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(54) **Title**: TOPICAL PHARMACEUTICAL COMPOSITIONS COMPRISING MINOXIDIL

(57) **Abstract**: A topical pharmaceutical composition comprising minoxidil and at least one or more pharmaceutically acceptable excipients.

TITLE:

Topical Pharmaceutical Compositions comprising Minoxidil

FIELD OF INVENTION:

The present invention relates to topical pharmaceutical compositions of minoxidil, methods for making the compositions, and methods for inducing and/or stimulating hair growth and/or reducing hair loss using the compositions.

BACKGROUND AND PRIOR ART:

Androgenic alopecia (AGA) is characterised by hereditary thinning of the hair induced by androgens in genetically susceptible men and women. This condition is also known as male pattern hair loss or common baldness in men and as female pattern hair loss in women. Thinning usually begins between the age of 12 and 40 years in both sexes, and at least 50% of the men by the age of 50 and 50% of women by the age of 60 are most affected. It is more common in men. The pattern of inheritance is polygenetic. Male pattern hair loss results from a combination of hereditary, acquired factors and hormones. Few references describe the interdependence of androgens, genetic factors and age which influences scalp hair growth. Androgens are important in regulating hair growth at puberty as they increase the size of follicles in beard, chest and limbs and decrease the size of follicle in bitemporal regions which reshapes the hair line in men and women. In susceptible hair follicle of the scalp dihydrotestosterone (DHT) binds to androgen receptor and this hormone receptor complex then activates the genes responsible for gradual transformation of large terminal follicle to miniaturized follicle. AGA susceptibility is largely determined by genetics, though the environment may also play a minor role. Androgen receptor polymorphisms probably make the key determination for androgen responsiveness, but 5α reductase, aromatase, and sex hormone binding globulin (SHBG) genes may also contribute along with other hormone metabolism associated genes.

Drug therapies specifically approved for treating AGA are limited to minoxidil and finasteride as major category products. Several other drugs are also used off label and a plethora of treatments with unsubstantiated hair growth claims can be obtained, however, looking at the number of

treatment options currently available to patients with AGA, though the clinical data supporting their use is often very limited.

Minoxidil (i.e., 2,4-diamino-6-piperidinylpyrimidine-3-oxide) is the active ingredient of the brand Rogaine® (in USA and Canada) and Regaine®(in Europe and Asia Pacific) as a treatment and prevention for androgenic alopecia (male and female pattern baldness) available as 5% minoxidil solution designed for men and 2% solutions designed for women. The preparation of minoxidil is described in U.S. Pat. No. 3,461,461. Methods and topical preparations for using the compound to grow hair and to treat male and female pattern baldness are described and claimed in U.S. Pat. Nos. 4,139,619 and 4,596,812.

Pharmaceutical compositions for topical application may take a variety of forms including, for example, solutions, gels, suspensions, and the like. Generally speaking, improved absorption may be achieved when the topical compositions are in the form of a solution or gel, i.e., where the active ingredient, for example, minoxidil, is dissolved in the carrier solution, in contrast to topical compositions which are in the form of suspensions, i.e., where the active ingredient is merely suspended in the composition.

Topical solutions have not been entirely satisfactory for use in treating the scalp, as these solutions do not remain on the scalp long enough for adequate amounts of the drug to be absorbed. Formulations in the form of jellies and ointments have also been proposed but, these compositions may not be pharmaceutically elegant, and also may not be suitable for use as treatments for stimulating the growth of hair, especially from a cosmetic point of view. Attempts to provide pharmaceutically appropriate thickened formulations containing higher concentrations of solubilized minoxidil are hampered, by various processing difficulties. For example, minoxidil is poorly soluble, and may precipitate out of solution by the addition of additional ingredients, such as thickening agents. Accordingly, high percentages of solvents (about 30 -50% or even more), such as propylene glycol and lower alcohols (for e.g. ethanol) may be required. Due to the viscosity and tack of propylene glycol, large amounts of propylene glycol are not pharmaceutically or cosmetically elegant which may further lead to local irritation and hypersensitivity where applied to the skin. Further, solvents such as propylene glycol have been

reported to contribute to various allergic reactions and lower alcohol (e.g. ethanol) presence causes dryness of scalp resulting in itching, flakes, dandruff, light sensitivity and inflammation. It has also been observed that after application of the topical products comprising either high percentages of solvents such as propylene glycol or ethanol tend to undergo recrystallization of the drug/active ingredient on the scalp thereby leading to poor patient compliance.

US2003/0157046 discloses a minoxidil-containing composition which can be prevented from coloring for a long period of time.

U. S. Pat. No. 6,946,120 discloses a pharmaceutical composition for topical administration including piperidinopyrimidine derivative or salt thereof, an acid and a solvent composition with atleast two solvents selected from water, ethanol and co-solvent which inturn includes propylene glycol.

US2005/0163811 discloses a method for achieving a novel solution comprising a high percentage of a piperidinopyrimidine derivative, more particularly minoxidil by way of specific processing.

Various of such topical therapies (e.g. such as gel based formulations) require an increased contact time which in turn leads to increase in local drug concentration because of: i) an effect where in ethanol evaporates quickly and the residue of the drug remains on the skin or ii) penetration enhancement affects wherein ethanol alters the physical integrity of stratum corneum barrier resulting in an increase in the ability of drug to penetrate the skin.

Hence, considering the conventional problems associated with use of potential solvents as discussed above, and keeping into consideration the contact time which in turn leads to increase in local drug concentration for specific formulations requiring presence of such potential solvents, there is a need to develop a suitable topical compositions which helps in inducing and/or stimulating hair growth and/or reducing hair loss without compromising on the aforementioned aspects that need be taken into consideration as well as which overcomes the drawbacks of the prior art compositions.

OBJECT OF THE INVENTION:

The object of the present invention is to provide a topical pharmaceutical composition comprising a solution of minoxidil with pharmaceutically suitable excipients which exhibits reduced or no irritation on application.

Another object of the present invention is to provide a topical pharmaceutical composition comprising a solution of minoxidil with pharmaceutically suitable excipients which does not form flakes or crystals on application.

Another object of the present invention is to provide a topical pharmaceutical composition comprising a solution of minoxidil with pharmaceutically suitable excipients wherein the said composition is devoid of higher amounts of propylene glycol and/ or lower alcohols.

Yet another object of the present invention is to provide a process for preparing a topical pharmaceutical composition comprising a solution of minoxidil with pharmaceutically suitable excipients.

Still another object of the present invention is to provide a method of inducing and/or stimulating hair growth by applying a topical pharmaceutical composition comprising a solution of minoxidil with pharmaceutically suitable excipients wherein the said composition is devoid of higher amounts of propylene glycol and/ or lower alcohols.

Still another object of the present invention is to provide a method of reducing hair loss by applying a topical pharmaceutical composition comprising a solution of minoxidil with pharmaceutically suitable excipients wherein the said composition is devoid of higher amounts of propylene glycol and/ or lower alcohols.

Another object of the present invention to provide a topical pharmaceutical composition comprising a solution of minoxidil with pharmaceutically suitable excipients for use in the treatment of androgenic alopecia.

SUMMARY OF THE INVENTION:

According to one aspect of the present invention, there is provided a topical pharmaceutical composition comprising minoxidil and at least one or more pharmaceutically acceptable excipients.

Preferably, the composition is suitable for topical administration. Preferably, the composition is an aqueous based solution. Preferably, the composition is an aqueous based solution comprising water.

Preferably, the composition is devoid of higher amounts of propylene glycol and/ or lower alcohols.

Preferably, the composition is free of propylene glycol. Preferably, the composition is free of lower alcohols.

According to another aspect of the invention, there is provided a composition of the invention for use in medicine. Preferably, the use comprises inducing and/or stimulating hair growth, reducing hair loss, and/or treating androgenic alopecia.

According to another aspect of the invention, there is provided the use of a topical pharmaceutical composition according to the invention in the manufacture of a medicament for inducing and/or stimulating hair growth, reducing hair loss, and/or treating androgenic alopecia.

According to another aspect of the invention, there is provided a method of inducing and/or stimulating hair growth, reducing hair loss, and/or treating androgenic alopecia, wherein the method comprises applying the composition of the invention to a patient in need thereof.

According to another aspect of the invention, there is provided a process for preparing a topical pharmaceutical composition of the present invention, wherein the process comprises blending minoxidil, with at least one or more pharmaceutically acceptable excipients.

DETAILED DESCRIPTION OF THE INVENTION:

The existing therapies for the treatment of androgenic alopecia require an increased contact time to attain increased drug concentration at the site of application. These therapies incorporate

higher amounts of potential solvents like propylene glycol and/ or lower alcohols to not only assist in solubilising the active ingredient but also promote the requisite activity.

The inventors of the present invention have observed that by avoiding use of higher amounts of the aforementioned potential solvents like propylene glycol or completely excluding propylene glycol and/ or lower alcohols, and by adjusting the acid concentration of the composition, the solubility of the active ingredient (minoxidil) significantly increases and wherein the composition may be proposed in the form of an aqueous solution which also exhibits a reduced contact time at the site of application.

The present invention provides a topical pharmaceutical composition comprising minoxidil with atleast one or more pharmaceutically suitable excipients.

The term “Minoxidil” or “active ingredient” or “active/s” or “active agent” is used in broad sense to include not only “Minoxidil” *per se* but also its pharmaceutically acceptable derivatives thereof. Suitable derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable anhydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable esters, pharmaceutically acceptable isomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc.

The term "topical pharmaceutical composition" may include liquid dosage forms (liquids, liquid dispersions, suspensions, solutions, emulsions, sprays, spot-on, pour-on), gels, foams, aerosols (propellant based or non-propellant based), ointments, creams, mousse, however, other dosage forms such as powders, capsules (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, (multi-unit pellet systems) MUPS, granules, and microspheres, multiparticulates), sachets (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, (multi-unit pellet systems) MUPS, granules, and microspheres, multiparticulates) and sprinkles may also be envisaged under the ambit of the present invention.

According to the present invention, there is provided a topical pharmaceutical composition comprising minoxidil along with at least one or more pharmaceutically suitable excipients

wherein the said composition is devoid of higher amounts of propylene glycol and/ or lower alcohols.

Preferably, the composition comprises less than 40% w/v of propylene glycol. More preferably, the composition comprises less than 30 % w/v of propylene glycol. More preferably, the composition comprises less than 20 % w/v of propylene glycol. More preferably, the composition comprises less than 10 % w/v of propylene glycol. Most preferably, the composition is free of propylene glycol.

Preferably, the composition is free of lower alcohols. The term "lower alcohol" would be understood by the skilled person in the broadest sense to mean an alcohol with 10 carbon atoms or less. Preferably, the composition of the invention is free of lower alcohols with 3 carbon atoms or less. Preferably, the composition is free of monohydric lower alcohols with 3 carbon atoms or less. Preferably, the composition is free of aliphatic monohydric lower alcohols with 3 carbon atoms or less. Preferably, the composition is free of methanol, ethanol and propanol. Preferably, the composition comprises less than 40% w/v of aliphatic monohydric alcohols with 3 carbon atoms or less. More preferably, the composition comprises less than 30% w/v of aliphatic monohydric alcohols with 3 carbon atoms or less. More preferably, the composition comprises less than 20% w/v of aliphatic monohydric alcohols with 3 carbon atoms or less. More preferably, the composition comprises less than 10% w/v of aliphatic monohydric alcohols with 3 carbon atoms or less. Most preferably, the composition is free of aliphatic monohydric alcohols with 3 carbon atoms or less.

Preferably, the composition comprises less than 40% w/v of propylene glycol and less than 40% w/v of monohydric alcohols with 3 carbon atoms or less. More preferably, the composition comprises less than 30% w/v of propylene glycol and less than 30% w/v of monohydric alcohols with 3 carbon atoms or less. Even more preferably, the composition comprises less than 20% w/v of propylene glycol and less than 20% w/v of monohydric alcohols with 3 carbon atoms or less. Even more preferably, the composition comprises less than 10% w/v of propylene glycol and less than 10% w/v of monohydric alcohols with 3 carbon atoms or less. Most preferably, the composition is free of propylene glycol and monohydric alcohols with 3 carbon atoms or less.

Alternatively, there is provided a topical pharmaceutical composition comprising minoxidil along with at least one or more pharmaceutically suitable excipients wherein the said composition may totally exclude propylene glycol and/ or lower alcohols.

The inventors of the present invention have also further observed that the solubility properties of minoxidil improved by nanosizing.

Nanonization of hydrophobic or poorly water-soluble drugs or drug-excipient premix generally involves the production of drug nanocrystals through either chemical precipitation (bottom-up technology) or disintegration (top-down technology). Different methods may be utilized to reduce the particle size of the hydrophobic or poorly water soluble drugs. [Huabing Chen *et al.*, discusses the various methods to develop nanoformulations in "Nanonization strategies for poorly water-soluble drugs," Drug Discovery Today, Volume 16, Numbers 7/8, April 2011].

The term "nanosize" as used herein refers to drug particles having an average particle size of less than or equal to about 2000 nm, preferably less than or equal to about 1000 nm.

Mostly all particles have a particle size of less than or equal to about 2000 nm, preferably less than or equal to about 1000 nm.

The term "particles" as used herein refers to individual particles of a drug or particles of drug or drug granules and/or mixtures thereof.

The nanosize particles of the present invention can be obtained by any of the process such as but not limited to milling, precipitation, homogenization, high pressure homogenization, spray-freeze drying, supercritical fluid technology, double emulsion/solvent evaporation, PRINT (Particle replication in non-wetting templates), thermal condensation, ultrasonication, spray drying or the like. Such nanoparticles obtained by any of these processes may further be formulated into desired dosage forms.

Suitably, the topical pharmaceutical composition, according to the present invention, is presented in a liquid dosage form, conveniently packaged in single or multiple units, which may further comprise one or more pharmaceutically acceptable excipients. The liquid dosage form as envisaged under the present invention may be aqueous-based, alcohol-based or hydro-alcohol based composition wherein the said alcohol refers to class of lower alcohols. Alternatively, the

topical pharmaceutical composition, according to the present invention, may include suitable excipients which may increase the viscosity of the composition to provide range of viscous liquid to semisolid consistency based composition.

Preferably, the topical pharmaceutical composition, according to the present invention, is aqueous based composition with minimum amount of alcohols (e.g. lower alcohols) or totally devoid of alcohols (e.g. lower alcohols). Alternatively, the topical pharmaceutical composition may be alcohol or hydro-alcohol based composition which may comprise pharmaceutically suitable amount of alcohol ranging from 0% to 10% with one or more pharmaceutically acceptable excipients.

Preferably, the topical pharmaceutical composition, according to the present invention, is an aqueous based composition which may comprise minoxidil with one or more of pharmaceutically acceptable excipients wherein the said composition i) is totally devoid of excipients like propylene glycol and/ or lower alcohols, or, ii) may comprise less than 10% of excipients like propylene glycol and/ or lower alcohols.

As envisaged under the present invention, one or more pharmaceutically acceptable excipients may be used for formulating the topical pharmaceutical composition according to the present invention.

Suitable excipients may comprise one or more of surfactants/wetting agents, acidifying agents, solubilizers, penetration enhancers, preservatives, humectants, moisturizers, anti-oxidants, de-tackifying agents, conditioning agents, proteins, fragrances and mixtures thereof.

According to the present invention, surfactants/wetting agents may be suitably selected from but not limited to anionic, cationic, nonionic, zwitterionic, amphoteric and ampholytic surfactants, as well as mixtures of these surfactants and suitable non-limiting examples may comprise one or more, but not limited to polyethoxylated fatty acids, fatty acid diesters, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglycerized fatty acids, sterol and sterol derivatives, polyethylene glycol sorbitan fatty acid esters/ Polysorbates; polyethylene glycol alkyl ethers, sugar esters, polyethylene glycol alkyl phenols, polyoxyethylene- polyoxypropylene block copolymers, sorbitan fatty acid esters and lower alcohol fatty acid esters; polyoxyethylene (POE) fatty acid esters, such as Myrj®;

polyoxyethylene alkylyl ethers, such as poly oxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, Brij®; Sodium dodecyl sulfate (sodium lauryl sulfate), Lauryl dimethyl amine oxide, Docusate sodium, Cetyl trimethyl ammonium bromide (CTAB); Octoxynol; N, N–dimethyldodecylamine–N–oxide; Hexadecyltrimethylammonium bromide; Polyoxyl 10 lauryl ether; Bile salts (sodium deoxycholate, sodium cholate); Methicones; Polyoxyl castor oil; Nonylphenol ethoxylated Cyclodextrins; Lecithins; Methylbenzethonium chloride; Glycol esters of fatty acids, Carboxylic amides, Monoalkanolamine condensates, Polyoxyethylene fatty acid amides, Quaternary ammonium salts, Polyoxyethylene alkyl and alicyclic amines or mixtures thereof. The topical pharmaceutical composition, according to the present invention may comprise one or more surfactants/wetting agents in an amount ranging from about 1% w/v to about 10% w/v.

Suitable solubilizers, according to the present invention, may comprise one or more of glycerols; glycols such as polyethylene glycols of various grades; aliphatic alcohols/ aromatic alcohols; Polyoxyl n castor oil (synonyms - ethoxylated castor oil, polyethylene glycol castor oil and wherein "n" is the number of oxyethylene units in the compound); Polyoxyl n hydrogenated castor oil or mixtures thereof. The topical pharmaceutical composition, according to the present invention may comprise one or more solubilizers in an amount ranging from about 1% w/v to about 50% w/v.

Suitable penetration enhancers, according to the present invention, may comprise one or more of glycol ether solvents such as Ethylene glycol monomethyl ether , Ethylene glycol monoethyl ether, Ethylene glycol monopropyl ether, Ethylene glycol monoisopropyl ether, Ethylene glycol monobutyl ether, Ethylene glycol monophenyl ether, Ethylene glycol monobenzyl ether, Diethylene glycol monomethyl ether, Diethylene glycol monoethyl ether, Diethylene glycol mono-n-butyl ether; dialkyl ethers and dialkyl ether esters such as ethylene glycol dimethyl ether, ethylene glycol diethyl ether, ethylene glycol dibutyl ether, and ethylene glycol methyl ether acetate, ethylene glycol monoethyl ether acetate, ethylene glycol monobutyl ether acetate or mixtures thereof. The topical pharmaceutical composition, according to the present invention may comprise one or more penetration enhancers in an amount ranging from about 1% w/v to about 20% w/v.

Suitable acidifying agents, according to the present invention, may comprise one or more of acetic acid, hydrochloric acid, salicylic acid, boric acid, sulfuric acid, lactic acid, and citric acid or mixtures thereof. The topical pharmaceutical composition, according to the present invention may comprise one or more acidifying agents in an amount ranging from about 0.5% w/v to about 10% w/v.

Suitable preservatives, according to the present invention, may comprise one or more of aliphatic or aromatic alcohols; glycols; parahydroxybenzoic acid derivatives (e.g. parabens); Vitamin E or its derivatives which may include, but are not limited to, ethyl alcohol, benzyl alcohol, propylene glycol, glycerin, benzoic acid/sodium benzoate, sorbic acid, methylparaben, propylparaben, benzalkonium chloride or mixtures thereof. The topical pharmaceutical composition, according to the present invention may comprise one or more preservatives in an amount ranging from about 0.1% w/v to about 10% w/v.

Suitable de-tackifying agents, according to the present invention, may comprise one or more of silanes; methicones; alkyl/aryl lactates or mixtures thereof. The topical pharmaceutical composition, according to the present invention may comprise one or more de-tackifying agents in an amount ranging from 0.1% w/v.to about 15% w/v.

The topical pharmaceutical composition may comprise one or more surfactants, one or more solubilisers, one or more penetration enhancers, one or more acidifying agents, one or more preservatives and one or more detackifying agents.

The topical pharmaceutical composition, according to the present invention, may further comprise at least one additional active ingredient effectively acting as hair re-growth agent such as, but not limited to, finasteride, dutasteride, ketoconazole, and in case of female androgenic alopecia, other drugs that may be used include, but are not limited to, spironolactone, alfatradiol or flutamide.

Additionally, for the purposes of hair re-growth and maintenance, the topical pharmaceutical composition may comprise one or more vitamins (water soluble or fat soluble or both) eg. Biotin, D-panthenol, niacinamide; herbal extracts and dietary supplements eg. saw palmetto (*Serenoa repens*), stinging nettle (*Urtica dioica*), turmeric (*Curcubita pepo*), and *Pygeum africanum*. Other herbs include black cohosh (*Actaea racemosa*), dong quai (*Angelica sinensis*), false

unicorn (*Chamaelirium luteum*), chasteberry (*Vitex agnus-castus*), red clover (Trifolium pratense), L-arginine, Boswellia serrata, L-Carnitine, curcumin, ginger, grape seed extract, *Grateloupia elliptica*, green tea, lycopene, pumpkin seed oil (*Curcurbitae pepo*), and resveratrol. It will be well acknowledged by a person skilled in the art that each of these additional active ingredients may be in the form of nano-size particles and may be processed by any of the aforementioned techniques.

Alternatively, it will be well acknowledged to the person skilled in the art that the above additional drugs may be presented in combination with the topical pharmaceutical composition as envisaged under the invention as a fixed and single presentation or as separate kit presentation either solely in the form of topical route or in the form of combination of topical route and other than topical route (which may include but is not limited to oral route) presentations.

According to another embodiment of the present invention, there is provided a process for preparing the topical pharmaceutical composition, which comprises blending minoxidil with at least one or more pharmaceutically suitable excipients wherein the said composition is devoid of higher amounts of propylene glycol and/ or lower alcohols.

Alternatively, according to another embodiment, there is provided a process for preparing topical pharmaceutical composition, as an aqueous based composition which comprises blending minoxidil with one or more of pharmaceutically acceptable excipients wherein the said composition i) is totally devoid of excipients like propylene glycol and/ or lower alcohols, or, ii) may comprise less than 30% of excipients like propylene glycol and/ or lower alcohols.

The process for preparing the topical pharmaceutical composition may comprise preparing a separate "active dispersion" comprising minoxidil with one or more active ingredients and optionally pharmaceutically acceptable excipients and a separate "excipient dispersion" comprising one or more pharmaceutically acceptable excipients and yielding batch-wise production of the topical solution as envisaged under the invention.

Preferably, there is provided a process for preparing the topical pharmaceutical composition which process comprises co-solvency technology or solvent blending. The term "Co-solvency" refers to a technique of using one or more co-solvents or a co-solvent system that may be used in liquid formulations to increase the solubility of poorly water soluble or sparingly water soluble

active ingredients/ drugs. Accordingly, the topical pharmaceutical composition, according to the present invention may be prepared by solvent blending in order to solubilize the active ingredient minoxidil and prevent re-crystallization of minoxidil.

Alternatively, the process of preparing the topical pharmaceutical composition, comprises preparing a separate "active dispersion" comprising minoxidil with one or more active ingredients and optionally pharmaceutically acceptable excipients and separate a "excipient dispersion" comprising one or more pharmaceutically acceptable excipients wherein the said composition i) is totally devoid of excipients like propylene glycol and/ or lower alcohols, or, ii) may comprise less than 30% of excipients like propylene glycol and/ or lower alcohols.

There is also provided a method of inducing and/or stimulating hair growth by applying a topical pharmaceutical composition according to the invention comprising minoxidil with one or more pharmaceutically suitable excipients wherein the said composition is devoid of higher amounts of propylene glycol and/ or lower alcohols.

There is also provided a method of inducing and/or stimulating hair growth by applying a topical pharmaceutical composition comprising minoxidil with one or more pharmaceutically suitable excipients wherein the said composition i) is totally devoid of excipients like propylene glycol and/ or lower alcohols, or, ii) may comprise less than 30% of excipients like propylene glycol and/ or lower alcohols.

There is also provided a method of reducing hair loss by applying a topical pharmaceutical composition according to the present invention comprising minoxidil with pharmaceutically suitable excipients wherein the said composition is devoid of higher amounts of propylene glycol and/ or lower alcohols.

There is also provided a method of reducing hair loss by applying a topical pharmaceutical composition of the present invention comprising minoxidil with pharmaceutically suitable excipients wherein the said composition i) is totally devoid of excipients like propylene glycol and/ or lower alcohols, or, ii) may comprise less than 30% of excipients like propylene glycol and/ or lower alcohols.

There is also provided a topical pharmaceutical composition of the present invention comprising minoxidil with pharmaceutically suitable excipients for use in reducing hair loss or treatment of androgenic alopecia wherein the said composition is devoid of higher amounts of propylene glycol and/ or lower alcohols.

There is also provided a topical pharmaceutical composition comprising minoxidil with pharmaceutically suitable excipients for use in reducing hair loss or treatment of androgenic alopecia wherein the said composition i) is totally devoid of excipients like propylene glycol and/ or lower alcohols, or, ii) may comprise less than 30% of excipients like propylene glycol and/ or lower alcohols.

The following example is for the purpose of illustration of the invention only and is not intended in any way to limit the scope of the present invention.

Example I:

Formula:

Sr. No.	**Ingredients**	**Minoxidil Solution 2% Quantity (%w/v)**	**Minoxidil Solution 5% Quantity (%w/v)**	**Minoxidil Solution 10% Quantity (%w/v)**
1.	Minoxidil	2.00	5.00	10.00
2.	Polyethylene glycol 400	40.00	40.00	35.00
3.	Glycerin	5.00	5.00	5.00
4.	Diethylene Glycol Monoethyl Ether	8.00	8.00	8.00

	(Transcutol P)			
5.	PEG 40 Hydrogenated Castor Oil (Cremophor RH 40)	1.00	1.00	1.00
6.	Citric acid (Anhydrous)	0.50	0.50	--
7.	Lactic acid	1.50	1.50	5.00
8.	Benzyl Alcohol	2.00	2.00	2.00
9.	Butylated Hydroxytoluene	0.01	0.01	0.01
10.	PEG-12 Dimethicone (DC 193C)	3.00	3.00	3.00
11.	(Bis-PEG-18 Methyl Ether Dimethyl Silane) (DC 2501)	1.00	1.00	1.00
12.	Hydrolyzed Keratin	1.00	1.00	1.00
13.	Fragrance	0.05	0.05	0.05
14.	Purified water	q. s. to 100% (Approx.	q. s. to 100% (Approx.	q. s. to 100% (Approx. 28.94%)

		34.94%)	31.94%)	

Manufacturing process:

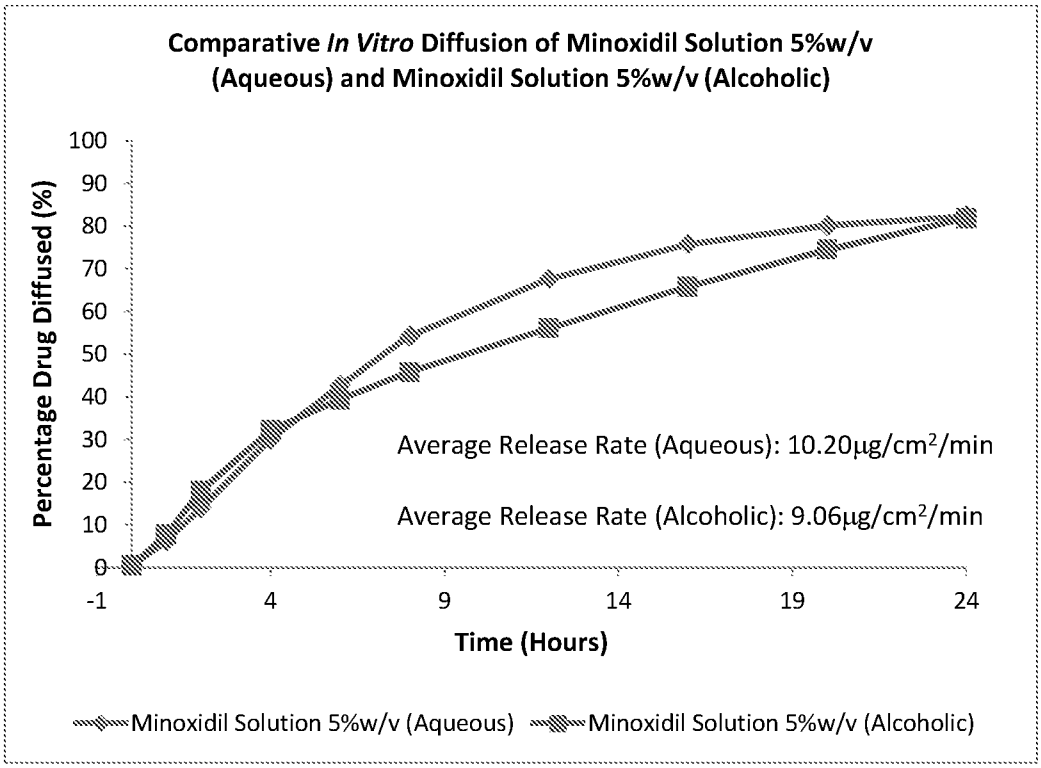
1. Batch quantity of citric acid and lactic acid were added and dissolved in part quantity of purified water.
2. Minoxidil, Glycerin, Polyethylene glycol 400, Transcutol P, and Cremophor RH40 were added and dispersed in the solution obtained in step (1) followed by heating under continuous stirring.
3. The solution obtained in step (2) was cooled.
4. Batch quantity of Butylated Hydroxytoluene in Benzyl alcohol was prepared and this solution was added to the solution obtained in step (3) under continuous stirring.
5. Suitable quantity of PEG-12 Dimethicone was added and dissolved in the solution obtained in step (4) under stirring followed by addition of Bis-PEG-18 Methyl Ether Dimethyl Silane.
6. Batch quantity of Hydrolyzed keratin was prepared in remaining quantity of purified water, and was added to the solution obtained in step (5) under stirring.
7. Suitable fragrance was added to the solution obtained in step (6) under stirring, and the volume was made up with purified water.
8.

The following studies have been conducted to compare the aqueous topical minoxidil composition of the present invention with a minoxidil composition comprising alcohol.

Study 1.

Comparative *In Vitro* Diffusion of Minoxidil Solution 5%w/v (Aqueous) and Minoxidil Solution 5%w/v (Alcoholic)

In Vitro diffusion of two solutions viz. Minoxidil Solution 5%w/v (Aqueous) and Minoxidil Solution 5%w/v (Alcoholic) were compared using a dialysis membrane.



As can be seen from the graph, average drug diffused in 4 hours from aqueous solution and alcoholic solution is 30.15% and 32.18% respectively. Similarly, average drug diffused in 24 hours from aqueous solution and alcoholic solution is 82.3% and 81.8% respectively. The average rate of drug diffusion over 24 hours was higher for the aqueous composition of the invention than for the alcoholic minoxidil formulation.

Conclusion:

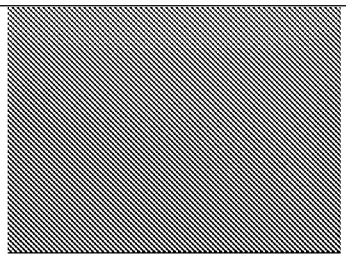
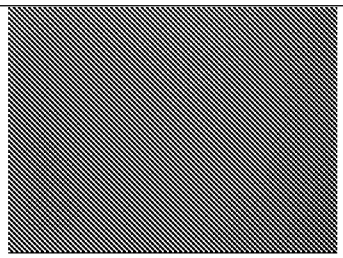
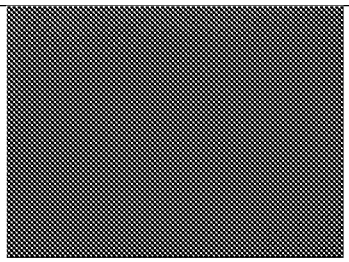
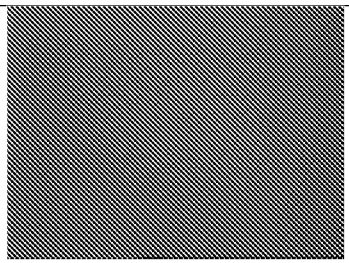
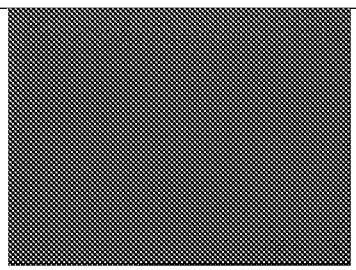
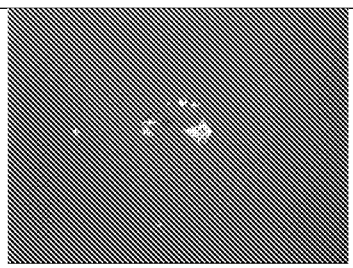
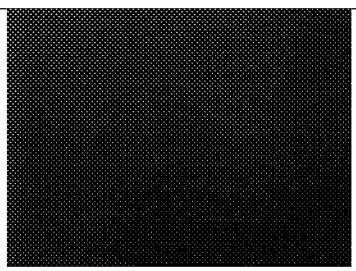
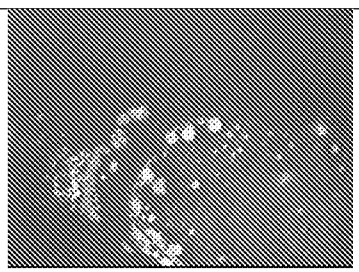
The average release rate of Minoxidil solution 5%w/v (aqueous) is nearly similar to average release rate of Minoxidil Solution 5%w/v (alcoholic).

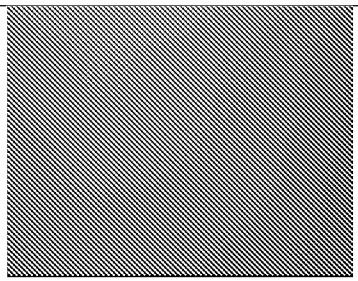
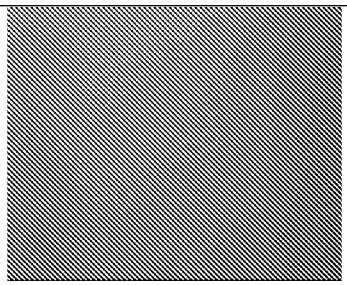
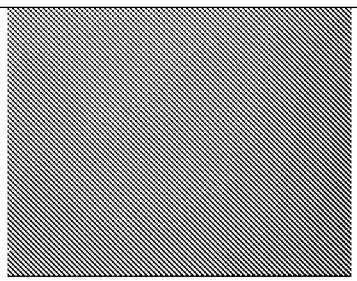
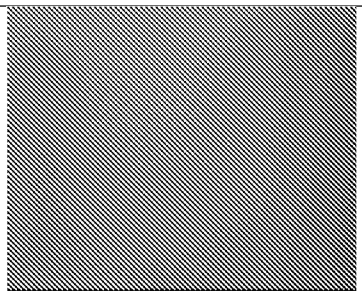
Study 2.

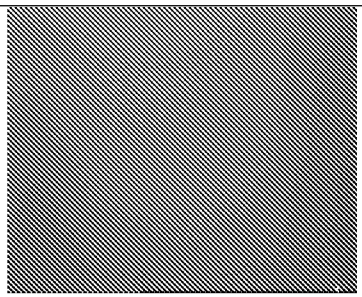
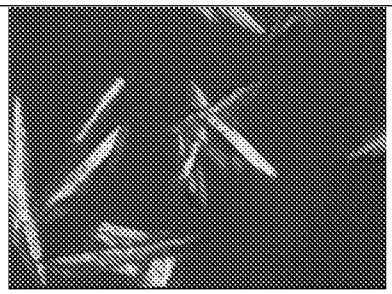
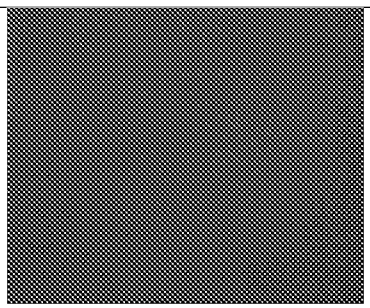
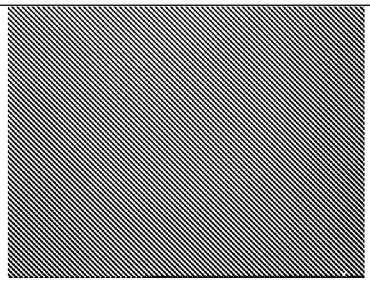
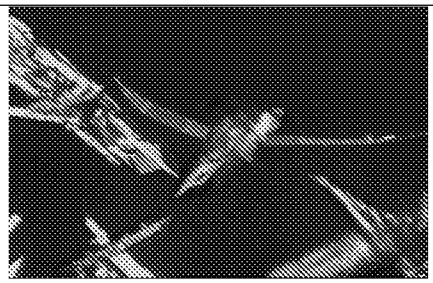
A further study compares the tendency of minoxidil solution to recrystallize. The aqueous composition of the invention is compared to the commercially available product Regaine.

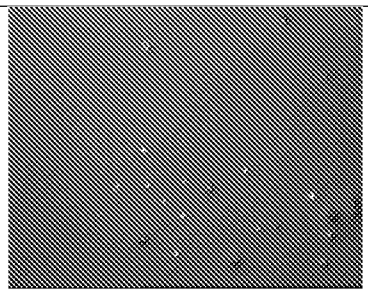
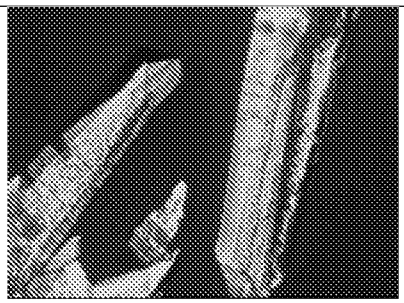
Comparative *In vitro* Recrystallization Study Data of Minoxidil Solution 5%w/v (Aqueous) with Minoxidil Solution 5%w/v (Alcoholic)

Sr.	Time	Minoxidil 5%w/v Solution	Minoxidil 5%w/v Solution

.No.	(Minutes/ Hours)	(Aqueous)	(Alcoholic)
1.	Initial		
		No crystals seen under polarized microscope	No crystals seen under polarized microscope
2.	15 minutes		
		No crystals seen under polarized microscope	No crystals seen under polarized microscope
3.	30 minutes		
		No crystals seen under polarized microscope	Initiation of crystals seen under polarized microscope
4.	1 hour		
		No crystals seen under polarized	Crystal growth seen under

		microscope	polarized microscope
5.	2 hours		
		No crystals seen under polarized microscope	Crystals seen under polarized microscope
6.	3 hours		
		No crystals seen under polarized microscope	Crystals seen under polarized microscope
7.	4 hours		
		No crystals seen under polarized microscope	Crystals seen under polarized microscope
8.	5 hours		

		No crystals seen under polarized microscope	Crystals seen under polarized microscope
9.	6 hours		
		No crystals seen under polarized microscope	Crystals seen under polarized microscope
10.	7 hours		
		No crystals seen under polarized microscope	Crystals seen under polarized microscope
11.	8 hours		
		No crystals seen under polarized microscope	Crystals seen under polarized microscope

12.	24 hours		
		Initiation of crystals seen under polarized light	Crystals seen under polarized microscope

Conclusion:

Minoxidil 5%w/v Solution (Aqueous) did not show recrystallization for 8 hours whereas Minoxidil 5%w/v Solution (Alcoholic) showed recrystallization at 30 minutes. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of “including,” “comprising,” or “having” and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to a “preservative" includes a single preservative as well as two or more different preservatives; reference to a "cosolvent" refers to a single cosolvent or to combinations of two or more cosolvents, and the like.

Claims

1. A topical pharmaceutical composition comprising minoxidil and at least one or more pharmaceutically acceptable excipients.

2. A topical pharmaceutical composition according to claim 1, wherein minoxidil is in the form of a pharmaceutically acceptable derivative which optionally comprises pharmaceutically acceptable salts, solvates, hydrates, isomers, esters, tautomers, anhydrates, enantiomers, complexes, polymorphs or prodrugs.

3. A topical pharmaceutical composition according to any preceding claim, wherein the composition is an aqueous based solution.

4. A topical pharmaceutical composition according to any preceding claim, wherein the composition comprises less than 40% w/v of solvents.

5. A topical pharmaceutical composition according to any preceding claim, wherein the composition comprises less than 30% w/v of solvents.

6. A topical pharmaceutical composition according to any preceding claim, wherein the composition comprises less than 20 % w/v solvents.

7. A topical pharmaceutical composition according to any preceding claim, wherein the composition comprises less than 10 % w/v of solvents.

8. A topical pharmaceutical composition according to any preceding claim, wherein the composition is free of solvents.

9. A topical pharmaceutical composition according to claims 4 to 8, wherein the solvents comprise one or more of propylene glycol and monohydric alcohols with 3 carbon atoms or less.

10. A topical pharmaceutical composition according to any preceding claim, wherein the at least one or more pharmaceutically acceptable excipients comprise one or more surfactants/wetting agents present in an amount of from 1 % w/v to 10 % w/v.

11. A topical pharmaceutical composition according to any preceding claim, wherein the at least one or more pharmaceutically acceptable excipients comprise one or more solubilisers present in an amount of from 1 % w/v to 50 % w/v.

12. A topical pharmaceutical composition according to any preceding claim, wherein the at least one or more pharmaceutically acceptable excipients comprise one or more penetration enhancers present in an amount of from 1 % w/v to 20 % w/v.

13. A topical pharmaceutical composition according to any preceding claim, wherein the at least one or more pharmaceutically acceptable excipients comprise one or more acidifying agents present in an amount of from 0.5 % w/v to 10 % w/v.

14. A topical pharmaceutical composition according to claim 13, wherein the one or more acidifying agents comprise one or more of acetic acid, hydrochloric acid, salicylic acid, boric acid, sulphuric acid, lactic acid, citric acid, or any combination thereof.

15. A topical pharmaceutical composition according to any preceding claim, wherein the at least one or more pharmaceutically acceptable excipients comprise one or more preservatives present in an amount of from 0.1 % w/v to 10 % w/v.

16. A topical pharmaceutical composition according to any preceding claim, wherein the at least one or more pharmaceutically acceptable excipients comprise one or more de-tackifying agents present in an amount of from 0.1 % w/v to 15 % w/v.

17. A topical pharmaceutical composition according to any preceding claim wherein the at least one or more pharmaceutically acceptable excipients comprise one or more surfactants, one or more solubilisers, one or more penetration enhancers, one or more acidifying agents, one or more preservatives and one or more detackifying agents.

18. A topical pharmaceutical composition according to any preceding claim, wherein the composition is in the form of a liquid dosage form such as liquid dispersions, suspensions, solutions, emulsions, sprays, spot-on, pour-on, gels, foams, propellant based or non-propellant based aerosols, ointments, creams, mousse, or solid dosage forms such as powders, capsules (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, multi-unit pellet systems (MUPS), granules, microspheres, and multiparticulates), sachets (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, multi-unit pellet systems (MUPS), granules, microspheres, and multiparticulates) and sprinkles.

19. A topical pharmaceutical composition according to any preceding claim, wherein, the average particle size of minoxidil is less than or equal to 2000 nm, preferably less than or equal to 1000 nm.

20. A topical pharmaceutical composition according to any preceding claim, wherein the composition further comprises at least one additional active ingredient effectively acting as a hair re-growth agent.

21. A topical pharmaceutical composition according to any preceding claim, wherein the minoxidil is present in the composition in an amount of from 2% to 15% by weight of the composition.

22. A topical pharmaceutical composition according to any preceding claim for use in medicine.

23. A topical pharmaceutical composition according to claim 22, wherein the use comprises inducing and/or stimulating hair growth, reducing hair loss, and/or treating androgenic alopecia.

24. Use of a topical pharmaceutical composition according to any one of claims 1 to 21 in the manufacture of a medicament for inducing and/or stimulating hair growth, reducing hair loss, and/or treating androgenic alopecia.

25. A method of inducing and/or stimulating hair growth, reducing hair loss, and/or treating androgenic alopecia, wherein the method comprises applying the topical pharmaceutical composition according to any one claims 1 to 21 to a patient in need thereof.

26. A process for preparing a topical pharmaceutical composition according to any one of claims 1 to 21, wherein the process comprises blending minoxidil, with at least one or more pharmaceutically acceptable excipients.

27. A topical pharmaceutical composition substantially as described herein with reference to the description and examples.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/050278

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61Q7/00 A61K31/506
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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 269 973 A1 (TAISHO PHARMA CO LTD [JP]) 2 January 2003 (2003-01-02) page 1, paragraph 1 page 1, paragraphs 1, 8-12 page 2, paragraph 13-20 -----	1-26
X	EP 2 233 139 A1 (FUJIFILM CORP [JP]) 29 September 2010 (2010-09-29)	1-3,8,9, 11-14, 17,20-26
Y	page 1, paragraphs 1-2, 6-10 page 2, paragraphs 21, 22, 26 page 4, paragraphs 35,37-41; example 1 -----	4-7
	-/--	

[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 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	Date of mailing of the international search report
28 May 2014	18/07/2014

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, Fax: (+31-70) 340-3016	Raposo, Antonio

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2014/050278

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 27
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:

see FURTHER INFORMATION sheet PCT/ISA/210

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:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional 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 report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-26(partially)

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.

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BALAKRISHNAN P ET AL: "Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER BV, NL, vol. 377, no. 1-2, 30 July 2009 (2009-07-30), pages 1-8, XP026281914, ISSN: 0378-5173, DOI: 10.1016/J.IJPHARM.2009.04.020 [retrieved on 2009-04-24] abstract item 2.2; page 2, right-hand column item conclusion; page 7, left-hand column -----	4-7,17
Y	WO 2007/070069 A1 (CELL MATRIX CORP [US]; MALEK SHANE [US]) 21 June 2007 (2007-06-21) page 1, paragraph 1 page 2, paragraphs 4, 6 page 4, paragraphs 2, 6 page 6, paragraphs 1, 7 page 7; claim 1 page 8; claims 13-14 -----	4-7,17
A	Anonymous: "Cosmetic Dermatology, Products&Procedures", 2010, Wiley-Blackwell, XP002723375, page 31 -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2014/050278

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1269973 A1	02-01-2003	AT 305765 T	15-10-2005
		AU 4473101 A	23-10-2001
		AU 2001244731 B2	17-02-2005
		BR 0110146 A	30-12-2003
		CA 2405452 A1	18-10-2001
		CN 1434698 A	06-08-2003
		DE 60113822 T2	03-08-2006
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		ES 2245980 T3	01-02-2006
		HK 1057708 A1	28-11-2008
		HU 0300417 A2	28-08-2003
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		US 2003108500 A1	12-06-2003
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		JP 5420946 B2	19-02-2014
		JP 2010222283 A	07-10-2010
		US 2010240684 A1	23-09-2010
WO 2007070069 A1	21-06-2007	CN 101365411 A	11-02-2009
		EP 1971308 A2	24-09-2008
		JP 2009519936 A	21-05-2009
		KR 20070064411 A	20-06-2007
		US 2007141004 A1	21-06-2007
		US 2007141015 A1	21-06-2007
		US 2010298365 A1	25-11-2010
		US 2012184575 A1	19-07-2012
		WO 2007070069 A1	21-06-2007
		WO 2007078796 A2	12-07-2007

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-26(partially)

   A topical composition comprising minoxidil and one or more pharmaceutical acceptable excipients, wherein the composition is in the form of a liquid dosage form.

   ---

2. claims: 1-26(partially)

   A topical composition comprising minoxidil and one or more pharmaceutical acceptable excipients, wherein the composition is in the form of a solid dosage form.

Continuation of Box II.2

Claims Nos.: 27

Claim 27 makes reference to the examples disclosed in the description. However, the claims must not, in respect of the technical features of the invention, rely on references to the description (Rule 6.2 PCT).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.