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(54) Title: EMULSION COMPRISING FINASTERIDE

(57) Abstract: The present invention concerns an emulsion comprising finasteride, a method of its preparation and a pharmaceutical formulation comprising said emulsion. In addition the invention relates said emulsion for the use in the treatment of androgenetic alopecia.



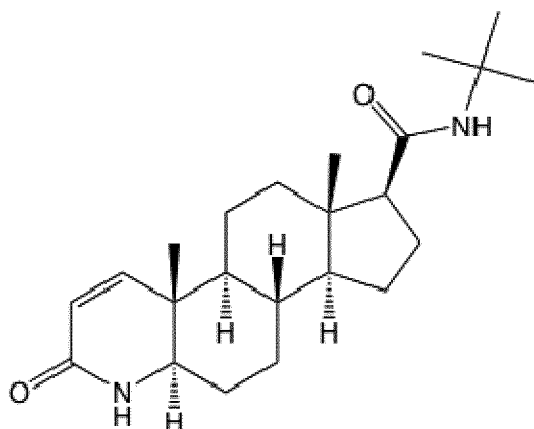
WO 2018/206077 A1

Emulsion comprising finasteride

The present invention concerns an emulsion comprising finasteride, a method of its preparation and a pharmaceutical formulation comprising said emulsion. In addition the invention relates said emulsion for the use in the treatment of androgenetic alopecia.

Finasteride is a 5α -reductase inhibitor and is regarded as a synthetic steroid. Due to its similar structure compared with testosterone, finasteride is reported to irreversibly inhibit 5α -reductase and, thus, prevents testosterone from being converted to dihydrotestosterone (DHT). Currently a specific kind of hair follicle is reported to reduce its anagen-phase (growth-phase) when brought into contact with DHT. By preventing the formation of DHT, the growth phase of the hair follicle can be enhanced and the beginning of androgenetic alopecia can be postponed for years. However, this treatment has to be applied continuously since in case of an abandonment of the finasteride administration the level of DHT rises and the grown hair falls out again. Further, finasteride can be used in the treatment of benign prostatic hyperplasia (BPH) also known as enlarged prostate, wherein finasteride eases the symptoms associated with BPH such as difficulty urinating, having to get up during the night to urinate, hesitation at the start of urination and decreased urinary flow.

The IUPAC name of finasteride is (1S,3aS,3bS,5aR,9aR,9bS,11aS)-N-tert-butyl-9a,11a-dimethyl-7-oxo-1,2,3,3a,3b,4,5,5a,6,9b,10,11-dodecahydroindeno[5,4-f]quinoline-1-carboxamide and the compound is represented by the following chemical Formula (I)



Formula (I)

Finasteride for the treatment of alopecia is marketed under the brand name "Propecia" and is administered 1 mg once daily. Further, finasteride is marketed under the brand name "Proscar" and administered 5 mg once daily for the treatment of benign prostatic hyperplasia.

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For the patient's convenience a topical formulation of finasteride is reported to be desirable. The preparation of such a topical formulation bears several problems. Finasteride is very poorly water-soluble and also the solubility in lipophilic substance is undesirably low. Suitable solvents for finasteride are alcohols such

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Example 1 of US 2011/0183016 A1 describes a film-forming solution consisting of 0.25 wt.% finasteride, 55 wt.% ethanol, 5 wt.% propylene glycol, 1 wt.% hydroxypropyl chitosan and 28.75 wt.% water. The obtained clear solution is reported to form a matte, non-sticky and elastic film which could adhere to the scalp surface.

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Alcohols, when applied in high concentrations, however, are reported to leave a cold sensation, which is considered to be unpleasant by many patients. In addition, alcohols might inappropriately remove the protecting fatty substances of the epidermis.

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Contrary, formulations containing a very high content of water might inadequately dissolve the active pharmaceutical ingredient and might be difficult to remove such that the hair remains wet after application.

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Thus, it was an object of the present invention to overcome the above-illustrated drawbacks.

In particular, it was an object of the invention to provide a topical finasteride formulation being advantageous compared to the formulation of the prior art. Sufficient concentration of dissolved finasteride should be provided at the target site. The scope of protection of US 2011/0183016 A1 should be avoided.

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Further, a finasteride formulation advantageously reducing an unpleasant sensation or a skin irritation upon administration should be provided.

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In addition, it was an object to provide a finasteride formulation which preferably completely volatilizes. Further, the formulation should not leave behind residues such as an oily film on the scalp or hair.

- 5 Further, a finasteride formulation should be provided which can be produced in a simple way and which might be administered in different forms.

The objects of the present invention have been unexpectedly solved by an emulsion comprising finasteride, organic solvent, non-ionic emulsifier, siloxane
10 having 2 to 5 silicon atoms and water in specific amounts, respectively.

The inventors found out that the emulsion of the present invention unexpectedly prevents an unpleasant sensation upon administration. In addition, the emulsion of the present invention does not leave behind any residues on the scalp or on the
15 hair.

Further, the above properties are achieved wherein the formulation additionally provides a sufficient concentration of dissolved active pharmaceutical ingredient at the target site.

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Summary of the Invention

This invention provides an emulsion comprising

- 25 (A) 0.025 to 1 wt.% finasteride
(B) 20 to 40 wt.% organic solvent
(C) 5 to 25 wt.% non-ionic emulsifier
(D) 1.0 to 7.0 wt.% of a siloxane having 2 to 5 silicon atoms
(E) 35 to 65 wt.% water

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In addition a method for the preparation of the emulsions according to the invention is provided, wherein the method comprises the steps of

- 35 (i) dissolving finasteride and optionally one or more additive(s) in the solvent and the siloxane having 2 to 5 silicon atoms,
(ii) preparing a mixture of the non-ionic emulsifier and optionally one or more additive(s) in water, and

- (iii) merging the solution from step (i) and the mixture of step (ii) to form the emulsion of the present invention

Further, this invention provides a pharmaceutical formulation comprising the emulsion according to the present invention.

Finally, a subject of the present invention is the emulsion or the pharmaceutical formulation of the present invention for use in the treatment of androgenetic alopecia.

Detailed Description of the Invention

An emulsion can be regarded herein as the dispersion of two incompletely miscible liquids or systems of liquids. Commonly one liquid or system of liquids can be an oil or a system of oil, wherein "oil" refers to any liquid which is essentially water-insoluble. The second liquid or system of liquids can be water or system of water miscible liquids. The average diameter of droplets in an emulsion, which is sometimes also referred to as macro-emulsion, can be close to one millimeter, i.e. 10^{-3} m. Generally, emulsions are thermodynamically instable and the average droplet size grows with time.

A micro-emulsion can be regarded herein as a thermodynamically stable and anisotropic emulsion. Its properties usually are time independent and not influenced by its method for preparation, such as order of mixing or mechanical energy. A micro-emulsion preferably comprises an emulsifier. The entities of the dispersed phase are preferably stabilized by an emulsifier and/or emulsifier-coemulsifier system, wherein the coemulsifier can be for example an aliphatic alcohol. The diameter of droplets of the dispersed phase can vary from 0.5 to 200 nm, 1 to 100 nm, or 10 to 50 nm. Further, in a micro-emulsion the domains of the dispersed phase can be either globular or interconnected to give a continuous micro-emulsion.

In a preferred embodiment the emulsion according to the present invention can be a micro-emulsion. In a preferred embodiment the intensity-weighted particle size distribution of the dispersed phase has a Z-average of 1 to 100 nm, preferably 5 to 80 nm, more preferably 10 to 60 nm, in particular 20 to 40 nm.

The intensity-weighted particle size distribution is determined by dynamic light scattering (DLS) with a Zetasizer Nano ZS by Malvern.

The Z-average can be expressed as the intensity based harmonic mean and can be calculated as follows:

$$D_z = \frac{\sum S_i}{\sum \left(\frac{S_i}{D_i} \right)}$$

wherein S_i corresponds to the scattered intensity from particle i ;

and D_i corresponds to the diameter of particle i .

The parameters for the set up of the corresponding device are described in the experimental section.

Component (A) comprised in the emulsion of the present invention is finasteride, which is referred to as the compound according to above Formula I.

Finasteride is contained in the emulsion of the present invention in amounts of from 0.025 to 1.0 wt.%, preferably from 0.10 to 0.75 wt.%, more preferably from 0.15 to 0.50 wt.%, in particular from 0.20 to 0.35 wt.%, based on the total weight of the emulsion.

Component (B) is an organic solvent. An organic solvent is referred herein to an organic compound which can preferably be liquid at 23°C at 1013 mbar. In that regard the term "organic compound" generally refers to a compound the skeleton of which predominately contains carbon atoms, nitrogen atoms and/or oxygen.

Examples of organic solvents are aliphatic mono- or divalent or trivalent alcohols having 1 to 6 carbon atoms such as methanol, ethanol, propanol, isopropanol, 1,2-propandiol or 1,3-propandiol, butanol, *tert.*butanol, 1,6-hexanediol, glycerol, ketones such as acetone, *tert.*butyl methylketone, methyl ethylketone, ethers such as diethylether, tetrahydrofuran and dioxane, dimethyl formamide, dimethyl sulfoxide, acetonitrile, carboxylic acid esters such as ethyl acetate, and mixtures thereof.

Preferred solvents are alcohols such as methanol, ethanol, propanol und isopropanol, more preferably ethanol and isopropanol, in particular ethanol.

5 The organic solvent (B) is contained in the emulsion of the present invention in amounts of from 20 to 40 wt.%, preferably from 22 to 37 wt.%, in particular from 25 to 34 wt.%, based on the total weight of the emulsion.

10 An emulsifier can be regarded as a compound which can enable the formation of emulsion from two non-miscible liquids and which can stabilize said emulsion preventing the separation of the liquids.

Generally, an emulsifier can comprise a polar as well as a non-polar part. The non-polar part can be for example an alkyl group having more than 8 carbon atoms or an alkyl phenyl group.

15 The polar part of the emulsifier can be composed of various functional groups being suitable to classify the emulsifier into the following four categories.

20 An anionic emulsifier bears a negatively charged polar group such as a sulfate, phosphate or carboxylate. Examples of anionic emulsifiers are alkyl sulfates such as ammonium lauryl sulfate and sodium lauryl sulfate and alkylcarboxylates such as sodium stearate.

25 A cationic emulsifier bears a positively charged polar group such as quaternary ammonium group. An example of a cationic emulsifier is cetyltrimethylammonium bromide.

30 A zwitterionic emulsifier bears both a negatively charged polar group, such as a carboxylate, and a positively charged polar group, such as a quaternary ammonium group. An example of a zwitterionic emulsifier is cocamidopropyl betaine.

35 The emulsion of the present invention can comprise a non-ionic emulsifier (C). A non-ionic emulsifier comprises a non-polar part and a polar part, wherein the polar part does not bear an ionic group.

In a preferred embodiment of the invention the non-polar part of the non-ionic emulsifier can comprise 4 to 40 carbon atoms, preferably 8 to 20 carbon atoms.

Further, the polar part of the non-ionic emulsifier can comprise for example one or a plurality of hydroxy or ether group(s), preferably polyether groups such as polyethoxyethylene groups. Examples for non-ionic emulsifiers can be for example polyoxyethylene glycol alkyl ethers, polyoxypropylene glycol alkyl ethers, polyoxyethylene glycol sorbitan alkylesters and fatty alcohols.

10 In a preferred embodiment the non-ionic emulsifier can be an ethoxylated fatty alcohol.

A fatty alcohol can preferably comprise an even number of carbon atoms, preferably from 4 to 26 carbon atoms. A fatty alcohol can be saturated or unsaturated. Further, fatty alcohols can preferably comprise a straight chain having a single alcohol group bonded to the terminal carbon atom.

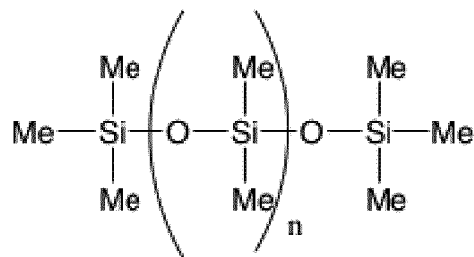
Examples of fatty alcohols are capryl alcohol (1-octanol), lauryl alcohol (1-dodecanol), cetyl alcohol (1-hexadecanol), stearyl alcohol (1-octadecanol), palmitoleyl alcohol (cis-9-hexadecen-1-ol) and oleyl alcohol (cis-9-octadecen-1-ol).

Ethoxylated fatty alcohol can comprise 1 to 10 ethoxyethylene groups, preferably 3 to 9 ethoxyethylene groups, wherein the corresponding residue can be also referred to as PEG-X-residue with X being the number of the ethoxyethylene groups.

In a particularly preferred embodiment of the invention the non-ionic emulsifier (C) is PEG-5-oleyether.

The non-ionic emulsifier (C) is contained in the emulsion of the present invention in amounts of from 5 to 25 wt.%, preferably from 8 to 22 wt.%, in particular from 12 to 18 wt.%, based on the total weight of the emulsion.

Component (D) is a siloxane having 2 to 5 silicon atoms. Preferably, component (D) can be represented by the following Formula (II)



wherein n is 0, 1, 2 or 3.

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It is preferred that the siloxane having 2 to 5 silicon atoms can have a boiling point at 1013 mbar from 85°C to 250°C, preferably from 90°C to 200°C, more preferably from 95° to 160°C.

- 10 In a particularly preferred embodiment component (D) comprised in the present emulsion is hexamethyldisiloxane. Hexamethyldisiloxane can be referred to as the component according to Formula (II) with n being 0.

- 15 In an alternatively particularly preferred embodiment component (D) comprised in the present emulsion is octamethyltrisiloxane. Octamethyltrisiloxane can be referred to the component according to Formula (II) with n being 1.

- 20 The siloxane having 2 to 5 silicon atoms (D) is contained in the emulsion of the present invention in amounts of from 1 to 7 wt.%, preferably from 1.5 to 5 wt.%, in particular from 2 to 4 wt.%, based on the total weight of the emulsion.

- Component (E) comprised in the emulsion of the present invention is water. Water can be preferably purified water, more preferably purified water according to Ph.Eur. 6. Supplement 6.3, pp. 4344-4346.

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The water, preferably the purified water, contained in the emulsion of the present invention is present in amounts of from 35 to 65 wt.%, preferably from 40 to 60 wt.%, in particular from 45 to 55 wt.%, based on the total weight of the emulsion.

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In a preferred embodiment of the invention the emulsion can comprise one or more additives. The emulsion can for example comprise additive(s) in an amount of from 0.001 wt.% to 40 wt.%, preferably from 0.01 wt.% to 35 wt.%, more

preferably 0.1 wt.% to 30 wt.%, in particular from 0.5 wt.% to 20 wt.%, based on the total weight of the emulsion.

In a preferred embodiment the emulsion of the present invention comprises

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- (A) finasteride,
- (B) ethanol,
- (C) PEG-5-oleyl-ether,
- (D) octamethyltrisiloxane, and
- 10 (E) purified water.

In another preferred embodiment of the invention the emulsion comprises

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- 0.025 to 1 wt.%, preferably 0.10 to 0.75 wt.%, more preferably 0.15 to 0.50 wt.%, in particular 0.20 to 0.3 wt.% finasteride
- 20 to 40 wt.%, preferably 22 to 37 wt.%, in particular 25 to 34 wt.% solvent
- 5 to 25 wt.%, preferably 8 to 22 wt.%, in particular 12 to 18 wt.% non-ionic emulsifier
- 1 to 7 wt.%, preferably 1.5 to 5 wt.%, in particular 2 to 4 wt.% siloxane
- 20 having 2 to 5 silicon atoms
- 35 to 65 wt.%, preferably 40 to 60 wt.%, in particular 45 to 55 wt.% water,

wherein wt.% is based on the total weight of the emulsion.

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In a particular preferred embodiment the emulsion of the present invention comprises

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- 0.025 to 1 wt.%, preferably 0.10 to 0.75 wt.%, more preferably 0.15 to 0.50 wt.%, in particular 0.20 to 0.3 wt.% finasteride
- 20 to 40 wt.%, preferably 22 to 37 wt.%, in particular 25 to 34 wt.% ethanol
- 5 to 25 wt.%, preferably 8 to 22 wt.%, in particular 12 to 18 wt.% PEG-5-oleyl-ether
- 1 to 7 wt.%, preferably 1.5 to 5 wt.%, in particular 2 to 4 wt.% octamethyltrisiloxane
- 35 - 35 to 65 wt.%, preferably 40 to 60 wt.%, in particular 45 to 55 wt.% purified water,

wherein wt.% is based on the total weight of the emulsion.

Additives are for example active substances, conditioning agents, preservatives, dyes, perfume substances, care substances, pH regulators and penetration enhancers. Each single additive can be present in an amount of from 0.001 wt.% to 10 wt.%, in particular from 0.01 wt.% to 5 wt.%, based on the total weight of the emulsion.

The term "active substances" means that besides finasteride a further substance having a pharmacological effect is contained in the formulation. Active substances can preferably be selected from the extracts of plants, synthetically produced substances corresponding to extracts and analogous derivatives thereof, vitamins as well as substances that influence the skin and mixture thereof.

Extracts of plants are, for example, those of ylang ylang, pine needles, cypress, thyme, mint, limes, oranges, grapefruit, mandarin oranges, juniper, valerian, lemon balm, eucalyptus, thyme, palmarosa, rosemary, lavender, rosewood, lemon grass, spruce needles, pine needles, ginger, currant, linden blossom, calendula extract, magnolia, algae, aloe vera, pineapple, guava, echinacea, ivy leaf, birch leaf, hibiscus extract, burdock root, witch hazel, hydrocotylidis herba, quince, water lily, cinnamon, or mixtures thereof.

Suitable vitamins are, for example, vitamins A, B, E, C, or suitable derivatives thereof, such as esters, e.g. palmitate, acetate, or phosphate.

Other suitable active substances that influence the skin can be minerals and trace elements such as copper, zinc, magnesium, or their derivatives, particularly salts, such as Zincidone[®] (zinc PCA), zinc gluconate, or copper gluconate.

Further, astringent and sebum-regulating substances, such as hydroxydecanoic acid, pyridoxine, niacinamide, glycerin, caproyl collagen amino acids, sebacic acid, cinnamonom zeylanicum, or cooling/soothing active substances such as menthyl lactate or sodium hyaluronate, wheat germ extract, saccharomyces cerevisiae extract can preferably be used.

Furthermore, active substances can preferably be active substances that promote blood circulation. Examples are nicotinic acid derivatives such as methyl nicotinate or tocopheryl nicotinate, alphahydroxy and betahydroxy acids and their derivatives.

- 5 Furthermore, substances having an antioxidant effect or a cell-protection effect, such as polyphenols, flavonoids, or isoflavones. Other active substances can preferably be UV filters such as UVB, WVA, and broadband filters, as they are generally known, e.g. cinnamic acid esters, salicylates, or inorganic UV filters. Further, active substances that can preferably be used are biotin, allantoin, panthenol, 10 niacinamide, urea and inositol. Depending on the purpose of use, active substances that are soluble in oil or water can also be used or combined for cosmetic and/or dermatological/pharmaceutical purposes.

- 15 Dermatologically/pharmaceutically active substances can be, in particular, anti-microbially active substances (antibiotics; antimycotics, antiviral substances), hormones or hormonally active substances such as sex hormones, wound cleansing agents, analgesics, cytokins, cytostatics, anti-acne agents, immune suppressives, pigmentation regulators, agents against photodermatoses, or the vasoactive/antiphlogistic substances named above, or combinations thereof.

- 20 In contrast, strongly oxidative substances such as hydrogen peroxide are preferably not used.

- 25 Examples of conditioning agents can be acrylamides; polysaccharide such as xanthan gum; cellulose and its derivatives such as methyl cellulose, ethyl cellulose hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose; carmellose-Na; starch and mixtures thereof.

- 30 Furthermore, complexing agents such as EDTA, compounds such as citric acid, soda lye, solvents such as propylene glycol or alcohols, salts such as NaCl, starch or starch derivatives, or mixtures thereof, can be contained as conditioning agents. Other conditioning agents are monoalkyl and dialkyl phosphates or glyceryl stearate.

- 35 A preservative is a substance that can be added to the emulsion of the present invention to protect the emulsion and its ingredients from disadvantageous reactions such as oxidation or damage caused by microorganisms. A preservative can be a natural or synthetic substance.

Example of suitable preservatives are imidazolidinyl urea, glutaraldehyde, formaldehyde, 2-phenoxyethanol, 1-phenoxy-propan-2-ol, undec-10-enoic acid iodopropynyl butyl carbamate, DMDM hydantoin, phenoxyethanol and other commonly used preservatives, such as sorbic acid and dehydracetic acid, and their salts, methyl dibromoglutaronitrile or combinations thereof; or other acids such as benzoic acid, propionic acid or salicylic acid, or benzyl alcohol or esters such as p-hydroxy benzoic acid esters, e.g. methyl paraben, ethyl paraben, propyl paraben, butyl paraben, isobutyl paraben, or climbazol or suitable combinations of the stated substances.

- 10 Dyes can preferably be naturally occurring and synthetically produced colouring agents. Examples are Acid Blue 7, disodium salt of 1-(3-sulfo- 1-phenylazo)-2-naphthol-6-sulfonic acid (Food Orange 2), disodium salt of 1-(4- sulfo-1-phenylazo)-2-naphthol-6-sulfonic acid (Food Orange 3), Acid Orange 10 (Food Orange 4) or derivatives thereof, trisodium salt of 1-(4-sulfo-1-naphthylazo)-2-naphthol-6,8-
 15 disulfonic acid (Acid Red), trisodium salt of 1-(4-sulfo-1-naphthyl- azo)-2-naphthol-3,6-disulfonic acid (Acid Red 27), tetrasodium salt of 1-(4-sulfo-1- naphthylazo)-2-naphthol-3,6,8-disulfonic acid (Acid Red 41), quinophthalonedisul- fonic acid or suited combinations thereof.
- 20 Suitable perfume substances are, for example, the ether oils named under active substances or commercially available perfume mixtures.

Particularly suitable care substances are phytosterols (essentially mixtures of β -sitosterol, campesterol, and stigmasterol or ethoxylated derivatives thereof), such as
 25 those from canola oil. Also lecithin (e.g. soybean lecithin), phosphatidyl choline, phosphatidyl serine or diethanolamine, or mixtures thereof with the aforementioned phytosterols can preferably be used.

Furthermore, silicone oils such as dimethicones or silicone (co)polymers, e.g. di-cyclo-
 30 methicone or divinyl dimethicone/dimethicone copolymers, C12-13 pareth-3/C12-13 pareth-23) can preferably be used.

Other care substances can be moisturizing agents such as glycerin, propylene glycol, or polyethylene glycols, propylene glycol, butylene glycol, sorbitol, or polymers, e.g.
 35 polyquaternium types such as polyquaternium 39, collagen or its hydrolysates, amino acids, urea, polysaccharide (biosaccharide gum 1), glucosaminoglycanes, e.g.

hyaluronic acid or sulfated glucosaminoglycans such as chondroitin sulfate, dermatane sulfate, keratane sulfate, heparane sulfate or mixtures thereof..

Substances to adjust the pH-value of the emulsion can be referred to as pH regulators. A pH regulator can preferably selected from indifferent und less irritated salts such as calcium chloride, barium chloride; or from acids, especially organic acids, such as acetic acid, citric acid, salicylic acid, lactic acid and other alpha hydroxy acids as well as inorganic acids such HCl, from buffering substances such as phosphate buffer, lactate buffer or citric buffer, or from slats such as NaOH and KOH and from other bases.

These regulators are used in amounts sufficient to provide the desired pH value of the composition of the invention. In a preferred embodiment the pH value of the claimed formulation is between 3 and 7, and more preferably between 4.5 and 5.5.

Penetration enhancers can be chosen amongst polyvalent alcohol(s) and derivatives thereof, preferably esters, such as glycerol alone or with its esters or suitable combinations thereof; mono- or polyvalent glycols or derivatives thereof, such as propylenglycol, ethoxydiglycol, preferably Transcutol[®], or azocycloheptanone, preferably 1-dodecyl azocycloheptan-2-one as in Azone[®].

Further, the present invention relates to a pharmaceutical formulation comprising the emulsion of the present invention.

The pharmaceutical formulation according to the present invention may be contained in and released from devices commonly used for emulsions. Such a container can preferably be a conventional disperser. Discharge and application in/with air leads to the finely distributed product on the skin with fine air bubbles or in the form of a foam.

In a preferred embodiment the pharmaceutical formulation can preferably be present as foamable composition which can be applied in form of a foam. To this end, it may e.g. be contained in a foam dispenser with a suitable pumping mechanism or together with a suitable propellant in an aerosol device. In this case, the product is obtained directly as a foam and is not post-foaming as described in the prior art discussed above. The aerosol device may comprise a compressed gas container containing foaming agent such as a propellant, a distribution device with a valve, spray nozzle as well as the composition.

Commercially available gasses or mixtures of gasses, like CO₂, N₂, N₂O, or mixtures thereof, like CO₂:N₂O 1:1 to 0.5:1, are suitable as propellant. Particularly preferred are gasses such as butane/propane/isobutane or mixtures thereof as commonly used for aerosols, e.g. 3-5:20-25:65-73 as available e.g. as Drivosol®
5 (35a). The gas may be present in compressed form in amounts of 2 to 20 wt.%, preferably 3-18 wt.%, in particular 5-15 wt.%, based on the finished product. These amounts may, however, be varied depending on the total amount of the product and/or the size of the container.

10 Suitable devices for administering the inventive composition as aerosol as well as for application without propellant are known. To this end, e.g. mechanical foam dispensers working according to the principle of air pumps may be used, such as Squeeze Foamer (F2 Finger Pump Foamer, commercially available), Rieke
15 Dispensing by Englass or foamers made by Airspray, into which the finished emulsion is filled in a suitable manner. Preferably, the composition is provided in common dispensers. In particular it is dispensed from a foam dispenser or an aerosol container filled with a propellant.

The present invention relates to a gas container containing a compressed mixture
20 comprising 80-98 wt.%, preferably 82-97 wt.%, in particular 85-95 wt.% of the emulsion of the present invention and 2 to 20 wt.%, preferably 3-18 wt.%, in particular 5-15 wt.% of propellant. As far as the emulsion and the propellant are concerned the same applies as described above.

25 Further, the present invention relates to the emulsion of the present invention or the pharmaceutical formulation of the present invention for use in the treatment of androgenetic alopecia.

In a preferred embodiment the pharmaceutical formulation of the present invention
30 can be used in a topical treatment, in particular a topical treatment of androgenetic alopecia.

The invention further relates to a foam for use in the treatment of androgenetic alopecia, wherein the foam is obtained by releasing a compressed mixture from a
35 gas container. The mixture can comprise 80-98 wt.%, preferably 82-97 wt.%, in particular 85-95 wt.% of the emulsion of the present invention and 2 to 20 wt.%, preferably 3-18 wt.%, in particular 5-15 wt.% of propellant.

Further, the present invention relates to the preparation of the emulsion of the present invention. Thus a subject of the invention is the method for preparing the emulsion of the invention comprising the steps of

- 5 (i) dissolving finasteride and optionally one or more additive(s) in the solvent and the siloxane having 2 to 5 silicon atoms,
(ii) preparing a mixture of the non-ionic emulsifier and optionally one or more additive(s) in water, and
(iii) merging the solution from step (i) and the mixture of step (ii) to form the
10 emulsion of the present invention

In step (i) finasteride can be dissolved, preferably completely dissolved, in the solvent and the siloxane having 2 to 5 silicon atoms.

Finasteride can be finasteride according to Formula (I) as shown above. Further, in line
15 with the method of the present invention finasteride also refers to any polymorphic form of finasteride as well as to solvates of finasteride.

Further, as far as the solvent and the siloxane having 2 to 5 silicon atoms are concerned the same as described above applies.

In a particularly preferred embodiment the solvent used in step (i) is ethanol.

20 Further, in step (i) one or more additive(s) can be dissolved, preferably completely dissolved in the solvent and the siloxane having 2 to 5 carbon atoms.

Step (i) can preferably be carried out under mechanical treatment such as stirring or ultrasonic treatment. Stirring can be preferably carried out at a stirring speed of 100 to 600 rpm (rotations per minute). Generally, ultrasonic treatment can be carried
25 out by immersing the mixture of step (i) into an ultrasonic device, for example an ultrasonic bath.

Further, step (i) can preferably be carried out at an elevated temperature. An elevated temperature as used herein can be a temperature which is above room temperature and
30 below the boiling point of the solvent at standard pressure. Room temperature and a temperature of 23°C can be used interchangeably. In a preferred embodiment step (i) can be carried out at a temperature of between 30°C and the boiling point of the solvent, preferably between 35°C and 60°C, in particular between 40°C and 55°C.

35 In a preferred embodiment the duration of step (i) can be preferably from 2 minutes to 240 minutes, preferably from 5 minutes to 60 minutes, in particular from 10 minutes to 30 minutes.

In step (ii) water and a non-ionic emulsifier can preferably be mixed. In a preferred embodiment the emulsifier can be added to the water for the preparation of the mixture.

5 Further, as far as water and non-ionic emulsifier is concerned the same as described above applies.

10 Further, in step (ii) one or more additive(s) can be further mixed with the mixture of water and emulsifier. In a preferred embodiment one or more additive(s) can be added to water before, together with or after the addition of the emulsifier to the water for the preparation of the mixture.

15 Step (ii) can preferably be carried out under mechanical treatment such as stirring or ultrasonic treatment. As far as stirring and ultrasonic treatment are concerned the same as described under step (i) applies.

20 Further, step (ii) can preferably be carried out at an elevated temperature. As far as elevated temperature as used herein is concerned the same as described under step (i) applies. In a preferred embodiment step (ii) can be carried out at a temperature of between 30°C and 100°C, preferably between 40°C and 95°C, in particular between 45°C and 90°C.

25 In a preferred embodiment the duration of step (ii) can be preferably from 1 minute to 60 minutes, preferably from 2 minutes to 30 minutes, in particular from 3 minutes to 15 minutes.

30 In step (iii) the solution of step (i) and the mixture of step (ii) can be merged to form the emulsion of the invention. Merging the solution of step (i) and the mixture of step (ii) can comprise adding the mixture of step (ii) to the solution of step (i) or vice versa, preferably adding the mixture of step (ii) to the solution of step (i).

Step (iii) can preferably be carried out under the same mechanical treatment as step (i) and step (ii), preferably under stirring.

35 Further, step (iii) can preferably be carried out at an elevated temperature like step (i) and step (ii), preferably at 50°C and 85°C.

Further, in case that the merging of the solution of step (i) and the mixture of step (ii) was carried out at an elevated temperature, step (iii) can preferably comprise cooling the emulsion to room temperature. Further, in a preferred embodiment one or more additive(s), preferably temperature-sensitive additive(s), can be added to the emulsion, when being at room temperature.

As the final product the emulsion, preferably the micro-emulsion, of the present invention is obtained.

The invention should be illustrated by the following examples. Further, the following analytical methods have been used.

Experimental section

15 Analytical methods:

1. Dynamic Light Scattering (DLS)

DLS is conducted by Wessling GmbH, Altenberge with the Zetasizer Nano ZS by Malvern using the following parameters:

Measurement parameters:

Temperature:	25°C
Count Rate (kcps):	230.4
25 Cell Description:	Disposable sizing cuvette
Attenuator:	7
Measurement Position (mm):	4.65
Duration Used (s):	20
Light source:	Standard laser (633 nm)

30

Samples parameters:(particle size)

Sample volume	1 ml
Record Number:	28
Material RI:	1.38
35 Viscosity (cP):	0.8872
Material Absorbtion:	0.100
Dispersant Name:	Water
Dispersant RI:	1.330

The samples were measured at 25°C and disposable sizing cuvettes were used for DLS measurement.

Examples

5

Example 1: Preparation of an emulsion according to the invention

At 23°C finasteride (0.25 g) was added to ethanol (30.0 g) and the mixture was stirred at 23°C until the finasteride was dissolved at visual inspection. PEG-5-
 10 oleyl-ether (15.0 g) was added and the resulting mixture was stirred until dissolution. Octamethyltrisiloxane (3.0 g) was added and the resulting mixture was stirred until dissolution. Finally, purified water (51.75 g) was added and the resulting mixture was stirred until dissolution. The obtained formulation was a clear and colorless liquid emulsion and has the following composition:

15

Finasteride	0.25 g (0.25 wt.%)
Ethanol (96%)	30.0 g (30.0 wt.%)
PEG-5-oleyl-ether	15.0 g (15.0 wt.%)
Octamethyltrisiloxane	3.0 g (3.0 wt.%)
20 Purified water	51.75 g (51.75 wt.%)

Data (particle size):

The Z-average of the intensity weighted particle size distribution of the present
 25 emulsion was determined by Dynamic Light Scattering (DLS) with the Zetasizer Nano ZS as described in the analytical section. The determination was carried out twice. The following results were obtained:

Emulsion	Z-average [nm]	PDI
1 st Determination	29.81	0.093
2 nd Determination	30.58	0.086

30

As can be seen the Z-average is about 30 nm and the PDI (poly dispersity index) is smaller than 0.1, indicating a homogenous distribution of the particles in the emulsion.

Claims:

1. Emulsion comprising
 - (A) 0.025 to 1 wt.% finasteride,
 - (B) 20 to 40 wt.% organic solvent,
 - (C) 5 to 25 wt.% non-ionic emulsifier,
 - (D) 1.0 to 7.0 wt.% of a siloxane having 2 to 5 silicon atoms,
 - (E) 35 to 65 wt.% water.
2. Emulsion according to claim 1 being a micro-emulsion.
3. Emulsion according to claim 1 or 2, wherein the organic solvent (B) is ethanol.
4. Emulsion according to any one of claims 1 to 3, wherein the non-ionic emulsifier (C) is an ethoxylated fatty alcohol.
5. Emulsion according to any one of claims 1 to 4, wherein the emulsifier (C) is PEG-5-oleyl-ether.
6. Emulsion according to any one of claims 1 to 5, wherein the siloxane (D) is octamethyltrisiloxane.
7. Emulsion according to any one of claims 1 to 6 further comprising at least one additive.
8. Pharmaceutical formulation comprising the emulsion according to any one of claims 1 to 7.
9. Emulsion according any one of claims 1 to 7 or pharmaceutical formulation according to claim 8 for use in the treatment of androgenetic alopecia.
10. Emulsion or pharmaceutical formulation for use according to claim 9, wherein the treatment is a topical treatment.
11. Method for preparing the emulsion according to any one of claims 1 to 7 comprising the steps of

- (i) dissolving finasteride and optionally one or more additive(s) in the solvent and the siloxane having 2 to 5 silicon atoms,
- (ii) preparing a mixture of the non-ionic emulsifier and optionally one or more additive(s) in water, and
- (iii) merging the solution from step (i) and the mixture of step (ii) to form the emulsion of the present invention.

12. Method according to claim 11, wherein in step (i) the organic solvent is ethanol.

13. Gas container containing a mixture comprising

- 85-95 wt.% of the emulsion according to any one of claims 1 to 10 and
- 5-15 wt.% propellant.

14. Foam for use in the treatment of androgenetic alopecia, wherein the foam is obtained by releasing a compressed mixture comprising 85-95 wt.% of the emulsion according to any one of claims 1 to 10 and 5-15 wt.% propellant from a gas container.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/060948

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K9/107 A61K8/89	A61K9/122 A61K8/06
	A61K31/58	A61K8/63
		A61Q7/00
ADD.		
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 A61Q		
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 practicable, search terms used) EPO-Internal, BIOSIS, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 2003/180278 A1 (HOPPE UDO [DE] ET AL) 25 September 2003 (2003-09-25) paragraphs [0150] - [0155], [0177] - [0179]; examples 27,28	1-14
Y	EP 2 891 486 A1 (BIOLAB SANUS FARMACÉUTICA LTDA [BR]; UNIV FED DO RIO GRANDE DO SUL [BR]) 8 July 2015 (2015-07-08) paragraph [0043]; example 1; tables 1,2	1-14
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☒ Further documents are listed in the continuation of Box C. ☒ 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 application or patent 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 6 December 2017		Date of mailing of the international search report 15/12/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Giménez Miralles, J

INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	EP 2 891 487 A1 (BIOLAB SANUS FARMACÉUTICA LTDA [BR]; UNIV FED DO RIO GRANDE DO SUL [BR] 8 July 2015 (2015-07-08) paragraphs [0076], [0077]; example 1.2 -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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