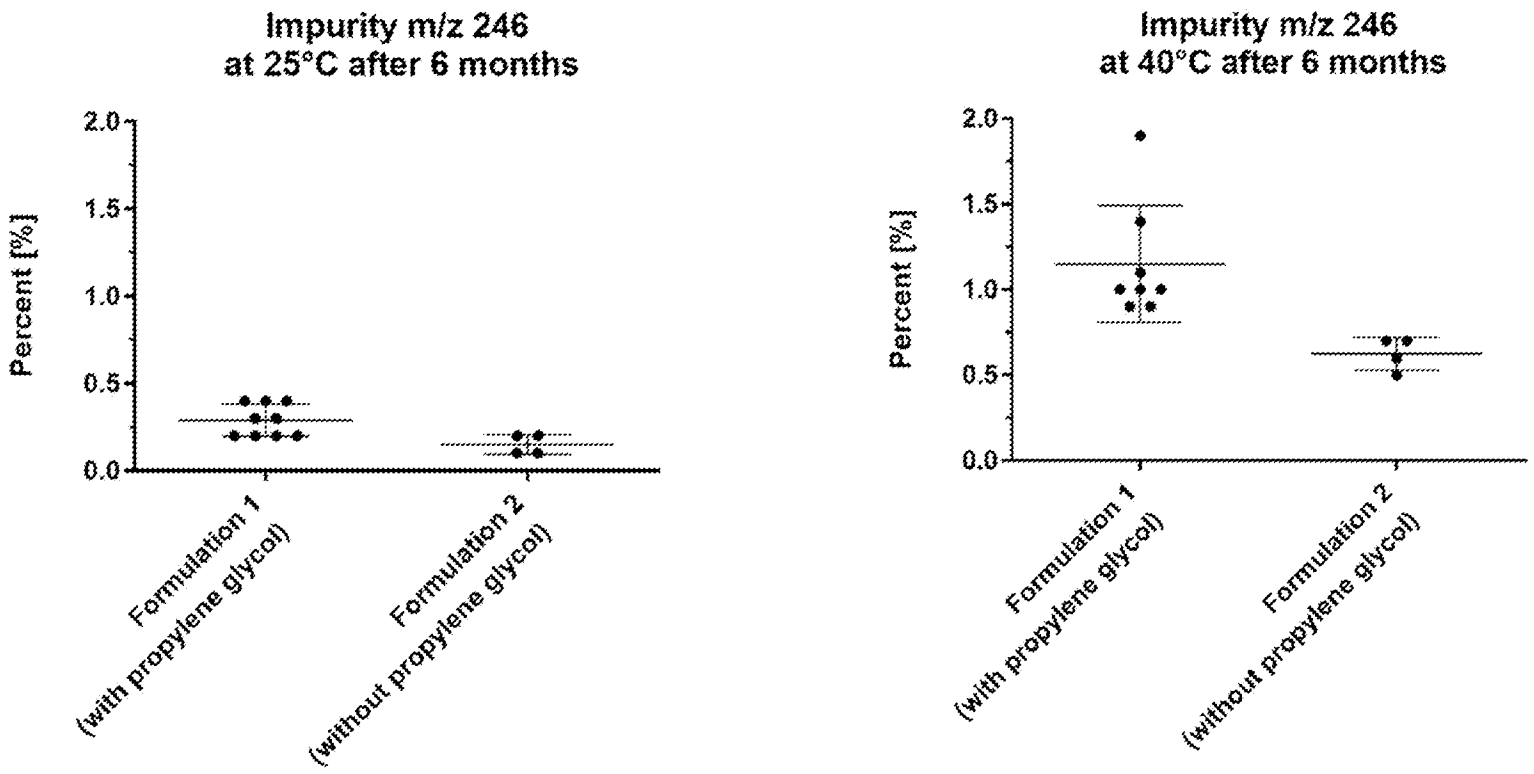


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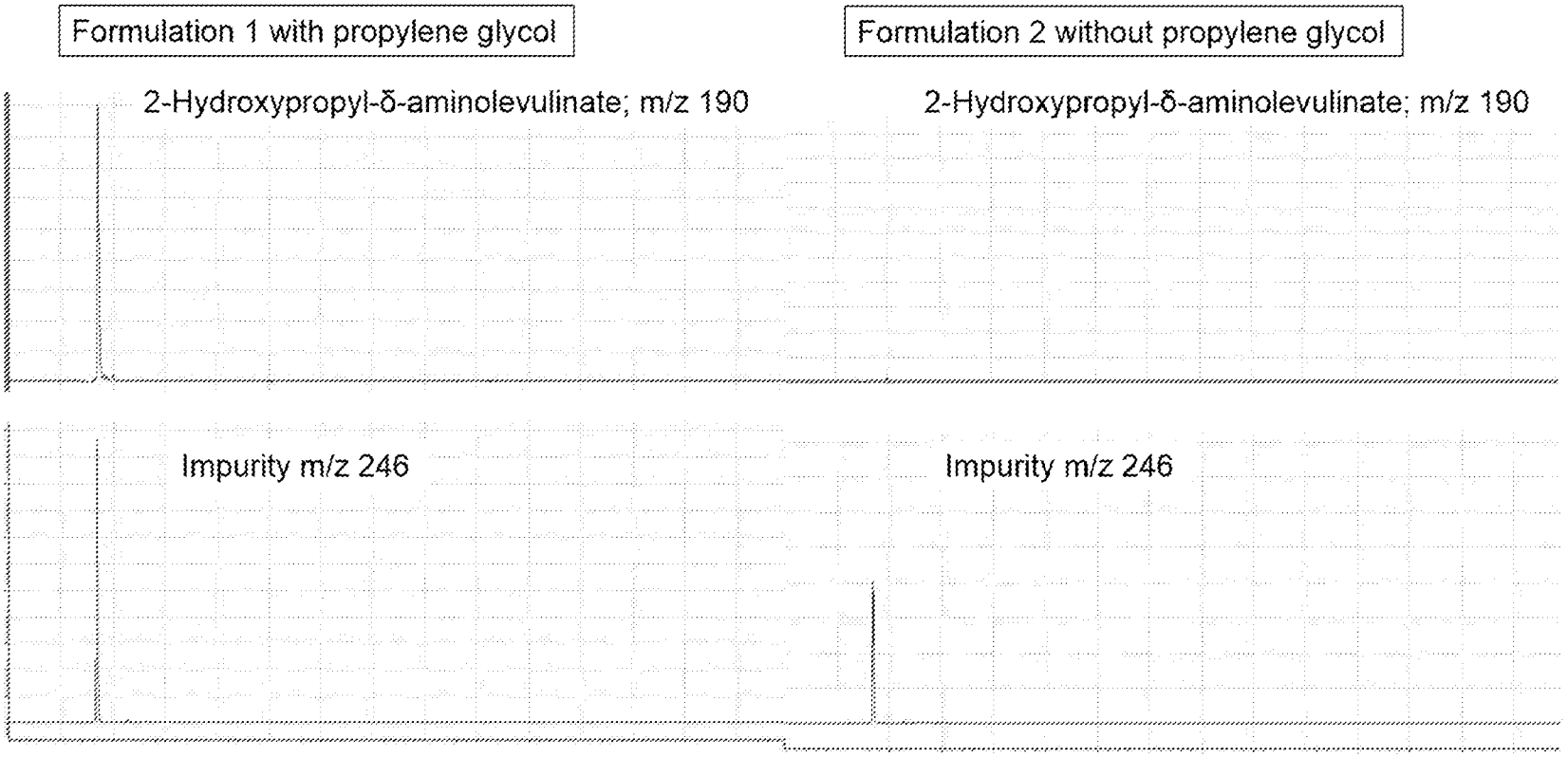

Formulation 1 with propylene glycol
Formulation 2 without propylene glycol
2-Hydroxypropyl-δ-aminolevulinate; m/z 190
2-Hydroxypropyl-δ-aminolevulinate; m/z 190
Impurity m/z 246
Impurity m/z 246

Figure 2

Figure 3

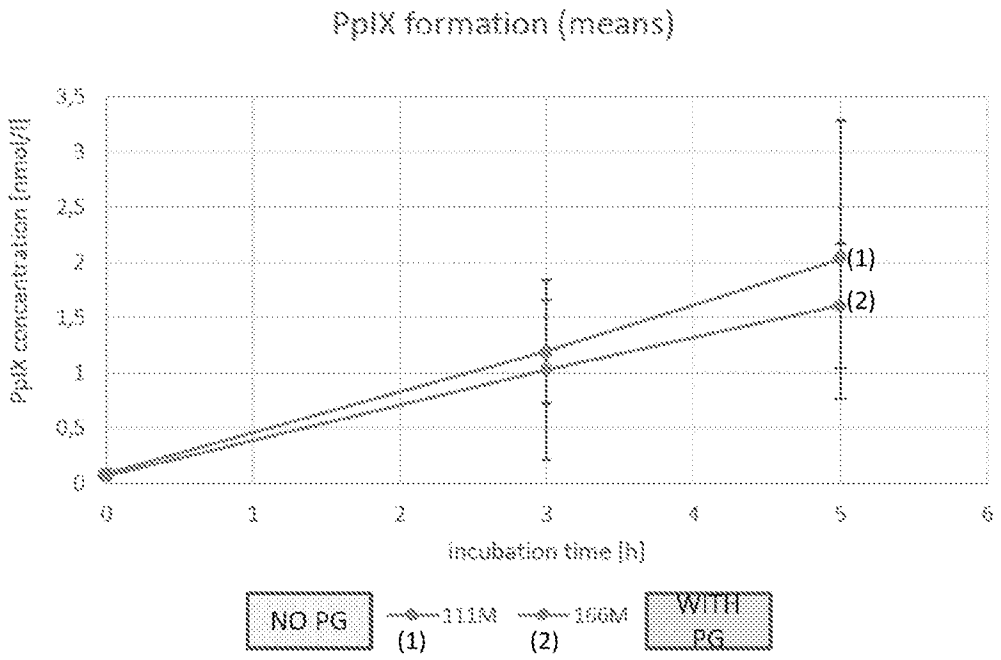
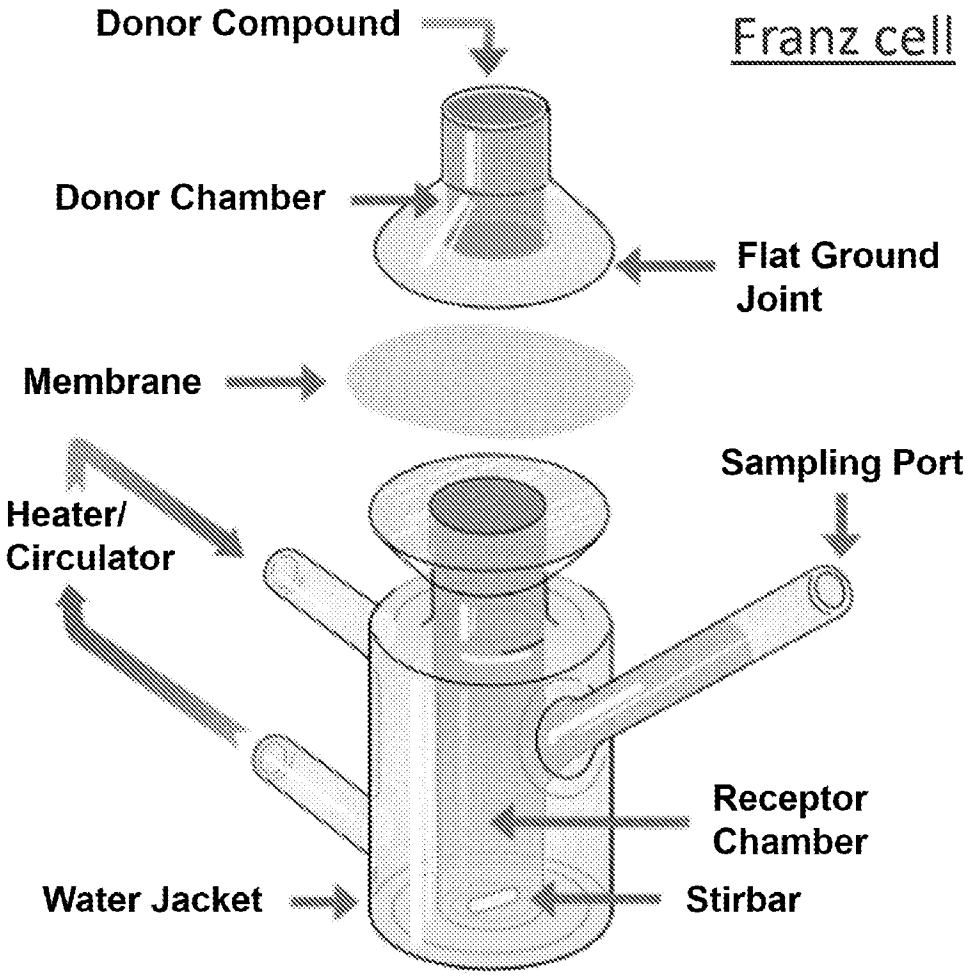
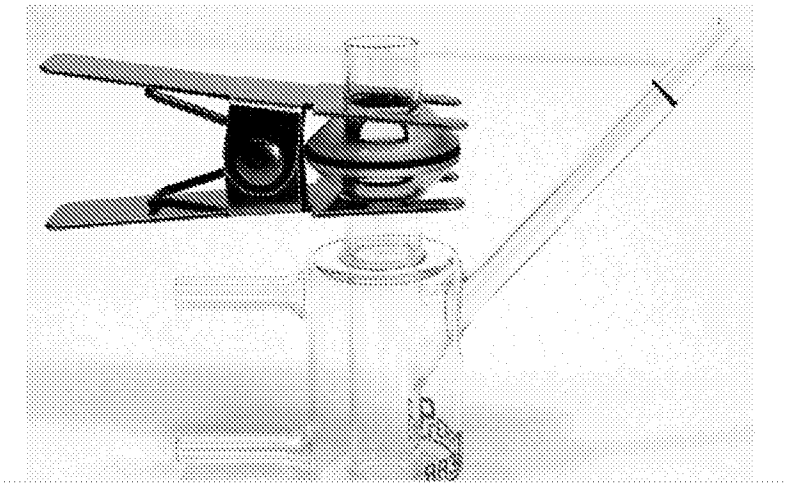

PpIX formation (means)
PpIX concentration [nmol/l]
3,5
3
2,5
2
1,5
1
0,5
0
0
1
2
3
4
5
6
incubation time [h]
(1)
(2)
NO PG
111M
166M
WITH PG

Figure 4


Donor Compound
Franz cell
Donor Chamber
Flat Ground Joint
Membrane
Sampling Port
Heater/ Circulator
Receptor Chamber
Water Jacket
Stirbar



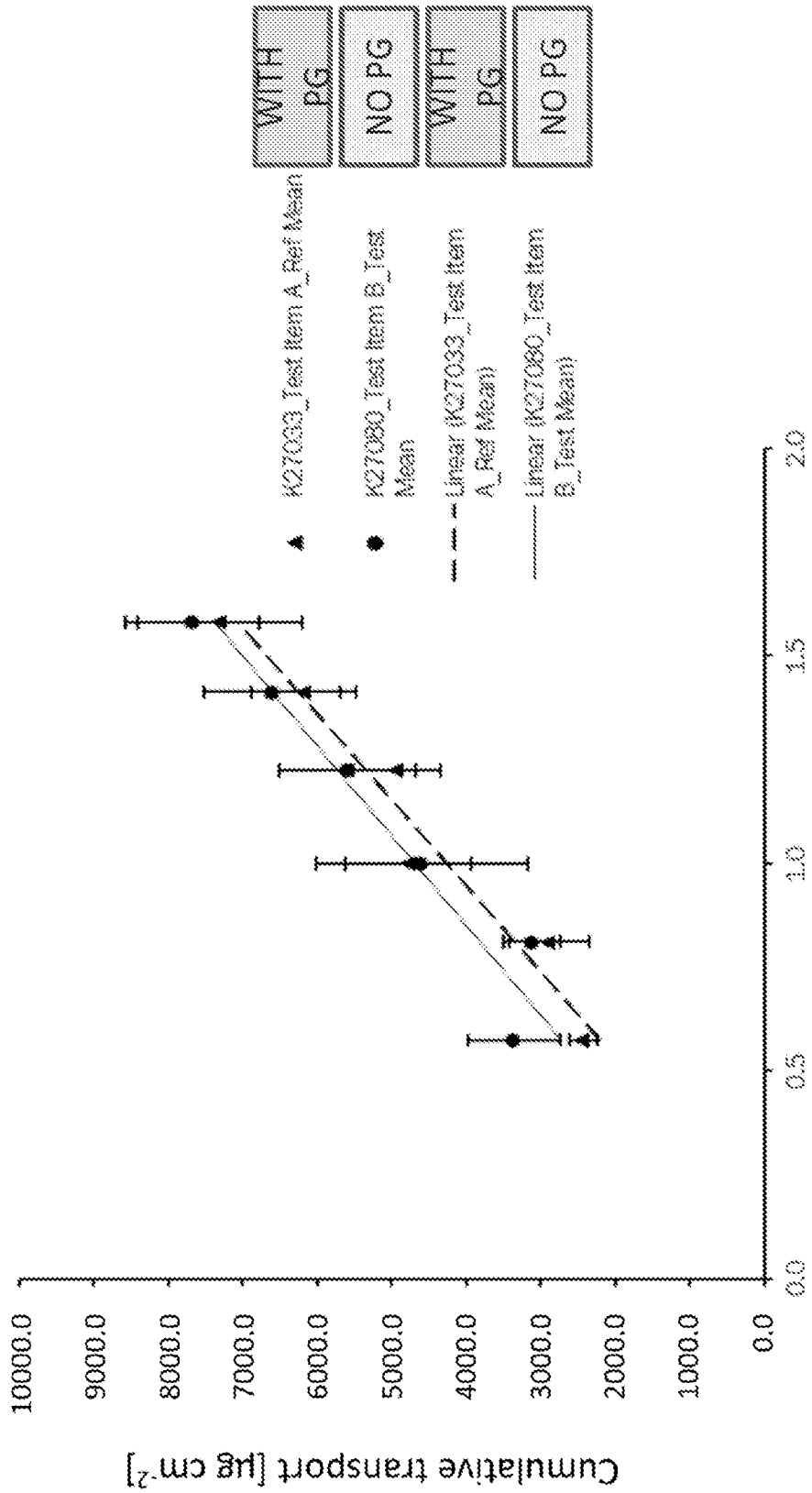

Cumulative transport [µg cm-2]
10000.0
9000.0
8000.0
7000.0
6000.0
5000.0
4000.0
3000.0
2000.0
1000.0
0.0
0.0
0.5
1.0
1.5
2.0
Square root of time [h 0.5]
K27033_Test Item A_Ref Mean
K27080_Test Item B_Test Mean
Linear (K27033_Test Item A_Ref Mean)
Linear (K27080_Test Item B_Test Mean)
WITH PG
NO PG
WITH PG
NO PG

Figure 5

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 claim 2, wherein the formulation comprises essentially no propylene glycol.

4. The formulation of claim 3, wherein the formulation comprises no propylene glycol.

5. The formulation of claim 4, 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 claim 5, 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 claim 1, 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;
   - 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; and/or

- 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.

8. The formulation of claim 1, 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).

9. The formulation of claim 1, 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).

10. The formulation of claim 1, wherein the active agent is a photosensitizer or a metabolic precursor thereof.

11. The formulation of claim 1, wherein the active agent is 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof.

12. The formulation of claim 1, 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.

13. The formulation of claim 1, 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.

14. The formulation of claim 1, 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.

15. The formulation of claim 1, 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.

16. The formulation of claim 1, which is essentially free of parabens.

17. A formulation comprising
    (a) a nanoemulsion comprising:
        (i) at least one aqueous component;
        (ii) a carrier component comprising:
            (4) at least one lipophilic component,
            (5) at least one surfactant, and
            (6) 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 active agent is a photosensitizer or a metabolic precursor thereof;
    wherein the formulation comprises essentially no propylene glycol.

18. The formulation of claim 17, wherein the active agent is 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof.

19. A formulation comprising
    (a) a nanoemulsion comprising:

(i) at least one aqueous component;

(ii) a carrier component comprising:

(7) at least one lipophilic component,

(8) at least one surfactant, and

(9) at least one alcohol; and

(b) 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

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

20. A method of treating a dermatological disease or condition, comprising administration of an effective amount of the formulation of claim 10 to a subject in need thereof.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	748419: BFR9-002
	Application Number	
Title of Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Montserrat		FOGUET	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Leverkusen	Country of Residence	DE

Mailing Address of Inventor:

Address 1	c/o Biofrontera Bioscience GmbH		
Address 2	Hemmelrather Weg 201		
City	Leverkusen	**State/Province**	
Postal Code	51377	**Country**	DE

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Lars		MÖLLMANN	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Leverkusen	Country of Residence	DE

Mailing Address of Inventor:

Address 1	c/o Biofrontera Bioscience GmbH		
Address 2	Hemmelrather Weg 201		
City	Leverkusen	**State/Province**	
Postal Code	51377	**Country**	DE

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	748419: BFR9-002
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Title of Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL	

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Customer Number	12779		
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Application Information:

Title of the Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL		
Attorney Docket Number	748419: BFR9-002	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	6	**Suggested Figure for Publication (if any)**	

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For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	748419: BFR9-002
	Application Number	
Title of Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL	

Domestic Benefit/National Stage Information:

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Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

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Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
PCT/EP2023/059291	EP	2023-04-06	

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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	748419: BFR9-002
	Application Number	
Title of Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

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NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	748419: BFR9-002
	Application Number	
Title of Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Biofrontera Bioscience GmbH		
Mailing Address Information For Applicant:			
Address 1	Hemmelrather Weg 201		
Address 2			
City	Leverkusen	**State/Province**	
Country	DE	Postal Code	51377
Phone Number		Fax Number	
Email Address			

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Assignee Information including Non-Applicant Assignee Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	748419: BFR9-002
	Application Number	
Title of Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

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Phone Number		Fax Number	
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See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/James H. Velema/			Date (YYYY-MM-DD)	2023-12-08
First Name	James	Last Name	Velema	Registration Number	56,130

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	748419: BFR9-002
	Application Number	
Title of Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL	

This collection of information is required by 37 CFR 1.76. 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 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

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Abstract

The present invention relates to oil in water nanoemulsions which are essentially free of propylene glycol. The nanovesicle formulations are particularly stable in regard to shelf life at different storage temperatures.

62898612v1

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/533,497

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	* 0			OR	x =	0
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x =	0
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1820

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

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Kathi Vidal

Kathi Vidal
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Derrick Brent
Deputy Under Secretary of Commerce for Intellectual Property and
Deputy Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002

CONFIRMATION NO. 6866

12779
Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

INFORMAL NOTICE

OC000000066134664

Date Mailed: 12/21/2023

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):

  Montserrat FOGUET
  Lars MÖLLMANN

  An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor must be submitted no later than the date on which the issue fee is paid in response to a notice requiring such fee. See 37 CFR 1.53(f).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/akidane/

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/533,497	12/08/2023		1980	748419: BFR9-002	20	3

CONFIRMATION NO. 6866

FILING RECEIPT

12779
Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

OC00000066134659

Date Mailed: 12/21/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Montserrat FOGUET, Leverkusen, GERMANY;
Lars MÖLLMANN, Leverkusen, GERMANY;

Applicant(s)

Biofrontera Bioscience GmbH, Leverkusen, GERMANY;

Power of Attorney: The patent practitioners associated with Customer Number 12779

Domestic Applications for which benefit is claimed - None.
A proper domestic benefit claim must be provided in an Application Data Sheet in order to constitute a claim for domestic benefit. See 37 CFR 1.76 and 1.78.

Foreign Applications (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) PCT/EP2023/059291 04/06/2023 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 12/20/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/533,497**

Projected Publication Date: 10/10/2024

Non-Publication Request: No

Early Publication Request: No
Title

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 01/18/2024

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
CENTRAL, DOCKET	

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
01/18/2024	ELECTRONIC

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):

bostonpatent@lathropgage.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 18/533,497	**Applicant(s)** FOGUET et al.	
	Examiner FIKIRTE A GEREMEW	**Art Unit** OMBL	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 08 December 2023 IS **GRANTED** .

   The above-identified application has met the requirements for prioritized examination
   - A. ☑ for an original nonprovisional application (Track I).
   - B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:
   - A. filing a **petition for extension of time** to extend the time period for filing a reply;
   - B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;
   - C. filing a **request for continued examination** ;
   - D. filing a notice of appeal;
   - E. filing a request for suspension of action;
   - F. mailing of a notice of allowance;
   - G. mailing of a final Office action;
   - H. completion of examination as defined in 37 CFR 41.102; or
   - I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to FIKIRTE GEREMEW at (703) 756-1930. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/FIKIRTE A GEREMEW/ PROGRAM SUPPORT ASSISTANT, OMBL	

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
18/533,497	2023-12-08

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 12779

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

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OR

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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Biofrontera Bioscience GmbH

☐ Inventor or Joint Inventor (title not required below)
☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)
☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)
☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	/ppa/	Date (Optional)	14. December 2023
Name	Manfredi Fagnet / Wiebke Meyer-Wirth		
Title	Managing Director / Vice President Quality Management		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL

As the below named inventor, I hereby declare that:

This declaration is directed to.

☐ The attached application, or

☒ United States application or PCT international application number 18/533,497

filed on December 8, 2023.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

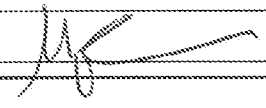
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Montserrat FOGUET Date (Optional): 14 December 2023

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0032. Public burden for this form is estimated to average 1 minute per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.** If filing this completed form by mail, send to: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Title of Invention	NANOEMULSION WITHOUT PROPYLENE GLYCOL

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 18/533,497

filed on December 8, 2023

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

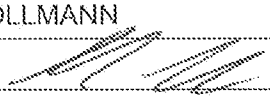
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Lars MÖLLMANN Date (Optional): 14.12.2023

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0032. Public burden for this form is estimated to average 1 minute per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.** If filing this completed form by mail, 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.

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P.O. Box 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**01/26/2024 12:06:27 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Leslie Roberts
PATENT CENTER #	64099687	FILING DATE	12/08/2023
CUSTOMER #	12779	FIRST NAMED INVENTOR	Montserrat FOGUET
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	James Velema

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
748419_BFR9-002_Executed_Declarations.pdf	2	Oath or Declaration filed	2448 KB
748419_BFR9-002_Executed_POA.pdf	1	Power of Attorney	1445 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
748419_BFR9-002_Executed_Declarations.pdf	86A3BAC28144BAD341BC208C79FCEA9BAA7C857CF1C18A832BCE457BEEB389A162095967CA2CF1FB58C89B3FD85B82E9719587FB743668F5EE9A005D2D9D1B57

748419_BFR9-002_Executed_POA.pdf

A200A96BA305B2BB0AD01442C8F613886BEB2761580C7AF02667B1263C24612BD165A2B0580F31E8978E9A34EDC1A2B4FB2C00C7747DB107F8837EBD852031E5

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 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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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002

CONFIRMATION NO. 6866

12779
Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

POA ACCEPTANCE LETTER

OC000000067893088

Date Mailed: 02/07/2024

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/26/2024.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/cnguyen/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 02/12/2024

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
02/12/2024	ELECTRONIC

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):

bostonpatent@lathropgage.com

Office Action Summary	Application No. 18/533,497	Applicant(s) FOGUET et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	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 2 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 08 December 2023.

☐ 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) 1-20 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) _____ is/are rejected.

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

9) ☑ Claim(s) 1-20 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 _____.

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

4) ☐ Other: _____.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-16, drawn to a nanoemulsion comprising less than 1 % propylene glycol, classified in A61K9/1075.

II. Claims 17-18, drawn to a nanoemulsion comprising essentially no propylene glycol, classified in A61K9/127.

III. Claim 19, drawn to a nanoemulsion comprising less than 1 % propylene glycol and 5-aminolevulinic acid, classified in A61K41/0061.

IV. Claim 20, drawn to a method of treating a dermatological disease or condition, classified in A61K47/110.

The inventions are independent or distinct, each from the other because:

Inventions I-III are directed to related products. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed can have a materially different design, mode of operation, function, or effect. For example, Inventions III requires 5-aminolevulinic acid, which is not required of Inventions I and II; Invention II excludes propylene glycol, which is not excluded by Inventions I and III. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Inventions I-III and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the product as claimed can be used in a materially different process. For example, nanoemulsions can be used in processes of treating tumors.

Restriction for examination purposes as indicated is proper because all the inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

1. The inventions have acquired a separate status in the art in view of their different classification.

2. The inventions have acquired a separate status in the art due to their recognized divergent subject matter.

3. The inventions require a different field of search (e.g., searching different classes /subclasses or electronic resources, or employing different search strategies or search queries).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancelation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

Notice of Potential Rejoinder

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained.

Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A RONEY whose telephone number is (571)272-5192. The examiner can normally be reached Monday-Friday; 8 AM-6 PM.

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, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

REMARKS

Claims 1-20 are pending. Group III (Claim 19) has been elected. Claims 1-18 have been cancelled. Claims 19 and 20 have been amended. Claims 21-26 are newly added. Support for the new claims can be found in the application as originally filed. There is no new matter.

Restriction Requirement

At page 2 of the Restriction Requirement, the Examiner requires Applicant to elect one of the following inventions under 35 U.S.C. § 121:

Group I. Claims 1-16 identified by the Office Action as being drawn to a nanoemulsion comprising less than 1% propylene glycol.

Group II. Claims 17 and 18, identified by the Office Action as being drawn to a nanoemulsion comprising essentially no propylene glycol.

Group III. Claim 19, identified by the Office Action as being nanoemulsion comprising less than 1% propylene glycol and 5-aminolevulinic acid.

Group IV. Claim 20, identified by the Office Action as being drawn to a method of treating a dermatological disease or condition.

In response, Applicant hereby elects **Group III**, *without traverse*. Claim 19 encompasses the elected invention.

Applicant expressly reserves the right to pursue any nonelected group or groups in this or one or more divisional applications claiming priority to this application.

CONCLUSION

An election of claims has been made herein and the Applicant submits that the application is in condition for examination and allowance, which is respectfully requested.

If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is invited to call Applicant's attorney at (312) 920-3357.

Dated: April 12, 2024

Respectfully submitted,

Electronic signature: /Laura A. Labeots/

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UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**04/12/2024 05:27:43 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Leslie Roberts
PATENT CENTER #	65078769	FILING DATE	12/08/2023
CUSTOMER #	12779	FIRST NAMED INVENTOR	Montserrat FOGUET
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Laura Labeots

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
748419_BFR9-002_Response_to_Restriction_Requirement.pdf		5	-	143 KB
748419_BFR9-002_Response_to_Restriction_Requirement-ELC..pdf	(1-1)	1	Response to Election / Restriction Filed	97 KB
748419_BFR9-002_Response_to_Restriction_Requirement-CLM.pdf	(2-3)	2	Claims	96 KB
748419_BFR9-002_Response_to_Restriction_Requirement-REM.pdf	(4-5)	2	Applicant Arguments/Remarks Made in an Amendment	119 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
748419_BFR9-002_Response_to_Restriction_Requirement.pdf	00F40D56B4CDE3923AD256A6109863632EFFC0EDD9D4765956EAB5637A16C67094EEADD9982F7325784F0E145CC857DC938A34B8A7956345FEF826B424C971A8
748419_BFR9-002_Response_to_Restriction_Requirement-ELC..pdf	CBF6604E5ABCC5A382FC1910E1420833516F09843CEB4353B36CFF60BE35328290F688799DA33AC5AB644321D7DC637E153F9DD0F745E5122A612C5C4687AE8B
748419_BFR9-002_Response_to_Restriction_Requirement-CLM.pdf	38FECDDD6E318E5F8521D7A1BD4144FF9BF52F6AC346593AD05884762C6BDA8A9C4F39FAC8B52E1CCAB9C621D643D8080DEAECC7E7B0CBB304823B7AED8AE9A8
748419_BFR9-002_Response_to_Restriction_Requirement-REM.pdf	F407F4EDF7D5F42C43ED10AA77840A50A3E7B92B8F7887535D75AFB2606BC19B57425C1BD7C65873FEAA696DDA801936009F9F7FC53A82C7CB9CA23783C4CF07

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 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Biofrontera Bioscience GmbH	Confirmation No.: 6866
Application No.: 18/533,497	Art Unit: 1612
Filed: December 8, 2023	Examiner: Roney, Celeste A.

Title: NANOEMULSION WITHOUT PROPYLENE GLYCOL

Via Patent Center
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT
AND PRELIMINARY AMENDMENT

Dear Commissioner:

This paper is filed in response to the Restriction Requirement having a mailing date of February 12, 2024. As this response is timely filed on April 12, 2024, Applicant believes no fees are due in connection with the filing of this Response. However, the Office is authorized to charge any additional fees deemed necessary in connection with this paper, or credit any overpayment, to Deposit Account No. 12-0600, Attorney Docket No. 748419: BFR9-002.

Amendments to the Claims begin on page 2.
Remarks begin on page 4.

AMENDMENTS TO THE CLAIMS

1-18. **(Cancel)**

19. **(Currently Amended)** A formulation comprising:

(a) a nanoemulsion comprising:

(i) at least one aqueous component;

(ii) a carrier component comprising:

~~(7)~~ (1) at least one lipophilic component,

~~(8)~~ (2) at least one surfactant, and

~~(9)~~ (3) at least one alcohol; and

(b) 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

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

20. **(Currently Amended)** A method of treating a dermatological disease or condition, comprising administration of an effective amount of the formulation of claim [[10]]19 to a subject in need thereof.

21. **(New)** The formulation of claim 19, wherein the formulation comprises less than 0.9% w/w of propylene glycol.

22. **(New)** The formulation of claim 19, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms; 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; essentially no non-cyclic polyol having 2 to 5 carbon atoms; or no non-cyclic polyol having 2 to 5 carbon atoms.

23. **(New)** The formulation of claim 19, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms; 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 12 carbon atoms; essentially no non-cyclic polyol having 2 to 12 carbon atoms; or no non-cyclic polyol having 2 to 12 carbon atoms.

24. (**New**) The formulation of claim 19, wherein:

the at least one alcohol comprises at least 3 carbon atoms; 3, 4 or 5 carbon atoms; or 1-propanol, 2-propanol, or mixtures thereof;

the at least one lipophilic component comprises triglycerides and/or mixtures thereof; or a caprylic, and/or a capric triglyceride, or a mixture thereof; and/or

the at least one surfactant comprises a phospholipid, a phosphatidylcholine, a lysophospholipid, a ceramide, a mixture thereof; and/or a polyoxyethylene-type surfactant.

25. (**New**) The formulation of claim 19, comprising an at least one aqueous component in an amount from 50% to 99% (w/w), from 70% to 95% (w/w), from 75% to 95% (w/w), or from 80% to 90% (w/w).

26. (**New**) The formulation of claim 24, comprising:

(a) the at least one lipophilic component in an amount from 0.1% to 30% (w/w), from 0.25% to 15% (w/w), from 0.25% to 10% (w/w), 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), from 0.5% to 5% (w/w), from 1% to 5% (w/w), or from 1% to 3%,

based on total weight of the nanoemulsion.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/011404

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/107 A61K9/12 A61K31/195 A61K47/10 A61K47/44

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 165 500 A (CEVC GREGOR [DE]) 26 December 2000 (2000-12-26) column 8, line 27 - line 31 column 9, line 41 - line 51 column 5, line 51 - line 65 column 3, line 6 - line 29	1-63
X	US 2002/155084 A1 (ROESSLER BLAKE J [US] ET AL) 24 October 2002 (2002-10-24) paragraphs [0004], [0006], [0039], [0041], [0044], [0069] - [0075], [0083], [0089], [0090], [0095], [0098], [0101], [0108], [0193]; claim 1	1-63

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2008	09/05/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giese, Hans-Hermann

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/011404

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/208083 A1 (ANNIS THEODORE C [US]) 22 September 2005 (2005-09-22) paragraphs [0008], [0009], [0029] - [0031], [0044], [0060] - [0067], [0076] - [0081]; claims 81-88,114	1-63
X	US 2005/158389 A1 (DOMB ABRAHAM J [IL]) 21 July 2005 (2005-07-21) paragraphs [0009] - [0014], [0025], [0037], [0044] - [0046], [0048]; claims 1,4,10,15	1-63
X	WO 2005/027872 A (NANOBIO CORP [US]; BAKER JAMES R [US]; ANNIS TED C [US]; HAMOUDA TAREK) 31 March 2005 (2005-03-31) paragraph [0034]; claims 1-6,27,41-33,36	1-63
X	EP 0 620 271 A (COLGATE PALMOLIVE CO [US]) 19 October 1994 (1994-10-19) page 2, line 9 - line 17; claim 1	60
X	WO 02/066589 A (COLGATE PALMOLIVE CO [US]) 29 August 2002 (2002-08-29) page 12, line 15 - line 23; claim 1	60
A	EP 1 655 021 A (NOVAGALI PHARMA SA [FR]) 10 May 2006 (2006-05-10) paragraphs [0008] - [0017], [0025], [0043], [0044]; claims 1-4,8,12	1-63
A	US 2006/140984 A1 (TAMARKIN DOV [IL] ET AL) 29 June 2006 (2006-06-29) paragraphs [0024], [0088], [0172] - [0216], [0240], [0262], [0281], [0285]; claim 1	1-20, 29-34

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/011404

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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 35, 36, 38, 58, 59 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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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 and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/011404

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6165500 A	26-12-2000	JP 3765579 B2	12-04-2006
		JP 2006052226 A	23-02-2006
US 2002155084 A1	24-10-2002	WO 0191728 A2	06-12-2001
US 2005208083 A1	22-09-2005	NONE	
US 2005158389 A1	21-07-2005	NONE	
WO 2005027872 A	31-03-2005	AU 2004273779 A1	31-03-2005
		CA 2528095 A1	31-03-2005
		EP 1633322 A2	15-03-2006
EP 0620271 A	19-10-1994	AU 675500 B2	06-02-1997
		AU 5948094 A	20-10-1994
		BR 9401481 A	18-10-1994
		CA 2117274 A1	15-10-1994
		CN 1093743 A	19-10-1994
		HU 66866 A2	30-01-1995
		JP 6330098 A	29-11-1994
		NZ 260307 A	28-03-1995
		PT 101489 A	04-05-1995
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2007/011404	21.12.2007	22.12.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/107 A61K9/12 A61K31/195 A61K47/10 A61K47/44

Applicant
BIOFRONTERA BIOSCIENCE GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Giese, Hans-Hermann Telephone No. +49 89 2399-8488

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☐ claims Nos.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	33-34,37,52-59
	No:	Claims	1-20,22-32,35,36,38-51,60-63
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-63
Industrial applicability (IA)	Yes:	Claims	1-63
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Claims 35, 36, 38, 58, 59 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.

Re Item V

The application concerns nanoemulsions having (a) an aqueous component and (b) a carrier, the latter comprising (i) a lipophilic component, (ii) a surfactant, (iii) an alcohol characterised in that at least one alcohol has at least three carbon atoms. Further, the active agent 5-aminolevulinic acid is mentioned and various uses and methods target at various diseases.

1. Reference is made to the following documents:

   D1: US 61 655 00
   D2: US 2002 166 084
   D3: US 2005 208 083
   D4: US 2005 158 389
   D5: US 2005 027 872
   D6: EP 0 620 271
   D7: WO 02/066589

2. **Patentability**

   Claims 35, 36, 38, 58, 59 relate to a subject-matter considered by the Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. However, the patentability of these claims is inter alia dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT. Their assessment will be carried out based on the alleged effects of the compounds/compositions searched in the International Search Report.

3. **Novelty**

   The independent claim 60 defines a nanoemulsion and an active agent. The monolayer of the active agent around the particles of the nanoemulsion constitutes a

result to be achieved and part of the claimed solution of the posed problem as explained on page 13, lines 18-21 (Art. 6 PCT, Guidelines 5.35 PCT) . Therefore, this features has not been considered. Consequently, search has resulted in an overflow of documents disclosing a nanoemulsion and an active agent. D6 and D7 are mentioned as examples.

Document D1 (see citations in the search report) discloses aqueous compositions for active agents in nanoemulsion with very small liq. droplets comprising a surfactant or the polyoxyethylene type, a phospholipid, a solvent selected from iso-propanol, iso-butanol or iso-pentanol and furthermore agents for therapeutic purposes such as delta-aminolevulinic acid.
Therefore, subject-matter of independent claims 1, 12, 13, 14, 17, 19, 22, 25, 38, 39, 45, 46, 49, 60, 62, 63 appears not to be novel (Art 33(2) PCT).

Document D2 (see citations in the search report) discloses nanoemulsions which are prepared by dispersing an oil (soybean oil, suflower oil, fish oil or rape oil) in an aqueous surfactant (polyoxyethylene-20) solution, adding the fourth component short chain-length alcohol (butanol, pentanol, or hexanol), The nanoemulsions deliver a biological agent to a subject for treating any type of disease including cancer etc..
Therefore, subject-matter of independent claims 1, 12, 13, 14, 17, 19, 22, 25, 29, 35, 36, 38, 60, 62, 63 appears not to be novel (Art 33(2) PCT).

Document D3 (see citations in the search report) describes nanoemulsions which comprise an aqueous phase and an oil phase comprising soybean oil, fish oil or sunflower oil, an organic solvent such as isopropyl alcohol and a polyoxyethylene-type surfactant such as TWEEN(R)-20. The therapeutic agent is an antimicrobial agent, an antifungal agent, an antiviral agent, an anti-mold agent, an anti-mildew agent for treating papilloma virus, inflammatory disease (psoriasis).
Therefore, subject-matter of independent claims 1, 12, 13, 14, 17, 19, 22, 25, 38, 60, 62, 63 appears not to be novel (Art 33(2) PCT).

Document D4 (see citations in the search report) discloses a microemulsion delivery system for pharmaceutical compounds for example for the treatment of cancer,

comprising an aqueous phase, a hydrophilic solvent, a surfactant of polyethylene glycol-type, soy/egg phospholipids or lecithin, a biologically active agent and solid component which can be fatty alcohol.
Therefore, subject-matter of independent claims 1, 12, 13, 14, 17, 19, 29, 35, 36, 38, 60, 62, 63 appears not to be novel (Art 33(2) PCT).

Document D5 (see citations in the search report) discloses nonanoemulsion comprising an aqueous phase, an oil phase comprising soybean, rapeseed, sunflower, fish oil, an organic solvent (such as isopropanol) and one or more surfactants (such as the nononic surfactant polyethylene ether). The nanoemulsion further has a therapeutic agent for treating papilloma virus.
Therefore, subject-matter of independent claims 1, 12, 13, 14, 17, 19, 22, 38, 60, 62, 63 appears not to be novel (Art 33(2) PCT).

Document D6 (see citations in the search report) discloses microemulsions comprising a lipophile, a surfactant, a cosurfactant and water. They are a thermodynamically stable phase in which the micelles have a particle size of less than 100nm (nanometers). Polyethylene glycol as a a nonionic detergent is present as well as 1 to 40% of an anionic organic surface active agent.
Therefore, subject-matter of independent claim 60 and insofar as they refer to claim 60 also claims 62, 63 appears not to be novel (Art 33(2) PCT).

Document D7 (see citations in the search report) discloses microemulsions having a particle size between 10 and 100 nanometers and the active agent is a softening active compound.
Therefore, subject-matter of independent claims 60 and insofar as they refer to claim 60 also claims 62, 63 appears not to be novel (Art 33(2) PCT).

4. **Inventive Step** (Article 33(3) PCT)

4.1. The problem to be solved in present application was to provide a nanoemulsion with improved stability as well as improved penetration into cells and tissues. The solution

proposed by the present application is a nanoemulsion comprising an aqueous phase and a carrier comprising a lipophilic component, a surfactant and at least one alcohol having at least three carbon atoms (see the application document on page 2, l. 29 to page 3, l. 13).

4.2. The documents D1, D2, D3, D4 or D5 also address the problem of stability and solve the problem with the nanoemulsions as defined in the present claims. Therefore, the independent product claims are not inventive (Article 33(3) PCT).

4.3. The claims 20-35 defines the use of a nanoemulsion as anti-aging agent, for the treatment of a virus-associated disease or a dermatological disease or a disease associated with cell proliferation or in the photodynamic therapy or the detection of proliferating cells or the diagnosis of dermatological and/or tumor diseases.
The respective uses have been either disclosed in the cited documents or it would be obvious for the skilled worker to administer such nanoemulsions for known purposes also for other purposes.

4.4. The same applies for method claim 37 and further use claims 45-58 (Article 56 EPC).

4.5. The documents D2 and D3 teach that the disclosed nanoemulsions are used for delivering biological agents to a subject for treating or preventing any type of disease (D2 see for example §108, 193; D3 see for example §§77-81). Therefore, also in light of documents D2 and D3 the present use claims 20-35 and 45-58 are not inventive (Article 56 EPC).

4.6. The dependent claim do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see documents D1 to D5 and the corresponding passages cited in the search report.

4.7. The applicant has failed to provide proves (e.g. examples) that the nanoemulsions cause a surprising effect or an unexpected advantage in such treatments or therapies in order to support an inventive step (Article 33(3) PCT).

Therefore, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of present claims 1-63 does not involve an inventive step in the sense of Article 33(3) PCT.

Re Item VII

As required by Rule 5.1(a)(ii) PCT, it is appropriate to identify the relevant documents and to discuss the relevant background art disclosed therein briefly (see also the Guidelines II, 4.4 PCT).

Re Item VIII

1. Claims 1, 12, 13, 16, 36, 38, 44, 59, 61 have been drafted as separate independent product claims, claims 11, 18, 37 as separate independent process/method claims and claims 20, 21, 24, 28, 32, 34, 35, 45,48, 51, 55, 57, 58, 62 as separate independent use claims.
   Under Article 6 PCT an application may contain more than one independent claim in a particular category. The Applicant is kindly asked to provide a well-founded reasoning and/or redraft the independent claims creating dependencies.

2. The subject-matter of claim 1 does not fulfil the requirements of Art. 6 PCT because the feature (iii) at least one alcohol does not exclude ethanol (see the application document page 2, lines 13+14 and line 29 to page 3, line 12).

3. The subject-matter of claims 21 and 22 does not fulfil the requirements of Art. 6 PCT because the "nanoemulsions of any of claims 1 to 11" do not comprise an active agent and therefore appear not to have anti-aging or anti-virus properties.

4. The statements with regard to independent claim 60 (see above) are also valid for claim 43 (Art. 6 PCT, Guidelines 5.35 PCT).

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**04/15/2024 08:00:24 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Allison Douglas
PATENT CENTER #	65103325	FILING DATE	12/08/2023
CUSTOMER #	12779	FIRST NAMED INVENTOR	Montserrat FOGUET
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	James Velema

Documents

TOTAL DOCUMENTS: 34

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
748419_BFR-002_Transmittal-Ltr_JHV.pdf	2	Transmittal Letter	107 KB
748419_BFR-002_IDS-SB08.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	199 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
EP0704209A1_FOR.pdf	9	Foreign Reference	632 KB
JP2002302414A_FOR.pdf	9	Foreign Reference	810 KB
EP1655021A1_FOR.pdf	18	Foreign Reference	1068 KB

JP2006273821A_FOR.pdf	11	Foreign Reference	675 KB
WO1997041855A1_FOR.pdf	28	Foreign Reference	1798 KB
WO2002066589A2_FOR.pdf	24	Foreign Reference	1467 KB
EP0620271A1_FOR.pdf	16	Foreign Reference	987 KB
WO1998021307A1_FOR.pdf	38	Foreign Reference	3114 KB
WO1996041647A1_FOR.pdf	88	Foreign Reference	6580 KB
WO2005110370A1_FOR.pdf	62	Foreign Reference	3732 KB
WO2005027872A2_FOR.pdf	72	Foreign Reference	5492 KB
EP1473367A1_FOR.pdf	188	Foreign Reference	14302 KB
INTL-FOOD-INFO-SERVICE_NPL.pdf	3	Non Patent Literature	175 KB
YUAN_2006_NPL.pdf	7	Non Patent Literature	381 KB
ABOOFAZELI_NPL.pdf	13	Non Patent Literature	924 KB
FRITSH_NPL.pdf	12	Non Patent Literature	998 KB
TADROS_NPL.pdf	16	Non Patent Literature	1159 KB
BINKS_NPL.pdf	11	Non Patent Literature	424 KB
KANG_NPL.pdf	5	Non Patent Literature	517 KB
MORENO_2003_NPL.pdf	10	Non Patent Literature	568 KB
ONEIL_NPL.pdf	8	Non Patent Literature	216 KB
SUPPASANSATORN_NPL.pdf	8	Non Patent Literature	534 KB

SARKER_NPL.pdf	14	Non Patent Literature	1372 KB
ISR-WO_PCT-EP2007-014404.pdf	13	Non Patent Literature	582 KB
DANIELSSON_NPL.pdf	2	Non Patent Literature	210 KB
SONNEVILLE-AUBRUN_NPL.pdf	5	Non Patent Literature	460 KB
FENDLER_NPL.pdf	12	Non Patent Literature	1239 KB
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SINKO_2009_NPL.pdf	34	Non Patent Literature	4494 KB
BAGWE_NPL.pdf	64	Non Patent Literature	7170 KB
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Digest

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BAGWE_NPL.pdf	270A73E602DFEB3BF08033C26B653D39626CE56525EA3572324BD1A60D910548E3C99D95F76C7A0723C591BB2869D6BF6D24C1B366147EA3F8F4F4FA93C13A34
KOSAR_2015_NPL.pdf	D75639C8A8316B5FA2F3F86DDE860D8EE6CD4E030B6B9EBAD357072A0DEC6526C4573B4AA85B5221B8A7F32C707D10C6983D50B87BFFCD09E499F9F41B812FF5

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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 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Biofrontera Bioscience GmbH	Examiner:	Celeste A. RONEY
Serial No.:	18/533,497	Group Art No.:	1612
Filed:	December 8, 2023	Confirmation No.:	6866
Title:	NANOEMULSION WITHOUT PROPYLENE GLYCOL		

VIA EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Dear Commissioner:

This Information Disclosure Statement is submitted:

☒ under 37 CFR 1.97(b), or
(Within three months of filing national application other than a CPA under §1.53(d); or within three months of date of entry of the national stage in international application; or before mailing date of first Office Action on the merits, or before mailing date of first Office Action after filing RCE under §1.114, whichever occurs last)

☐ under 37 CFR 1.97(c) together with either a:
- ☐ Statement under 37 CFR 1.97(e), or
- ☐ a $260 fee under 37 CFR 1.17(p), or

(After the CFR 1.97(b) time period, but before final action or notice of allowance, whichever occurs first)

☐ under 37 CFR 1.97(d) together with a Statement under 37 CFR 1.97(e)(1) or (2), and a $260 fee set forth in 37 CFR 1.17(p).
(Filed after final action, a notice of allowance, on or before payment of issue fee)

For an information disclosure statement under § 1.97(c) or (d), please charge any unpaid required fee set forth in § 1.17(p) or credit any overpayment to Deposit Account 12-0600 pursuant to 37 CFR 1.25.

Applicant(s) submit herewith PTO Form SB/08 – Information Disclosure Statement together with copies of non-U.S. patents, publications or other information (if any) of which

applicant(s) are aware, which applicant(s) believe(s) may be material to the examination of the application and for which there may be a duty to disclose in accordance with 37 CFR 1.56.

Applicant calls to the attention of the Examiner to the following patents and applications, and in the interest of completeness, the instant application is also included in the listing below.

Patents/Applications				
Appl'n No. Publ'n No. Patent No.	**Filing Date Publ'n Date Grant Date**	**First Named Inventor**	**Title**	**Docket No.**
12/520,759 2009/0324727 11,540,981	12/22/2006 12/21/2007 01/03/2023	Montserrat Foguet ROCA	Nanoemulsion Formulation with Improved Stability and Cell Penetration	602825: BFR9-001US
18/071,733 2023/0201087	11/30/2022 06/29/2023	Montserrat Foguet ROCA	Nanoemulsion	729364: BFR9-001USDIV
*18/533,497	12/08/2023	Montserrat FOUGET	Nanoemulsion Without Propylene Glycol	748419: BFR9-002
18/533,521	12/08/2023	Montserrat FOUGET	Pressurized Nanoemulsion	748420: BFR9-003

*Instant Application

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references. It is requested that the information disclosed herein be made of record in this application.

Date: April 15, 2024

Respectfully submitted,

Signature: /James H. Velema/
James H. Velema, Esq.
LATHROP GPM LLP
Reg. No. 56,130
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Telephone: (857) 300-4000
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Customer No: 12779

INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	18/533,497
				Filing Date/371(c) Date	December 8, 2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	1	of	4	*Attorney Docket Number*	748419: BFR9-002

U.S. PATENTS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Issue Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 5891490 A	04/06/1999	MERABET	
	2.	US 6165500 A	12/26/2000	CEVC	
	3.	US 6245349 B1	06/12/2001	YIV et al.	
	4.	US 6274150 B1	08/14/2001	SIMONNET et al.	
	5.	US 6375960 B1	04/23/2002	SIMONNET et al.	
	6.	US 6413527 B1	07/02/2002	SIMONNET et al.	
	7.	US 6500862 B1	12/31/2002	ZANELLO	
	8.	US 6559183 B1	05/06/2003	SCHMID et al.	
	9.	US 6602511 B2	08/05/2003	VON CORSWANT	
	10.	US 6897238 B2	05/24/2005	CHEN et al.	
	11.	US 7314624 B2	01/01/2008	BAKER et al.	
	12.	US 11540981 B2	01/03/2023	ROCA et al.	

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Publication Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 20020155084 A1	10/24/2002	ROESSLER et al.	
	2.	US 20030167033 A1	09/04/2003	CHEN et al.	
	3.	US 20030190347 A1	10/09/2003	SUPERSAXO et al.	
	4.	US 20050158389 A1	07/21/2005	DOMB	
	5.	US 20050208083 A1	09/22/2005	ANNIS	
	6.	US 20060140984 A1	06/29/2006	TAMARKIN et al.	
	7.	US 20060078525 A1	04/13/2006	TOMOKUNI	
	8.	US 20110060042 A1	03/10/2011	ITO	
	9.	US 20090324727 A1	12/21/2007	ROCA et al.	
	10.	US 20230201087 A1	06/29/2023	ROCA et al.	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	18/533,497
				Filing Date/371(c) Date	December 8, 2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	2	of	4	*Attorney Docket Number*	748419: BFR9-002

FOREIGN PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Foreign Patent Document Country Code Number Kind Code (*if known*)	Publication Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Translation
	1.	EP 0620271 A1	10/19/1994	COLGATE PALMOLIVE CO.	
	2.	EP 0704209 A1	04/03/1996	JOHNSON & JOHNSON MEDICAL, INC.	
	3.	EP 1473367 A1	11/03/2004	NEURONOVA A.G.	
	4.	EP 1655021 A1	05/10/2006	NOVAGALI PHARMA S.A.	
	5.	JP 2002-302414 A	10/18/2002	KOKURIYUUDOU	
	6.	JP 2006-273821 A	10/12/2006	NARIS COSMETICS CO. LTD.	
	7.	WO 1996/041647 A1	12/27/1996	BARNES JEWISH HOSPITAL D.B.A.	
	8.	WO 1997/041855 A1	11/13/1997	NEW YORK BLOOD CENTER INC.	
	9.	WO 1998/021307 A1	05/22/1998	PROCTER & GAMBLE	
	10.	WO 2002/066589 A2	08/29/2002	COLGATE PALMOLIVE CO.	
	11.	WO 2005/027872 A2	03/31/2005	NANBIO CORP.	
	12.	WO 2005/110370 A1	11/24/2005	NESTEC S.A.	

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.	Translation
	1.	ABOOFAZELI et al., "Particle Size Analysis of Concentrated Phospholipid Microemulsions: I. Total Intensity Light Scattering", AAPS PharmSci, 2000, 2(2): 1-13.	
	2.	ALAM et al., "Design and Characterization of Nanostructured Topical Gel of Betamethasone Dipropionate for Psoriasis," Journal of Applied Pharmaceutical Science, 2012, 2(10): 148-158.	
	3.	BAGWE et al., "Improved Drug Delivery Using Microemulsions: Rationale, Recent Progress, and New Horizons", Critical Reviews in Therapeutic Drug Carrier Systems, 2001, 18(1): 77-140.	
	4.	BINKS et al., "Phase Behaviour of microemulsions stabilised by double chain cationic surfactants and alcohol co-surfactants", Colloids and Surfaces A: Physicochem. Eng. Aspects, January 23, 2003, 212(2-3): 135-145.	
	5.	DANIELSSON et al., "The Definition of Microemulsion", Colloids and Surfaces, December 1981, 3(4): 391-392.	
	6.	FENDLER et al., "Liposomes as Drug Carriers", Life Sciences, April 1, 1977, 20(7):1109-1120.	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/533,497
				Filing Date/371(c) Date	December 8, 2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	3	of	4	Attorney Docket Number	748419: BFR9-002

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.	Translation
	7.	FRITSCH et al., "Fluorescence Diagnosis and Photodynamic Therapy of Skin Diseases", Atlas and Handbook, 2003, pages 23-31.	
	8.	International Food Information Service, "Dictionary of Food Science and Technology", 2nd ed. 2009, p. 250.	
	9.	International Search Report and Written Opinion for PCT International Patent Application No. PCT/EP2007/011404, dated May 9, 2008.	
	10.	KANG et al., "Preparation and Characterization of Nano-Liposomes Using Phosphatidylcholine", International Journal of Industrial and Engineering Chemistry, November 2005, 11(6): 847-851.	
	11.	KOSAR et al., "Exogenously-applied 5-aminolevulinic acid modulates some key physiological characteristics and antioxidative defense system in spring wheat (Triticum aestivum L.) seedlings under water stress," Journal of Botany, 2015, 96: 71-77.	
	12.	MORENO, "Lecithin-Based Oil-in-Water Microemulsions for Parenteral Use: Pseudoternary Phase Diagrams, Characterization and Toxicity Studies", Wiley-Liss Journal of Pharmaceutical Science, 2003, 92(7): 1428-1437.	
	13.	O'NEIL et al., "The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals," Merck & Co., Inc.; entries for "aminolevulinic acid," "Lecithins," and "Polysorbates," 2006, pp. 1-8 (as provided).	
	14.	SARKER, "Engineering of Nanoemulsions for Drug Delivery", Current Drug Delivery, October 2005, 2(4): 297-310.	
	15.	SINKO et al., "MARTIN'S PHYSICAL PHARMACY AND PHARMACEUTICAL SCIENCES", Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences, 15th ed., 2009, Chapter 18, "Coarse Dispersions" pp. 499-530.	
	16.	SONNEVILLE-AUBRUN et al., "Nanoemulsions: a new vehicle for skincare products", Advanced Colloid and Interface Science, May 20, 2004, 108-109: 145-149.	
	17.	SUPPASANSATORN et al., "Microemulsions as topical delivery vehicles for the anti-melanoma prodrug, temozolomide hexyl ester (TMZA-HE)", Journal of Pharmacy and Pharmacology, June 2007, Vol. 59, pp. 787-794.	
	18.	TADROS et al., "Formation and stability of nano-emulsions", Advances in Colloid and Interface Science, May 20, 2004, Vol. 108-109, pp. 303-318.	
	19.	WEISS et al., "Nanostructured Encapsulation Systems: Food Antimicrobials", Global Issues in Food Science and Technology, 2009, Chapter 24, pp. 425-479.	
	20.	YUAN et al., "Investigation of microemulsion system for transdermal delivery of meloxicam", International Journal of Pharmaceutics, September 14, 2006, 321(1-2): 117-123.	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/533,497
				Filing Date/371(c) Date	December 8, 2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	4	of	4	Attorney Docket Number	748419: BFR9-002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James H. Velema/	Date (YYYY-MM-DD)	2024-04-15
Name/Print	James H. Velema, Esq.	Registration Number	56,130

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 1.14. This collection is estimated to take 1 hour 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 require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, VA 22313-1450.**

Examiner Signature		Date Considered	

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

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	11	((("BIOFRONTERA") near3 ("BIOSCIENCE") near3 ("GMBH"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/04/24 01:15 PM
L2	4	((("FOGUET") near3 ("Montserrat")) OR (("MÖLLMANN") near3 ("Lars"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/04/24 01:15 PM
L3	24	"5" adj2 aminolevulinic adj2 acid WITH nanoemulsion	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/04/24 01:17 PM
L4	2084128	"5" adj2 aminolevulinic adj2 acid WITH nanoemulsion AND propylene glycol	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/04/24 01:17 PM
L5	8	"5" adj2 aminolevulinic adj2 acid WITH nanoemulsion AND propylene adj2 glycol	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/04/24 01:17 PM
L6	8	L5 AND ((A61K41/0061 OR A61K2800/21 OR A61K2800/413 OR A61K8/06 OR A61K8/34 OR A61K8/375 OR A61K8/44 OR A61K8/4993 OR A61K8/553 OR A61K9/0014 OR A61K9/107 OR A61K41/008 OR A61K47/10 OR A61K47/24 OR A61K47/6923 OR A61K47/6929 OR A61K9/0019 OR A61K9/1075 OR A61K47/183).cpc.)	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/04/24 01:18 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Web Search History

date, time	web site	search string
4/24/2024 1:19:58 PM	Google Scholar	(5-aminolevulinic-acid)(nanoemulsion)(propylene-glycol)
4/24/2024 1:19:58 PM	Google Patents	Search Term 1 (5-aminolevulinic-acid)(nanoemulsion)(propylene-glycol)

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/533,497	FOGUET et al.
	Examiner	Art Unit
	CELESTE A RONEY	1612

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
A61K9/1075; A61K9/127; A61K41/0061; A61K47/10; A61K47/12; A61K47/14; A61K47/24; A61K47/26; A61K47/36 further limited by nanoemulsion and 5-aminolevulinic acid and propylene glycol	04/24/2024	CR

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.

Search Notes		
Search Notes	Date	Examiner
palm inventor search. filing receipt search. google (patents and scholar) and PE2E searches further limited by nanoemulsion and 5-aminolevulinic acid and propylene glycol	04/24/2024	CR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/CELESTE A RONEY/ Primary Examiner, Art Unit 1612	

Bibliographic Data

Application No: 18/533,497

Foreign Priority claimed: ◉ Yes ○ No

35 USC 119 (a-d) conditions met: ☑ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /CELESTE A RONEY/ Examiner's Signature | Initials

Title: NANOEMULSION WITHOUT PROPYLENE GLYCOL

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/08/2023	424	1612	748419: BFR9-002
RULE			

APPLICANTS

Biofrontera Bioscience GmbH, Leverkusen, GERMANY

INVENTORS

Montserrat FOGUET, Leverkusen, GERMANY

Lars MÖLLMANN, Leverkusen, GERMANY

CONTINUING DATA

FOREIGN APPLICATIONS

PCT/EP2023/059291 04/06/2023

IF REQUIRED, FOREIGN LICENSE GRANTED**

12/20/2023

STATE OR COUNTRY

GERMANY

ADDRESS

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109
UNITED STATES

FILING FEE RECEIVED

$6,320

Notice of References Cited	Application/Control No. 18/533,497	Applicant(s)/Patent Under Reexamination FOGUET et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-20090324727-A1	2009-12-31	Foguet Roca; Montserrat	A61K9/107	514/561
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Biofrontera Bioscience GmbH	Examiner:	Celeste A. RONEY
Serial No.:	18/533,497	Group Art No.:	1612
Filed:	December 8, 2023	Confirmation No.:	6866
Title:	NANOEMULSION WITHOUT PROPYLENE GLYCOL		

VIA EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Dear Commissioner:

This Information Disclosure Statement is submitted:

☒ under 37 CFR 1.97(b), or
(Within three months of filing national application other than a CPA under §1.53(d); or within three months of date of entry of the national stage in international application; or before mailing date of first Office Action on the merits, or before mailing date of first Office Action after filing RCE under §1.114, whichever occurs last)

☐ under 37 CFR 1.97(c) together with either a:
- ☐ Statement under 37 CFR 1.97(e), or
- ☐ a $260 fee under 37 CFR 1.17(p), or

(After the CFR 1.97(b) time period, but before final action or notice of allowance, whichever occurs first)

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Applicant(s) submit herewith PTO Form SB/08 – Information Disclosure Statement together with copies of non-U.S. patents, publications or other information (if any) of which

/CELESTE A RONEY/

04/23/2024

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

applicant(s) are aware, which applicant(s) believe(s) may be material to the examination of the application and for which there may be a duty to disclose in accordance with 37 CFR 1.56.

Applicant calls to the attention of the Examiner to the following patents and applications, and in the interest of completeness, the instant application is also included in the listing below.

Patents/Applications				
Appl'n No. Publ'n No. Patent No.	**Filing Date Publ'n Date Grant Date**	**First Named Inventor**	**Title**	**Docket No.**
12/520,759 2009/0324727 11,540,981	12/22/2006 12/21/2007 01/03/2023	Montserrat Foguet ROCA	Nanoemulsion Formulation with Improved Stability and Cell Penetration	602825: BFR9-001US
18/071,733 2023/0201087	11/30/2022 06/29/2023	Montserrat Foguet ROCA	Nanoemulsion	729364: BFR9-001USDIV
*18/533,497	12/08/2023	Montserrat FOUGET	Nanoemulsion Without Propylene Glycol	748419: BFR9-002
18/533,521	12/08/2023	Montserrat FOUGET	Pressurized Nanoemulsion	748420: BFR9-003

*Instant Application

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references. It is requested that the information disclosed herein be made of record in this application.

Date: April 15, 2024

Respectfully submitted,

Signature: /James H. Velema/
James H. Velema, Esq.
LATHROP GPM LLP
Reg. No. 56,130
28 State Street, Suite 0700
Boston, Massachusetts 02109
Telephone: (857) 300-4000
Facsimile: (857) 300-4001
Customer No: 12779

04/23/2024

/CELESTE A RONEY/

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	18/533,497
				Filing Date/371(c) Date	December 8, 2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	1	of	4	*Attorney Docket Number*	748419: BFR9-002

U.S. PATENTS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Issue Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 5891490 A	04/06/1999	MERABET	
	2.	US 6165500 A	12/26/2000	CEVC	
	3.	US 6245349 B1	06/12/2001	YIV et al.	
	4.	US 6274150 B1	08/14/2001	SIMONNET et al.	
	5.	US 6375960 B1	04/23/2002	SIMONNET et al.	
	6.	US 6413527 B1	07/02/2002	SIMONNET et al.	
	7.	US 6500862 B1	12/31/2002	ZANELLO	
	8.	US 6559183 B1	05/06/2003	SCHMID et al.	
	9.	US 6602511 B2	08/05/2003	VON CORSWANT	
	10.	US 6897238 B2	05/24/2005	CHEN et al.	
	11.	US 7314624 B2	01/01/2008	BAKER et al.	
	12.	US 11540981 B2	01/03/2023	ROCA et al.	

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Publication Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 20020155084 A1	10/24/2002	ROESSLER et al.	
	2.	US 20030167033 A1	09/04/2003	CHEN et al.	
	3.	US 20030190347 A1	10/09/2003	SUPERSAXO et al.	
	4.	US 20050158389 A1	07/21/2005	DOMB	
	5.	US 20050208083 A1	09/22/2005	ANNIS	
	6.	US 20060140984 A1	06/29/2006	TAMARKIN et al.	
	7.	US 20060078525 A1	04/13/2006	TOMOKUNI	
	8.	US 20110060042 A1	03/10/2011	ITO	
	9.	US 20090324727 A1	12/21/2007	ROCA et al.	
	10.	US 20230201087 A1	06/29/2023	ROCA et al.	

Examiner Signature	/CELESTE A RONEY/	Date Considered	04/24/2024

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/533,497
				Filing Date/371(c) Date	December 8, 2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	2	of	4	Attorney Docket Number	748419: BFR9-002

FOREIGN PATENT DOCUMENTS					
Examiner Initials*	Cite No.	Foreign Patent Document Country Code Number Kind Code (if known)	Publication Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Translation
	1.	EP 0620271 A1	10/19/1994	COLGATE PALMOLIVE CO.	
	2.	EP 0704209 A1	04/03/1996	JOHNSON & JOHNSON MEDICAL, INC.	
	3.	EP 1473367 A1	11/03/2004	NEURONOVA A.G.	
	4.	EP 1655021 A1	05/10/2006	NOVAGALI PHARMA S.A.	
	5.	JP 2002-302414 A	10/18/2002	KOKURIYUUDOU	
	6.	JP 2006-273821 A	10/12/2006	NARIS COSMETICS CO. LTD.	
	7.	WO 1996/041647 A1	12/27/1996	BARNES JEWISH HOSPITAL D.B.A.	
	8.	WO 1997/041855 A1	11/13/1997	NEW YORK BLOOD CENTER INC.	
	9.	WO 1998/021307 A1	05/22/1998	PROCTER & GAMBLE	
	10.	WO 2002/066589 A2	08/29/2002	COLGATE PALMOLIVE CO.	
	11.	WO 2005/027872 A2	03/31/2005	NANBIO CORP.	
	12.	WO 2005/110370 A1	11/24/2005	NESTEC S.A.	

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.	Translation
	1.	ABOOFAZELI et al., "Particle Size Analysis of Concentrated Phospholipid Microemulsions: I. Total Intensity Light Scattering", AAPS PharmSci, 2000, 2(2): 1-13.	
	2.	ALAM et al., "Design and Characterization of Nanostructured Topical Gel of Betamethasone Dipropionate for Psoriasis," Journal of Applied Pharmaceutical Science, 2012, 2(10): 148-158.	
	3.	BAGWE et al., "Improved Drug Delivery Using Microemulsions: Rationale, Recent Progress, and New Horizons", Critical Reviews in Therapeutic Drug Carrier Systems, 2001, 18(1): 77-140.	
	4.	BINKS et al., "Phase Behaviour of microemulsions stabilised by double chain cationic surfactants and alcohol co-surfactants", Colloids and Surfaces A: Physicochem. Eng. Aspects, January 23, 2003, 212(2-3): 135-145.	
	5.	DANIELSSON et al., "The Definition of Microemulsion", Colloids and Surfaces, December 1981, 3(4): 391-392.	
	6.	FENDLER et al., "Liposomes as Drug Carriers", Life Sciences, April 1, 1977, 20(7):1109-1120.	

Examiner Signature	/CELESTE A RONEY/	Date Considered	04/24/2024

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
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				Filing Date/371(c) Date	December 8, 2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	3	of	4	Attorney Docket Number	748419: BFR9-002

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.	Translation
	7.	FRITSCH et al., "Fluorescence Diagnosis and Photodynamic Therapy of Skin Diseases", Atlas and Handbook, 2003, pages 23-31.	
	8.	International Food Information Service, "Dictionary of Food Science and Technology", 2nd ed. 2009, p. 250.	
	9.	International Search Report and Written Opinion for PCT International Patent Application No. PCT/EP2007/011404, dated May 9, 2008.	
	10.	KANG et al., "Preparation and Characterization of Nano-Liposomes Using Phosphatidylcholine", International Journal of Industrial and Engineering Chemistry, November 2005, 11(6): 847-851.	
	11.	KOSAR et al., "Exogenously-applied 5-aminolevulinic acid modulates some key physiological characteristics and antioxidative defense system in spring wheat (Triticum aestivum L.) seedlings under water stress," Journal of Botany, 2015, 96: 71-77.	
	12.	MORENO, "Lecithin-Based Oil-in-Water Microemulsions for Parenteral Use: Pseudoternary Phase Diagrams, Characterization and Toxicity Studies", Wiley-Liss Journal of Pharmaceutical Science, 2003, 92(7): 1428-1437.	
	13.	O'NEIL et al., "The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals," Merck & Co., Inc.; entries for "aminolevulinic acid," "Lecithins," and "Polysorbates," 2006, pp. 1-8 (as provided).	
	14.	SARKER, "Engineering of Nanoemulsions for Drug Delivery", Current Drug Delivery, October 2005, 2(4): 297-310.	
	15.	SINKO et al., "MARTIN'S PHYSICAL PHARMACY AND PHARMACEUTICAL SCIENCES", Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences, 15th ed., 2009, Chapter 18, "Coarse Dispersions" pp. 499-530.	
	16.	SONNEVILLE-AUBRUN et al., "Nanoemulsions: a new vehicle for skincare products", Advanced Colloid and Interface Science, May 20, 2004, 108-109: 145-149.	
	17.	SUPPASANSATORN et al., "Microemulsions as topical delivery vehicles for the anti-melanoma prodrug, temozolomide hexyl ester (TMZA-HE)", Journal of Pharmacy and Pharmacology, June 2007, Vol. 59, pp. 787-794.	
	18.	TADROS et al., "Formation and stability of nano-emulsions", Advances in Colloid and Interface Science, May 20, 2004, Vol. 108-109, pp. 303-318.	
	19.	WEISS et al., "Nanostructured Encapsulation Systems: Food Antimicrobials", Global Issues in Food Science and Technology, 2009, Chapter 24, pp. 425-479.	
	20.	YUAN et al., "Investigation of microemulsion system for transdermal delivery of meloxicam", International Journal of Pharmaceutics, September 14, 2006, 321(1-2): 117-123.	

Examiner Signature	/CELESTE A RONEY/	Date Considered	04/24/2024

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/533,497
				Filing Date/371(c) Date	December 8, 2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	4	of	4	Attorney Docket Number	748419: BFR9-002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James H. Velema/	Date (YYYY-MM-DD)	2024-04-15
Name/Print	James H. Velema, Esq.	Registration Number	56,130

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 1.14. This collection is estimated to take 1 hour 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 require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, VA 22313-1450.**

Examiner Signature	/CELESTE A RONEY/	Date Considered	04/24/2024

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 05/01/2024

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
05/01/2024	ELECTRONIC

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):

bostonpatent@lathropgage.com

Office Action Summary	Application No. 18/533,497	Applicant(s) FOGUET et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	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 April 2024.

☐ 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) 19-26 is/are pending in the application.

5a) Of the above claim(s) 20 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 19 and 21-26 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 4/15/24 (2).

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

4) ☐ Other: _____.

DETAILED ACTION

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. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Election/Restrictions

Applicant's election without traverse of Group III, claim 19, drawn to a nanoemulsion comprising less than 1 % propylene glycol and 5-aminolevulinic acid, in the reply filed on 04/12/2024, is acknowledged.

Claim 20 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/12/2024.

Claim Rejections - 35 USC § 103 - Obviousness

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.

Claim(s) 19 and 21-26 are rejected under 35 U.S.C. 103 as being unpatentable over Roca et al (US 2009/0324727 A1).

Roca taught a nanoemulsion comprising (a) at least one aqueous component and (b) a carrier, which comprises (i) at least one lipophilic component (e.g., triglyceride; caprylic, capric triglycerides at [0014]) being present in an amount of from 0.1% by weight to 15% by weight, (ii) at least one surfactant (e.g., phosphatidylcholine; phospholipid, ceramide at [0015]), and (iii) at least one alcohol (e.g., isopropyl alcohol; alcohols having at least 3-5 carbons at [0012]), wherein the alcohol was present in an amount of from 0.1% by weight to 10% by weight and wherein the aqueous component was present in an amount of from 50% by weight to 98% by weight, based on the total weight of the nanoemulsion.

Roca further related to a composition comprising said nanoemulsion and an active agent. In particular, the active agent was 5-aminolevulinic acid [abstract, claims 1-9]. At Tables 4-6, Roca taught compositions comprising 0.009 % propylene glycol (reads on less than 1 % propylene glycol) (e.g., 9 mg propylene glycol ÷ 1000 mg total composition = 0.009 % pg).

Claim 19 is rendered *prima facie* obvious over the teachings of Roca, because it is *prima facie* obvious to combine prior art elements according to known methods, in order to yield predictable results. In the instant case, all the claimed elements (e.g., nanoemulsion comprising 5-aminolevulinic acid) were known in the prior art (e.g., Roca), and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing

more than predictable results (e.g., a nanoemulsion) to one of ordinary skill in the art. MPEP 2143.A.

Roca reads on claims 19, 21 and 24-26.

The instant claim 19 recites less than 1 % propylene glycol.

The instant claim 21 recites less than 0.9 % propylene glycol.

The instant claim 25 recites an aqueous component of 50-99 %.

The instant claim 26 recites a lipophilic component of 0.1-30 % and an alcohol amount of 0.1 to 10 %.

Roca taught 0.009 % propylene glycol; a lipophilic component of from 0.1% by weight to 15% by weight; an aqueous component of from 50% by weight to 98%; and, an alcohol amount of from 0.1% by weight to 10% by weight. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a *prima facie* case of obviousness exists. MPEP 2144.05 A.

Claims 22-23 are rendered *prima facie* obvious because Roca does not disclose non-cyclic polyols as required ingredients.

Nonstatutory Double Patenting

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 provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* 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 filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual 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/apply/applying-online/eterminal-disclaimer.

Claims 19 and 21-26 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 18/533,521, in view of Roca et al (US 2009/0324727 A1).

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims require less than 1 % of propylene glycol, which is not recited by the copending claims.

Roca taught a nanoemulsion comprising (a) at least one aqueous component and (b) a carrier, which comprises (i) at least one lipophilic component, (ii) at least one surfactant, and (iii) at least one alcohol. Roca further related to a composition comprising said nanoemulsion and an active agent. In particular, the active agent was 5-aminolevulinic acid [abstract, claims 1-9]. At Tables 4-6, Roca taught compositions comprising 0.009 % propylene glycol (reads on less than 1 % propylene glycol) (e.g., 9 mg propylene glycol ÷ 1000 mg total composition = 0.009 % pg).

It would have been *prima facie* obvious to one of ordinary skill in the art to include, within the copending claims, less than 1 % propylene glycol, as taught by Roca. The ordinarily skilled artisan would have been motivated to form the nanoemulsion, as taught by Roca.

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

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A RONEY whose telephone number is (571)272-5192. The examiner can normally be reached Monday-Friday; 8 AM-6 PM.

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, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 18/533,497	Filing Date 12/08/2023	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $480 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/01/2024	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 17	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MONICA D FRANCIS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 1.14. This collection is estimated to take 12 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.

REMARKS

Claims 19-26 are pending. Claim 20 is withdrawn. Claim 20 has been cancelled. Claims 19 and 21-26 have been amended. Claims 27-36 are newly added. Support for the amended and new claims can be found in the application as originally filed. *There is no new matter*.

Claim Rejections – 35 § U.S.C. 103

Claim 19 and 21-26 are rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Roca et al. (U.S. Patent Appl. Pub. No. 2009/0324727 A1)(hereinafter "Roca").[1]

The Office asserts that Roca teaches the elements of the formulation of the claims. The Office refers to Tables 4-6 from Roca and alleges that Roca teaches formulations comprising 9 mg of propylene glycol per 1000 mg of formulation, which allegedly corresponds to a propylene glycol concentration of ***0.009% w/w*** based on the total weight of the formulation. Applicant respectfully disagrees and traverses the rejection with respect to the claims as currently amended.

While Applicant respectfully disagrees with the rejection, Applicant has amended the claims without prejudice or disclaimer in the interest of advancing prosecution to encompass a formulation comprising "essentially no propylene glycol." Applicant asserts that the claims are nonobvious over the cited reference Roca.

Roca does not teach all the elements of the instant claims. Roca is silent regarding a formulation comprising essentially no propylene glycol as required by the instant claims. Roca at Tables 4-6 discloses formulations comprising 9 mg of propylene glycol per gram (i.e., 1000 mg) of formulation. This corresponds to a propylene glycol concentration of 0.009 w/w or ***0.9%* w/w** based on the total weight of the formulation, which is higher than the propylene glycol concentration from the formulation of the instant claims. Therefore, because Roca fails to teach or suggest each limitation of the claimed formulation, the formulation *as a whole* could not have been obvious to the skilled artisan at the time the subject Application was filed.

Furthermore, the objective evidence presented in Applicant's specification demonstrate that the features of the formulation recited in the instant claims impart significant and unexpected

[1] *See*, Action at page 2.

advantages for the claimed formulation that are sufficient to rebut any *prima facie* case of obviousness. In particular, the results in the specification show that:

- first, purity of formulations after storage surprisingly improves when the ***formulations comprise essentially no propylene glycol***. This is illustrated in Figures 1 and 2 and Example 6 of the application as originally filed that show the impurities of different formulations after storage. In these figures, a formulation comprising essentially no propylene glycol (*see* Formulation 2, comprising no propylene glycol) is shown after storage to have lower concentrations in m/z = 246 and m/z = 190 impurities when compared with a formulation comprising propylene glycol at a concentration higher than 0.9% w/w (*see* Formulation 2, comprising 1.0% w/w of propylene glycol) after the same storage;
- second, skin penetration of 5-aminolevulinic (5-ALA) from formulations comprising same surprisingly improves when the ***formulations comprise essentially no propylene glycol.*** This is illustrated in Figure 3 and Example 6 of the application as originally filed that show the 5-ALA skin penetration of different formulations. Figure 3 shows protoporphyrin IX (PpIX) concentrations in skin tissues treated with formulations comprising 5-ALA, which drives the synthesis of PpIX in the tissues. In this figure, a skin tissue treated with a formulation comprising 5-ALA and essentially no propylene glycol (*see* NO PG formulation, comprising no propylene glycol) is shown to have a higher PpIX concentration and therefore a higher penetration of 5-ALA compared with a tissue treated with a formulation comprising 5-ALA and more than 0.9% w/w of propylene glycol (*see* WITH PG formulation, comprising 1.0% w/w of propylene glycol). This finding is surprising because propylene glycol is a known penetration enhancer used in topical pharmaceutical formulations;[2] and
- third, formulations comprising 5-ALA surprisingly release more 5-ALA when the ***formulations comprise essentially no propylene glycol.*** This is illustrated in Figure 5 and Example 6 of the application as originally filed that show the release *in vitro* of 5-ALA from different formulations. In this figure, a formulation comprising essentially no propylene glycol (*see* NO PG formulation, comprising no propylene glycol) is shown to have a higher cumulative transportation and therefore a higher release of 5-ALA compared with a formulation comprising more than 0.9% w/w of propylene glycol (*see* WITH PG formulation,

[2] *See*, see page 52, line 26 of the application as originally filed.

comprising 1.0% w/w of propylene glycol). This finding is surprising because the addition of propylene glycol is expected to improve adhesion and thus improve drug release.[3]

Overall, these results are evidence that the claimed invention yields unexpectedly improved properties and properties not present in the prior art.

Accordingly, Applicant submits that the instant claims are nonobvious and respectfully requests favorable reconsideration and withdrawal of the 35 U.S.C. § 103 rejection over Roca.

Nonstatutory Double Patenting

Claims 19 and 21-26 are provisionally rejected on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1-20 of copending U.S. Patent Application No. 18/533,521 (hereinafter "the '521 application"), in view of Roca.[4]

The Office alleges that Roca renders claims 19 and 21-26 obvious, thus its combination with the '521 application claims supports obviousness. Applicant respectfully traverses this rejection.

Applicant notes that the '521 application claims, alone or combined Roca, do not teach or suggest the formulation of the instant claims. The '521 application claims are directed 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) a propellant, wherein the formulation is comprised in a pressurized container, and wherein the formulation comprises essentially no fatty alcohol. The '521 application claims are directed to a different formulation than the instant claims. None of the claims of the '521 application recite a formulation comprising: a nanoemulsion comprising: at least one aqueous component; a carrier component comprising: (1) at least one lipophilic component, (2) at least one surfactant, and (3) at least one alcohol; and a 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof, wherein the formulation comprises essentially no propylene glycol, as required by the instant claims. One of ordinary skill in the art would not arrive at the instant claims based on the claims of the '521 application.

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[3] *See*, page 6, line 13 of the application as originally filed.

[4] *See*, Action at page 6.

One of ordinary skill in the art would not have had a reasonable expectation of success at arriving at the subject matter of instant claims based on the claims of the '521 application alone or combined with Roca. As provided above, the '521 application alone are directed to a different formulation than the instant claims. Roca does not cure the deficiencies of the '521 application claims.

As indicated above, Roca does not teach or suggest all the elements of the claimed formulation. Roca is silent regarding a formulation comprising essentially no propylene glycol as required by the instant claims. Furthermore, as indicated above the objective evidence presented in Applicant's specification demonstrate that the features of the formulation recited in the instant claims impart significant and unexpected advantages for the claimed formulation that are sufficient to rebut any *prima facie* case of obviousness. In particular, the results in the specification show that purity of formulations after storage surprisingly improves when the formulations comprise essentially no propylene glycol, skin penetration of 5-ALA from formulations comprising same surprisingly improves when the formulations comprise essentially no propylene glycol, and formulations comprising 5-ALA surprisingly release more 5-ALA when the formulations comprise essentially no propylene glycol. These results are evidence that the claimed invention yields unexpectedly improved properties and properties not present in the prior art.

Accordingly, the instant claims are patentably distinct over the claims of the 'the '521 application. Applicant requests withdrawal of the double patenting rejection.

CONCLUSION

An election of claims has been made herein and the Applicant submits that the application is in condition for examination and allowance, which is respectfully requested.

If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is invited to call Applicant's attorney at (312) 920-3357.

Dated: August 1, 2024

Respectfully submitted,

Electronic signature: /Laura A. Labeots/
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64194186v2

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**08/01/2024 03:06:11 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Lauren Schmitt
PATENT CENTER #	66613799	FILING DATE	12/08/2023
CUSTOMER #	12779	FIRST NAMED INVENTOR	Montserrat FOGUET
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Laura Labeots

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
748419_Response_to_NFOA_us.pdf		9	-	157 KB
748419_Response_to_NFOA_us-A...pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	105 KB
748419_Response_to_NFOA_us-CLM.pdf	(2-4)	3	Claims	89 KB
748419_Response_to_NFOA_us-REM.pdf	(5-9)	5	Applicant Arguments/Remarks Made in an Amendment	144 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
748419_Response_to_NFOA_us.pdf	40469D8DE2563E119F544E6C8966C5E5DAFA77E37D287B37426DC56EE1278633630A20CE2B6ED4189182D14DCA30E22D5F0A6E7289ACB89ABD65FCE4E92D4BFC
748419_Response_to_NFOA_us-A....pdf	18943D67A96EDCDC40BC9F54A3C41AC4AA3440D59DA45010BA82E14470D2F2B65132A26DE552237175CA5C01A75F3259BF448849D7173817561BE5F5827778FF
748419_Response_to_NFOA_us-CLM.pdf	988E222F4C56B42B99F53E45E6C4F0B76BF8B314561AE31776346BB39F5E48A856899522F85A133E4A56E8E6CC26E7F52128480186A5F0300F2B332D8C8FC3BE
748419_Response_to_NFOA_us-REM.pdf	069B11A2C260F30151015C021E3F65A7DF9400D66C464DF2FED95A77168E4F1D5CC4EA88E5FCFC833E5EEB0A98591C63D2B3573F822B40868214A2A0EDA488F1

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 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.

AMENDMENTS TO THE CLAIMS

1-18. **(Canceled)**

19. **(Currently Amended)** 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) 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

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

20. **(Cancel)**

21. **(Currently Amended)** The formulation of claim 19, wherein the formulation comprises less than 0.9% w/w of the propylene glycol.

22. **(Currently Amended)** The formulation of claim 19, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms~~; 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, essentially no non-cyclic polyol having 2 to 5 carbon atoms, or no non-cyclic polyol having 2 to 5 carbon atoms~~.

23. **(Currently Amended)** The formulation of claim 19, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms~~; 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 12 carbon atoms; essentially no non-cyclic polyol having 2 to 12 carbon atoms; or no non-cyclic polyol having 2 to 12 carbon atoms~~.

24. **(Currently Amended)** The formulation of claim 19, wherein[[:]] the at least one alcohol comprises: at least 3 carbon atoms; 3, 4, or 5 carbon atoms; or 1-propanol, 2-propanol, or mixtures thereof~~;~~

~~the at least one lipophilic component comprises triglycerides and/or mixtures thereof; or a caprylic, and/or a capric triglyceride, or a mixture thereof; and/or~~

~~the at least one surfactant comprises a phospholipid, a phosphatidylcholine, a lysophospholipid, a ceramide, a mixture thereof; and/or a polyoxyethylene-type surfactant~~.

25. **(Currently Amended)** The formulation of claim 19, comprising [[an]] the at least one aqueous component in an amount from 50% to 99% (w/w), from 70% to 95% (w/w), from 75% to 95% (w/w), or from 80% to 90% (w/w).

26. **(Currently Amended)** The formulation of claim 24, comprising[[:]]

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

~~(a) the at least one alcohol in an amount from 0.1% to 10% (w/w), from 0.5% to 5% (w/w), from 1% to 5% (w/w), or from 1% to 3%;~~

based on total weight of the nanoemulsion.

27. **(New)** The formulation of claim 19, wherein the formulation comprises no propylene glycol.

28. **(New)** The formulation of claim 19, wherein the formulation further comprises 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.

29. **(New)** The formulation of claim 19, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 5 carbon atoms.

30. **(New)** The formulation of claim 19, wherein the formulation further comprises no non-cyclic polyol having 2 to 5 carbon atoms.

31. **(New)** The formulation of claim 19, wherein the formulation further comprises 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 12 carbon atoms.

32. **(New)** The formulation of claim 19, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 12 carbon atoms.

33. **(New)** The formulation of claim 19, wherein the formulation further comprises no non-cyclic polyol having 2 to 12 carbon atoms.

34. **(New)** The formulation of claim 19, wherein the at least one lipophilic component comprises: triglycerides and/or mixtures thereof; or a caprylic and/or a capric triglyceride, or a mixture thereof.

35. **(New)** The formulation of claim 19, wherein the at least one surfactant comprises: a phospholipid, a phosphatidylcholine, a lysophospholipid, a ceramide, and/or a mixture thereof; and/or a polyoxyethylene-type surfactant.

36. **(New)** The formulation of claim 24, wherein the at least one alcohol is in an amount from 0.1% to 10% (w/w), from 0.5% to 5% (w/w), from 1% to 5% (w/w), or from 1% to 3% based on total weight of the nanoemulsion.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Biofrontera Bioscience GmbH	Confirmation No.: 6866
Application No.: 18/533,497	Art Unit: 1612
Filed: December 8, 2023	Examiner: Roney, Celeste A.

Title: NANOEMULSION WITHOUT PROPYLENE GLYCOL

Via Patent Center
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION
AND AMENDMENT

Dear Commissioner:

This paper is filed in response to the Non-Final Office Action having a mailing date of May 1, 2024. As this response is timely filed on August 1, 2024, Applicant believes no fees are due in connection with the filing of this Response. However, the Office is authorized to charge any additional fees deemed necessary in connection with this paper, or credit any overpayment, to Deposit Account No. 12-0600, Attorney Docket No. 748419: BFR9-002.

Amendments to the Claims begin on page **2**; and
Remarks begin on page **5**.

Web Search History

date, time	web site	search string
8/27/2024 9:16:14 AM	Google Scholar	(nanoemulsion)(5-aminolevulinic-acid)
8/27/2024 9:16:14 AM	Google Patents	Search Term 1 (nanoemulsion)(5-aminolevulinic-acid)

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	87	nanoemulsion WITH aminolevulinic adj2 acid	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/27 09:20 AM
L2	80	L1 AND ((A61K41/0061 OR A61K9/0014 OR A61K9/1075 OR A61K31/197 OR A61K9/107 OR A61K2800/21 OR A61K2800/413 OR A61K8/06 OR A61K8/34 OR A61K8/375 OR A61K8/44 OR A61K8/4993 OR A61K8/553 OR A61K47/10 OR A61K47/24 OR A61K9/0019 OR A61K47/183 OR A61K49/0021 OR A61K9/06 OR A61K41/0052 OR A61K47/555 OR A61K31/337 OR A61K47/545 OR A61K47/557 OR A61K47/585 OR A61K47/68 OR A61K49/0043 OR A61K51/04 OR A61K51/0482 OR A61K51/0497 OR A61K51/088 OR A61K47/26 OR A61K45/06 OR A61K47/34 OR A61K47/44 OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/08/27 03:43 PM

		A61K47/6907 OR A61K31/655 OR A61K31/19 OR A61K31/195 OR A61K31/355 OR A61K31/75 OR A61K41/0071 OR A61K41/008 OR A61K47/38 OR A61K47/551 OR A61K47/6923 OR A61K47/6929 OR A61K49/0036 OR A61K49/0082 OR A61K9/08 OR A61K31/60 OR A61K47/14 OR A61K47/36).cpc.)					
L3	12	((("BIOFRONTERA") near3 ("BIOSCIENCE") near3 ("GMBH"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/27 03:43 PM
L4	4	((("FOGUET") near3 ("Montserrat")) OR (("MÖLLMANN") near3 ("Lars"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/08/27 03:44 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/533,497	FOGUET et al.
	Examiner	Art Unit
	CELESTE A RONEY	1612

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
A61K9/1075; A61K9/127; A61K41/0061; A61K47/10; A61K47/12; A61K47/14; A61K47/24; A61K47/26; A61K47/36 further limited by nanoemulsion and 5-aminolevulinic acid and propylene glycol	04/24/2024	CR
A61K9/1075; A61K9/127; A61K41/0061; A61K47/10; A61K47/12; A61K47/14; A61K47/24; A61K47/26; A61K47/36 further limited by nanoemulsion and 5-aminolevulinic acid	08/27/2024	CR

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.

Search Notes		
Search Notes	Date	Examiner
palm inventor search. filing receipt search. google (patents and scholar) and PE2E searches further limited by nanoemulsion and 5-aminolevulinic acid and propylene glycol	04/24/2024	CR
palm inventor search. filing receipt search. google (patents and scholar) and PE2E searches further limited by nanoemulsion and 5-aminolevulinic acid	08/27/2024	CR

/CELESTE A RONEY/ Primary Examiner, Art Unit 1612	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/533,497	FOGUET et al.
	Examiner	Art Unit
	CELESTE A RONEY	1612

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/CELESTE A RONEY/ Primary Examiner, Art Unit 1612	

Notice of References Cited	Application/Control No. 18/533,497	Applicant(s)/Patent Under Reexamination FOGUET et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-6559183-B1	2003-05-06	Schmid; Hans W.	A61P17/06	514/561
*	B	US-5152923-A	1992-10-06	Weder; Hans G.	A61Q19/00	424/455
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 09/06/2024

Lathrop GPM LLP
28 State Street
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EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/06/2024	ELECTRONIC

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):

bostonpatent@lathropgage.com

Office Action Summary	Application No. 18/533,497	Applicant(s) FOGUET et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	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 01 August 2024.

☐ 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) 19 and 21-36 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) 19 and 21-36 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 _____.

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

4) ☐ Other: _____.

DETAILED ACTION

Previous Rejections

Applicant's arguments, filed 08/01/2024, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 – Improper Dependency

The following is a quotation of 35 U.S.C. 112(d):

> (d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of pre-AIA 35 U.S.C. 112, fourth paragraph:

> Subject to the following paragraph [i.e., the fifth paragraph of pre-AIA 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claim 21 is rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

Claim 21 recites "less than 0.9 % of the propylene glycol." Claim 19, from which claim 21 depends, recites "essentially no propylene glycol." Claim 21 is of improper dependency because the claim scope cannot comprise "less than 0.9 % of the propylene glycol" if it depends from a claim reciting "essentially no propylene glycol."

Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections - 35 USC § 103 - Obviousness

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.

Claim(s) 19, 21-25 and 27-36 are rejected under 35 U.S.C. 103 as being unpatentable over Schmid et al (USP 6,559,183 B1).

Schmid taught [abstract] a composition comprising a nano-emulsion that contained 5-aminolevulinic acid, an aqueous phase, a carrier, triglyceride (reads on a lipophilic component; see Examples 1 and 2 (e.g., Miglyol 812)), polysorbatum 80 and egg lecithin (e.g., phosphatidylcholine) (e.g., reads on a surfactant, see Example 1) and, stearyl alcohol (reads on an alcohol, see Example 1).

Schmid did not teach propylene glycol.

Claim 19 is rendered *prima facie* obvious over the teachings of Schmid et al, because it is *prima facie* obvious to combine prior art elements according to known methods, in order to yield predictable results. In the instant case, all the claimed elements (e.g., nanoemulsion, aqueous component, carrier, lipophilic component, surfactant, alcohol, 5-aminolevulinic acid) were known in the prior art (e.g., Schmid) and one skilled

in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results (e.g., a nanoemulsion of 5-aminolevulinic acid) to one of ordinary skill in the art. MPEP 2143.A.

Schmid et al reads on claims 19, 21, 24, 27 and 34-35.

Claims 22-23 and 28-33 are rendered prima facie obvious because Schmid was silent polyols, as instantly recited.

Claim 25 is rendered prima facie obvious over the teachings of Schmid et al. At col 4, lines 27-33, Schmid taught that the composition can be formulated as either a gel or as a lotion, with 1-25 % active, 40-60 % carrier, 0-10 % adjuvants, with the remainder being water; or, with 1-25 % active, 10-30 % carrier, 10-30 % adjuvants, with the remainder being water.

The instant claim 25 recites an aqueous component in an amount from 50-99 %; from 70-95 %; from 75-95 %; or, from 80-90 %.

Schmid taught that the composition can be formulated as either a gel or as a lotion, with 1-25 % active, 40-60 % carrier, 0-10 % adjuvants, with the remainder being water; or, with 1-25 % active, 10-30 % carrier, 10-30 % adjuvants, with the remainder being water. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claim 36 is rendered prima facie obvious because Schmid taught 1.0 % stearyl alcohol [see Table 2 of Example 1].

The instant claim 36 recites at least one alcohol in an amount from 0.1-10 %; from 0.5-5 %; from 1-5 %; or, from 1-3 %. Schmid taught 1.0 %. A prima facie case of obviousness exists because of overlap, as discussed above.

Response to Arguments

Applicant's arguments with respect to the instant claim(s) have been considered but are moot because the new ground of rejection does not rely on any reference applied in the prior rejection of record for any teaching or matter specifically challenged in the argument.

Claim 26 is rejected under 35 U.S.C. 103 as being unpatentable over Schmid et al (USP 6,559,183 B1), in view of Weder et al (USP 5,152,923).

The 35 U.S.C. 103 rejection over Schmid et al was previously discussed.

Schmid taught nanoemulsions formulated with triglycerides, as discussed above. At Examples 1 and 2, Schmid incorporated, by reference, Weder *et al*, to teach nanoemulsions, generally formulated with triglycerides (e.g., Miglyol 812).

Although Schmid taught triglycerides, Schmid was silent the amount of lipophilic content, as recited in claim 26.

Nevertheless, Weder taught a process for the production of a nanoemulsion of oil particles in an aqueous phase, comprising a triglyceride as oil [abstract]. Weder's emulsion comprised 9.83 % triglyceride (e.g., soybean oil) [Example 1 at Table 1].

Since Schmid incorporated the teachings of Weder *et al* by reference, it would have been *prima facie* obvious to one of ordinary skill in the art to use, within the teachings

of Schmid, 9.83 % triglyceride, as taught by Weder. The ordinarily skilled artisan would have been motivated to formulate the nanoemulsion, as taught by Weder at Table 1.

The instant claim 1 taught a lipophilic component in an amount from 0.1-30 %; from 0.25-15 %; from 0.25-10 %; from 2-10 % or, from 3-8 %. Weder taught triglycerides at 9.83 %. A prima facie case of obviousness exists because of overlap, as discussed above.

Response to Arguments

Applicant's arguments with respect to the instant claim(s) have been considered but are moot because the new ground of rejection does not rely on any reference applied in the prior rejection of record for any teaching or matter specifically challenged in the argument.

Nonstatutory Double Patenting

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 provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* 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 filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual 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/apply/applying-online/eterminal-disclaimer.

Claims 19 and 21-36 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 18/533,521.

Although the claims at issue are not identical, they are not patentably distinct from each other because the species (pressurized nanoemulsion) recited in the claims of the copending application falls within the genus (nanoemulsion without propylene glycol) recited in the claims of the instant application, and thus read on the instant claims.

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

Response to Arguments

Applicant's arguments with respect to the instant claim(s) have been considered but are moot because the new ground of rejection does not rely on any reference applied in the prior rejection of record for any teaching or matter specifically challenged in the argument.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). 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 date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A RONEY whose telephone number is (571)272-5192. The examiner can normally be reached Monday-Friday; 8 AM-6 PM.

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, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx

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/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002

CONFIRMATION NO. 6866

12779
Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

PUBLICATION NOTICE

OC000000079187717

Date Mailed: 10/10/2024

Title:NANOEMULSION WITHOUT PROPYLENE GLYCOL

Publication No.US-2024-0335380-A1
Publication Date:10/10/2024

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be viewed using the USPTO's publicly available Searchable Databases via the Patent Public Search tool at www.uspto.gov. The direct link to access the Patent Public Search tool is currently https://ppubs.uspto.gov/pubwebapp/static/pages/ppubsbasic.html.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through Patent Center, the USPTO's electronic patent application filing and management system. The direct link to access this status information is currently https://patentcenter.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of Patent Center.

Further assistance in electronically accessing the publication, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 18/533,497	Filing Date 12/08/2023	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $480 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	11/06/2024	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/LISA R EPPS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 1.14. This collection is estimated to take 12 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.

REMARKS

Claims 19 and 21-36 are pending. Claims 19, 24, and 34 are amended, claim 21 is canceled, and new claims 37-39 are added herein. Support for the amended and new claims can be found in the application as originally filed. *No new matter has been added.* Upon entry of this Response, claims 19 and 22-39 will be pending.

All amendments presented herein are made without prejudice to the possibility of future reinstatement of any excluded matter and/or the subsequent filing of continuation and/or divisional applications based on any matter contained in the application as filed.

Applicant respectfully requests entry of these amendments and new claims.

Claim Rejections – 35 U.S.C. § 112

Claim 21 is rejected under 35 U.S.C. § 112(d) as allegedly being of improper dependent form. Without acquiescing to the rejection, and solely for the purpose of expediting prosecution, claim 21 has been cancelled, thereby rendering this rejection moot.

Claim Rejections – 35 U.S.C. § 103

I. Claims 19, 21-25, and 27-36 over Schmid

Claims 19, 21-25, and 27-36 are rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Schmid et al. (U.S. Patent No. 6,559,183; hereinafter "Schmid").[1] Claim 21 is canceled without prejudice or disclaimer, thereby rendering this rejection moot as it pertains to this claim. Applicant respectfully disagrees and traverses the rejection with respect to the claims as currently amended.

The Office asserts that Schmid discloses a composition comprising a nanoemulsion that contains 5-aminolevulinic acid, an aqueous phase, a carrier, a lipophilic component, a surfactant, and an alcohol, and Schmid does not disclose propylene glycol. The Office alleges that all claimed elements were known in the prior art at the time of the invention and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results.

[1] *See* Action at page 3.

Applicant has amended the claims without prejudice or disclaimer in the interest of advancing prosecution. Amended claim 19 and claims 22-25 and 27-36 depending therefrom recite a "formulation … wherein the formulation comprises essentially no propylene glycol and ***essentially no sorbitol***." Applicant submits that Schmid does not disclose, teach, or suggest the formulation set forth in the present claims.

Schmid does not disclose, teach, or suggest a formulation having each and every feature of the current claims arranged in the same way as recited in the claims. The Office acknowledges that Schmid is silent regarding a formulation comprising essentially no propylene glycol as required by the claims. Schmid is also silent regarding a formulation comprising essentially no sorbitol as required by the instant claims. Schmid is directed to nanoemulsions of 5-aminolevulinic acid ***comprising*** sorbitol.[2] For this reason alone, the instant claims are nonobvious over the cited reference.

Furthermore, the Office has failed to establish a *prima facie* case of obviousness for the claimed formulation as a whole. The Office combines different elements of different formulations having different properties from two examples of Schmid to arrive at the claimed formulation. In particular, the Office refers to Schmid at Examples 1 and 2 and states that the reference discloses a lotion and a gel comprising a lipophilic component (triglyceride) and the Office refers to Schmid at Example 1 and states that the reference discloses a lotion comprising a surfactant (polysorbatum 80 and egg lecithin) and an alcohol (stearyl alcohol).[3] The Office has not identified or articulated any reason to select these different elements from Schmid and combine them to formulate the formulation of the instant claims. The Office is picking and choosing elements disclosed by Schmid while using the Applicant's formulation as a guide using hindsight. In other words, there is no satisfactory articulation by the Office of why one of ordinary skill would be driven to choose each of those elements disclosed by Schmid, and, in addition, would be driven to choose each of those particular elements from the multitude of elements within each of the two examples from Schmid to be combined.

It is well understood that "[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

[2] *See* Schmid at Table 2.

[3] *See* Action at page 3.

underpinning to support the legal conclusion of obviousness."[4] Always, but "[e]ven when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference."[5] Furthermore, "we cannot allow hindsight bias to be the thread that stitches together prior art patches into something that is the claimed invention."[6] Applicant notes that improper hindsight can be inferred when the Office has not explained why the skilled artisan – unaware of Applicant's invention – would make the modification required to meet the claims.[7]

Applicant notes that it must be recognized that creating a new drug formulation is a complex process. Each ingredient must be carefully chosen, not only for efficacy but for compatibility with other ingredients, then utilized in precise concentration in order for the drug formulation to be effective and safe. However, the Office trivialized this process by stating it was obvious to indiscriminately pluck ingredients from different formulations and examples that describe many chemically and physically different compositions, then combine those, in stating a basis for obviousness of the present composition. This is hindsight reasoning.

Accordingly, Applicant submits that the instant claims are nonobvious and respectfully requests favorable reconsideration and withdrawal of the 35 U.S.C. § 103 rejection over Schmid.

II. Claim 26 over Weder

Claim 26 is rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Schmid in view of Weder et al. (U.S. Patent No. 5,152,923; hereinafter "Weder").[8] Applicant respectfully disagrees and traverses the rejection with respect to the claims as currently amended.

Claim 26 depends from claim 19, which is patentable for the reasons provided above, and is therefore patentable for being in dependent form.

Applicant notes that Weder does not bridge the gap in the teaching of Schmid. Weder is silent regarding a formulation comprising essentially no propylene glycol as required by the instant

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[4] *KSR Int 'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006))

[5] *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000)

[6] *Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017)

[7] See *In re Rouffet*, 149 F.3d 1350, 1358 (Fed. Cir. 1998).

[8] *See* Action at page 5.

claims and acknowledged by the Office. Weder is also silent regarding a formulation comprising essentially no sorbitol as required by the instant claims.

Accordingly, Applicant submits that the instant claim is nonobvious and respectfully requests favorable reconsideration and withdrawal of the 35 U.S.C. § 103 rejection over Schmid.

Nonstatutory Double Patenting

Claims 19 and 21-36 are provisionally rejected on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1-20 of copending U.S. Patent Application No. 18/533,521 (hereinafter "the '521 application").[9] Claim 21 is canceled, thereby rendering this rejection moot as it pertains to this claim.

The Office asserts that although the claims at issue are not identical, they are not patentably distinct from each other because the species (pressurized nanoemulsion) recited in the claims of the copending application falls within the genus (nanoemulsion without propylene glycol) recited in the claims of the instant application, and thus read on the instant claims. Applicant respectfully traverses this rejection.

Applicant notes that the '521 application claims do not disclose, teach, or suggest the formulation of the instant claims. The '521 application claims are directed 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) a propellant, wherein the formulation is comprised in a pressurized container, and wherein the formulation comprises essentially no fatty alcohol. The '521 application claims are directed to a different formulation than the instant claims. None of the claims of the '521 application recite a formulation comprising: a nanoemulsion comprising: at least one aqueous component; a carrier component comprising: (1) at least one lipophilic component, (2) at least one surfactant, and (3) at least one alcohol; and a 5-aminolevulinic acid and/or a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof, wherein the formulation comprises essentially no propylene glycol and essentially no sorbitol, as required by the instant claims. One of ordinary skill in the art would not arrive at the instant claims based on the claims of the '521 application.

One of ordinary skill in the art would not have had a reasonable expectation of success at arriving at the subject matter of instant claims based on the claims of the '521 application. As provided above, the claims of the '521 application are directed to a different formulation than the instant claims.

Accordingly, the instant claims are patentably distinct over the claims of the '521 application. Applicant requests withdrawal of the double patenting rejection.

CONCLUSION

An election of claims has been made herein and the Applicant submits that the application is in condition for examination and allowance, which is respectfully requested.

If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is invited to call Applicant's attorney at (312) 920-3357.

Dated: November 6, 2024

Respectfully submitted,

Electronic signature: /Laura A. Labeots/
Laura A. Labeots, Ph.D., J.D.
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Customer No: 12779

64962815v1

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**11/06/2024 05:36:59 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Leslie Roberts
PATENT CENTER #	67869567	FILING DATE	12/08/2023
CUSTOMER #	12779	FIRST NAMED INVENTOR	Montserrat FOGUET
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Laura Labeots

Documents

TOTAL DOCUMENTS: 4

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
748419_BFR9-002_Response_to_FOA.pdf		10	-	173 KB
748419_BFR9-002_Response_to_FOA-A.NE.pdf	(1-1)	1	Response After Final Action	104 KB
748419_BFR9-002_Response_to_FOA-CLM.pdf	(2-5)	4	Claims	101 KB
748419_BFR9-002_Response_to_FOA-REM.pdf	(6-10)	5	Applicant Arguments/Remarks Made in an Amendment	147 KB
748419_BFR9-002_AFCP.pdf		2	After Final Consideration Program Request	221 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
748419_BFR9-002_Response_to_FOA.pdf	F0F1A6A45DB545F567E08AD53535C6F83DAF4DF9144BA4F7F F2C97D8B551B3E619F79DBE4FBB72E9B0FDD57A2A6417311 F176C6D0420B36A2465F58C29E6E916
748419_BFR9-002_Response_to_FOA-A.NE.pdf	65054C03B12BEE9C0720EFCB99AB1B0D994B8735BEAD798C BCC46B83D424DD5966635F56A71BCE53C8AAEE797AD55AE B99A4966FFFA74BBD42901E852ACE7A1A
748419_BFR9-002_Response_to_FOA-CLM.pdf	C2DE7C2E51C17CB40E33715D489FC6E3B969FF8A6AC8555F 8B82439ADCF7D29AF472D3197AF51D70E89E39C68FAE2F947 E30DD06AFA46CD2FD5519433CB23A35
748419_BFR9-002_Response_to_FOA-REM.pdf	0C3C0A12CC50E892E2E5F26BC750D5B5B1640ED546301870A 20B2C9F9FBA09CD30B9BE1A119299F308436DDA39D1957BA 0BE59F45DAB2EE50E71AE2448EC6868
748419_BFR9-002_AFCP.pdf	B21E58BC3985EE59A0C16FE7092EAE12964BEAE016BBABC6 1602C28132D37226CB999F0D4555513C8438E92519B1BD93D7 0E900CB749A51B8068A8D15D77D3F8

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 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.

AMENDMENTS TO THE CLAIMS

1-18. **(Canceled)**

19. **(Currently Amended)** 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) 5-aminolevulinic acid[[,]] and/or a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

wherein the formulation comprises essentially no propylene glycol and essentially no sorbitol.

20. **(Canceled)**

21. **(Cancel)**

22. **(Previously Presented)** The formulation of claim 19, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 5 carbon atoms.

23. **(Previously Presented)** The formulation of claim 19, wherein the formulation further comprises less than 1% w/w of a non-cyclic polyol having 2 to 12 carbon atoms.

24. **(Currently Amended)** The formulation of claim 19, wherein the at least one alcohol comprises: ~~at least 3 carbon atoms;~~ 3, 4, or 5 carbon atoms; or 1-propanol, 2-propanol, or a mixture[[s]] thereof.

25. (**Previously Presented**) The formulation of claim 19, comprising the at least one aqueous component in an amount from 50% to 99% (w/w), from 70% to 95% (w/w), from 75% to 95% (w/w), or from 80% to 90% (w/w).

26. (**Previously Presented**) The formulation of claim 24, comprising the at least one lipophilic component in an amount from 0.1% to 30% (w/w), from 0.25% to 15% (w/w), from 0.25% to 10% (w/w), from 2% to 10% (w/w), or 3% to 8% (w/w) based on total weight of the nanoemulsion.

27. (**Previously Presented**) The formulation of claim 19, wherein the formulation comprises no propylene glycol.

28. (**Previously Presented**) The formulation of claim 19, wherein the formulation further comprises 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.

29. (**Previously Presented**) The formulation of claim 19, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 5 carbon atoms.

30. (**Previously Presented**) The formulation of claim 19, wherein the formulation further comprises no non-cyclic polyol having 2 to 5 carbon atoms.

31. (**Previously Presented**) The formulation of claim 19, wherein the formulation further comprises 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 12 carbon atoms.

32. (**Previously Presented**) The formulation of claim 19, wherein the formulation further comprises essentially no non-cyclic polyol having 2 to 12 carbon atoms.

33. (**Previously Presented**) The formulation of claim 19, wherein the formulation further comprises no non-cyclic polyol having 2 to 12 carbon atoms.

34. (**Currently Amended**) The formulation of claim 19, wherein the at least one lipophilic component comprises: triglycerides and/or mixtures thereof; or a caprylic triglyceride, ~~and/or~~ a capric triglyceride, or a mixture thereof.

35. (**Previously Presented**) The formulation of claim 19, wherein the at least one surfactant comprises: a phospholipid, a phosphatidylcholine, a lysophospholipid, a ceramide, and/or a mixture thereof; and/or a polyoxyethylene-type surfactant.

36. (**Previously Presented**) The formulation of claim 24, wherein the at least one alcohol is in an amount from 0.1% to 10% (w/w), from 0.5% to 5% (w/w), from 1% to 5% (w/w), or from 1% to 3% based on total weight of the nanoemulsion.

37. (**New**) The formulation of claim 19, wherein the formulation further comprises essentially no monosaccharides and disaccharides.

38. (**New**) 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) 5-aminolevulinic acid and/or a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

wherein the formulation comprises less than or equal to 0.9% w/w propylene glycol and less than or equal to 0.1% w/w sorbitol.

39. (**New**) 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 having 3, 4, or 5 carbon atoms; and

(b) 5-aminolevulinic acid and/or a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,

wherein the formulation comprises less than or equal to 0.9% w/w propylene glycol and less than or equal to 0.1% w/w sorbitol.

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
748419: BFR9-002	18/533,497	December 8, 2023
First Named Inventor:	**Title:**	
Montserrat FOGUET	NANOEMULSION WITHOUT PROPYLENE GLYCOL	

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:
    - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
    - The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
        - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
        - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
            - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
            - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	Date
/Laura A. Labeots/	November 6, 2024
Name (Print/Typed)	**Practitioner Registration No.**
Laura A. Labeots, Ph.D., J.D.	62,235

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

☐ * Total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Biofrontera Bioscience GmbH	Confirmation No.: 6866
Application No.: 18/533,497	Art Unit: 1612
Filed: December 8, 2023	Examiner: Roney, Celeste A.

Title: NANOEMULSION WITHOUT PROPYLENE GLYCOL

Via Patent Center
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Dear Commissioner:

In response to the Final Office Action mailed September 6, 2024, Applicant submits the following Amendment and Response. As this response is timely filed on or before the deadline of December 6, 2024, no fees are believed to be due in connection with this filing. However, the Commissioner is authorized to charge any fees that may be due to Deposit Account No. 12-0600, Attorney Docket No. 748419: BFR9-002.

Amendments to the Claims begin on page **2**; and
Remarks begin on page **6**.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Biofrontera Bioscience GmbH	Examiner:	Celest A. RONEY
Serial No.:	18/533,497	Group Art No.:	1612
Filed:	December 8, 2023	Confirmation No.:	6866
Title:	NANOEMULSION WITHOUT PROPYLENE GLYCOL		

Via Patent Center
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Dear Commissioner:

This Information Disclosure Statement is submitted:

☐ under 37 CFR 1.97(b), or

☐ under 37 CFR 1.97(c) together with either a:
- ☐ Statement under 37 CFR 1.97(e), or
- ☐ a $260 fee under 37 CFR 1.17(p), or

☒ under 37 CFR 1.97(d) together with a Statement under 37 CFR 1.97(e)(1) or (2), that no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement, see 37 CFR 1.97(e)(2), and a $260 fee set forth in 37 CFR 1.17(p).
(Filed after final action, a notice of allowance, on or before payment of issue fee)

For an information disclosure statement under § 1.97(c) or (d), please charge any unpaid required fee set forth in § 1.17(p) or credit any overpayment to Deposit Account 12-0600 pursuant to 37 CFR 1.25.

Applicant(s) submit herewith PTO Form SB/08 – Information Disclosure Statement together with copies of non-U.S. patents, publications or other information (if any) of which

applicant(s) are aware, which applicant(s) believe(s) may be material to the examination of the application and for which there may be a duty to disclose in accordance with 37 CFR 1.56.

Applicant calls to the attention of the Examiner to the following patents and applications, and in the interest of completeness, the instant application is also included in the listing below.

Patents/Applications				
Appl'n No. Publ'n No. Patent No.	**Filing Date Publ'n Date Grant Date**	**First Named Inventor**	**Title**	**Docket No.**
12/520,759 2009/0324727 11,540,981	12/22/2006 12/21/2007 01/03/2023	Montserrat Foguet ROCA	Nanoemulsion Formulation with Improved Stability and Cell Penetration	602825: BFR9-001US
18/071,733 2023/0201087	11/30/2022 06/29/2023	Montserrat Foguet ROCA	Nanoemulsion	729364: BFR9-001USDIV
*18/533,497 2024/0335380	12/08/2023 10/10/2024	Montserrat FOUGET	Nanoemulsion Without Propylene Glycol	748419: BFR9-002
18/533,521 2023/0201087	12/08/2023 06/29/2023	Montserrat FOUGET	Pressurized Nanoemulsion	748420: BFR9-003

*Instant Application

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references. It is requested that the information disclosed herein be made of record in this application.

Date: November 6, 2024

Respectfully submitted,

Signature: /James H. Velema/
James H. Velema, Esq.
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Boston, Massachusetts 02109
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UNITED STATES
PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**11/06/2024 06:39:32 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Allison Douglas
PATENT CENTER #	67870373	AUTHORIZED BY	James Velema
CUSTOMER #	12779	FILING DATE	12/08/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Montserrat FOGUET

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 3154	**E2024A6I40005805**	**Allison Douglas**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
120600	**37 CFR 1.19 (Document supply fees); 37 CFR 1.21 (Miscellaneous fees and charges)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	260.00	1	260.00
			TOTAL AMOUNT:	**$260.00**

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

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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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**11/06/2024 06:39:32 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Allison Douglas
PATENT CENTER #	67870373	FILING DATE	12/08/2023
CUSTOMER #	12779	FIRST NAMED INVENTOR	Montserrat FOGUET
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	James Velema

Documents

TOTAL DOCUMENTS: 5

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
748419_BFR9-002_IDS-SB08.pdf	2	Information Disclosure Statement (IDS) Form (SB08)	180 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
748419_BFR9-002_Transmittal-Ltr_JHV.pdf	2	Transmittal Letter	134 KB
ACHARYA_2002_NPL.pdf	8	Non Patent Literature	751 KB
DESPIEGELEER_2006_NPL.pdf	11	Non Patent Literature	895 KB
CHANGEZ_2006_NPL.pdf	8	Non Patent Literature	943 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
748419_BFR9-002_IDS-SB08.pdf	25E185530075B8FA9CFED319C732FDAADCC13CC004E15696F9F3177B38EAAA8E85EB2DBE4349773685B752E43002956CE7D2D72F5DC543E523B5629A6F743281
748419_BFR9-002_Transmittal-Ltr_JHV.pdf	51C548FB3664D27A9BF77DC3AC78B5D2CBED0E6D3A950DEB135D0B4F03DCACED0D9B21901B894B6F0C3D52F1DEFF84BF7C5578EE3CA8B9E343A45FC11163C092
ACHARYA_2002_NPL.pdf	98BDA33EE6FB6CC539EA302A28459579EEC5F3B8F4D1E3A59A2B0B52BE87DE1F3BBCC0714A86516374C5D68B64C98AB65DFC0932A99539D0C2CAF7FF13A96FC9
DESPIEGELEER_2006_NPL.pdf	1553CC64CC6B1D0749BAF485BA85196F0A47A6F9560B9CEFC2BE8FE345F92B685CFB3249CEC0BCC9C3FD661EE7A3F518E6B71E2246A157B63862CF47CAC6DA70
CHANGEZ_2006_NPL.pdf	B2BB9AB47FE7F79E9D73396172AA9651C06DB093D3CAD1CE8C5BF3B56444AE6E987224ECA22444AEBD2B96F083168763AFF8292087D0087D02E071F7D197C685

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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	18/533,497
				Filing Date/371(c) Date	12/08/2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	1	of	2	*Attorney Docket Number*	748419: BFR9-002

U.S. PATENTS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Issue Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.				

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Publication Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 20030148927 A1	08/07/2003	PATT et al.	
	2.	US 20090110703 A1	04/30/2009	TOLLA et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document Country Code Number Kind Code *(if known)*	Publication Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Translation
	1.				

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.	Translation
	1.	ACHARAYA et al., "Physicochemical Investigations of Microemulsification of Coconut Oil and Water Using Polyoxyethylene 2-Cetyl Ether (Brij 52) and Isopropanol or Ethanol", Journal of Colloid and Interface Science, 2002, 245: 163-170.	
	2.	CHANGEZ et al., "Effect of the composition of lecithin/n-propanol/isopropyl myristate/water microemulsions on barrier properties of mice skin for transdermal permeation of tetracaine hydrochloride: In vitro", Colloids and Surfaces B: Biointerfaces, 2006, 50: 18-25.	
	3.	DE SPIEGELEER et al., "The Importance of the Cosolvent Propylene Glycol on the Antimicrobial Preservative Efficacy of a Pharmaceutical Formulation by DOE-Ruggedness Testing", Informa Healthcare; Pharmaceutical Development and Technology, 2006, 11: 275-284.	

Examiner Signature		Date Considered	

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/533,497
				Filing Date/371(c) Date	12/08/2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	2	of	2	Attorney Docket Number	748419: BFR9-002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James H. Velema/	Date (YYYY-MM-DD)	2024-11-06
Name/Print	James H. Velema, Esq.	Registration Number	56,130

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 1.14. This collection is estimated to take 1 hour 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 require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, VA 22313-1450.**

Examiner Signature		Date Considered	

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

Web Search History

date, time	web site	search string
12/7/2024 6:24:40 AM	Google Scholar	(5-aminolevulinic-acid)(nanoemulsion)(sorbitol)(propylene-glycol)
12/7/2024 6:24:40 AM	Google Patents	Search Term 1 (5-aminolevulinic-acid)(nanoemulsion)(sorbitol)(propylene-glycol)
12/7/2024 6:24:59 AM	Google Scholar	(5-aminolevulinic-acid)(nanoemulsion)(sorbitol)(propylene-glycol)(propanol)
12/7/2024 6:24:59 AM	Google Patents	Search Term 1 (5-aminolevulinic-acid)(nanoemulsion)(sorbitol)(propylene-glycol)(propanol)
12/7/2024 6:25:24 AM	Google Scholar	(5-aminolevulinic-acid)(nanoemulsion)(sorbitol)(propylene-glycol)(propanol)(phosphatidylcholine)
12/7/2024 6:25:24 AM	Google Patents	Search Term 1 (5-aminolevulinic-acid)(nanoemulsion)(sorbitol)(propylene-glycol)(propanol)(phosphatidylcholine)

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	100	aminolevulinic adj2 acid WITH nanoemulsion	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/12/06 12:16 PM
L2	91	L1 AND ((A61K41/0061 OR A61K9/0014 OR A61K9/1075 OR A61K31/197 OR A61K2800/21 OR A61K8/375 OR A61K9/107 OR A61K8/06 OR A61K8/4993 OR A61K8/553 OR A61K47/10 OR A61K2800/413 OR A61K47/24 OR A61K8/34 OR A61K8/44 OR A61K9/0019 OR A61K49/0021 OR A61K9/06 OR A61K47/183 OR A61K41/0052 OR A61K47/26 OR A61K47/555 OR A61K31/337 OR A61K47/545 OR A61K47/557 OR A61K47/585 OR A61K47/68 OR A61K49/0043 OR A61K51/04 OR A61K51/0482 OR A61K51/0497 OR A61K51/088 OR A61K45/06 OR A61K47/14 OR A61K47/34 OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/12/06 12:50 PM

		A61K47/44 OR A61K47/6907 OR A61K31/196 OR A61K31/655 OR A61K47/551 OR A61K49/0036 OR A61K49/0082 OR A61K8/046 OR A61K2800/30 OR A61K2800/592 OR A61K2800/87 OR A61K31/19 OR A61K31/195 OR A61K31/355 OR A61K31/75 OR A61K41/0071 OR A61K41/008 OR A61K47/36 OR A61K47/38 OR A61K47/6923 OR A61K47/6929 OR A61K8/068 OR A61K8/37 OR A61K8/731 OR A61K8/90 OR A61K9/08 OR A61K9/7015 OR A61K31/436 OR A61K31/60 OR A61K47/12 OR A61K49/0019 OR A61K49/1809 OR A61K8/062 OR A61K9/122 OR A61K9/124 OR A61K9/127).cpc.)					
L3	23	aminolevulinic adj2 acid WITH nanoemulsion AND sorbitol AND propylene adj2 glycol	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/12/06 12:50 PM
L4	14	((("BIOFRONTERA") near3 ("BIOSCIENCE") near3 ("GMBH"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/12/06 12:51 PM
L5	6	((("FOGUET") near3	(US-PGPUB; USPAT;	OR	ON	ON	2024/12/06

		("Montserrat")) OR (("MÖLLMANN") near3 ("Lars"))).INV.	USOCR; EPO; JPO; DERWENT)				12:52 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	23	L1 AND ((A61K41/0061 OR A61K9/0014 OR A61K9/1075 OR A61K31/197 OR A61K2800/21 OR A61K8/375 OR A61K9/107 OR A61K8/06 OR A61K8/4993 OR A61K8/553 OR A61K47/10 OR A61K2800/413 OR A61K47/24 OR A61K8/34 OR A61K8/44 OR A61K9/0019 OR A61K49/0021 OR A61K9/06 OR A61K47/183 OR A61K41/0052 OR A61K47/26 OR A61K47/555 OR A61K31/337 OR A61K47/545 OR A61K47/557 OR A61K47/585 OR A61K47/68 OR A61K49/0043 OR A61K51/04 OR A61K51/0482 OR A61K51/0497 OR A61K51/088 OR A61K45/06 OR A61K47/14 OR A61K47/34 OR A61K47/44 OR A61K47/6907 OR A61K31/196 OR A61K31/655 OR A61K47/551 OR A61K49/0036 OR A61K49/0082 OR A61K8/046 OR A61K2800/30 OR A61K2800/592 OR A61K2800/87 OR A61K31/19 OR A61K31/195 OR	(US-PGPUB; USPAT)	OR	ON	ON	2024/12/06 12:50 PM

		A61K31/355 OR A61K31/75 OR A61K41/0071 OR A61K41/008 OR A61K47/36 OR A61K47/38 OR A61K47/6923 OR A61K47/6929 OR A61K8/068 OR A61K8/37 OR A61K8/731 OR A61K8/90 OR A61K9/08 OR A61K9/7015 OR A61K31/436 OR A61K31/60 OR A61K47/12 OR A61K49/0019 OR A61K49/1809 OR A61K8/062 OR A61K9/122 OR A61K9/124 OR A61K9/127).cpc.)					
N2	7	L3 AND ((A61K2800/21 OR A61K8/375 OR A61K8/06 OR A61K8/4993 OR A61K8/553 OR A61K2800/413 OR A61K8/34 OR A61K8/44 OR A61K9/107 OR A61K31/197 OR A61K47/10 OR A61K47/14 OR A61K9/0014 OR A61K9/1075 OR A61K31/196 OR A61K41/0061 OR A61K47/24 OR A61K47/26 OR A61K8/046 OR A61K2800/30 OR A61K2800/592 OR A61K2800/87 OR A61K41/008 OR A61K47/6923 OR A61K47/6929 OR A61K8/068 OR A61K8/37 OR A61K8/731 OR A61K8/90 OR A61K9/06 OR A61K9/7015 OR A61K31/436 OR A61K47/12 OR	(US-PGPUB; USPAT)	OR	ON	ON	2024/12/06 12:51 PM

		A61K47/36 OR A61K8/062 OR A61K9/122 OR A61K9/124 OR A61K9/127).cpc.)					

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/533,497	FOGUET et al.
	Examiner	Art Unit
	CELESTE A RONEY	1612

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
A61K9/1075; A61K9/127; A61K41/0061; A61K47/10; A61K47/12; A61K47/14; A61K47/24; A61K47/26; A61K47/36 further limited by nanoemulsion and 5-aminolevulinic acid and propylene glycol	04/24/2024	CR
A61K9/1075; A61K9/127; A61K41/0061; A61K47/10; A61K47/12; A61K47/14; A61K47/24; A61K47/26; A61K47/36 further limited by nanoemulsion and 5-aminolevulinic acid	08/27/2024	CR
A61K9/1075; A61K9/127; A61K41/0061; A61K47/10; A61K47/12; A61K47/14; A61K47/24; A61K47/26; A61K47/36 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR

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.

/CELESTE A RONEY/ Primary Examiner, Art Unit 1612	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/533,497	FOGUET et al.
	Examiner	Art Unit
	CELESTE A RONEY	1612

Search Notes		
Search Notes	**Date**	**Examiner**
palm inventor search. filing receipt search. google (patents and scholar) and PE2E searches further limited by nanoemulsion and 5-aminolevulinic acid and propylene glycol	04/24/2024	CR
palm inventor search. filing receipt search. google (patents and scholar) and PE2E searches further limited by nanoemulsion and 5-aminolevulinic acid	08/27/2024	CR
palm inventor search. filing receipt search. google (patents and scholar) and PE2E searches further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
A61K9	1075 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR
A61K9	127 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR
A61K14	0061 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR
A61K47	10 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR
A61K47	12 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR
A61K47	14 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR
A61K47	24 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR
A61K47	26 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR
A61K47	36 further limited by nanoemulsion and 5-aminolevulinic acid	12/07/2024	CR

/CELESTE A RONEY/ Primary Examiner, Art Unit 1612	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/533,497	FOGUET et al.
	Examiner	**Art Unit**
	CELESTE A RONEY	1612

CPC						
Symbol					**Type**	**Version**
A61K	/	9	/	1075	F	2013-01-01
A61K	/	9	/	127	I	2013-01-01
A61K	/	41	/	0061	I	2013-01-01
A61K	/	47	/	10	I	2013-01-01
A61K	/	47	/	12	I	2013-01-01
A61K	/	47	/	14	I	2013-01-01
A61K	/	47	/	24	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	36	I	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	17	
/CELESTE A RONEY/ Primary Examiner, Art Unit 1612	07 December 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office

Part of Paper No.: 20241206

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/533,497	FOGUET et al.
	Examiner	**Art Unit**
	CELESTE A RONEY	1612

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K9/107	/	9	/	107

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 17	
/CELESTE A RONEY/ Primary Examiner, Art Unit 1612 (Primary Examiner)	07 December 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/533,497	FOGUET et al.
	Examiner	**Art Unit**
	CELESTE A RONEY	1612

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	19	10	30												
2	22	11	31												
3	23	12	32												
4	24	13	33												
5	25	14	34												
6	26	15	35												
7	27	16	36												
8	28	17	37												
9	29														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 17	
/CELESTE A RONEY/ Primary Examiner, Art Unit 1612 (Primary Examiner)	07 December 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No.: 20241206

Examiner-Initiated Interview Summary	**Application No.** 18/533,497	**Applicant(s)** FOGUET et al.		
	Examiner CELESTE A RONEY	**Art Unit** 1612	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
CELESTE A RONEY	Primary Examiner	Telephonic
Laura Labeots	Attorney	

Date of Interview: 06 December 2024

Issues Discussed:

Other

Applicant's representative (Ms. Labeots) and the Examiner discussed the claimed subject matter, in order to ready the claims for allowance. The Examiner did not agree that the claims were in condition for allowance, and suggested the cancellation of claims 38-39. The Examiner agreed to await Ms. Labeots' response before proceeding with the next round of prosecution.

/CELESTE A RONEY/ Primary Examiner, Art Unit 1612	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Bibliographic Data

Application No: 18/533,497

Foreign Priority claimed: (•) Yes ( ) No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /CELESTE A RONEY/ Examiner's Signature | Initials

Title: NANOEMULSION WITHOUT PROPYLENE GLYCOL

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/08/2023	424	1612	748419: BFR9-002
RULE			

APPLICANTS

Biofrontera Bioscience GmbH, Leverkusen, GERMANY

INVENTORS

Montserrat FOGUET, Leverkusen, GERMANY

Lars MÖLLMANN, Leverkusen, GERMANY

CONTINUING DATA

FOREIGN APPLICATIONS

PCT/EP2023/059291 04/06/2023

IF REQUIRED, FOREIGN LICENSE GRANTED**

12/20/2023

STATE OR COUNTRY

GERMANY

ADDRESS

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109
UNITED STATES

FILING FEE RECEIVED

$6,320

AFCP 2.0 Decision	Application No.	Applicant(s)	
	18/533,497	FOGUET et al.	
	Examiner	Art Unit	AIA (FITF) Status
	CELESTE A RONEY	1612	Yes

This is in response to the After Final Consideration Pilot request filed 06 November 2024.

1. **Improper Request** – The AFCP 2.0 request is improper for the following reason(s) and the after final amendment submitted with the request will be treated under pre-pilot procedure.

   ☐ An AFCP 2.0 request form PTO/SB/434 (or equivalent document) was not submitted.

   ☐ A non-broadening amendment to at least one independent claim was not submitted.

   ☐ The request is not the first proper AFCP 2.0 request submitted in response to the most recent final rejection.

   ☐ Other: _____

2. **Proper Request**

   A. After final amendment submitted with the request will not be treated under AFCP 2.0.
   The after final amendment cannot be reviewed and a search conducted within the guidelines of the pilot program.

   ☐ The after final amendment will be treated under pre-pilot procedure.

   B. Updated search and/or completed additional consideration.
   The examiner performed an updated search and/or completed additional consideration of the after final amendment within the time authorized for the pilot program. The result(s) of the updated search and/or completed additional consideration are:

   ☐ 1. All of the rejections in the most recent final Office action are overcome and a Notice of Allowance is issued herewith.

   ☐ 2. The after final amendment would not overcome all of the rejections in the most recent final Office action . See attached interview summary for further details.

   ☐ 3. The after final amendment was reviewed, and it raises a new issue(s). See attached interview summary for further details.

   ☑ 4. The after final amendment raises new issues, but would overcome all of the rejections in the most recent final Office action. A decision on determining allowability could not be made within the guidelines of the pilot. See attached interview summary for further details, including any newly discovered prior art.

   ☐ 5. Other: _____

   Examiner Note: Please attach an interview summary when necessary as described above.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	18/533,497
				Filing Date/371(c) Date	12/08/2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	1	of	2	*Attorney Docket Number*	748419: BFR9-002

U.S. PATENTS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Issue Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.				

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Publication Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 20030148927 A1	08/07/2003	PATT et al.	
	2.	US 20090110703 A1	04/30/2009	TOLLA et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document Country Code Number Kind Code *(if known)*	Publication Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Translation
	1.				

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.	Translation
	1.	ACHARAYA et al., "Physicochemical Investigations of Microemulsification of Coconut Oil and Water Using Polyoxyethylene 2-Cetyl Ether (Brij 52) and Isopropanol or Ethanol", Journal of Colloid and Interface Science, 2002, 245: 163-170.	
	2.	CHANGEZ et al., "Effect of the composition of lecithin/n-propanol/isopropyl myristate/water microemulsions on barrier properties of mice skin for transdermal permeation of tetracaine hydrochloride: In vitro", Colloids and Surfaces B: Biointerfaces, 2006, 50: 18-25.	
	3.	DE SPIEGELEER et al., "The Importance of the Cosolvent Propylene Glycol on the Antimicrobial Preservative Efficacy of a Pharmaceutical Formulation by DOE-Ruggedness Testing", Informa Healthcare; Pharmaceutical Development and Technology, 2006, 11: 275-284.	

Examiner Signature		Date Considered	

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

12/07/2024 /CELESTE A RONEY/

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/533,497
				Filing Date/371(c) Date	12/08/2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	2	of	2	Attorney Docket Number	748419: BFR9-002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James H. Velema/	Date (YYYY-MM-DD)	2024-11-06
Name/Print	James H. Velema, Esq.	Registration Number	56,130

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 1.14. This collection is estimated to take 1 hour 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 require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, VA 22313-1450.**

Examiner Signature		Date Considered	

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

/CELESTE A RONEY/ 12/07/2024
ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

12779 7590 12/24/2024

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	
ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 12/24/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

TITLE OF INVENTION: NANOEMULSION WITHOUT PROPYLENE GLYCOL

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	03/24/2025

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

12779 7590 12/24/2024

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

TITLE OF INVENTION: NANOEMULSION WITHOUT PROPYLENE GLYCOL

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	03/24/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
RONEY, CELESTE A	1612	424-450000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 12/24/2024

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	
ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 12/24/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 1.14. This collection is estimated to take 30 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 18/533,497	Applicant(s) FOGUET et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	AIA (FITF) Status Yes

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to amended claims 11/6/24.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☑ The allowed claim(s) is/are 19 and 22-37 . As a result of the allowed claim(s), 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.**

4. ☐ 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)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 11/6/24.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 12/6/24.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☑ Other PTO-2323.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Laura Labeots on 12/10/2024.

The application has been amended as follows:

1. Claims 38-39 have been cancelled without prejudice thereunto.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

The closest prior art, Schmid et al (USP 6,559,183), is excluded by the claimed subject matter of essentially no propylene glycol and essentially no sorbitol (See Schmid at Table 2, comprising 0.25 % sorbitol).

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A RONEY whose telephone number is (571)272-5192. The examiner can normally be reached Monday-Friday; 8 AM-6 PM.

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, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 01/08/2025

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
01/08/2025	ELECTRONIC

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.

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bostonpatent@lathropgage.com

Corrected ***Notice of Allowability***	**Application No.** 18/533,497	**Applicant(s)** FOGUET et al.	
	Examiner CELESTE A RONEY	**Art Unit** 1612	**AIA (FITF) Status** Yes

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to Printer query form, dated 12/28/2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☐ The allowed claim(s) is/are _____ . As a result of the allowed claim(s), 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.**

4. ☑ 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)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 01/22/2025

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
01/22/2025	ELECTRONIC

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Corrected ***Notice of Allowability***	**Application No.** 18/533,497	**Applicant(s)** FOGUET et al.	
	Examiner CELESTE A RONEY	**Art Unit** 1612	**AIA (FITF) Status** Yes

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1. ☑ This communication is responsive to printer rush, 1/8/25.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☑ The allowed claim(s) is/are 19 and 22-37 . As a result of the allowed claim(s), 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.**

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   1. ☑ Certified copies of the priority documents have been received.
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6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CELESTE A RONEY/
Primary Examiner, Art Unit 1612

Bibliographic Data

Application No: 18/533,497

Foreign Priority claimed: (•) Yes ( ) No

35 USC 119 (a-d) conditions met: [ ] Yes [✓] No [ ] Met After Allowance

Verified and Acknowledged: /CELESTE A RONEY/ Examiner's Signature [ ] Initials

Title: NANOEMULSION WITHOUT PROPYLENE GLYCOL

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/08/2023	424	1612	748419: BFR9-002
RULE			

APPLICANTS

Biofrontera Bioscience GmbH, Leverkusen, GERMANY

INVENTORS

Montserrat FOGUET, Leverkusen, GERMANY

Lars MÖLLMANN, Leverkusen, GERMANY

CONTINUING DATA

FOREIGN APPLICATIONS

PCT/EP2023/059291 04/06/2023

IF REQUIRED, FOREIGN LICENSE GRANTED**

12/20/2023

STATE OR COUNTRY

GERMANY

ADDRESS

Lathrop GPM LLP
28 State Street
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Boston, MA 02109
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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**01/24/2025 02:21:05 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	James Velema
PATENT CENTER #	68901112	FILING DATE	12/08/2023
CUSTOMER #	12779	FIRST NAMED INVENTOR	Montserrat FOGUET
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
CorrectedADS.pdf	3	Application Data Sheet to update/correct info	63 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
CorrectedADS.pdf	D99A77D6DD7F8CF6C8EB2DD7A1BA6CC41BE540739C23BFA4FFD88F5FA5F6FEDD2D174FD18A90D0CE80D59593F30B7A39166817017988F5869E011F4F683D20DF

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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 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

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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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Corrected Application Data Sheet

18533497 : NANOEMULSION WITHOUT PROPYLENE GLYCOL

~~Strike-through~~ indicates removal of data from existing record Underline indicates new data being added to the application If no data is shown, no data has been corrected

Inventor Information

Data of record	Updated Data
No data change in this section	

Application Information

Title of Invention	**NANOEMULSION WITHOUT PROPYLENE GLYCOL**
Attorney Docket Number	**748419: BFR9-002**
Entity Status	**Regular Undiscounted**

Domestic Benefit/National Stage Information

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c), 386(c), or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be

made part of the specification.

Data of record	Updated Data
No data change in this section	

Foreign Priority Information

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the Application Data Sheet constitutes the claim for priority as required by 35 U.S.C. 119 (b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Data of record		Updated Data	
Application number	PCT/EP2023/059291		
Country	EP		
Filing date	04/06/2023		
Access code	~~null~~	Access code	8CCF

Applicant Information

The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46.

Data of record	Updated Data
No data change in this section	

Assignee Information including Non-Applicant Assignee Information

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Data of record	Updated Data
No data change in this section	

Signature

NOTE:

This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See CFR 1.4(d) for the manner of making signatures and certifications.

Signature	First name	Last name	Registration #	Date
/James H. Velema/	James	Velema	56130	01/24/2025

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Application number: PCT/EP2023/059291

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Bescheinigung

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Certificate

The attached documents are exact copies of the international patent application described on the following page, as originally filed.

Attestation

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet internationale spécifiée à la page suivante.

Anmeldenummer Nr. Application No Demande de brevet n°

PCT/EP2023/059291

Der Präsident des Europäischen Patentamts, i.A.
For the President of the European Patent Office
Le Président de l'Office européen des brevets, p.o.

V. Joseph

Europäisches Patentamt
European Patent Office
Office européen des brevets

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldenummer - Application no. - Demande n°
PCT/EP2023/059291

Anmelder - Applicant(s) - Demandeur(s)
1) BIOFRONTERA BIOSCIENCE GMBH - Leverkusen, Germany

Bezeichnung der Erfindung - Title of the invention - Titre d'invention
NANOEMULSION WITHOUT PROPYLENE GLYCOL

Anmeldetag - Date of filing - Date de dépôt
06 April 2023 (06.04.2023)

In Anspruch genommene Priorität(en) - Priority(ies) claimed - Priorité(s) revendiquée(s)

Nanoemulsion without propylene glycol

The present invention relates to a composition for topical use comprising an oil in water nanoemulsion and an active ingredient, wherein the composition is essentially free of propylene glycol. The formulation shows less impurities and side products of the active ingredient over time and therefore ensures a higher quality standard and an improved shelf-life.

Background of the invention

Dispersions are colloidal systems, which include micelles, liposomes, virosomes, emulsions and micro-, nanoemulsions, suspensions and polymer solutions. Emulsions or micro emulsions can be oil in water, water in oil or middle phased dispersions, often dispersed with surfactants as emulsifiers. Nanoemulsions are a subgroup of the emulsions that contain very fine oil in water dispersions. Nanoemulsions are highly homogeneous, transparent, and slightly opalescent dispersions (or emulsions) of oil and water. The dispersed droplets (liquid) or vesicles in such emulsions are composed of a lipid core surrounded by at least one surfactant or emulsifier monolayer. Nanoemulsions are characterized by a mean particle or vesicle size of less than 200 nm, often less than 100 nm and a narrow monodisperse particle or vesicle size distribution.

Nanoemulsions are thermodynamically more stable than conventional emulsions, making them a favorable vehicle for pharmaceutical compositions, which have to maintain stability for long periods of time. Nanoemulsions can be in a metastable state and the structure depends often of the manufacturing process, making them a fragile system and complicated to formulate to a pharmaceutical composition with a long shelf-life under different storage conditions. If destabilized they can become heterogeneous, milky and/or exhibit phase separation. However, they can provide useful applications in skin care in that they may exhibit good textural and sensual properties due to the very fine droplet or globule size.

Nanoemulsions are generally manufactured by mechanical fragmentation of an oily phase in an aqueous phase in the presence of a surfactant. The very small size of the oily globules is often obtained by virtue of at least one pass through a high-pressure homogenizer or a sonicator.

Formulations comprising nanoemulsions as vehicles for the delivery of active ingredients often contain adjuvants, such as organic molecules or solvents, e.g., propylene glycol. Propylene glycol is known to have advantageous properties, such as penetration enhancing or preservative effects (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 of the invention

A first aspect of the invention 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 aspect of the invention 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 aspect of the invention 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.

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 of any other integer or step or group of integer or step. As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural referents, unless the content clearly dictates otherwise.

Formulating a topical pharmaceutical gel composition is a highly complex process, which needs to take account of different aspects, such as pH, solubility, polymorphism, applicability, and overall stability of the pharmaceutical composition. Additionally, one must consider the benefits and constraints of the active pharmaceutical ingredient (API), excipients, the interaction of all components and the manufacturing process. In oil in water nanoemulsion formulations, there are two different phases, which may need to be stabilized and compliant with patients: one is the hydrophobic carrier component, which is usually the carrier and needs to stabilize and release the API and the other one the aqueous component. All these aspects lead to complex formulations with a large number of ingredients. However, the more ingredients a composition has, the more problems/pitfalls may arise during formulation, such as undesired side reactions/interactions of ingredients or higher impurity profiles. Additionally, patients may have allergic reactions or skin irritations to various components after application on the skin. Therefore, a pharmaceutical composition should only have the necessary ingredients and omit as many adjuvants and/or excipients as possible. One very popular class of excipients in cosmetics, pharmaceutical or food products are polyols, in particular propylene glycol. It may be used as a solvent, humectant, preservative agent or emulsion stabilizer. One rather attractive property in topical pharmaceuticals is its ability to enhance penetration of active ingredients.

The prior art fails to teach a pharmaceutical composition comprising a nanoemulsion composition containing an active agent comprising a carboxylic acid group or a derivative, or pharmaceutically acceptable salt of a carboxylic acid group, being free of propylene glycol.

In the context of the present specification, the term “propylene glycol” refers to propane-1,2-diol (also known as 1,2-propanediol, α-propylene glycol, 1,2-dihydroxypropane, methyl ethyl glycol or methylethylene glycol).

As described above, nanoemulsions tend to coalesce under certain circumstances, such as exposure to extreme temperature differences, leading to bigger droplet sizes and harm the nanoemulsion quality.

These aspects make it clear that design and formulation of a composition with a high penetration and improved impurity profile is highly desirable.

The examples of the present invention demonstrate that the omission of propylene glycol in a pharmaceutical formulation comprising an active agent, in particular an hydrophilic active agent and/or an active agent comprising a carboxylic acid group or a derivative, or pharmaceutically acceptable salt of a carboxylic acid shows a better impurity profile without restricting the penetration properties of the topical pharmaceutical composition compared to a pharmaceutical formulation comprising propylene glycol. Surprisingly, the penetration of the vehicles is improved by the omission of propylene glycol, which is a non-obvious discovery for a person skilled in the art.

The terms “active agent” and “active ingredient” are used interchangeably herein. As used herein, “active agent”, includes an active pharmaceutical agent (herein also termed “pharmaceutical active agent” or “active pharmaceutical ingredient”, “API”) and an active cosmetic agent (herein also termed “cosmetic active agent”). As used herein, an active pharmaceutical agent is defined as the chemical, biological, mineral or any other entity or component responsible for the therapeutic (pharmacological, physiological, physical, etc.) effects in a product. As used herein, an active cosmetic agent is defined as the chemical, biological, mineral or any other entity or component responsible for the cosmetic effects in a product. The active agent may be a plant extract. The active agent may be present as a pharmaceutically acceptable salt. The active agent may be present as a cosmetically acceptable salt.

In the following specification, unless specifically mentioned otherwise, the term “active agent comprising a carboxylic acid group” also refers to active agents comprising a derivative of a carboxylic acid group, or a salt of a carboxylic acid group.

Preferably, the active agent comprising a carboxylic acid group is a hydrophilic active agent. It is preferred that the hydrophilic active agent has a logP value equal to or lower than 1, lower than 0.5, lower than 0.4, lower than 0.3, lower than 0.2, lower than 0.1 or a negative lg P value, wherein P is the octanol-water partition-coefficient.

In the context of the present specification, the term “derivative of a carboxylic acid group” refers to a carboxylic acid group that has formed a chemical compound by reacting with another chemical moiety, in particular a carboxylic acid group that has formed an ester by reacting with a hydroxy group.

Without wishing to be bound by theory, active agents comprising a carboxylic acid group may undergo nucleophilic reactions to form undesired products, such as esters, with propylene glycol. In instances where the active agent comprises a derivative of carboxylic acid group in the form of an ester, the active agent may still undergo nucleophilic reactions to form undesired products, such as esters, with propylene glycol, e.g. via transesterification. Omission of propylene glycol may thus lead to less undesired side products.

In addition to an extinction of the expected esters formed by 5-ALA and propylene glycol, the examples show that in a 5-ALA gel formulation of the invention, being free of propylene glycol, a previously detected impurity with m/z of 246 was surprisingly greatly reduced. This reduction is a meaningful improvement in view of prior art formulations: Firstly, this impurity poses the highest probability for “out-of-specification” results during stability testing. Secondly, the amount of this impurity increases at higher temperatures and after longer storage. A reduction of this impurity, as observed in the formulation of the invention, being free of propylene glycol, improves stability under stressed conditions and allows for longer storage. Additionally, the unknown impurities may

be harmful for patients, since it is impossible to predict their metabolism and long-term influence on the human body.

Furthermore, functional in vitro tests described in the Examples revealed that omission of propylene glycol does not impair the drug release and skin penetration qualities of the formulation at any rate. Improved penetration results of ALA were achieved with the formulation of the invention without propylene glycol compared to comparative formulation with propylene glycol. The formulation without propylene glycol has non-inferior penetration properties compared to the formulation containing propylene glycol. This finding is surprising, as propylene glycol is a well-known and highly effective penetration enhancer used in topical pharmaceutical formulations.

In an in-vitro release assay, the formulation of the invention, being free of propylene glycol, released more 5-ALA than the comparative formulation comprising propylene glycol. This finding is surprising since the addition of polyols, in particular glycerol or propylene glycol, which does not evaporate upon application, is expected to improve adhesion and thus improves drug release.

The formulations of the invention comprise two phases:

(I) an aqueous phase or aqueous component,

(II) a lipid carrier phase.

A first aspect of the invention 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.

In preferred embodiments, the formulation is a pharmaceutical formulation.

In preferred embodiments, the formulation is for topical use.

In preferred embodiments of the formulations described in the present invention, the aqueous component comprises an aqueous phase or forms an aqueous phase. Preferably, the active agent is dissolved in the aqueous phase.

In preferred embodiments of the formulations described in the present invention, the carrier component comprises or consists of nanovesicles. Preferably, the active agent is capable to interact with the surface of the nanovesicles.

The active agent may be present as a salt. Examples in which the active agent is present as a salt are e.g. 5-aminolevulinic acid HCl, and 5-aminolevulinic acid phosphate.

In even more preferred embodiments of the formulations described in the present invention, the active agent is dissolved in the aqueous phase and is capable to interact with the surface of the nanovesicles. The active agent preferably comprises a carboxylic acid group, a derivative of a carboxylic acid group, or pharmaceutically acceptable salt of a carboxylic acid group.

Examples in which the active agent comprises a derivative of a carboxylic acid group are e.g. esters of 5-aminolevulinic acid such as methyl δ-aminolevulinate (MAL), and hexyl δ-aminolevulinate (HAL).

Examples in which the active agent comprises a pharmaceutically acceptable salt of a derivative of a carboxylic acid group are e.g. methyl δ-aminolevulinate hydrochloride, hexyl δ-aminolevulinate hydrochloride.

In all embodiments described herein, the salt of a carboxylic acid group is preferably a pharmaceutically acceptable salt of a carboxylic acid group. As used herein "capable to interact with the surface of the nanovesicles" includes non-covalently binding of the active agent to the nanovesicles, in particular to the surface of the nanovesicles. For example, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 70%, at least 80%, or at least 90%, of the total amount of active agent interacts with the surface of the nanovesicles, the balance being dissolved in the aqueous phase.

In the context of the present specification, the expression "the formulation comprises less than or equal to 0.9% w/w of propylene glycol" is meant to include embodiments in which the formulation comprises essentially no propylene glycol.

In preferred embodiments, the formulation comprises essentially no propylene glycol.

As used herein, the expressions "essentially free of compound X", "does essentially not comprise compound X", or "comprises essentially no compound X" with respect to a formulation are interchangeable. In particular, these expressions specify that the formulation is either free of compound X or comprises less than 0.1% (w/w), less than 0.08% (w/w), less than 0.07% (w/w), less than 0.06% (w/w), less than 0.05% (w/w), less than 0.04% (w/w), less than 0.03% (w/w), less than 0.02% (w/w), or less than 0.01% (w/w) of compound X based on the total weight of the formulation.

As used herein, the expression "the composition comprises less than X% of compound X", is meant to include embodiments in which the composition is free of compound X.

The formulation may comprise 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 propylene glycol or no propylene glycol.

In particular, the formulation may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of propylene glycol.

More particular, the formulation may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of propylene glycol.

Most particular, the formulation may comprise less than or equal to 0.3% or 0.1% w/w of propylene glycol.

In preferred embodiments, the formulation comprises no propylene glycol.

In addition to comprising no propylene glycol or only small amounts of propylene glycol as defined above, it is preferred that 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 3 carbon atoms (i.e., having not more than 3). Preferably, 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 4, 2 to 5, 2 to 6, 2 to 7, 2 to 8, 2 to 9 or 2 to 10 carbon atoms (i.e., having not more than 4, 5, 6, 7, 8, 9, or 10 carbon atoms, respectively). More preferably, 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 4, 2 to 5, 2 to 6, 2 to 7, 2 to 8, 2 to 9, 2 to 10, 2 to 11 or 2 to 12 carbon atoms (i.e., having not more than 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms, respectively). More preferably, 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 15, 2 to 20, 2 to 25 or 2 to 30 carbon atoms (i.e., having not more than 15, 20, 25 or 30 carbon atoms, respectively). Even more preferably, 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 15, 2 to 20, 2 to 25 or 2 to 30 carbon atoms (i.e., having not more than 15, 20, 25 or 30 carbon atoms, respectively). Even more preferably, 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.

"Non-cyclic polyol" in the context of the present specifications means that the polyol does not comprise any cyclic hydrocarbon moieties, in particular no cyclic sugar moieties. The non-cyclic polyol may be linear or branched. The non-cyclic polyol may be a diol, a triol or may comprise more than three OH groups.

In preferred embodiments, the formulation of the invention comprises no, essentially no or less than 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 a molecular weight of less than 100 g/mol, less than 200 g/mol, less than 300 g/mol, less than 400

g/mol, less than 500 g/mol, less than 600 g/mol, less than 700 g/mol, less than 800 g/mol, less than 900 g/mol, or less than 1000 g/mol.

The formulation of the present invention may be essentially free of glycerin.

The formulation of the present invention may be essentially free of diglycerin.

The formulation of the present invention may be essentially free of polyglycerin.

The formulation of the present invention may be essentially free of diethylene glycol.

The formulation of the present invention may be essentially free of dipropylene glycol.

The formulation of the present invention may be essentially free of butylene glycol.

The formulation of the present invention may be essentially free of pentylene glycol.

The formulation of the present invention may be essentially free of hexylene glycol.

The formulation of the present invention may be essentially free of 1,3-propanediol.

The formulation of the present invention may be essentially free of 1,5-pentanediol.

The formulation of the present invention may be essentially free of octane-1,2-diol.

The formulation of the present invention may be essentially free of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups.

The formulation of the present invention may be essentially free of monosaccharides and disaccharides such as sorbitol, mannitol, and mixtures thereof.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of glycerin or no glycerin. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of glycerin. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of glycerin. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of glycerin. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of diglycerin or no diglycerin. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of diglycerin. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of diglycerin. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of diglycerin. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of polyglycerin or no polyglycerin. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of polyglycerin. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of polyglycerin. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of polyglycerin. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of diethylene glycol or no diethylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of diethylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of diethylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of diethylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of dipropylene glycol or no dipropylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of dipropylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of dipropylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of dipropylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of butylene glycol or no butylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of butylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of butylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of butylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of pentylene glycol or no pentylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of pentylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of pentylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of pentylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of hexylene glycol or no hexylene glycol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of hexylene glycol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of hexylene glycol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of hexylene glycol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of 1,3-propanediol or no 1,3-propanediol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of 1,3-propanediol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of 1,3-propanediol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of 1,3-propanediol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of 1,5-pentanediol or no 1,5-pentanediol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of 1,5-pentanediol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of 1,5-pentanediol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of 1,5-pentanediol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of octane-1,2-diol or no octane-1,2-diol. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of octane-1,2-diol. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of octane-1,2-diol. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of octane-1,2-diol. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups or no polyethyleneglycols. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may comprise less than or equal to 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% w/w of monosaccharides and disaccharides such as sorbitol, mannitol and mixtures thereof or no sugars such as sorbitol, mannitol and mixtures thereof. This formulation may be free of a paraben, as described herein.

In particular, the formulation of the present invention may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of monosaccharides and disaccharides such as sorbitol, mannitol and mixtures thereof. This formulation may be free of a paraben, as described herein.

More particular, the formulation of the present invention may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of monosaccharides and disaccharides such as sorbitol, mannitol and mixtures thereof. This formulation may be free of a paraben, as described herein.

Most particular, the formulation of the present invention may comprise less than or equal to 0.3% or 0.1% w/w of monosaccharides and disaccharides such as sorbitol, mannitol and mixtures thereof. This formulation may be free of a paraben, as described herein.

The formulation of the present invention may be free of, may be essentially free of, or may comprise less than an indicated amount, such as less than 1%, less than 0.99%, less than 0.95%, less than 0.9%, less than 0.8%, less than 0.7%, less than 0.6%, less than 0.5%. less than 0.4%, less than 0.3%, less than 0.2% or less than 0.1% of one polyol, all polyols or any chosen number

of polyols selected from the group consisting of glycerin, diglycerin, polyglycerin, diethylene glycol, propylene glycol, dipropylene glycol, butylene glycol, pentylene glycol, hexylene glycol, 1,3-propanediol, 1,5-pentanediol, octane-1,2-diol, polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups, and monosaccharides or disaccharides such as sorbitol, mannitol and mixtures thereof. The formulation of the present invention may be essentially free of one polyol or any chosen number of polyols selected from the group consisting of glycerin, diglycerin, polyglycerin, diethylene glycol, propylene glycol, dipropylene glycol, butylene glycol, pentylene glycol, hexylene glycol, 1,3-propanediol, 1,5-pentanediol, octane-1,2-diol, polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups, and monosaccharides or disaccharides such as sorbitol, mannitol and mixtures thereof, but may comprise another polyol. The formulation of the present invention may be essentially free of a polyol which is linear or branched, but non-cyclic. The formulation of the present invention may be essentially free of a polyol having a carbon atom number of 2 to 30, more preferably 2 to 20, even more preferably 2 to 10 or 2 to 8, most preferably 2 to 6 or 2 to 3.

The formulation may comprise 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 or no polyol. The polyol may be a polyol as described herein.

The formulation may comprise less than or equal to 0.7%, 0.5%, 0.3% or 0.1% w/w of a polyol. The polyol may be a polyol as described herein.

The formulation may comprise less than or equal to 0.5%, 0.3% or 0.1% w/w of a polyol. The polyol may be a polyol as described herein.

The formulation may comprise less than or equal to 0.3% or 0.1% w/w of a polyol. The polyol may be a polyol as described herein.

The formulation may comprise no polyol.

The small size of the nanovesicles and their high homogeneity confers on them advantageous properties which distinguish them from conventional emulsions: The nanoemulsions and formulations comprising nanoemulsions of the present invention are transparent. Further, the nanoemulsion and formulations comprising nanoemulsions of the present invention can carry active agents more efficiently and, thus, become increasingly important in the field of medicine and pharmacy.

“Aging” as used herein, refers to alteration, disintegration and/or degradation of the formulation, affecting chemical and physical stability during storage, in particular under stressed conditions. Such physical or chemical changes due to storage may include, but are not limited to Ostwald ripening, flocculation, coalescence and/or breaking, which may lead to a change in vesicle size or polydispersity index. “Aging” as used herein, may include the formation of impurities after storage, for example for 6 months at 25°C or 40°C. Typical impurities of formulations comprising

5-aminolevulinic acid as active agent are 2-hydroxypropyl-δ-aminolevulinate and an impurity characterized by m/z = 246.

The inventors have found that the formulations of the present invention are surprisingly stable and resistant to aging. In particular, the formulations of the present invention comprise fewer impurities than prior art formulations, even after storage, for example for 6 months at 25°C or 40°C.

As used herein, “stressed conditions” for storage are temperatures significantly exceeding room temperature (e.g., 40°C).

As used herein, a “nanovesicle emulsion” or a “nanoemulsion” is a dispersion of oil in water (oil-in-water dispersion, oil-in-water emulsion, O/W emulsion). The nanoemulsion can be monophasic, transparent and/or slightly opalescent. The nanoemulsions of the present invention can be colloidal systems, which include dispersed nanovesicles comprising a lipid core surrounded by at least one surfactant or emulsifier monolayers. The nanoemulsions and the formulations comprising the nanoemulsions of the present invention are characterized by a mean particle or nanovesicle size of less than 500 nm less, than 200 nm, or less than 100 nm. The nanoemulsions and the formulations comprising the nanoemulsions of the present invention has a narrow (homogeneous) nanovesicle size distribution, for example a nanovesicle size distribution characterized by a polydispersity index of less than or equal to 0.4.

As used herein, “nanovesicle”, “nano vesicle”, “lipid vesicles”, “oil droplets”, “droplets” and “oil globules" are interchangeable and refer to small oil droplets in an oil in water emulsion. A lipid vesicle of an average size (see above, e.g., below 500, 200, 100 nm) that is compiled of a monolayer of a surfactant and a lipid core. In the present invention, the nanovesicles can have a size of less than or equal to 500 nm, or less than or equal to 300 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 100 nm.

As used herein, the term “nanoparticle” or “nano particle”, is distinguished form “nanovesicles”, and refers to solid particles, which are not described in this invention. The formulation of the present invention may be a formulation which is essentially free of nanoparticles. “Essentially free of nanoparticles” means, that the formulation comprises less than or equal to 2% by weight, or less than or equal to 1% by weight of, or does not comprise nanoparticles. Nanoparticles are mainly inorganic, solid lipids or polymeric solid particles may have a size of below 100 nm, below 200 nm, or below 500. The size can be determined by the methods as described herein. For example, the formulation may be essentially free of nanoparticles with a diameter of less than 100 nm, as determined by dynamic light scattering.

As used herein, “topical use” of the formulation of the invention describes an application to a particular place on or in the body, in particular the human body. This includes, but is not limited to administration of the formulation to body surfaces such as the skin or mucous membranes. The

topical use can be epicutaneous, meaning that the formulation is directly administered to the skin. In particular the topical use is a pharmaceutical use.

As used herein, the "stability" of a formulation comprising nanovesicles, as described herein, includes, but is not limited to the physical and chemical stability. In particular, in the present invention, a formulation is stable if the integrity of the nanovesicles is found to be stable. A measure known to the skilled person to describe integrity of the nanovesicles is the size, as for example determined by dynamic light scattering, as described herein. The nanovesicles produced according to the invention can have a size below 100 nm, preferably below 50 nm, more preferably in the range of 20-30 nm, immediately after manufacture. For example, the formulation as described herein is stable if the nanovesicles in the formulation of the present invention have a size (or diameter) of less than or equal to 500 nm or less than or equal to 300 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 100 nm.

"Stability" can also refer to the absence of processes above described as aging, leading to a loss of pharmaceutical functionality or quality. The composition described in this invention is functional or pharmaceutically functional, as long as the vesicle size is less than or equal to 500 nm or less than or equal to 300 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 100 nm.

Furthermore, "stability" can refer to the stable content of the hydrophilic active compound, in particular 5-ALA. During storage, the content of 5-ALA is, for example, considered stable if at least 70%, at least 80% or at least 90% of the content of the active agent is still present, when stored, for example, at stressed conditions, as described herein.

In a formulation of the invention, the 5-ALA content may be

(i) at least 95% after storage for 3 months at 40°C, and/or

(ii) at least 95% or at least 97% after storage for 3, 6, 9 or 12 months at 25°C, and/or

(iii) at least 95%, at least 97% or at least 99% after storage for 12, 18, 24 or 36 months at 5°C.

As used herein "stability" of the compositions also refers to a low content of impurities to a small amount of impurities. For example, the formulation of the invention is stable if it contains an entity of m/z= 246 in an amount of less than or equal to 1.5%, 1.0% or 0.75% when stored for 6 months at 40°C, or in an amount of less than or equal to 0.5%, 0.4%, 0.3% or 0.2% when stored for 6 months at 25°C.

In the present invention, the formulation can be stable for at least one month, at least 3 months, at least 6 months, at least 9 months, at least 12 months, e.g., at room temperature (e.g., 15-25°C). In particular, the formulation of the invention can be stable for at least one month, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 24 months, or at least 36 months, at 2-8°C, or at about 5°C.

The formulation of the present invention may have a nanovesicle size of less than or equal to 500 nm, or less than or equal to 300 nm, or less than or equal to 200 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 150 nm, when stored for one month at 40°C.

The formulation of the present invention may have a nanovesicle size of less than or equal to 500 nm, or less than or equal to 300 nm, or less than or equal to 200 nm, preferably in the range of 5 nm to 200 nm, when stored for six months at 25°C.

The size or diameter of the nanovesicles as described herein can be expressed as the Z-average (also termed "z-average"). The size distribution of the nanovesicles can be characterized by the polydispersity index. These parameters are well known to the skilled person, and are widely used in the art to characterize particle or vesicles in emulsions, suspensions and/or polymeric solutions.

In the present invention, the size of the nanovesicles (e.g., z-average in nm) and/or the heterogeneity of nanovesicle formulations (characterized by the polydispersity index) can be determined by dynamic light scattering (also referred as Photon Correlation Spectroscopy (PCS) or Quasi-Elastic Light Scattering (QELS)). Dynamic light scattering is well known in the art and well established to determine size of nano or micro particles or vesicles in emulsions, suspensions and/or polymeric solutions with a laser.

In the formulation as described herein, the total aqueous component can present in an amount of 50% to 99% w/w, based on the total weight of the nanoemulsion (a), preferably from 70% to 95% (w/w), and more preferably from 75% to 95% (w/w), or 80% to 95%.

As used herein, "weight per weight", "weight/weight" or "w/w" means the weight concentration or mass concentration of a component in a formulation described herein. The weight or mass of a component is expressed as a percentage of a reference formulation. For example, the weight or mass of a component can be expressed as a percentage of the total weight or mass of the formulation of the invention, or as a percentage of the total weight or mass of the nanoemulsion (a).

The aqueous component can comprise at least one pH buffering agent. Any suitable buffering agent may be used. Suitable buffering agents are known to the skilled person. For example, the at least one pH buffering agent can be selected from the group consisting of citrate, phosphate, acetate and carbonate.

The pH of the aqueous component can be in the range of 2-9. The pH of the aqueous component can also be preferably in the range of 2-6, such as 2, 3, 4, 5 or 6, more preferably in the range of 4-6, such as 4, 5 or 6, or 2-4, such as 2, 3 or 4.

In the formulation as described herein, the at least one lipophilic component can be selected from triglycerides and mixtures thereof.

Preferably, the at least one lipophilic component is a lipid, a synthetic oil, a vegetable oil and/or an animal oil. Suitable lipids according to the present invention are physiologically acceptable lipids such as ceramide, mono-, di- and triacylglycerin (triglycerides). In particular, the at least one lipophilic component is a triglyceride, preferably a triglyceride comprising a C_{8-10} fatty acid, or a mixture thereof. More particular, the at least one lipophilic component is a caprylic and/or capric triglyceride and/or a mixture thereof, particularly preferably Miglyol (such as Miglyol 812, available e.g., from IOI Oleochemical) or Myritol (such as Myritol 318, available e.g., from BASF). Suitable vegetable and animal oils e.g., are sunflower oil, soybean oil, peanut oil, rape oil, fish oil and/or cetaceum.

In the formulation as described herein, the at least one lipophilic component can be present in an amount of from 0.1% to 30% (w/w) based on the total weight of the nanoemulsion (a), preferably from 0.25% to 15% (w/w), preferably from 0.25% to 10% (w/w), and more preferably from 0.5% to 8% (w/w) or 3% to 8% (w/w). Also preferred is the at least one lipophilic component being present in an amount of from 10% to 30% (w/w) based on the total weight of the nanoemulsion (a), more preferably 15-30%, or 10-20%.

In the formulation as described herein, a triglyceride or triglycerides can be present in an amount of from 2% to 10% (w/w), based on the total weight of nanoemulsion(a), preferably from 3% to 8% (w/w).

In the formulation as described herein, the at least one surfactant may be any suitable surfactant known to the skilled person.

Surfactants, also referred as surface active agents or emulsifiers, are well-known in the art and include any agent linking oil and water in the composition to form an emulsion. They lower the surface tension of two liquids and are amphiphilic. In emulsions they are referred as emulsifiers and coat the droplets preventing coalescing. Emulsifiers can be described with the hydrophilic/lipophilic balance (HLB), which expresses their affinity towards water or oil. Low HLB (e.g., HLB=1) refers to lipophilic emulsifiers and high (e.g., HLB=20) to hydrophilic emulsifiers. In general, lipophilic emulsifiers are used for water-in-oil emulsions and hydrophilic emulsifiers for oil-in-water emulsions. Persons skilled in the art will identify which emulsifiers or mixtures of them are suited for the preferred vehicles and purpose of the composition. In certain emulsions, combinations of emulsifiers might be advantageous.

A suitable membrane-forming surfactant is a phospholipid, a lysophospholipid, a ceramide and/or a mixture thereof. Preferably, the phospholipid is lecithin or cephalin from soybeans or hens' eggs. More preferably the at least one surfactant is lecithin, most preferably soy lecithin.

In the formulation as described herein, the phospholipid, the lysophospholipid, the ceramide and/or the mixture thereof can be present in an amount of from 0.1% to 10% (w/w), based on the

total weight of nanoemulsion(a), preferably from 0.15% to 5% (w/w), more preferably from 1% to 5% and even more preferably from 0.2% to 3% (w/w).

Preferably, the lecithin has a phosphatidylcholine content of at least 80% by weight, more preferably of at least 90% by weight, and most preferably of at least 94% by weight. The quality of the lecithin, namely its phosphatidylcholine content, plays a crucial role for the size of the vesicles of the nanoemulsion. The higher the phosphatidylcholine content of the lecithin, the smaller is the size of the vesicles of the nanoemulsion.

As O/W emulsion-forming surfactant, anionic, nonionic, cationic and/or amphoteric surfactants are suitable as well as block copolymers. Suitable anionic surfactants are soaps, alkylbenzene sulphonates, alkane sulphonates, alkylsulfates and/or alkyl ether sulfates. Suitable cationic surfactants are quaternary ammonium compounds, preferably having one or two hydrophobic groups (e.g., cetyltrimethylammonium bromide and cetyltrimethylammonium chloride) and/or salts of tong-chain primary amines. A suitable amphoteric surfactant is N-(acylamidoalkyl)betaine, N-alkyl-β-aminopropionate, phosphate-alkyl-ammonium compounds, and/or amine-N-oxide. A suitable copolymer building block, for example, is propylene oxide. In the present invention, a nonionic surfactant is particularly preferred as O/W emulsion-forming surfactant.

In the formulation as described herein, the at least one surfactant can be any a polyoxyethylene-type surfactant. A suitable nonionic surfactant can be selected from the group consisting of fatty alcohol polyglycolether, alkylphenol polyglycolether, alkylpolyglucoside, fatty acid glucamide, fatty acid polyglycolether, ethylen oxide-propylene oxide-block polymer, polyglycerol fatty acid ester, fatty acid alcanolamide and (ethoxylated) sorbitane fatty acid ester (sorbitane). A particularly preferred ethoxylated sorbitane fatty acid ester is polyoxyethylene sorbitane monooleate, most preferably Polysorbate 80.

The at least one surfactant, such as the polyoxyethylene-type surfactant, can be present in an amount of from 0.1% to 10% (w/w), based on the total weight of the nanoemulsion (a), more preferably from 2% to 10% (w/w), even more preferably from 0.2% to 5% (w/w), and most preferably from 1% to 5% (w/w) or 0.5% to 5% (w/w).

The formulation of the invention can comprise as least one hydrophilic surfactant with an HLB of 9 to 17, more preferably 12-16, particularly polysorbate 80 to form a nanoemulsion.

The at least one surfactant can be a sugar-based surfactant. Sugar-based surfactants are a group of non-ionic surfactants using hydrophilic sugars to which hydrophobic tails are bound. One common substance of this class is n-dodecyl-β-D-maltoside, a member of the maltoside surfactants so named because the sugar unit used is maltose. An example of a pyranoside surfactant is n-octyl-β-D-thioglucopyranoside. This class uses pyranose as the sugar unit. Examples of the glycoside surfactants are octyl glucoside, decyl glucoside, and lauryl glucoside. An example of a polysugar surfactant is digitonin.

Another very important group of sugar-based surfactants are the Tween surfactants, most notable Tween 20 (also termed herein Polysorbate 20) and Tween 80 (also termed herein Polysorbate 80). These surfactants are based on a sorbitan sugar, which is why they are commonly referred to as polysorbate surfactants. Three oligo(ethylene glycol) side groups of varying lengths are bound to the sugar increasing the hydrophilicity of the head group. This structure forms the core of all Tween surfactants. They deviate in the hydrophobic tail, which is a fatty acid coupled via an ester to four oligo(ethylene glycol) tail. In Tween 20 this fatty acid is lauric acid; in Tween 80 it is oleic acid.

In preferred embodiments, the at least one alcohol comprises at least three carbon atoms.

In the formulation as described herein, the at least one alcohol preferably independently has 3-5 (i.e. no more than 5) or 3-4 (i.e. no more than 4) carbon atoms. The at least one alcohol can be at least one monohydric alcohol. Particularly suitable alcohols having 5 carbon atoms are 1-pentanol and/or 4-methyl-2-pentanol. Suitable alcohols having 4 carbon atoms are 1-butyl alcohol, *iso*-butyl alcohol (2-methyl-1-propanol), *tert*-butyl alcohol (2-methyl-2-propanol) and/or *sec*-butyl alcohol (2-butanol). The alcohol is not propylene glycol.

Preferably, the at least one alcohol has 3 carbon atoms, i.e. is selected from the group consisting of 1-propanol or 2-propanol (isopropyl alcohol) and mixtures thereof. A preferred alcohol is 2-propanol.

In the formulation as described herein, the alcohol may present in an amount of from 0.1% to 10% w/w based on the total weight of the nanoemulsion (a), preferably from 1% to 5% (w/w) or 0.5% to 5% (w/w), and more preferably from 1% to 2% (w/w).

The formulation as described herein may comprise a gelling agent. Any suitable gelling agent may be used. Suitable gelling agents and mixtures thereof are known to the skilled person. In the formulation as described herein, the gelling agent may be 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.

It is preferred that the gelling agent is selected from poloxamer, xanthan and/or mixtures thereof.

It is also preferred that the gelling agent is xanthan (xanthan gum).

It is also preferred that the gelling agent is a poloxamer.

Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). Commercially available are Poloxamer 407 and Poloxamer 188. Poloxamer 407 can have an average molecular weight of about 12600 Dalton. Poloxamer 188

can have an average molecular weight of about 8400 Dalton. In the formulation as described herein, a preferred poloxamer is Poloxamer 407.

In the formulation as described herein, the gelling agent may be present in an amount of from 0.1% to 10% (w/w), based on the total weight of the formulation, preferably from 0.25% to 5% (w/w), and more preferably from 0.5% to 4% (w/w) or 1% to 4% (w/w).

The formulation as described herein may comprise a preservative. Any suitable preservative may be used. Suitable preservatives are known to the skilled person. The preservative can be selected from benzoate, citric acid, EDTA, potassium sorbate, vitamin C and/or derivatives and any mixtures thereof, wherein the preservative is preferably sodium benzoate. Suitable aqueous mixtures of sodium benzoate and potassium sorbate are commercially available, for example Euxyl™ K 712 preservative (Ashland).

The preservative can be present in the formulation as described herein in an amount of from 0.01% to 3% (w/w) based on the total weight of the formulation, preferably from 0.2% to 2% (w/w) or 0.1-2% (w/w), and more preferably from 0.2% to 1.5% (w/w).

In particular, the formulation of the present invention is essentially free of parabens, preferably free of parabens. The class of paraben compounds include *p*-hydroxybenzoates and PHB esters (esters of *p*-hydroxybenzoic acid, also known as 4-hydroxybenzoic acid).

Parabens are only slightly soluble in water. In the preparation of an aqueous formulation or a formulation comprising an aqueous component, parabens must be dissolved in a solvent suitable to introduce the parabens in the aqueous phase. A suitable solvent may be a polyol, in particular propylene glycol (1,2-propanediol). In the present invention, this preparation of a solution of a paraben in propylene glycol is not needed, so the formulation of the present invention can be free of a polyol, and/or a mixture of two or more polyols, such as propylene glycol.

The formulation of the present invention can be essentially free of a polyol and/or a mixture of two or more polyols, and a paraben, preferably free of propylene glycol and a paraben.

The formulation of the present invention may be a gel formulation. As used herein, a ”gel” is a two-phase elastic colloidal material, consisting of a dispersed liquid incorporated in the solid phase often constituted by a gelling agent. Suitable gelling agents, such as xanthan, are described herein.

The formulation of the present invention may be provided in a container or dispenser. Suitable dispensers and containers are known to the skilled person. For example, the dispenser may be a squeeze tube, comprising the formulation as described herein. The squeeze tube may contain the gel formulation as described herein. The dispenser may also be a metered dose dispenser or a foam dispenser or spray dispenser.

The container or dispenser may comprise a propellant, wherein the propellant is provided to pressurize the container or dispenser. Any suitable propellant may be used. Suitable propellants and mixtures thereof are known to the skilled person. Preferably, the propellant is selected from propane, isobutane, n-butane and mixtures thereof.

The formulation of the present invention may be prepared as a foamable formulation.

The formulation of the present invention may be prepared as a pressurized formulation, wherein a propellant is provided to pressurize the formulation. Any propellant as described herein can be used.

The formulation of the present invention may be prepared as a pressurized, foamable formulation, wherein a propellant is provided to pressurize the formulation. Any propellant as described herein can be used.

The formulation of the invention may be provided in a foam dispenser, as described herein, The foam dispenser comprises a container, wherein said container comprises the formulation as described herein, and a propellant. The propellant is provided to pressurize the foam dispenser. Any suitable propellant may be used, as described herein. A foam-generating device is mounted on the container. In particular, the formulation is prepared as a foamable formulation.

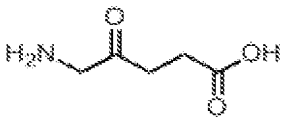
The invention also provides a foam, comprising the formulation of the present invention, as described herein.

In preferred embodiments, the active agent in the formulation of the invention comprises at least one carboxylic acid group, capable of undergoing esterification reactions. Preferably, the active agent is a small molecule containing a carboxylic acid group, having a molecular weight of 50 to 1000 g/mol, more preferably a molecular weight of 50 to 900 g/mol, most preferably from 100 to 850 g/mol.

The active agent may be present in an amount of from 0.001% to 50% w/w, based on the total weight of the formulation. In particular, the active agent may be present in an amount of from 0.01% to 30% w/w, based on the total weight of the formulation, or 0.1% to 25% w/w, 0.5% to 25% w/w, 1% to 25% w/w, or 5% to 25% w/w, based on the total weight of the formulation.

In particular the active agent in the formulation of the invention is a hydrophilic compound, which has one carboxylic acid group. The active agent may be a photosensitizer or a metabolic precursor thereof, most preferably **5-aminolevulinic acid (also termed herein "ALA" or "5-ALA"),** a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof. A preferred salt of 5-aminolevulinic acid is 5-aminolevulinic acid hydrochloride. Another preferred salt of 5-aminolevulinic acid is 5-aminolevulinic acid phosphate.

5-Aminolevulinic acid has the following chemical structure:



Molecular Weight: 131,13 g/mol

5-Aminolevulinic acid is a hydrophilic agent, which may interact with the surface of the nanovesicles when dissolved in the aqueous phase.

5-Aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof may be present in an amount of from 0.001% to 50% w/w, based on the total weight of the formulation. In particular, 5-Aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof may be present in an amount of from 0.01% to 30% w/w, based on the total weight of the formulation, or 0.1% to 25% w/w, 0.5% to 25% w/w, 1% to 25% w/w, or 5% to 25% w/w, based on the total weight of the formulation.

In particular, the formulation of the present invention may comprise or consist of:

(a) a nanoemulsion comprising

  (i) an aqueous component, present in an amount of 70% to 95% w/w, based on the total weight of the nanoemulsion (a).

  (ii) nanovesicles, comprising

    (1) 1-5% of at least one phospholipid, based on the total weight of the nanoemulsion (a);

    (2) 2-10% of at least one polyoxyethylene-type surfactant, based on the total weight of the nanoemulsion (a);

    (3) 1-5% C_3 to C_5 alcohol, based on the total weight of the nanoemulsion (a); and

    (4) 2-10% triglycerides, based on the total weight of the nanoemulsion (a);

(b) 0.1-20% of an active agent, preferably an active agent comprising a carboxylic acid group, based on the total weight of the formulation; and

(c) 0.1-2% of at least one preservative, based on the total weight of the formulation;

wherein the formulation comprises essentially no propylene glycol, and wherein the formulation preferably has a pH of 2-4. Preferably, the formulation can comprise two surfactants, more preferably soy lecithin and Polysorbate 80.

In this formulation, the at least one phospholipid, the at least one polyoxyethylene-type surfactant, the C_3 to C_5 alcohol, the triglycerides, and the at least one preservative may be independently selected according to the herein-described disclosure.

In particular, the formulation of the present invention may comprise, essentially consist of or consist of:

(a) an emulsion of nanovesicles comprising

(i) an aqueous component, present in an amount of 70% to 95% w/w, based on the total weight of the nanoemulsion (a).

(ii) nanovesicles, comprising

(1) 1-5% of at least one phospholipid, based on the total weight of the nanoemulsion (a);

(2) 2-10% of at least one polyoxyethylene-type surfactant, based on the total weight of the nanoemulsion (a);

(3) 1-5% C_3 to C_5 alcohol, based on the total weight of the nanoemulsion (a); and

(4) 2-10% triglycerides, based on the total weight of the nanoemulsion (a);

(b) 0.1-20% of an active agent, preferably a hydrophilic active agent, preferably a photosensitizer or a metabolic precursor thereof, most preferably 5-aminolevulinic acid hydrochloride, based on the total weight of the formulation;

(c) 0.1-2% of at least one preservative, based on the total weight of the formulation; and

wherein the formulation essentially does not comprise propylene glycol, and wherein the formulation preferably has a pH of 2-4.

Preferably, the formulation can comprise two surfactants, more preferably soy lecithin and Polysorbate 80.

In this formulation, the at least one phospholipid, the at least one polyoxyethylene-type surfactant, the C_3 to C_5 alcohol, the triglycerides, and the at least one preservative may be independently selected according to the herein-described disclosure.

The present invention also relates to a nanovesicle, comprising, essentially consisting of or consisting of

(i) 16-19% w/w of soy lecithin,

(ii) 32-36% w/w of Polysorbate 80,

(iii) 32-36% w/w of caprylic/capric triglycerides, and

(iv) 12-16% w/w of isopropyl alcohol.

A preferred nanovesicle of the invention comprises essentially consists of or consists of

(i) 17% w/w of soy lecithin

(ii) 34% w/w of Polysorbate 80

(iii) 35% w/w of caprylic/capric triglycerides

(iv) 14% w/w of isopropyl alcohol.

The present invention also relates to a nanoemulsion, comprising, essentially consisting of or consisting of

(a) 1.6-3.6% w/w of soy lecithin
(b) 3.3-6.9% w/w of Polysorbate 80
(c) 3.3-7.0% w/w of caprylic/capric triglycerides
(d) 1.3-2.9% w/w of isopropyl alcohol
(e) aqueous phosphate buffer, for example aqueous 5-20 mM phosphate buffer, pH 2-8, preferably pH 2-7, more preferably pH 3-6, ad 100%.

A preferred nanoemulsion of the present invention comprises, essentially consists of or consists of:

(a) 1.7% w/w of soy lecithin
(b) 3.4% w/w of Polysorbate 80
(c) 3.5% w/w of caprylic/capric triglycerides
(d) 1.4% w/w of isopropyl alcohol
(e) aqueous 10 mM phosphate buffer, pH 6, ad 100%.

This formulation is termed herein "BF200". The BF200 nanoemulsion can be obtained by contacting a mixture of ingredients (a)-(d) in a total amount of 10% w/w and 90% w/w of an aqueous 10 mM phosphate buffer, pH 6, under condition allowing formation of a nanoemulsion, thereby forming the nanoemulsion. An exemplary method for manufacture of the BF200 formulation is described in Example 1.

Another preferred nanoemulsion of the present invention comprises, essentially consists of or consists of:

(a) 2-3% w/w of soy lecithin
(b) 4.5-5.5% w/w of Polysorbate 80
(c) 4.5-5.5% w/w of caprylic/capric triglycerides
(d) 2-3% w/w of isopropyl alcohol
(e) aqueous 10 mM phosphate buffer, pH 6 or less, ad 100%.

This formulation is termed herein "BF215". The BF215 nanoemulsion can be obtained by contacting a mixture of ingredients (a)-(d) in a total amount of 15% w/w and 85% w/w of an aqueous 10 mM phosphate buffer, pH 6, under condition allowing formation of a nanoemulsion, thereby forming the nanoemulsion. An exemplary method for manufacture of the BF215 formulation is described in Example 1.

Yet another preferred nanoemulsion of the present invention comprises, essentially consists of or consists of:

(a) 3-4% w/w of soy lecithin
(b) 6-7% w/w of Polysorbate 80
(c) 6-8% w/w of caprylic/capric triglycerides
(d) 2-4% w/w of isopropyl alcohol

(e) aqueous 10 mM phosphate buffer, pH 6, ad 100%.

This formulation is termed herein "BF220". The BF220 nanoemulsion can be obtained by contacting a mixture of ingredients (a)-(d) in a total amount of 20% w/w and 80% w/w of an aqueous 10 mM phosphate buffer, pH 6, under condition allowing formation of a nanoemulsion, thereby forming the nanoemulsion. An exemplary method for manufacture of the BF220 formulation is described in Example 1.

A preferred formulation of the present invention being essentially free of propylene glycol, comprises, essentially consists of or consists of:

(1) 17.5% w/w of nanoemulsions BF200, as described herein
(2) 2.9% w/w Xanthan,
(3) 0.24% w/w sodium benzoate,
(4) 10% w/w 5-ALA hydrochloride, and
(5) water, ad 100%

This formulation may have a pH of 2-3. Preparation of this formulation is described in Example 3.

An exemplary comparative formulation, not covered by the claims, can comprise, essentially consist of or consist of:

(1) 17.5% w/w nanoemulsions BF200, as described herein
(2) 2.9% w/w Xanthan,
(3) 1% w/w propylene glycol,
(4) 0.24% w/w sodium benzoate,
(5) 10% w/w 5-ALA hydrochloride, and
(6) water, ad 100%

This formulation may have a pH of 2-3. Preparation of this formulation is described in Example 2.

All definitions and embodiments described for the first aspect are also envisioned for all other aspects described herein, where applicable.

Yet another aspect of the present invention relates to the formulations, as described herein, for use in medicine.

Yet another aspect of the present invention relates to the formulations as described herein, for use in a method of treatment and/or prevention of a dermatological disease or condition in a subject.

The treatment and/or prevention of the dermatological disease or condition may also comprise:

(a) topically administering to the subject, a pharmaceutically effective amount of the formulation comprising a photosensitizer or a metabolic precursor thereof, preferably 5-aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof, as described herein, to a diseased or affected area and optionally an area surrounding the diseased or affected area of the skin, and

(b) optionally incubating the pharmaceutically formulation on the skin of the subject with or without occlusion of the area of the skin to which the formulation was administered, the occlusion preferably performed using low density polyethylene or polyurethane film, to enhance deep layer tissue penetration.

The treatment and/or prevention of the dermatological disease or condition may also comprise:

(a) topically administering to the subject, a pharmaceutically effective amount of the formulation comprising a photosensitizer or a metabolic precursor thereof, preferably 5-aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof, as described herein, to a diseased or affected area and optionally an area surrounding the diseased or affected area of the skin, and

(b) optionally incubating the pharmaceutically formulation on the skin of the subject with or without occlusion of the area of the skin to which the formulation was administered, the occlusion preferably performed using low density polyethylene or polyurethane film, to enhance deep layer tissue penetration, and

(c) irradiating the skin area to which the formulation was administered with light.

The light spectrum used for irradiation in step (c) may match the absorption spectrum of a fluorescent porphyrin. For example, the light spectrum may match the absorption peaks of protoporphyrin IX. In particular, the light used for irradiation in step (c) may comprise any visible wavelength in the range of 380 nm to 780 nm, preferably with equal irradiance throughout or irradiance peak(s) at around 410 nm and/or 505 nm and/or 542 nm and/or 575 nm and/or 635 nm. The wavelength spectrum may be essentially free of radiation with a wavelength of less than 380 nm and/or larger than 780 nm. In particular, the light used for irradiation in step (c) may comprise any visible wavelength in the range of 380-440 nm and/or 580-650 nm. The light used for irradiation in step (c) may further be capable to induce red fluorescence of accumulated porphyrins.

The light used in step (c) may be red light, blue light, green light and/or violet light, preferably red light and/or violet light, more preferably wherein (a) the red light results in a radiant exposure of 10-75 J/cm^2, preferably of 25-45 J/cm^2; and/or the violet light results in a radiant exposure of 1-30 J/cm^2, preferably 5 to 15 J/cm^2.

Irradiation in step (c) may be performed with sunlight and/or daylight or with an artificial light source emitting light with a wavelength spectrum and preferably also irradiance similar or identical to sun light. The light with a wavelength spectrum and preferably also irradiance similar or identical to sun light may have a wavelength spectrum of 100 nm to 1000 nm, a wavelength spectrum of 380 nm to 780 nm, preferably with equal irradiance throughout or irradiance peak(s) at around 410 and/or 505 and/or 635 nm, or a wavelength spectrum of 570 nm to 650 nm or 570 nm to 630 nm, and/or a wavelength spectrum of 380 nm to 440 nm. Artificial light may be provided

by an LED. A suitable device providing artificial light is described, for example, in US patent No. 11235169 B1 and US patent No. 11219781 B2, the disclosure of which is incorporated herein by reference.

The area surrounding the diseased or affected area of the skin may include a surrounding area not affected, to ensure that the diseased or affected area is adequately treated in the peripheral diseased or affected areas. For example, the area surrounding the diseased or affected area of the skin may include an area of at least about 5 mm width.

The dermatological disease or condition to be treated with the formulation as described herein, may include, but is not limited to, diseases or conditions of the skin, skin appendages or mucosa.

The dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of inflammatory, neoplastic, proliferative, infectious, and/or autoimmune diseases or conditions, and/or the cutaneous manifestation thereof, and/or diseases associated with single lesions or fields of lesions, neoplastic, proliferative and/or inflammatory changes.

The inflammatory dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of dermatitis, contact dermatitis, acne, atopic dermatitis, eczema, pustular dermatitis, seborrheic dermatitis, perioral dermatitis, chronic wound, urticaria, skin ulcer, rosacea, rash, drug eruptions, toxic epidermal necrolysis; erythema multiforme, erythema nodosum, granuloma annulare, and other cutaneous manifestations of inflammation.

The neoplastic and/or proliferative dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of basal cell carcinoma, preferably superficial basal cell carcinoma or nodular basal cell carcinoma; squamous cell carcinoma, preferably Morbus Bowen or invasive squamous cell carcinoma; vulvar intraepithelial neoplasia (VIN); cutaneous T-cell lymphoma; Merkel cell carcinoma; hemangioma; a nodular or subcutaneous cancer disease; field cancerization; non-melanoma skin cancer in organ transplant recipients; and prevention of non-melanoma skin cancer in organ transplant recipients.

The infectious dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of bacterial infections, viral infections, fungal infections, parasitic infections, and combinations thereof.

The autoimmune dermatological disease or condition, or the cutaneous manifestation of the autoimmune condition to be treated with the formulation as described herein, may be selected from the group consisting of psoriasis, pemphigus, systemic lupus erythematodes, lichen planus, morphea, sclerodermia, epidermolysis bullosa, dermatomyositis, graft-versus-host syndrome.

The dermatological disease or condition to be treated with the formulation as described herein, may be selected from the group consisting of disorders of sweating, pigmentation disorders including hypopigmentation such as vitiligo, albinism and post inflammatory hypopigmentation and hyperpigmentation such as melasma, reactions to sunlight, such as sunburn, skin ageing, photosensitivity, disorders of hair follicles and sebaceous glands such as hypertrichosis, alopecia, male pattern baldness.

The pharmaceutical as described herein, in particular a pharmaceutical composition comprising a photosensitizer or a metabolic precursor thereof, preferably 5-aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof, as described herein, may be used in a method of photodynamic diagnosis of a neoplastic and/or proliferative dermatological disease or condition, such as benign or malignant neoplasia or precursors thereof; an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation such as acne.

The formulation as described herein, may be used in the treatment of a disease or condition, as described herein, for example neoplastic and/or proliferative dermatological diseases or conditions, such as benign or malignant skin neoplasia or precursors thereof, inflammatory dermatological diseases or conditions such as atopic dermatitis, eczema, psoriasis, rosacea or chronic wounds, and conditions associated with bacterial proliferation such as acne.

Yet another aspect of the present invention is 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 step (b), the conditions allowing formation of the nanoemulsion may include mixing both phases at an appropriate temperature and stirring in a fashion to form nanovesicle. The skilled person knows suitable temperature and stirring conditions. A vesicle size of less than or equal to 500 nm or less than or equal to 300 nm, preferably in the range of 5 nm to 200 nm, more preferably in the range of 5 nm to 100 nm can be obtained. In particular, the nanoemulsion of the present invention according to step (b) can be prepared without the use of high energy methods, which are well known in the art. High energy method includes high-pressure homogenization, microfluidization, and ultrasonication (Prev Nutr Food Sci. 2019 Sep; 24(3): 225–234).

The method comprises a step of adding the active agent. Preferably, the active agent is a hydrophilic active pharmaceutical ingredient.

A hydrophilic compound, such as an amino acid, preferably a photosensitizer or a metabolic precursor, such as ALA, or/and a pharmaceutically acceptable salt thereof (such as ALA hydrochloride), can be added to the aqueous component before contacting the mixture obtained in step (a) with an aqueous component in step (b), such that the active agent may be non-covalently bound to the nanovesicles (in particular to the nanovesicle surface) in step (b).

A hydrophilic compound, such as an amino acid, preferably a photosensitizer or a metabolic precursor, such as ALA, or/and a pharmaceutically acceptable salt thereof (such as ALA hydrochloride), can also be added to the nanoemulsion obtained in step (b), such that the active agent may be non-covalently bound to the nanovesicles (in particular to the nanovesicle surface).

The method for the preparation the pharmaceutical formulation of the present invention can further comprise:

(i) adding a gelling agent, and/or

(ii) adding a preservative.

Yet another aspect of the present invention is a dispenser product or container product, comprising the formulation as described herein. In the dispenser product or container product, the formulation of the present invention is provided in a container or dispenser. Suitable dispensers and containers are known to the skilled person. For example, the dispenser may be a squeeze tube, comprising the formulation as described herein. The squeeze tube may contain the gel formulation as described herein. The dispenser may also be a metered dose dispenser or a foam dispenser.

The container or foam dispenser may comprise a propellant, wherein the propellant is provided to pressurize the container or foam dispenser. Any suitable propellant may be used. Suitable propellants and mixtures thereof are known to the skilled person. Preferably, the propellant is selected from propane, isobutane, n-butane and mixtures thereof.

The dispenser product may be a foam dispenser product, comprising a foam dispenser, as described herein. The foam dispenser comprises a container, wherein said container comprises the formulation as described herein, and a propellant. The propellant is provided to pressurize the foam dispenser. Any suitable propellant may be used, as described herein. A foam-generating device is mounted on the container. In particular, the formulation is prepared as a foamable formulation.

Yet another aspect of the present invention is the use of the formulation of the present invention, as described herein, for the manufacture of a medicament for the treatment and/or prevention of a dermatological disease or condition in a subject. In particular, the dermatological disease is a dermatological disease or condition as described herein.

Yet another aspect of the present invention is a method of treatment and/or prevention of a dermatological disease or condition in a subject, said method comprising administering to the

subject, a pharmaceutically effective amount of the formulation as described herein. In particular, the dermatological disease is a dermatological disease or condition as described herein.

Yet another aspect of the present invention is a method of photodynamic diagnosis of a neoplastic and/or proliferative dermatological disease or condition, such as benign or malignant neoplasia or precursors thereof; an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation such as acne.

ALA (and derivatives) containing drugs drive the synthesis of fluorescent porphyrins that accumulate preferentially in cells/tissues with increased metabolic activity. This can be exploited in the method of photodynamic diagnostics, which can be applied to neoplastic diseases of the skin, such as benign or malignant neoplasia or precursors thereof, inflammatory conditions or conditions associated with bacterial proliferation such as acne. For photodynamic diagnosis, a ALA (or derivative) containing formulation is applied to the skin area to be diagnosed and incubated for an appropriate time (e.g., 1-3 h). Subsequently, blue spectrum light is applied to induce red fluorescence of accumulated porphyrins. The fluorescence can be detected by visual inspection or appropriate technical devices for qualitative or quantitative assessment.

The method of photodynamic diagnoses may comprise:

(i) administering the formulation comprising a photosensitizer or a metabolic precursor, such as 5-aminolevulinic acid, a pharmaceutically acceptable salt, a derivative, precursor and/or metabolite thereof, as described herein to the skin area to be diagnosed, under conditions allowing synthesis of fluorescent porphyrins in the cells and/or tissues, and

(ii) irradiating the skin area to which the formulation was administered, under conditions inducing fluorescence of accumulated porphyrins,

wherein increased fluorescence of porphyrins indicates increased metabolic activity, being indicative for a neoplastic and/or proliferative dermatological disease or condition, an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation.

In step (i), the formulation may be incubated on the skin for e.g., 1-3 h.

in step (ii), the skin can be irradiated with light capable to induce red fluorescence of accumulated porphyrins. Suitable irradiation conditions are described herein.

Diagnosis of the neoplastic and/or proliferative dermatological disease or condition, can be performed by detection of increased fluorescence (e.g., compared with healthy tissue and/or skin, e.g., adjacent to the suspected area). Detection of fluorescence can be performed by visual inspection or appropriate technical devices for qualitative or quantitative assessment.

Diagnosis according to the method described herein may be performed for demarcation of tumor borders to assist surgery, to assess treatment efficacy, and/or the assessment of light induced photobleaching for light dosimetry in photodynamic therapy.

An alternative aspect of the invention relates to a formulation as described in the first aspect of the invention, but comprising propylene glycol. The formulation of the alternative aspect may be free of, may be essentially free of, or may comprise less than an indicated amount, such as less than 1%, less than or equal to 0.99%, less than or equal to 0.95%, less than or equal to 0.9%, less than or equal to 0.8%, less than or equal to 0.7%, less than or equal to 0.6%, less than or equal to 0.5%. less than or equal to 0.4%, less than or equal to 0.3%, less than or equal to 0.2% or less than or equal to 0.1% of one polyol, all polyols or any chosen number of polyols selected from the group consisting of glycerin, diglycerin, polyglycerin, diethylene glycol, dipropylene glycol, butylene glycol, pentylene glycol, hexylene glycol, 1,3-propanediol, 1,5-pentanediol, octane-1,2-diol, polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups, and monosaccharides or disaccharides such as sorbitol, mannitol and mixtures thereof. The formulation of the alternative aspect may be essentially free of one polyol or any chosen number of polyols selected from the group consisting of glycerin, diglycerin, polyglycerin, diethylene glycol, dipropylene glycol, butylene glycol, pentylene glycol, hexylene glycol, 1,3-propanediol, 1,5-pentanediol, octane-1,2-diol, polyethyleneglycols, particularly having from 2 to 50 ethylene oxide groups, and monosaccharides or disaccharides such as sorbitol, mannitol and mixtures thereof.

The invention also pertains to the following embodiments:

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 embodiment 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 embodiment 1 or 2, preferably 2, wherein the formulation comprises essentially no propylene glycol.

4. The formulation of any one of embodiments 1 to 3, preferably 3, wherein the formulation comprises no propylene glycol.

5. The formulation of any one of embodiments 1 to 4, preferably 4, 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 embodiments 1 to 5, preferably 5, 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 embodiments 1 to 6, 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;
- 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; and/or
- 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.

8. The formulation of any one of embodiments 1 to 7, 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).

9. The formulation of any one of embodiments 1 to 8, 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).

10. The formulation of any one of embodiments 1 to 9, wherein the active agent is a photosensitizer or a metabolic precursor thereof.

11. The formulation of any one of embodiments 1 to 10, wherein the active agent is 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof.

12. The formulation of any one of embodiments 1 to 11, 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.

13. The formulation of any one of embodiments 1 to 12, 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.

14. The formulation of any one of embodiments 1 to 13, 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.

15. The formulation of any one of embodiments 1 to 14, 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.

16. The formulation of any one of embodiments 1 to 15, which is essentially free of parabens.

17. A formulation comprising
    (a) a nanoemulsion comprising:
        (i) at least one aqueous component;
        (ii) a carrier component comprising:
            (4) at least one lipophilic component,
            (5) at least one surfactant, and
            (6) 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 active agent is a photosensitizer or a metabolic precursor thereof;
    wherein the formulation comprises essentially no propylene glycol.

18. The formulation of embodiment 17, wherein the active agent is 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof.

19. A formulation comprising
    (a) a nanoemulsion comprising:
        (i) at least one aqueous component;
        (ii) a carrier component comprising:
            (7) at least one lipophilic component,
            (8) at least one surfactant, and
            (9) at least one alcohol; and
    (b) 5-aminolevulinic acid, a derivative, a precursor, a metabolite, and/or a pharmaceutically acceptable salt thereof,
    wherein the formulation comprises less than 1% w/w of propylene glycol or no propylene glycol.

20. A method of treating a dermatological disease or condition, comprising administration of an effective amount of the formulation of embodiment 10 to 12 to a subject in need thereof.

The invention also pertains to the following items:

1. A formulation comprising
    (a) a nanoemulsion, said emulsion 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 agentcomprising 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, preferably less than or equal to 0.99%, 0.95% or 0.9% w/w of propylene glycol or no propylene glycol.

2. The formulation of item 1, wherein the formulation comprises essentially no propylene glycol.

3. The formulation of any of the preceding items, 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 3 carbon atoms, preferably 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.

4. The formulation of any of the preceding items, 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 5 carbon atoms, preferably 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.

5. The formulation of any of the preceding items, wherein the at least one alcohol comprises at least three carbon atoms, preferably 3, 4 or 5 carbon atoms.

6. The formulation of any of the preceding items, wherein the active agent is a photosensitizer or a metabolic precursor thereof.

7. The formulation of any of the preceding items, wherein the active agent is present in an amount of from 0.01% to 25% (w/w), preferably 0.1% to 25% (w/w), more preferably 1% to 25% (w/w), based on the total weight of the formulation.

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

9. The formulation of item 8, wherein the 5-aminolevulinic acid, the derivative, the precursor, the metabolite thereof, and/or the pharmaceutically acceptable salt thereof, is present in an

amount of from 0.01% to 25% (w/w), preferably 0.1% to 25% (w/w), more preferably 1% to 25% (w/w), based on the total weight of the formulation.

10. The formulation of any one of the items 8 or 9, wherein the formulation comprises an entity characterized by m/z= 246 in an amount of less than or equal to 1.5%, 1.0% or 0.75% when stored for 3 months at 40°C.

11. The formulation of any one of the items 8 to 10, wherein the formulation comprises an entity characterized by m/z= 246 in an amount of less than or equal to 1.5%, 1.0%, 0.5% or 0.2% when stored for 6 months at 25°C.

12. The formulation of any of the preceding items, wherein formulation is a pharmaceutical formulation.

13. The formulation of any of the preceding items, wherein formulation is for topical use.

14. The formulation of any of the preceding items, wherein the active agent is dissolved in the aqueous phase and/or is capable to interact with the surface of the nanovesicles.

15. The formulation of any of the preceding items, wherein the active agent is a hydrophilic active agent

16. The formulation of any one of the preceding items, wherein the nanoemulsion comprises nanovesicles, wherein the nanovesicles have a size of less than or equal to 500 nm, preferably in the range of 5 nm to 200 nm when stored for one month at 40°C.

17. The formulation of any one of the preceding items, wherein the nanoemulsion comprises nanovesicles, wherein the nanovesicles have a size of less than or equal to 500 nm, preferably in the range of 5 nm to 200 nm when stored for six months at 25°C.

18. The formulation of any one of the preceding items, wherein the aqueous component is present in an amount of 50% to 99% w/w, based on the total weight of the nanoemulsion (a), preferably from 70% to 95% (w/w), and more preferably from 80% to 95% (w/w).

19. The formulation of any one of the preceding items, wherein the aqueous component comprises at least one pH buffering agent.

20. The formulation of item 19, wherein the pH buffering agent is selected from the group consisting of citrate, phosphate, acetate and carbonate.

21. The formulation of any one of the preceding items, having a pH of 2-6.

22. The formulation of any one of the preceding items, having a pH of 2-4.

23. The formulation of any one of the preceding items, wherein the at least one lipophilic component is selected from triglycerides and mixtures thereof.

24. The formulation of any one of the preceding items, wherein the at least one lipophilic component comprises a caprylic and/or a capric triglyceride or a mixture thereof.

25. The formulation of any one of the preceding items, wherein the at least one lipophilic component is present in an amount of from 0.1% to 30% (w/w), based on the total weight of the nanoemulsion (a), preferably from 0.25% to 10% (w/w), and more preferably from 0.5% to 8% (w/w) or 3% to 8% (w/w).

26. The formulation of any one of the preceding items, wherein the at least one surfactant comprises (a) a phospholipid, a lysophospholipid, a ceramide and/or a mixture thereof, and/or (b) a polyoxyethylene-type surfactant.

27. The formulation of any one of the preceding items, wherein the at least one surfactant comprises lecithin, preferably soy lecithin.

28. The nanoemulsion of item 27, wherein the lecithin has a phosphatidylcholine content of at least 80% by weight.

29. The formulation of any one of items 26-28, wherein the phospholipid, the lysophospholipid, the ceramide and/or the mixture thereof is present in an amount of from 0.1% to 10% (w/w), based on the total weight of nanoemulsion (a), preferably from 0.15% to 5% (w/w), and more preferably from 0.2% to 3% (w/w).

30. The formulation of any one of the items 26-29, wherein the polyoxyethylene-type surfactant comprises Polysorbate 80.

31. The formulation of any one of items 26-30, wherein the polyoxyethylene-type surfactant is present in an amount of from 0.1% to 10% (w/w), based on the total weight of the nanoemulsion (a), more preferably from 0.2% to 5% (w/w), and most preferably from 0.5% to 5% (w/w).

32. The formulation of any one of the preceding items, wherein at least one alcohol is selected from the group consisting of 1-propanol or 2-propanol and a mixture thereof.

33. The formulation of any one of the preceding items, wherein the at least one alcohol is present in an amount of from 0.1% to 10% (w/w), based on the total weight of the nanoemulsion (a), preferably from 0.5% to 5% (w/w), and more preferably from 1% to 2% (w/w).

34. The formulation of any one of the preceding items, comprising at least one gelling agent.

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

36. The formulation of item 34 or 35, wherein the gelling agent is selected from poloxamer, xanthan and/ or mixtures thereof.

37. The formulation of any one of the preceding items, wherein the gelling agent is present in an amount of from 0.1% to 10% (w/w), based on the total weight of the formulation, preferably from 0.25% to 5% (w/w), and more preferably from 1% to 4% (w/w).

38. The formulation of any one of the preceding items, further comprising at least one preservative.

39. The formulation of item 38, wherein the preservative is benzoate, preferably sodium benzoate.

40. The formulation of item 38 or 39, wherein the preservative is present in an amount of from 0.01% to 3% w/w, based on the total weight of the formulation, preferably from 0.2% to 2% (w/w), and more preferably from 0.2% to 1.5% (w/w).

41. The formulation of any one of the preceding items, which is essentially free of parabens.

42. The formulation of any one of the preceding items, characterized by a polydispersity index of less than or equal to 0.8, wherein the polydispersity index is determined by dynamic light scattering.

43. The formulation of any one of the items 1-42, comprising:

(a) an emulsion of nanovesicles comprising

(i) an aqueous component, present in an amount of 70% to 95% w/w, based on the total weight of the nanoemulsion (a).

(ii) nanovesicles, comprising

(1) 1-5% of at least one phospholipid, based on the total weight of the nanoemulsion (a);

(2) 2-10% of at least one polyoxyethylene-type surfactant, based on the total weight of the nanoemulsion (a);

(3) 1-5% C_3 to C_5 alcohol, based on the total weight of the nanoemulsion (a); and

(4) 2-10% triglycerides, based on the total weight of the nanoemulsion (a);

(b) 0.1-20% of a photosensitizer or a metabolic precursor thereof, preferably 5-aminolevulinic acid hydrochloride, based on the total weight of the formulation;

(c) 0.1-2% of at least one preservative, based on the total weight of the formulation; and

wherein the formulation essentially does not comprise propylene glycol, and wherein the formulation preferably has a pH of 2-4.

44. The formulation of any one of the preceding items, provided in a container, wherein the container further comprises a propellant, and wherein the propellant is provided to pressurize the container and/or to pressurize the formulation in the container.

45. The formulation of any one of the preceding items, for use in medicine.

46. The formulation of any one of the preceding items, for use in a method of treatment and/or prevention of a dermatological disease or condition in a subject.

47. The formulation of any one of the preceding items, for use in a method of treatment and/or prevention of a dermatological disease or condition in a subject, wherein the treatment and/or prevention of the dermatological disease or condition comprises:

(a) topically administering to the subject, a pharmaceutically effective amount of the formulation of any one of the items 1-46, to a diseased or affected area and optionally an area surrounding the diseased or affected area of the skin, and

(b) incubating the pharmaceutically formulation on the skin of the subject with or without occlusion of the area of the skin to which the formulation was administered, the occlusion preferably performed using low density polyethylene or polyurethane film, to enhance deep layer tissue penetration.

48. The formulation for use of item 47, further comprising the step:

(c) irradiating the skin area to which the formulation was administered, with light.

49. The formulation for use of any one of the items 47-48, wherein the area surrounding the diseased or affected area of the skin includes an area of at least about 5 mm width.

50. The formulation for use of any one of the items 46-49, wherein the dermatological disease or condition includes diseases or conditions of the skin, skin appendages or mucosa.

51. The formulation for use of any one of the items 46-50, wherein the dermatological disease or condition is selected from the group consisting of inflammatory, neoplastic, proliferative, infectious, and/or autoimmune diseases or conditions, and/or the cutaneous manifestation thereof, and/or diseases associated with single lesions or fields of lesions, neoplastic, proliferative and/or inflammatory changes.

52. The formulation for use of item 51, wherein the inflammatory dermatological disease or condition is selected from the group consisting of dermatitis, contact dermatitis, acne, atopic dermatitis, eczema, pustular dermatitis, seborrheic dermatitis, perioral dermatitis, chronic wound, urticaria, skin ulcer, rosacea, rash, drug eruptions, toxic epidermal necrolysis; erythema multiforme, erythema nodosum, granuloma annulare, and other cutaneous manifestations of inflammation.

53. The formulation for use of item 51, wherein the neoplastic and/or proliferative dermatological disease or condition is selected from the group consisting of basal cell carcinoma, preferably superficial basal cell carcinoma or nodular basal cell carcinoma; squamous cell carcinoma, preferably Morbus Bowen or invasive squamous cell carcinoma; vulvar intraepithelial neoplasia (VIN); cutaneous T-cell lymphoma; Merkel cell carcinoma; hemangioma; a nodular or subcutaneous cancer disease; field cancerization; non-melanoma skin cancer in organ transplant recipients; and prevention of non-melanoma skin cancer in organ transplant recipients.

54. The formulation for use of item 51, wherein the infectious dermatological disease or condition is selected from the group consisting of bacterial infections, viral infections, fungal infections, parasitic infections, and combinations thereof.

55. The formulation for use of item 51, wherein the autoimmune dermatological disease or condition, or the cutaneous manifestation of the autoimmune condition is selected from the group consisting of psoriasis, pemphigus, systemic lupus erythematodes, lichen planus, morphea, sclerodermia, epidermolysis bullosa, dermatomyositis, graft-versus-host syndrome.

56. The formulation for use of any one of the items 47-50, wherein the dermatological disease or condition is selected from the group consisting of disorders of sweating, pigmentation disorders including hypopigmentation such as vitiligo, albinism and post inflammatory hypopigmentation and hyperpigmentation such as melasma, reactions to sunlight, such as sunburn, skin ageing, photosensitivity, disorders of hair follicles and sebaceous glands such as hypertrichosis, alopecia, male pattern baldness.

57. The formulation of any one of the preceding items, for use in a method of photodynamic diagnosis of a neoplastic and/or proliferative dermatological disease or condition, such as benign or malignant neoplasia or precursors thereof; an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation such as acne.

58. A method for the preparation the formulation of any one of the items 1-57, 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.

59. The method of item 58, further comprising
    (i) adding a gelling agent, and/or
    (ii) adding a preservative.

60. A dispenser product, comprising the formulation of any one of the items 1-57.

61. A container, comprising the formulation of any one of the items 1-57.

62. Use of the formulation according to any one of the items 1-57, for the manufacture of a medicament for the treatment and/or prevention of a dermatological disease or condition in a subject.

63. A method of treatment and/or prevention of a dermatological disease or condition in a subject, said method comprising administering to the subject, a pharmaceutically effective amount of the formulation of any one of the items 1 to 57.

64. A method of photodynamic diagnosis of a neoplastic and/or proliferative dermatological disease or condition, such as benign or malignant neoplasia or precursors thereof; an

inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation such as acne, said method comprising

(i) administering the formulation according to any one of the items 1-57 to the skin area to be diagnosed, under conditions allowing synthesis of fluorescent porphyrins in the cells and/or tissues, and

(ii) irradiating the skin area to which the formulation was administered, under conditions inducing fluorescence of accumulated porphyrins,

wherein increased fluorescence of porphyrins indicates increased metabolic activity, being indicative for a neoplastic and/or proliferative dermatological disease or condition, an inflammatory dermatological disease or condition; and/or a condition associated with bacterial proliferation.

The present invention is further illustrated by the following figures and Examples.

Figure legends

Figure 1: Content of known impurity (2-hydroxypropyl-δ-aminolevulinate, m/z 190) and m/z 246-impurity in Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) after storage for 6 months at 25°C or 40°C.

Figure 2: Chromatograms of known impurity (2-hydroxypropyl-δ-aminolevulinate; m/z 190) and m/z 246-impurity in Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) after storage for 3 months at 40°C.

Figure 3: Skin penetration of Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) in ex vivo human skin. PpIX: protoporphyrin IX. Error bars indicate standard deviation.

Figure 4: Franz cell (top: scheme, bottom: photograph)

Figure 5: Release of 5-ALA from Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) after 2.5 hours (linear range of Higuchi plot). The values shown are the mean values from the experiment six-fold. The cumulative transport into the acceptor compartment is expresses as µg per cm^2 of membrane area against square root of time.

Examples

Example 1: Preparation of Nanoemulsions BF200, BF215 and BF220

Table 1: Lipophilic content of nanoemulsions used in the Examples

BF200	10% lipophilic content
BF215	15% lipophilic content
BF220	20% lipophilic content

The qualitative and quantitative compositions of the nanoemulsions BF200, BF215 and BF220 are given in **Table 2**.

Table 2: Composition of nanoemulsions BF200, BF215 and BF220

	Ingredient	**Content (% w/w) BF200**	**Content (% w/w) BF215**	**Content (% w/w) BF220**	**Function**	**Quality**
1	Soy lecithin	1.7	2.0-3.0	3.0-4.0	surfactant	>90% phosphadidylcholine, for pharmaceutical use, USP
2	Polysorbate 80 (polyoxyethylene sorbitol monooleate)	3.4	4.5-5.5	6.0-7.0	surfactant	Ph. Eur.
3	Caprylic/capric triglycerides	3.5	4.5-5.5	6.0-8.0	lipid core	Ph. Eur.
4	Isopropyl alcohol	1.4	2.0-3.0	2.0-4.0	solvent	Ph. Eur.
	Content (% w/w) ingredients 1-4	**10.0**	**15.0**	**20.0**		
	10 mM phosphate buffer, pH 6	ad 100.00	ad 100.00	ad 100.00	solvent	Water for injection: Ph. Eur.; Disodium phosphate and sodium hydrogen phosphate: Ph. Eur.

The manufacturing process for the nanoemulsions in a typical batch size consists of the following steps 1-4:

Step 1: Preparation of a 10 mM phosphate buffer (aqueous component)

10 mM phosphate buffer (1000 g), pH 6, was prepared and the phosphate buffer optionally sterilized by filtration through a sterile filter.

Step 2: Preparation of a carrier containing the lipophilic component, the surfactants and the alcohol

Table 3: Carrier component

Ingredient	***Weight (g)***
Soy lecithin	17
Polysorbate 80	34

(polyoxyethylene sorbitol monooleate)	
Caprylic/capric triglycerides	35
Isopropyl alcohol	14

Soy lecithin (17 g) was weighed in a suitable vessel, isopropyl alcohol (14 g) was added and the vessel was covered to avoid alcohol evaporation. Soy lecithin was dissolved under continuous stirring with a suitable stirrer at room temperature. Caprylic/capric triglycerides (35 g) and Polysorbate 80 (34 g) were weighed and added to the solution of soy lecithin. The mixture was stirred with a suitable stirrer at room temperature until a homogenous clear solution was obtained. This solution is the carrier phase to be included in the nanoemulsion containing all emulsifiers and lipid components of the nanoemulsion BF200. According to this procedure BF215 and BF220 was prepared by adapting the amount of the components (see Table 2).

In all examples shown herein, nanoemulsion BF200 was used.

Step 3: Manufacturing of the nanoemulsion by mixing the aqueous component from Step 1 and the carrier from Step 2 for a lipid content of 10% (BF200)

Manufacturing of an emulsion by mixing 900 g phosphate buffer (from Step 1) and 100 g carrier (from Step 2). First, the aqueous component comprising the phosphate buffer was heated to approximately 45-60°C in a suitable vessel. Then, the carrier (concentrate) of step 2 was heated to approximately 45-60°C. Subsequently, the carrier was poured to the phosphate buffer under continuous stirring with a propeller mixer resulting in the formation of a stable trombe (or spout) having the maximal possible diameter without causing foaming or sputtering. The resulting nanoemulsion is stirred for 15 min. Finally, the nanoemulsion was cooled down to room temperature.

In nanoemulsion BF215, 850 g phosphate buffer (from Step 1) and 150 g carrier were mixed. In nanoemulsion BF220, 800 g phosphate buffer (from Step 1) and 200 g carrier were mixed.

Step 4: Preparation of the final formulation and primary packaging

Optionally, the nanoemulsion can be sterilized by filtration.

Depending on the purpose of the nanoemulsion, one may add adjuvants and/ or excipients and/or active ingredients (at the appropriate step according to the description) and/or dilute the nanoemulsion with in a way to get a suitable pharmaceutical formulation, e.g., by adding water, a suitable buffer, or an additional aqueous gel base with e.g. poloxamer 407 or xanthan gum.

The pharmaceutical formulations with different nanoemulsions BF200, BF215 and BF220 were filled into a conventional glass container or into a squeeze tube with an appropriate size, respectively.

Example 2: Preparation of gel Formulation 1, containing propylene glycol (comparative example)

Step 1: Preparation of Nanoemulsion

Nanoemulsion BF200 is produced according to Example 1. Sodium benzoate, 5-ALA and propylene glycol were added under stirring to nanoemulsion BF200.

Table 4: Composition of Nanoemulsion, based upon BF200

Component	**Nanoemulsion**	
	per 287.35 mg of emulsion	
BF200		
Soybean Phosphatidylcholine	3.00 mg	
Polysorbate 80	6.00 mg	
Triglycerides, medium chain (Miglyol 812)	6.00 mg	
Isopropyl alcohol	2.50 mg	
Disodium phosphate dihydrate	0.03 mg	
Sodium dihydrogen phosphate dihydrate	0.22 mg	
Purified water	**157.25 mg**	**175.00 mg**
Components added to BF200		
5-aminolevulinic acid hydrochloride	100.000 mg	
Propylene glycol	10.000 mg	
Sodium benzoate	2.35 mg	**112.350 mg**
		287.35 mg

Step 2: Preparation of gel base with Xanthan gum (XT).

A round bottom flask was disinfected with isopropanol. Water was put into the bowl and then Xanthan was spread thereon. The resulting basis gel was filled in an appropriate beaker.

Table 5: Composition of Gel base

Component	**Gel base**	
	per 712.65 mg of gel base	
Xanthan gum	28.50 mg	4.0%
Purified water	**684.15 mg**	96.0%

Step 3: Preparation of Formulation 1.

28.74% of the nanoemulsion produced in step 1 (including 17.5% of nanoemulsion BF200), and 71.26% of Xanthan gel base produced in step 2 are mixed and homogenized, resulting in Formulation 1.

Table 6: Components of gel Formulation 1 (nanoemulsion BF200, gel base, 5-ALA, propylene glycol), mg per g gel

Component	Formulation 1
	per 1 g of gel
5-aminolevulinic acid hydrochloride	100.000 mg
Xanthan gum	28.50 mg
Soybean Phosphatidylcholine	3.00 mg
Polysorbate 80	6.00 mg
Triglycerides, medium chain (Miglyol 812)	6.00 mg
Isopropyl alcohol	2.50 mg
Disodium phosphate dihydrate	0.03 mg
Sodium dihydrogen phosphate dihydrate	0.22 mg
Propylene glycol	**10.000 mg**
Sodium benzoate	2.350 mg
Purified water	**841.4 mg**

Formulation 1 was filled in a 2 g squeeze tube.

Example 3: Preparation of gel Formulation 2, free of propylene glycol

Step 1: Preparation of Nanoemulsion

Nanoemulsion BF200 is produced according to Example 1. Sodium benzoate and 5-ALA were added under stirring to nanoemulsion BF200. Formulation 2 is free of propylene glycol. In view of Formulation 1, the propylene glycol was replaced by the corresponding amount of xanthan gel base (10 mg/g, 1%).

Table 7: Composition of Nanoemulsion based upon BF200

Component	Nanoemulsion	
	per 277.35 mg of emulsion	
BF200		
Soybean Phosphatidylcholine	3.00 mg	
Polysorbate 80	6.00 mg	
Triglycerides, medium chain (Miglyol 812)	6.00 mg	
Isopropyl alcohol	2.50 mg	
Disodium phosphate dihydrate	0.03 mg	
Sodium dihydrogen phosphate dihydrate	0.22 mg	
Purified water	**157.25 mg**	**175.00 mg**
Components added to BF200		
5-aminolevulinic acid hydrochloride	100.000 mg	
Propylene glycol	0.000 mg	
Sodium benzoate	2.350 mg	**102.350 mg**
		277.35 mg

Step 2: Preparation of gel base with Xanthan gum (XT).

The gel based in produced as described in Step 2 of Example 1.

Table 8: Composition of Gel base

Component	Gel base	
	per 722.65 mg of gel base	
Xanthan gum	28.90 mg	4.0%
Purified water	**693.75 mg**	96.0%

Step 3: Preparation of Formulation 2.

27.74% of the nanoemulsion produced in step 1 (including 17.5% of nanoemulsion BF200), and 72.26% of Xanthan gel base produced in step 2 are mixed and homogenized, resulting in Formulation 2.

Table 9: Components of gel Formulation 2 (nanoemulsion BF200, gel base, 5-ALA), mg per g gel

Component	Formulation 2
	per 1 g of gel
5-aminolevulinic acid hydrochloride	100.000 mg
Xanthan gum	**28.90 mg**
Soybean Phosphatidylcholine	3.0 mg
Polysorbate 80	6.00 mg
Triglycerides, medium chain (Miglyol 812)	6.00 mg
Isopropyl alcohol	2.5 mg
Disodium phosphate dihydrate	0.03 mg
Sodium dihydrogen phosphate dihydrate	0.22 mg
Propylene glycol	**0.000 mg**
Sodium benzoate	2.350 mg
Purified water	**851.000 mg**

Formulation 2 was filled in a 2 g squeeze tube.

Example 4: Determination of vesicle size and polydispersity index by dynamic light scattering

The size of the nanovesicles, expressed as the z-average size (e.g., in nm), and the homogeneity of nanovesicle formulations, expressed as polydispersity index was determined by dynamic light scattering (sometimes referred as Photon Correlation Spectroscopy (PCS) or Quasi-Elastic Light Scattering (QELS)). The technique is well known in the art and well established to determine size of nano or micro particles or vesicles in emulsions, suspensions or polymeric solutions with a laser. Measurements were conducted with an Zetasizer Nano ZS (Malvern Instruments Ltd, Malvern, Worcestershire, UK). The measurement was performed according to the manufacturer's instructions.

The Zetasizer Nano ZS is instrumented with a 633 nm green laser and optics with a 173°scattering detector angle for size measurement. The device may be operated under vacuum for measurements, but in these cases, vacuum was not applied to the samples for size and homogeneity measurements.

Example 5: Determination of impurity

Qualitative and quantitative analysis of impurities was performed by LC-MS using positive electrospray ionisation (ESI+). The scan change covered degradation products in a range of 100-2000 m/z.

Example A

Content of impurities in an 5-ALA nanoemulsion gel (compared with a comparative formation containing propylene glycol) after storage for 6 months

Formulation 1 (containing 1% propylene glycol) was prepared as described in Example 2. Formulation 1 (free of propylene glycol) was prepared as described in Example 3.

10-ml glass vials, containing either Formulation 1 or Formulation 2 were stored for six months at 25°C or 40°C.

Impurities were detected with mass spectroscopy, as described in Example 5.

The results are summarized in **Figure 1**. As expected, the ester of 5-ALA and propylene glycol (2-Hydroxypropyl-δ-aminolevulinate) is not present in Formulation 2 (without propylene glycol). An impurity with m/z=246 was found to be present in the comparative Formulation 1 (with propylene glycol) in a mean amount of about 0.3% after storage at 25°C and 1.2% after storage at 40°C. Unexpectedly, the impurity was found to be present in Formulation 2 (without of propylene glycol) in a mean amount of about 0.15% after storage at 25°C and 0.6% after storage at 40°C.

This behavior is also illustrated in **Figure 2**. Chromatograms of known impurity (2-hydroxypropyl-δ-aminolevulinate; m/z 190) and impurity m/z 246 in Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol) after storage for 3 months at 40°C.

Conclusion: A 5-ALA formulation, being free of propylene glycol, is safer / pharmaceutically more tolerable than a comparative 5-ALA formulation, containing propylene glycol.

Example B

Ex-vivo skin penetration study with human eye lid skin

Formulation 1 (with propylene glycol) was prepared as described in Example 2. Formulation 2 (without of propylene glycol) was prepared as described in Example 3.

Objective

- Comparison of skin penetration properties of Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol)
- Assess the amount of protoporphyrin IX (PpIX) in skin biopsy samples in fresh, vital skin samples after drug application.

Experimental set-up

Test material

- Human upper eyelid skin from routine blepharoplastic surgeries (eyelid tightening)
- Formulation 1 with propylene glycol (batch no. 166M, (1) in Figure 3)
- Formulation 2 without propylene glycol (batch no. 111M, (2) in Figure 3)

Methodology

- Incubation of skin explants with formulation for 0, 1, 3 h
- Cryosectioning, extraction of protoporphyrin IX from skin sections
- PpIX extraction from tissues and fluorimetric analysis of PpIX content in lysates

Results

The results are summarized in **Figure 3**.

- Means of n=5 plotted against (incubation) time
- PpIX concentrations increase with incubation time
- Although propylene glycol is a well-known penetration enhancer, equivalent penetration results were achieved with new Formulation 2 without propylene glycol compared to comparative Formulation 1 with propylene glycol (the formulation without propylene glycol is non-inferior to formulation with propylene glycol).
- Differences between formulations at different time points were not statistically significant (Mann-Whitney's U-test)

Conclusion: A 5-ALA formulation, being free of propylene glycol, which is found to be more stable that a comparative 5-ALA formulation, containing propylene glycol (Example 1), provides equivalent penetration efficacy.

Example C

In vitro release test of 5-aminolevulinic acid from Formulation 1 (with propylene glycol) and Formulation 2 (without propylene glycol)

Formulation 1 (with propylene glycol) was prepared as described in Example 2 (Batch 166M). Formulation 2 (without propylene glycol) was prepared as described in Example 3 (Batch 110M).

Objective

- Method development and evaluation of in vitro release (acc. to SUPAC-SS guideline (FDA, SUPAC, 1997)) of ALA from gel formulations (GMP GLP)

Experimental set-up

Test material

- Synthetic membranes (nylon, 0.20 µm)
- IVRT (in vitro release test) with so-called "Franz diffusion cell", **Figure 4**
- Formulation 1 with propylene glycol (comparative gel)
- Formulation 2 without propylene glycol

Methodology

- Analytical method for quantification of ALA: HPLC-MS/MS

Drug application, sampling and analysis

- Application of 300 mg ALA nanoemulsion to nylon membrane (0.20 µm)
- Incubation at 32 +-1 °C and sampling at t= 20, 40, 60, 90, 120, and 150 min
- n = 6 for each formulation (with/without propylene glycol) → 12 Franz cells
- HPLC-MS/MS for quantification of ALA in receptor compartiment

Results

The results are described in **Figure 5**:

- Higuchi plot (Takeru Higuchi 1961: "Rate of release of medicaments from ointment bases containing drugs in suspension" (DOI: 10.1002/jps.2600501018), cumulative transport of 5-ALA (in µg cm^{-2}), against square root of time (in $h^{-0.5}$).
- Transported amount is higher for Formulation 2 without propylene glycol
- The standard deviations two curves overlap completely.
- There is no significant difference between the two tested formulations

Statistical comparison of the slopes of the release curve:

Table 10:

Formulation 1	Formulation 2	Limits of the 90% confidence interval		
with propylene glycol	without propylene glycol	Lower Limit 8th value (0.75)	Upper-limit 29th value (1.33)	Significant difference
Batch 166M K27033 Test Item A	Batch 110M K27080 Test Item B	0.816	1.036	No

- There is no significant difference between the two tested formulations.
- The formulation without propylene glycol is to be considered at least as good as the formulation with propylene glycol in terms of drug release.

Conclusion: A 5-ALA gel formulation, being free of propylene glycol, which is found to be more stable that a comparative 5-ALA formulation, containing propylene glycol (Example 1), provides an equivalent in vitro release profile.

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.

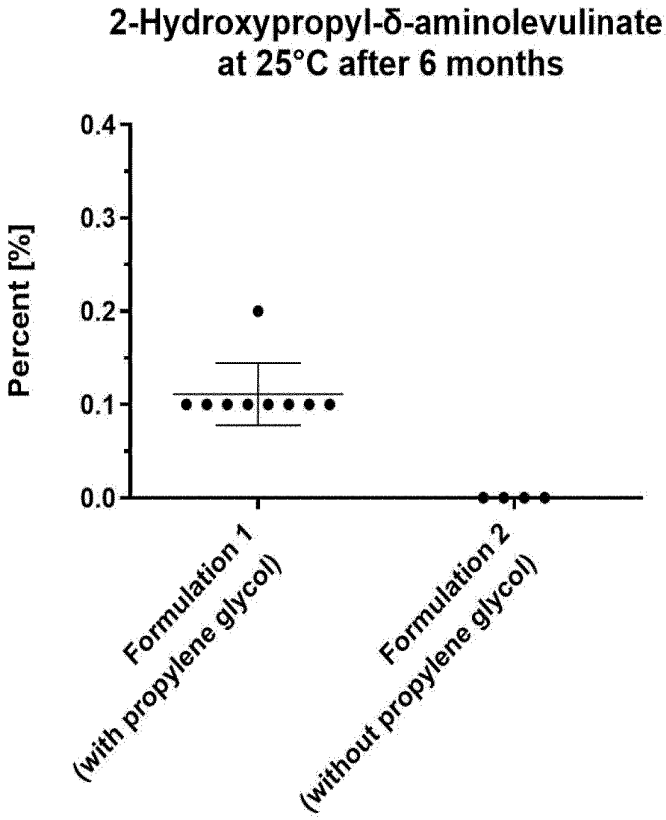
19. The formulation of any one of the preceding claims, which is essentially free of parabens.

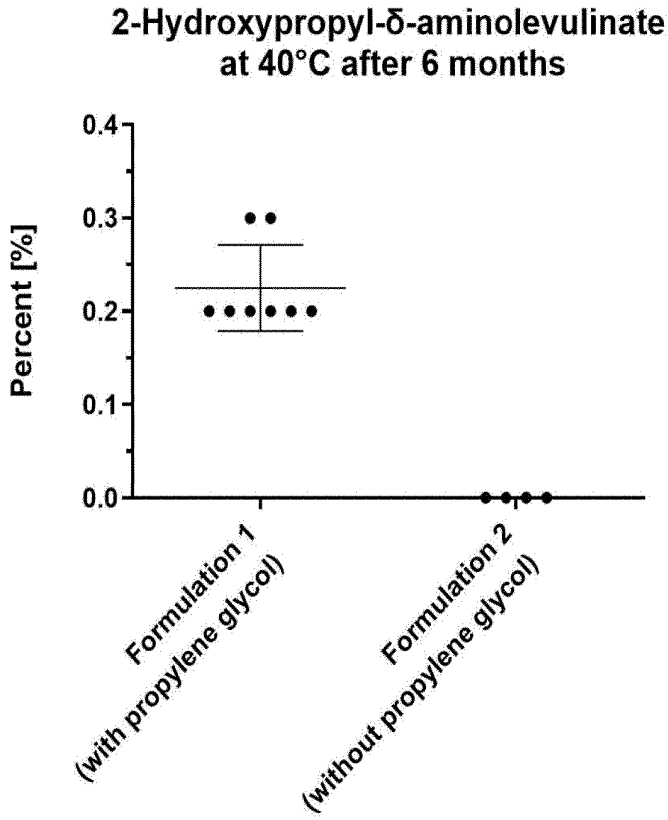
20. The formulation of any one of the preceding claims, for use in medicine, in particular for use in a method of treatment and/or prevention of a dermatological disease or condition.

Abstract

The present invention relates to oil in water nanoemulsions which are essentially free of propylene glycol. The nanovesicle formulations are particularly stable in regard to shelf life at different storage temperatures.

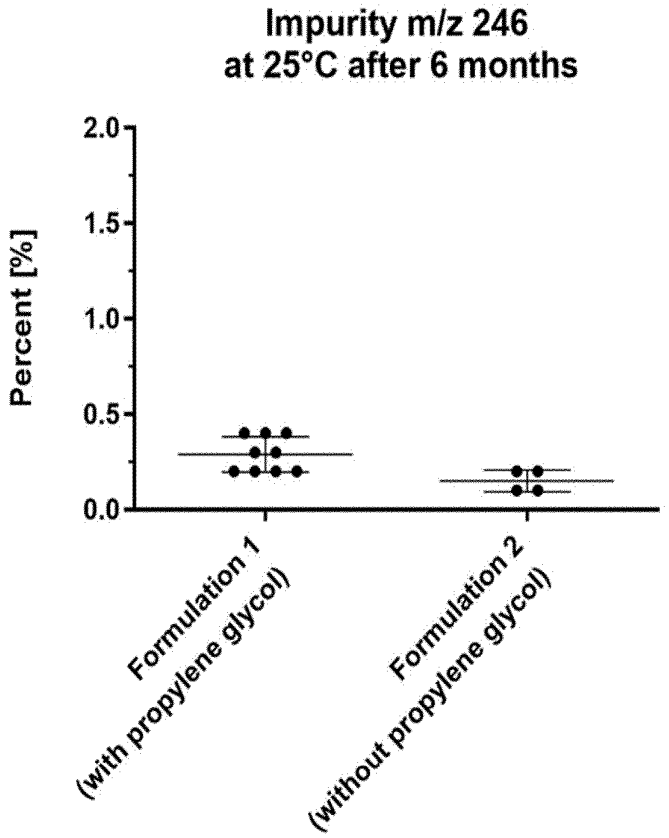
Figure 1





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Our Ref.: 501-25 PCT

Figure 1 (continued)



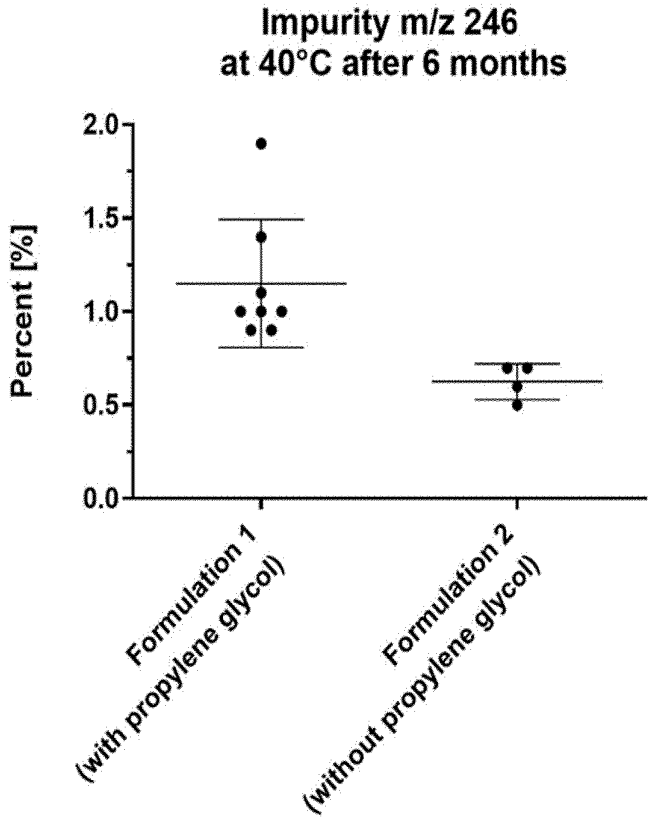


Figure 2

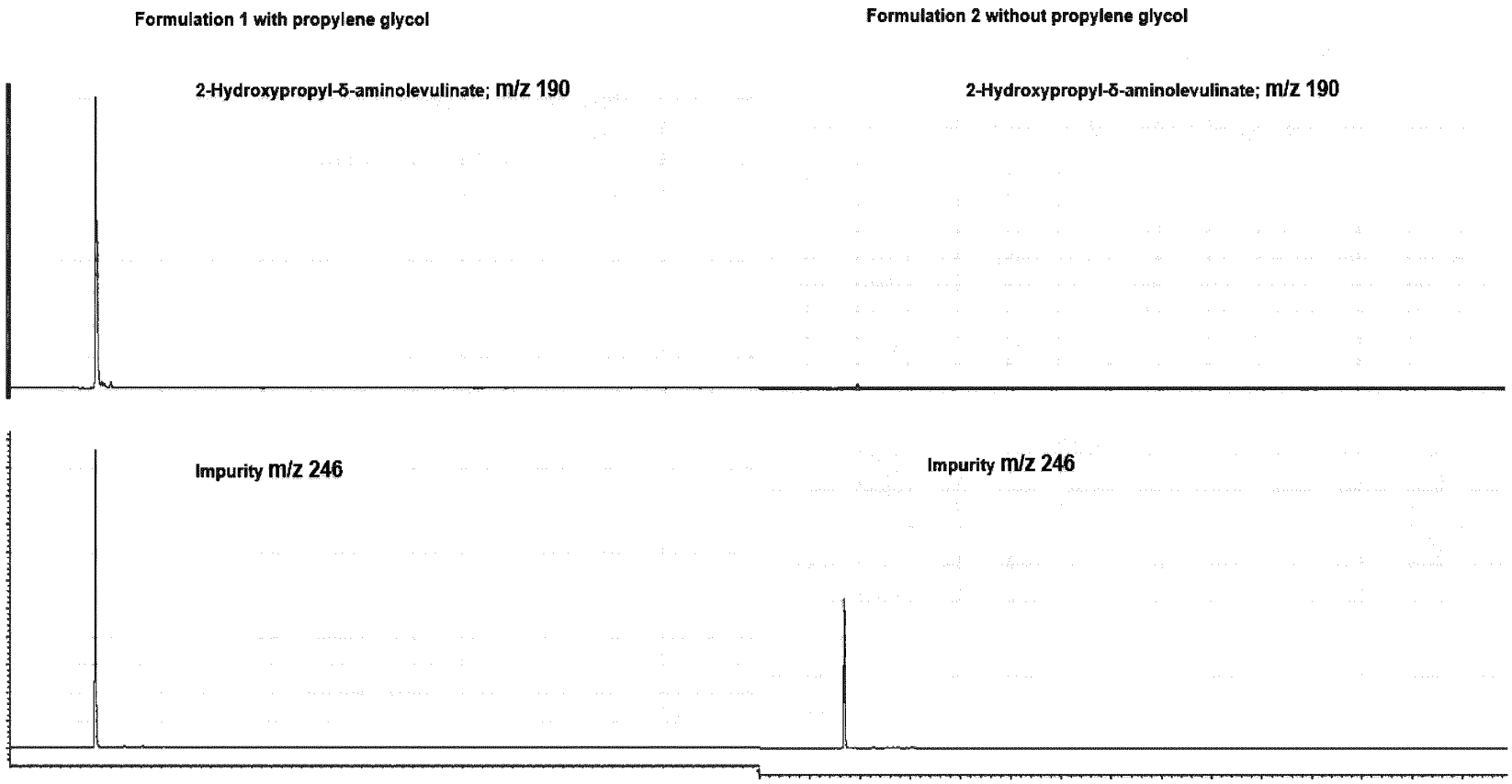

Formulation 1 with propylene glycol
Formulation 2 without propylene glycol
2-Hydroxypropyl-δ-aminolevulinate; m/z 190
2-Hydroxypropyl-δ-aminolevulinate; m/z 190
Impurity m/z 246
Impurity m/z 246

Figure 3

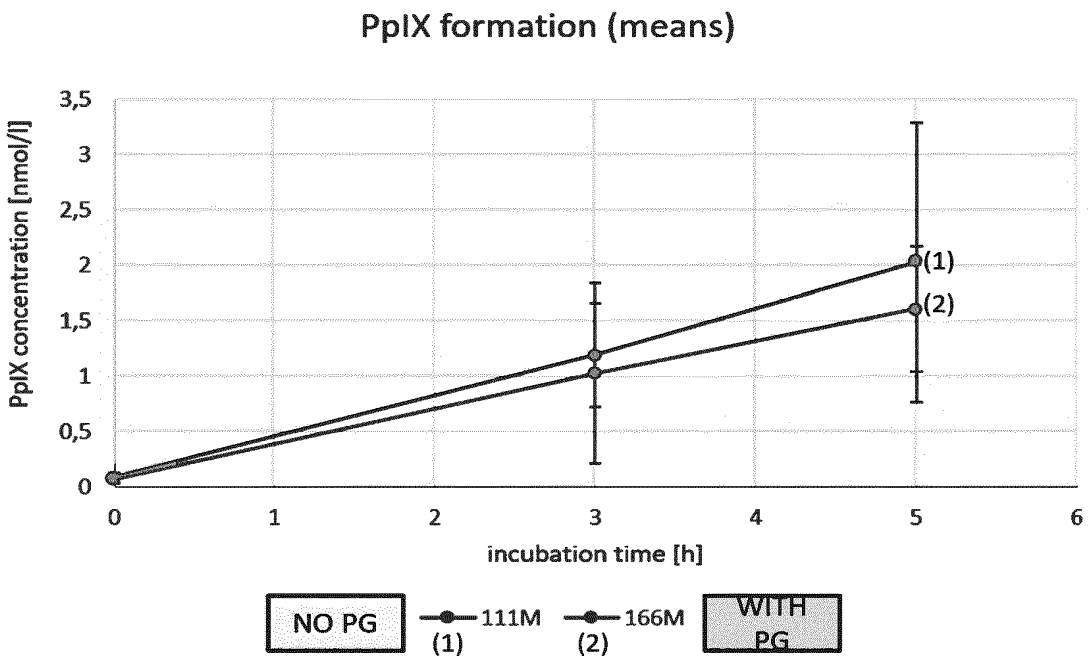
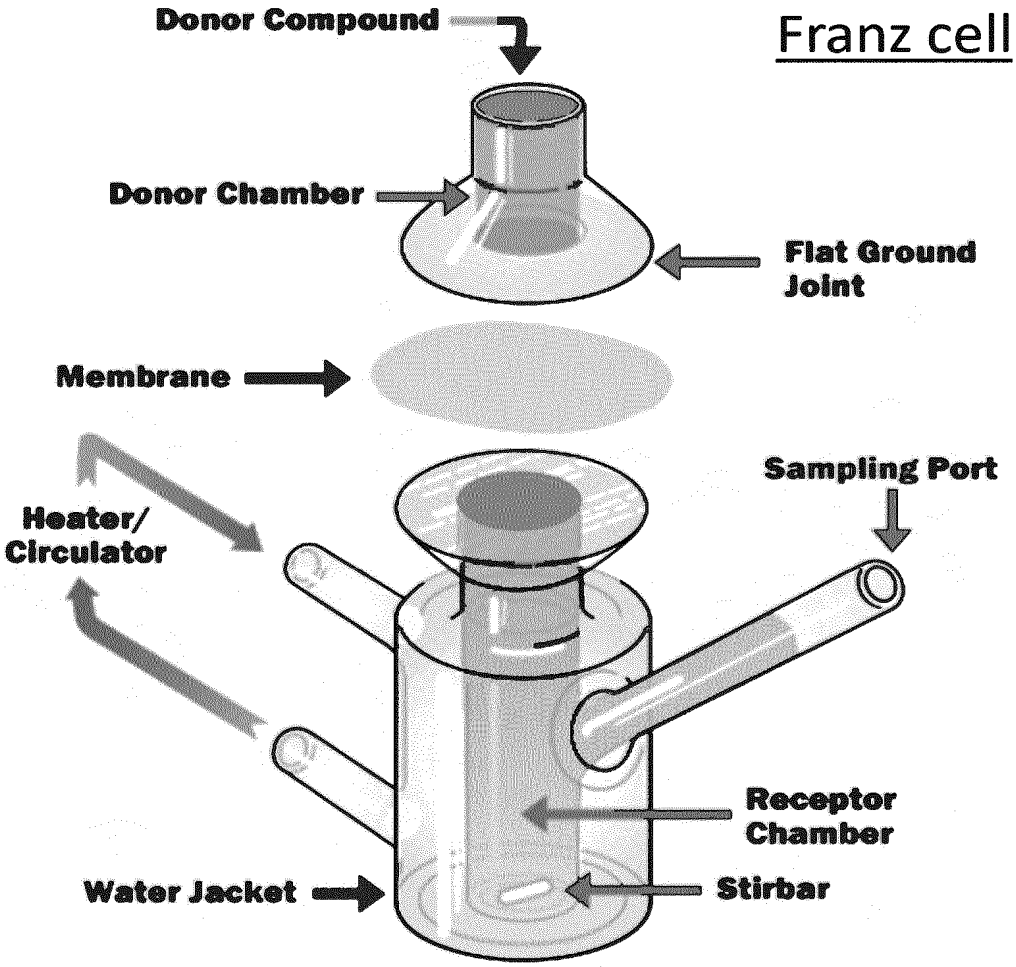

PpIX formation (means)
PpIX concentration [nmol/l]
3,5
3
2,5
2
1,5
1
0,5
0
0
1
2
3
4
5
6
incubation time [h]
(1)
(2)
NO PG
111M
(1)
166M
(2)
WITH PG

Figure 4


Franz cell
Donor Compound
Donor Chamber
Flat Ground Joint
Membrane
Sampling Port
Heater/ Circulator
Receptor Chamber
Water Jacket
Stirbar

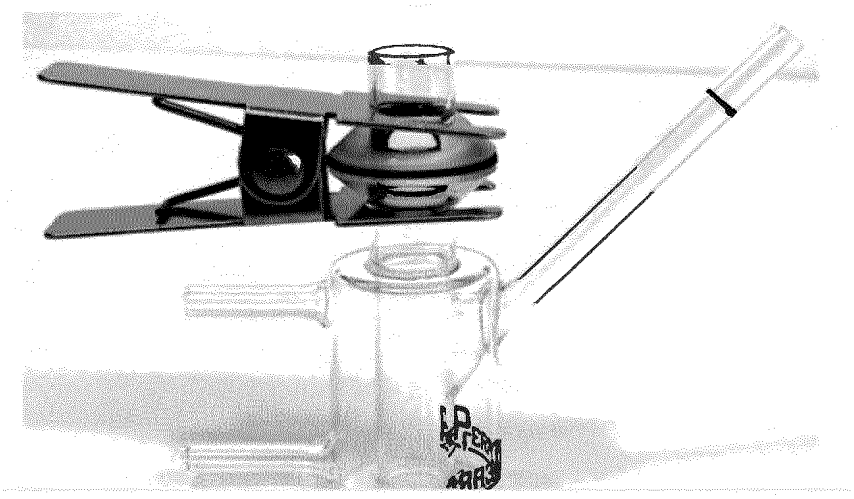
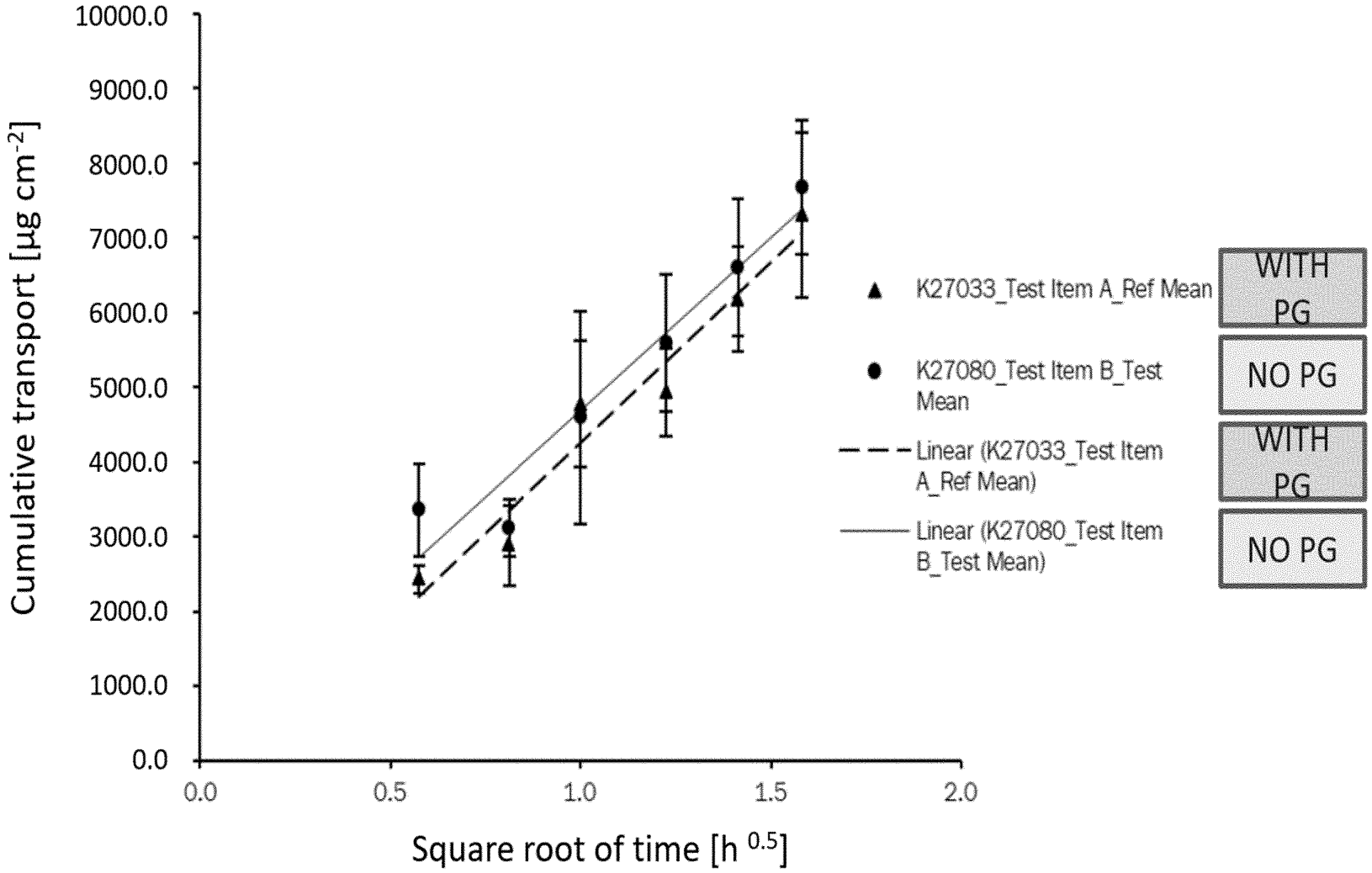


Figure 5


Cumulative transport [µg cm-2]
10000.0
9000.0
8000.0
7000.0
6000.0
5000.0
4000.0
3000.0
2000.0
1000.0
0.0
0.0
0.5
1.0
1.5
2.0
Square root of time [h 0.5]
K27033_Test Item A_Ref Mean
K27080_Test Item B_Test Mean
Linear (K27033_Test Item A_Ref Mean)
Linear (K27080_Test Item B_Test Mean)
WITH PG
NO PG
WITH PG
NO PG

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 01/28/2025

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
01/28/2025	ELECTRONIC

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):

bostonpatent@lathropgage.com

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United States Patent and Trademark Office
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Application No. : 18533497
Applicant : Foguet
Filing Date : 12/08/2023
Date Mailed : 01/28/2025

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

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The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Julia Walsh/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 18533497 **Drawings filed: 12/08/2023**

IDENTIFICATION OF DRAWING DEFICIENCIES

- [ ] There is a hole or the image thereof within the illustration. FIG(s)
- [ ] The illustration is penetrated or traversed by a solid or broken line that is not intended to be part of the drawing, such as a dark line caused by a flaw in the copying process. FIG(s)
- [ ] An ink stamp or the image thereof obscures part of the illustration. FIG(s)
- [ ] The drawing is marred by black smudges, obliterations, or fax/copier marks (for example, speckles or dots in a substantial portion of the drawing). FIG(s)
- [ ] Figure numbers are duplicated or missing. FIG(s)
- [ ] Drawing sheet or figure is missing. FIG(s)
- [ ] Numbers, letters, or reference characters in the drawing have been crossed out or are illegibly handwritten. FIG(s)
- [ ] The character of the lines, numbers, and letters is poor. FIG(s)
- [ ] The drawing's background shows that the original drawing was made on graph paper or other paper with a pattern or decoration. FIG(s)
- [ ] The FIG. number label is placed in a location that causes the drawing to be read upside down. FIG(s)
- [ ] Data, a reference number, or part of the drawing is truncated or missing, or a lead line has no reference number. FIG(s)
- [ ] The drawing and/or the FIG. label contain(s) foreign language. FIG(s)
- [X] This utility application contains a photograph of a view that is capable of being illustrated as a line drawing. FIG(s) 4
- [ ] A petition under 37 CFR 1.84(a)(2) to accept color drawings has been granted, but the brief description of the drawings in the specification does not contain (or has not been amended to contain) the paragraph required by 37 CFR 1.84(a)(2)(iii).
- [ ] This reissue application contains added and/or amended drawings that are not labeled as “New” or “Amended” or “Canceled” as required by 37 CFR 1.173(b)(3). FIG(s)
- [ ] This Design reissue application contains a drawing that is labeled as “Canceled” but is not surrounded by brackets, or a drawing that is surrounded by brackets but is not labeled as “Canceled.” See 37 CFR 1.173(b)(3). FIG(s)
- [ ] OTHER:
- [ ] COMMENTS:

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/533,497	12/08/2023	1612	1980	748419: BFR9-002	20	3

CONFIRMATION NO. 6866

UPDATED FILING RECEIPT

12779
Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

OC00000083600069

Date Mailed: 01/28/2025

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Montserrat FOGUET, Leverkusen, GERMANY;
Lars MÖLLMANN, Leverkusen, GERMANY;

Applicant(s)

Biofrontera Bioscience GmbH, Leverkusen, GERMANY;

Power of Attorney: The patent practitioners associated with Customer Number 12779

Domestic Applications for which benefit is claimed - None.
A proper domestic benefit claim must be provided in an Application Data Sheet in order to constitute a claim for domestic benefit. See 37 CFR 1.76 and 1.78.

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) PCT/EP2023/059291 04/06/2023 Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted: 12/20/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/533,497**

Projected Publication Date: Not Applicable.

Non-Publication Request: No

Early Publication Request: No

Title

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

7590 01/31/2025

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	
ART UNIT	PAPER NUMBER
1612	

DATE MAILED : 01/31/2025

FOREIGN PRIORITY ACKNOWLEDGMENT

☒ 1. Certified Copy Timely Received Before Payment of the Issue Fee:

Applicant previously submitted a claim for foreign priority under 35 U.S.C. 119(a)-(d) or (f).

☒ Certified copies of the priority documents have been received.

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

❑ Some of the certified copies of the priority documents have not been received: _____.

If the certified copy of a foreign application that has not been received is filed after the date the issue fee is paid, the patent will not include the priority claim unless corrected by a certificate of correction under 35 U.S.C. 255 and 37 CFR 1.323.

❑ 2. Certified Copy Received After Payment of the Issue Fee:

Applicant previously submitted a claim for foreign priority under 35 U.S.C. 119(a)-(d) or (f). Applicant submitted the certified copy after payment of the issue fee. The patent will not include the priority claim unless corrected by a certificate of correction under 35 U.S.C. 255 and 37 CFR 1.323.

Note: For utility or plant applications filed under 35 U.S.C. 111(a) on or after March 16, 2013, the certified copy may be timely received if the certified copy was filed within the later of four months from the filing date or sixteen months from the filing date of the prior foreign application (the 4/16 month time period) or if one of the exceptions in 37 CFR 1.55 (i.e., certified copy in a prior-filed nonprovisional application under 37 CFR 1.55(h), priority document exchange under 37 CFR 1.55(i), or interim copy under 37 CFR 1.55(j) is applicable. The 4/16 month time period does not apply to design applications.

\CB\

for 571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Patents Stakeholder Experience (OPSE)
Stakeholder Support Division (SSD)

U.S. Patent and Trademark Office
PTOL-147 (Rev. 08-2021)

DocCode - SCORE

Placeholder Sheet for Supplemental Content

Application Number: 18533497 Document Date: 02/05/2025

The presence of this form indicates that the following document type was received in electronic format on the date identified above. This document is stored separately from the typical case contents which are stored in image format.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded and no paper documents or physical media exist.

- Drawing

At the time of document entry (noted above):

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**02/05/2025 03:25:07 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Lauren Schmitt
PATENT CENTER #	69062814	FILING DATE	12/08/2023
CUSTOMER #	12779	FIRST NAMED INVENTOR	Montserrat FOGUET
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Laura Labeots

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
748419_Response.pdf	1	Amendment after Notice of Allowance (Rule 312)	154 KB
748419- BFR9-002_Replacement_Sheet.pdf	1	Drawings-other than black and white line drawings	261 KB
Miscellaneous Communication to Applicant - No Action Count.pdf	3	Miscellaneous Incoming Letter	108 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
748419_Response.pdf	D440F98620435D242C63129897CFDFDD50C7C9FCB5979C4C

	8CB8664A0C13F7EE82BD8485541BE86AF40BC624601EA431A B7C9528748ADCB630E4381BF989AE06
748419- BFR9- 002_Replacement_Sheet.pdf	510D4961EF70E09DD851A439DB8847A11D82D4068394BF71F C13707C7DCADD1CC2BE30ADB6643A7DA89FD57A3635FD9F 56306EAA092DB7247FF2E34811818D3D
Miscellaneous Communication to Applicant - No Action Count.pdf	D6D9DD195D5446C53DAB2C72441ADE45B2FC9C8A458D12A D270099DB572643CD283948AD312A45AF58CA1A127F7081E2 95ED915AB9DB99768313D3BD0CD2BA35

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 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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 01/28/2025

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28 State Street
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Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

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bostonpatent@lathropgage.com

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Application No. : 18533497
Applicant : Foguet
Filing Date : 12/08/2023
Date Mailed : 01/28/2025

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See attachment(s).

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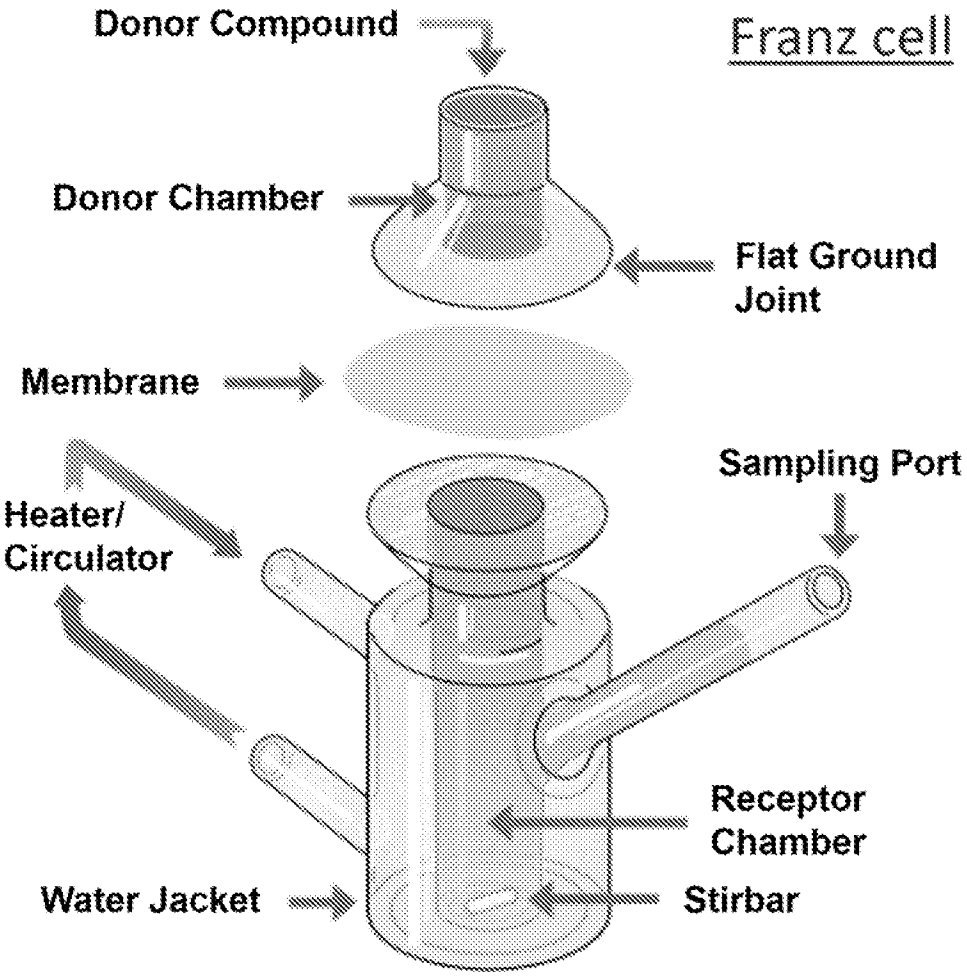
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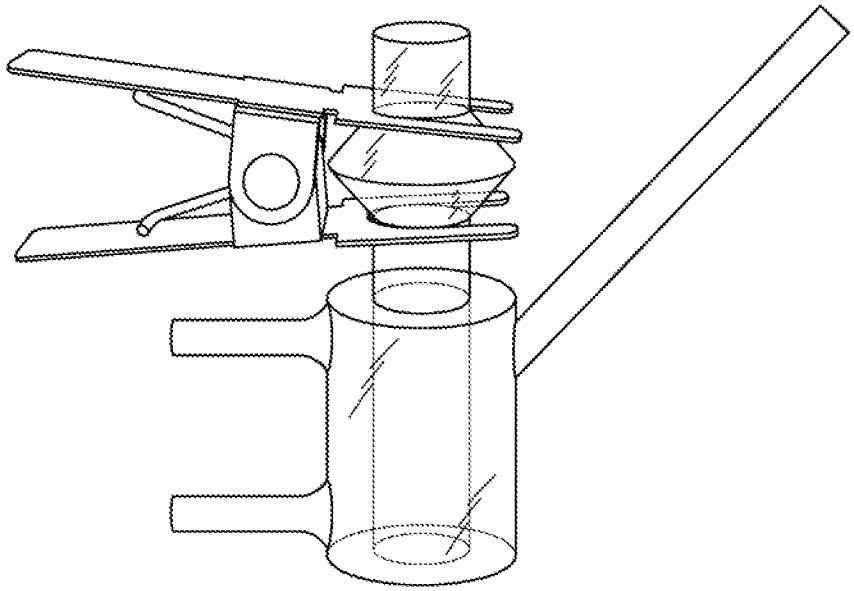
Application No. 18533497 **Drawings filed: 12/08/2023**

IDENTIFICATION OF DRAWING DEFICIENCIES

- [ ] There is a hole or the image thereof within the illustration. FIG(s)
- [ ] The illustration is penetrated or traversed by a solid or broken line that is not intended to be part of the drawing, such as a dark line caused by a flaw in the copying process. FIG(s)
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- [ ] Figure numbers are duplicated or missing. FIG(s)
- [ ] Drawing sheet or figure is missing. FIG(s)
- [ ] Numbers, letters, or reference characters in the drawing have been crossed out or are illegibly handwritten. FIG(s)
- [ ] The character of the lines, numbers, and letters is poor. FIG(s)
- [ ] The drawing's background shows that the original drawing was made on graph paper or other paper with a pattern or decoration. FIG(s)
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- [ ] The drawing and/or the FIG. label contain(s) foreign language. FIG(s)
- [X] This utility application contains a photograph of a view that is capable of being illustrated as a line drawing. FIG(s) 4
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- [ ] This reissue application contains added and/or amended drawings that are not labeled as “New” or “Amended” or “Canceled” as required by 37 CFR 1.173(b)(3). FIG(s)
- [ ] This Design reissue application contains a drawing that is labeled as “Canceled” but is not surrounded by brackets, or a drawing that is surrounded by brackets but is not labeled as “Canceled.” See 37 CFR 1.173(b)(3). FIG(s)
- [ ] OTHER:
- [ ] COMMENTS:

Figure 4


Donor Compound
Franz cell
Donor Chamber
Flat Ground Joint
Membrane
Sampling Port
Heater/ Circulator
Receptor Chamber
Water Jacket
Stirbar



Attorney Docket No:
748419: BFR9-002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Montserrat FOGUET	Confirmation No.: 6866
Application No.: 18/533,497	Art Unit: 1612
Filed: December 8, 2023	Examiner: CELESTE A RONEY

Title: NANOEMULSION WITHOUT PROPYLENE GLYCOL

Via Patent Center
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

Dear Commissioner:

In response to the post-allowance Notice to File Corrected Application Papers having a mailing date of January 28, 2025, submitted herewith is a Replacement Drawing which addresses the deficiencies outlined in the Notice. *No new matter has been added.* As this response is timely filed on or before March 28, 2025, Applicant believes that no fees are due in connection with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees that may be due or refund any fees to Deposit Account No. 12-0600, Reference No. 748419: BFR9-002.

Date: February 5, 2025

Respectfully submitted,

Electronic signature: /Laura A. Labeots/

Laura A. Labeots, Ph.D., J.D.
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LATHROP GPM
155 N. Wacker Drive
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(312) 920-3357
Attorney for Applicant
Customer No: 12779

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/533,497	**03/21/2025 03:20:11 PM Z ET**	**748419: BFR9-002**

Title of Invention

NANOEMULSION WITHOUT PROPYLENE GLYCOL

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6866	FILED BY	Lauren Schmitt
PATENT CENTER #	69685453	AUTHORIZED BY	Laura Labeots
CUSTOMER #	12779	FILING DATE	12/08/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Montserrat FOGUET

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 3154	**E20253KF20377004**	**Lauren Schmitt**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
120600	**37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1501	UTILITY ISSUE FEE	1200.00	1	1200.00
			TOTAL AMOUNT:	**$1,200.00**

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 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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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

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18/533,497	**03/21/2025 03:20:11 PM Z ET**	**748419: BFR9-002**

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CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Laura Labeots

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
748419- BFR9-002_Issue_Fee_Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	297 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
748419- BFR9-002_Issue_Fee_Transmittal.pdf	2BB329C5AAE1E436185EF7CC2C4CBC4C683AB876F3B0A994B38FF13C96456AEA5DB55AC2C05F4EEFAF113A099DB474D4EBE23C838380F63005197B7DA993E406

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

12779 7590 12/24/2024

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Laura A. Labeots, Ph.D., J.D.	(Typed or printed name)
/Laura A. Labeots/	(Signature)
March 21, 2025	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

TITLE OF INVENTION: NANOEMULSION WITHOUT PROPYLENE GLYCOL

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	03/24/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
RONEY, CELESTE A	1612	424-450000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Lathrop GPM LLP
2 James H. Velema
3 Laura A. Labeots, Ph.D., J.D.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Biofrontera Bioscience GmbH

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Leverkusen, Germany

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 12-0600

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Laura A. Labeots/ Date March 21, 2025

Typed or printed name Laura A. Labeots, Ph.D., J.D. Registration No. 62,235

INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				Complete if Known	
				Application Number	18/533,497
				Filing Date/371(c) Date	December 8, 2023
				First Named Inventor	Montserrat FOGUET
				Art Unit	1612
				Examiner Name	Celeste A. RONEY
Sheet	1	of	4	*Attorney Docket Number*	748419: BFR9-002

U.S. PATENTS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Issue Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 5891490 A	04/06/1999	MERABET	
	2.	US 6165500 A	12/26/2000	CEVC	
	3.	US 6245349 B1	06/12/2001	YIV et al.	
	4.	US 6274150 B1	08/14/2001	SIMONNET et al.	
	5.	US 6375960 B1	04/23/2002	SIMONNET et al.	
	6.	US 6413527 B1	07/02/2002	SIMONNET et al.	
	7.	US 6500862 B1	12/31/2002	ZANELLO	
	8.	US 6559183 B1	05/06/2003	SCHMID et al.	
	9.	US 6602511 B2	08/05/2003	VON CORSWANT	
	10.	US 6897238 B2	05/24/2005	CHEN et al.	
	11.	US 7314624 B2	01/01/2008	BAKER et al.	
	12.	US 11540981 B2	01/03/2023	ROCA et al.	

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.	Document Number Number-Kind Code *(if known)*	Publication Date MM/DD/YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 20020155084 A1	10/24/2002	ROESSLER et al.	
	2.	US 20030167033 A1	09/04/2003	CHEN et al.	
	3.	US 20030190347 A1	10/09/2003	SUPERSAXO et al.	
	4.	US 20050158389 A1	07/21/2005	DOMB	
	5.	US 20050208083 A1	09/22/2005	ANNIS	
	6.	US 20060140984 A1	06/29/2006	TAMARKIN et al.	
	7.	US 20060078525 A1	04/13/2006	TOMOKUNI	
Change(s) applied	8.	US 20110060042 A1	03/10/2011	ITO	
to document,	9.	US 20090324727 A1	12/21/2009	~~ROCA et al.~~ Foguet Roca	
/K.P./	10.	US 20230201087 A1	06/29/2023	ROCA et al.	
1/22/2025					

Examiner Signature	/CELESTE A RONEY/	Date Considered	04/24/2024

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.A.R/

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/533,497	04/22/2025	12280146	748419: BFR9-002	6866

12779 7590 04/02/2025

Lathrop GPM LLP
28 State Street
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Boston, MA 02109

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Montserrat FOGUET, Leverkusen, GERMANY;
Lars MÖLLMANN, Leverkusen, GERMANY;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Biofrontera Bioscience GmbH, Leverkusen, GERMANY;

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18/533,497	12/08/2023	Montserrat FOGUET	748419: BFR9-002	6866

12779 7590 04/22/2025

Lathrop GPM LLP
28 State Street
7th Floor
Boston, MA 02109

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/22/2025	ELECTRONIC

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):

bostonpatent@lathropgage.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/533,497	22-Apr-2025	12280146

Lathrop GPM LLP
28 State Street
Boston, MA 02109

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants