Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3085973 A1 2019/07/11

(21) 3 085 973

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2018/12/05
(87) Date publication PCT/PCT Publication Date: 2019/07/11
(85) Entrée phase nationale/National Entry: 2020/06/16
(86) N° demande PCT/PCT Application No.: IB 2018/059683
(87) N° publication PCT/PCT Publication No.: 2019/135123
(30) Priorité/Priority: 2018/01/02 (US62/612,853)

(51) Cl.Int./Int.Cl. *A61K 45/00* (2006.01),
A61K 9/00 (2006.01), *A61K 9/08* (2006.01),
A61K 9/10 (2006.01)

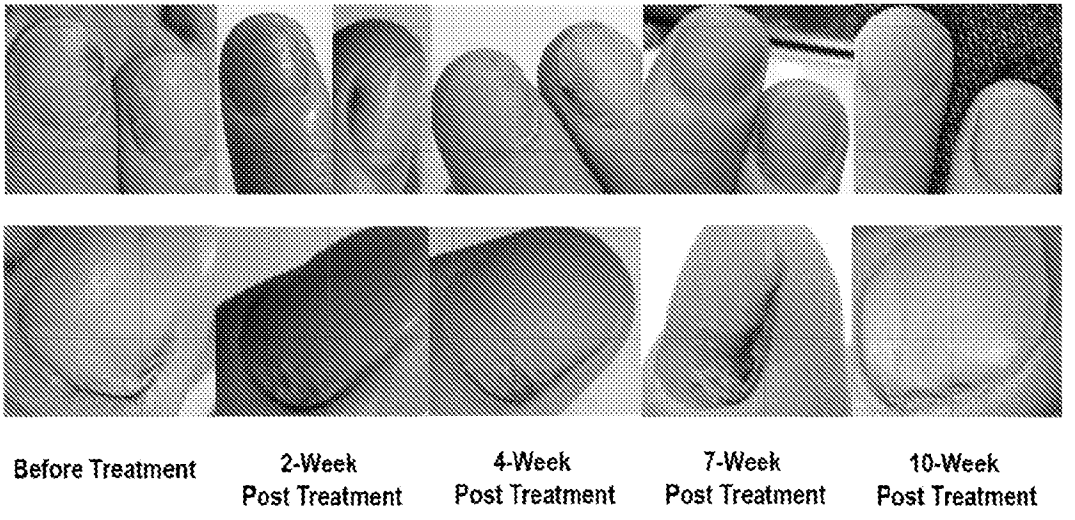
(71) Demandeur/Applicant:
NAL PHARMACEUTICAL GROUP LIMITED, CN

(72) Inventeurs/Inventors:
MO, Y. JOSEPH, US;
CHU, CHUN KWONG, CN

(74) Agent: BERESKIN & PARR LLP/S.E.N.C.R.L.,S.R.L.

(54) Titre : FORME POSOLOGIQUE LIQUIDE POUR APPLICATION TOPIQUE
(54) Title: LIQUID DOSAGE FORM FOR TOPICAL APPLICATION

FIGURE 1



(57) Abrégé/Abstract:
It relates to topical liquid compositions comprising at least one penetration enhancer that promotes permeation of pharmaceutically active agent through nail or skin. In particular, it relates to pharmaceutical formulations of, but not limited to, terbinafine for treating onychomycosis. The liquid topical compositions further comprise a secondary absorption enhancer selected from glycerol or terpenes. In addition, the liquid topical compositions further comprise a surfactant, a humectant, an emulsifier, a solubilizing agent, a solvent, a base polymer, a diluent, an antioxidant, a preservative and optionally a film forming agent. It also provides a method of drug delivery applying the topical composition on the skin of a subject in need thereof, wherein at least a fraction of 1% to 80% or greater of the drug is delivered to and absorbed by the skin or nail and absorbed systemically.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 July 2019 (11.07.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/135123 A1

(51) International Patent Classification:
A61K 45/00 (2006.01) *A61K 9/10* (2006.01)
A61K 9/08 (2006.01) *A61K 9/00* (2006.01)

(21) International Application Number:
PCT/IB2018/059683

(22) International Filing Date:
05 December 2018 (05.12.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/612,853 02 January 2018 (02.01.2018) US

(71) Applicant: **NAL PHARMACEUTICAL GROUP LIMITED** [CN/CN]; Rooms 2906-08, 29/F, Windsor House, 311 Gloucester Road, Causeway Bay, Hong Kong (CN).

(72) Inventors: **MO, Y. Joseph**; 1 Belleview Terrace, Princeton, New Jersey 08540 (US). **CHU, Chun Kwong**; RM 1531, Herring Gull House, Shakok Estate, Shatin, Hong Kong (CN).

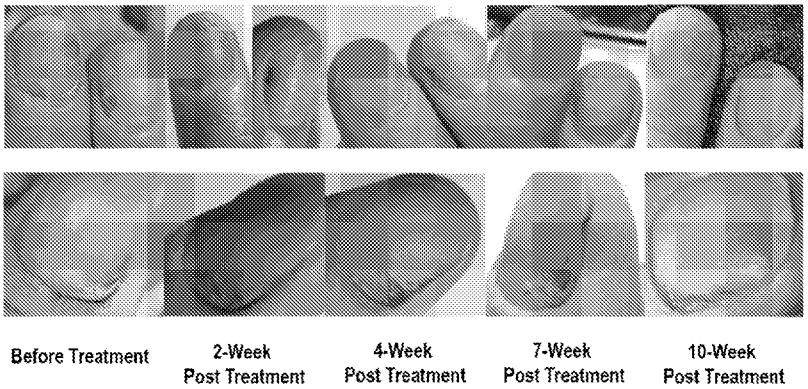
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** LIQUID DOSAGE FORM FOR TOPICAL APPLICATION

FIGURE 1



(57) **Abstract:** It relates to topical liquid compositions comprising at least one penetration enhancer that promotes permeation of pharmaceutically active agent through nail or skin. In particular, it relates to pharmaceutical formulations of, but not limited to, terbinafine for treating onychomycosis. The liquid topical compositions further comprise a secondary absorption enhancer selected from glycerol or terpenes. In addition, the liquid topical compositions further comprise a surfactant, a humectant, an emulsifier, a solubilizing agent, a solvent, a base polymer, a diluent, an antioxidant, a preservative and optionally a film forming agent. It also provides a method of drug delivery applying the topical composition on the skin of a subject in need thereof, wherein at least a fraction of 1% to 80% or greater of the drug is delivered to and absorbed by the skin or nail and absorbed systemically.

WO 2019/135123 A1

LIQUID DOSAGE FORM FOR TOPICAL APPLICATION

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of priority from U.S. Provisional Application Serial No. 62/612,853, filed January 2, 2018, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to novel topical compositions comprising at least one penetration enhancer that promotes permeation of pharmaceutically active agent through nail or skin.

BACKGROUND OF THE INVENTION

Onychomycosis is a fungal infection of nail that affects 10% of the general population. The most common cause of Onychomycosis is dermatophyte, which probably account for more than 85% of all cases. Onychomycosis is difficult to treat and has a high recurrence rate. Treatment for onychomycosis is commercially available in oral or topical dosage form, which involves terbinafine (Lamisil®), itraconazole (Sopranox®), ciclopirox (Penlac®), and amorolfine (Loceryl®). Lamisil®, marketed by Novartis, is very effective against onychomycosis administrated systemically, however, oral administration is associated with side effects such as liver toxicity.

Topical therapy is an alternative to oral therapy to diminish the side effects. Topical application of medications on nails allows active agents to penetrate through nail plate, reach nail bed, and eventually enter the systemic circulation bypassing the first-pass metabolism. Commercially available nail lacquer like Penlac® and Loceryl® have been developed for nail fungal infection, but the treatment times are relatively long and cure rate are relatively low either compared with oral administration. Probably, the poor drug penetration is the bottleneck of these products. The 1% Lamisil® cream is for treating skin fungal infection instead, terbinafine, being an effective antifungal agent, is not available in topical dosage form yet. The unmet medical need urges the development of effective topical therapies for nail fungal infection.

The nail comprises the nail plate, the nail matrix, and the nail bed. The nail plate is the hard, thin, translucent, slight elastic structure sitting on the nail bed, composed of keratin. The nail plate is made of dead keratinized cells which is formed by the cell division of nail matrix. The penetration of the drug through the nail plate, where the medication applies on, is the key determining the effectiveness of the topical therapy. The keratin binding affinity of drugs correlate to its penetration through the keratin matrix in nail plate. Low keratin binding efficiency contributes to increased permeability, which is a desirable physiochemical property of drugs as higher proportion of administrated drug can be targeted to the lower nail layer. Many antifungal drugs are reported to bind strongly to keratin and thus developing formulations that dwindle the interactions between the drugs and keratin is necessary.

SUMMARY OF THE INVENTION

The present invention relates to novel liquid topical compositions comprising at least one penetration enhancer that promotes permeation of pharmaceutically active agent through nail or skin. In particular, the invention relates to pharmaceutical formulations of but not limited to terbinafine for treating onychomycosis.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a human case study of the Terbinafine Lacquer formulation 1I on treating fingernail onychomycosis.

Figure 2 shows the cumulative amount of minoxidil penetrated-time curve.

DETAILED DESCRIPTION OF THE INVENTION

The detailed description is merely exemplary in nature and is not intended to limit application and uses. The following examples further illustrate the present invention without, however, limiting the scope of the invention thereto. Various changes and modifications can be made by those skilled in the art on the basis of the description of the invention, and such changes and modifications are also included in the present invention.

In one embodiment, the present invention provides a liquid topical composition comprising a matrix comprising an effective amount of a pharmaceutically active agent and one or more penetration enhancer having a combined hydrophilic- lipophilic balance of about

1 to about 16, wherein the matrix is a liquid such as solution, suspension, emulsion and lacquer.

In other embodiment of the invention, the pharmaceutically active agent is such as antifungal agents, hair growth promoting agents, anesthetic agents, nonnarcotic analgesics such as the nonsteroidal anti-inflammatory agent (NSAIDS), erectile dysfunction agents, female sexual dysfunction agents, antihistamine and anti-cold agents, cough suppressant agents, respiratory disorder agents, antiemetic agents, oral hygiene agents, antagonists of Calcitonin Gene Related Peptide (CGRP) receptors, drugs for hormone replacement, Alzheimer's disease agent, caffeine and caffeine salt compounds and corticosteroid. In particular embodiment of the invention, pharmaceutically active agent is such as terbinafine hydrochloride, efinaconzole, minoxidil, sildenafil, tadalafil, vardenafil, cetirizine, donepezil, galantamine, rivastigmine, tacrine, and memantine.

In another embodiment of the invention, the liquid topical composition further comprises enhancers. Enhancers are selected from among PEG-8 beeswax, PEG-75 stearate, pegoxol-7 stearate, propylene glycol monocaprylate, propylene glycol monolaurate, propylene glycol monostearate, propylene glycol dioleate, 2-hydroxypropyl stearate, 2-hydroxypropyl laurate, propylene glycol oleate, propylene glycol distearate, propylene glycol dicaprylate, propylene glycol dilaurate, polypropylene glycol (17) dioleate, propyleneglycol monolaurate, propylene glycol monomyristate, dipropylene glycol dipelargonate, polypropylene glycol monobutyl ether oleate, propylene glycol dipelargonate, propylene glycol didecanoate, dipropylene glycol dipelargonate, propylene glycol bis(9,10-epoxystearate), propylene glycol monoisostearate, propylene glycol diundecanoate, glycol monoethyl ether, diethylene glycol monobutyl ether, oleoyl macrogolglycerides, lauroyl macrogolycerides, stearoyl macrogolgylycerides, caprylocaproyl macrogolglycerides, triglycerides medium-chain, polyglyceryl-3 diisostearate, polyglyceryl oleate, ethylene glycol paimitostearate, dissopropyl adipate, di-n-butyl adipate, dimethyl adipate, dimethyl isosorbide and diethylene glycol monoethyl ether. In a particular embodiment, liquid topical composition of the invention contains one or more penetration enhancers in an amount of from about 0.1% by weight to about 20%, about 0.1% by weight to about 15%, or about 1% by weight to about 10% by weight of the liquid dosage form.

The inventive liquid topical composition further comprises a secondary absorption enhancer which is selected from among glycerol and terpenes.

In a still further embodiment, the inventive liquid topical composition comprises a

surfactant, a humectant, an emulsifier, a solubilizing agent, a solvent, a base polymer, a diluent, an antioxidant, a preservative and optionally a film forming agent.

The invention also provides a method of drug delivery applying the topical composition of the invention topically on the skin of a subject in need thereof, wherein at least a fraction of 1% to 80% or greater of the drug is delivered to and absorbed by the skin or nail and absorbed systemically.

Pharmaceutical Active Agent

The pharmaceutical active agent is such as antifungal agents, hair growth promoting agents, anesthetic agents, nonnarcotic analgesics such as NSAIDS, erectile dysfunction agents, female sexual dysfunction agents, antihistamine and anti-cold agents, cough suppressant agents, respiratory disorder agents, antiemetic agents, oral hygiene agents, antagonists of CGRP receptors, drugs for hormone replacement, Alzheimer's disease agent, caffeine and caffeine salt compounds and corticosteroid. For example, the antifungal agent is terbinafine, terbinafine hydrochloride, butenafine, butenafine hydrochloride, efinaconazole or other pharmaceutically acceptable salts thereof; the hair growth promoting agent is minoxidil or its pharmaceutically acceptable salts thereof; the anesthetic agent is lidocaine (xylocaine), procaine, benzocaine or its pharmaceutically acceptable salts thereof; the nonnarcotic analgesics such as NSAIDS is acetaminophen, Ibuprofen, ketoprofen, indomethacin, aspirin (low dose for cardiovascular), naproxen sodium, ketorolac, diclofenac, meloxicam, piroxicam or its pharmaceutically acceptable salts thereof; the erectile dysfunction agent is sildenafil, tadalafil, vardenafil or its pharmaceutically acceptable salts thereof; the female sexual dysfunction agent is sildenafil, tadalafil, vardenafil or its pharmaceutically acceptable salts thereof; the antihistamine and anti-cold agent is cetirizine hydrochloride, loratadine, chlorcyclizine hydrochloride, chlorpheniramine maleate, dextrochlorpheniramine maleate, dexbrompheniramine maleate, diphenhydramine citrate, diphenhydramine hydrochloride, doxylamine succinate, ketotifen fumarate, phenindamine tartrate, pheniramine, pyrilamine maleate, triprolidine hydrochloride, thonzylamine hydrochloride, clemastine fumarate or other pharmaceutically acceptable salts thereof; the cough suppressant agent is menthol, camphor, dextromethorphan hydrobromide, guaifenesin, codeine phosphate, codeine or its pharmaceutically acceptable salts thereof; the respiratory disorder agent is pseudoephedrine

hydrochloride, phenylephrine hydrochloride, guaifenesin, dextromethorphan hydrobromide, ephedrine or its pharmaceutically acceptable salts thereof; the antiemetic agent is granisetron, ondansetron, AZ-001 (Staccato® prochlorperazine, proprietary product of Alexza), AZ-004 (Staccato® loxapine; proprietary product of Alexza), Levadex® (dihydroergotamine, proprietary product of Allergan, Inc.), Zelrix™ (sumatriptan; proprietary product of NuPathe Inc.), VR-147 (proprietary product of Vectura), ROX-828 (ketorolac tromethamine containing 6% lidocaine, proprietary product of ROXRO PHARMA, Inc.), COL-144 (lasmiditan, proprietary product of Colucid Pharmaceuticals), BF-1(proprietary product of Biofrontera), diphenhydramine, scopolamine or other pharmaceutically acceptable salts thereof; the drug for hormone replacement is estradiol, testosterone or its pharmaceutically acceptable salts thereof; the Alzheimer's agent is donepezil, galantamine, rivastigmine, tacrine, memantine or its pharmaceutically acceptable salts thereof; and the corticosteroid is triamcinolone acetonide or its pharmaceutically acceptable salts thereof.

Enhancer

The present invention comprises one or more enhancers. The enhancer is selected from among PEG-8 beeswax, PEG-75 stearate, pegoxol-7 stearate, propylene glycol monocaprylate, propylene glycol monolaurate, propylene glycol monostearate, propylene glycol dioleate, 2-hydroxypropyl stearate, 2-hydroxypropyl laurate, propylene glycol oleate, propylene glycol distearate, propylene glycol dicaprylate, propylene glycol dilaurate, polypropylene glycol (17) dioleate, propyleneglycol monolaurat

e, propylene glycol monomyristate, dipropylene glycol dipelargonate, polypropylene glycol monobutyl ether oleate, propylene glycol dipelargonate, propylene glycol didecanoate, dipropylene glycol dipelargonate, propylene glycol bis(9,10-epoxystearate), propylene glycol monoisostearate, propylene glycol diundecanoate, glycol monoethyl ether, diethylene glycol monobutyl ether, oleoyl macrogolglycerides, lauroyl macrogolycerides, stearoyl macrogolgylycerides, caprylocaproyl macrogolglycerides, triglycerides medium-chain, polyglyceryl-3 diisostearate, polyglyceryl oleate, ethylene glycol paimitostearate, dissopropyl adipate, di-n-butyl adipate, dimethyl adipate, dimethyl isosorbide and diethylene glycol monoethyl ether. The liquid topical composition further comprises a secondary absorption enhancer such as glycerol and terpenes. The liquid topical composition of the invention further

contains one or more penetration enhancers in an amount of from about 0.1% by weight to about 20%, about 0.1% by weight to about 15%, or about 1% by weight to about 10% by weight of the liquid dosage form.

Surfactant

The liquid topical composition further comprises the surfactant. The surfactant is such as anionic, cataionic, nonionic, amphoteric, saturated and unsaturated higher aliphatic acid salts including but not limited to sodium laurate, sodium stearate, sodium oleate, and sodium linolenate, long-chain alkyl sulfate salts, alkylbenzenesulfonic acids such as hexylbenzenesulfonic acid, octylbenzenesulfonic acid dodecylbenzenesulfonic acid and their salts thereof, polyoxyalkylene alkyl ether sulfate salts, polyoxyalkylene alkenyl ether sulfate salts, the salts of polyoxyethylene alkyl sulfate esters, the salts of the alkyl esters of sulfosuccinic acid, polyoxyalkylene sulfosuccinate salts, the salts of the alkyl esters of polyoxyalkylene sulfosuccinic acid, the alkali metal salts of the polyoxyalkylene-modified dimethylpolysiloxane esters of sulfosuccinic acid, polyoxyalkylene alkylphenyl ether sulfate salts, long-chain alkanesulfonic acid salts, long-chain alkylsulfonates, polyoxyethylene alkylphenyl ether sulfate salts, polyoxyalkylene alkyl ether acetate salts, long-chain alkyl phosphate salts, polyoxyalkylene alkyl ether phosphate salts, acylglutamate salts, alpha-acylsulfonate salts, long-chain alkylsulfonate salts, alkylarylsulfonate salts, long-chain alpha-olefinsulfonate salts, alkylnaphthalenesulfonate salts, long-chain alkanesulfonic acid salts, long-chain alkyl or alkenyl sulfate salts, long-chain alkylamide sulfate salts, long-chain alkyl or alkenyl phosphate salts, alkylamide phosphate salts, alkyloylalkyltaurate salts, N-acylamino acid salts, sulfosuccinate salts, alkyl alkyl ether carboxylate salts, amide ether carboxylate salts, the salts of esters of alpha-sulfofatty acids, alanine derivatives, glycine derivatives, and arginine derivatives; salts can be exemplified by alkali-metal salts such as the sodium salt and potassium salt, alkanolamine salts such as the triethanolamine salt, and the ammonium salt, the sodium salt; alkyltrimethylammonium chloride, stearyltrimethylammonium chloride, lauryltrimethylammonium chloride, cetyltrimethylammonium chloride, beef tallow alkyltrimethylammonium chloride, behenyltrimethylammonium chloride, octyltrimethylammonium hydroxide, dodecyltrimethylammonium hydroxide, stearyltrimethylammonium bromide, behenyltrimethylammonium bromide,

distearyldimethylammonium chloride, dicocoyldimethylammonium chloride, dioctyldimethylammonium chloride, di(POE)oleylmethylammonium (2EO) chloride, benzalkonium chloride, alkylbenzalkonium chloride, alkyldimethylbenzalkonium chloride, benzethonium chloride, stearyldimethylbenzylammonium chloride, lanolin-derived quaternary ammonium salts, diethylaminoethylamide of stearic acid, dimethylaminopropylamide of stearic acid, behenamidopropyldimethylhydroxypropylammonium chloride, stearoylcolaminoformylmethylpyridinium chloride, cetylpyridinium chloride, tall oil alkylbenzylhydroxyethylimidazolinium chloride, and benzylammonium salts; phospholipids, such as lecithin, phosphatidylethanolamine, phosphatidic acid, phosphatidylinositol, phosphatidylserine, phosphatidylcholine, phosphatidylglycerol, sphingomyelin, and cardiolipin, and the hydrogenates of the preceding. Particularly preferred are the hydrogenated natural lecithins as yielded by the hydrogenation of, for example, soy lecithin, egg yolk lecithin, corn lecithin, cottonseed oil lecithin, rapeseed lecithin; polyoxyalkylene ethers, polyoxyalkylene alkyl ethers, polyoxyalkylene fatty acid esters, polyoxyalkylene fatty acid diesters, polyoxyalkylene resin acid esters, polyoxyalkylene (hardened) castor oils, polyoxyalkylene alkylphenols, polyoxyalkylene alkylphenyl ethers, polyoxyalkylenephenyl phenyl ethers, polyoxyalkylene alkyl esters, polyoxyalkylene alkyl esters, sorbitan fatty acid esters, polyoxyalkylene sorbitan alkyl esters, polyoxyalkylene sorbitan fatty acid esters, polyoxyalkylene sorbitol fatty acid esters, polyoxyalkylene glycerol fatty acid esters, polyglycerol alkyl ethers, polyglycerol fatty acid esters, sucrose fatty acid esters, fatty acid alkanolamides, alkyl glucosides, polyoxyalkylene fatty acid bisphenyl ethers, polypropylene glycol, polyether-modified silicones such as polyoxyalkylene-modified diorganopolysiloxanes, polyglycerol-modified silicones, glycerol-modified silicones, saccharide-modified silicones, perfluoropolyether-type surfactants, polyoxyethylene-polyoxypropylene block copolymers, alkyl polyoxyethylene-polyoxypropylene block copolymer ethers and mixtures thereof.

Humectant

The liquid topical composition of the invention further comprises the humectant. The humectant is such as sorbitol, mineral oil, vegetable oil, glycerol, betaine, guanidine, urea, glycolic acid, glycolate salts, ammonium glycolate, quaternary alkyl ammonium glycolate, lactic acid, lactate salts, ammonium lactate, quaternary alkyl ammonium lactate, aloe vera, aloe

vera gel, allantoin, urazole, alkoxylated glucose, hyaluronic acid, lactamide monoethanolamine, acetamide monoethanolamine and derivatives, esters, salts and mixtures thereof, collagen, gelatin, aloe vera, hyaluronic acid or volatile water-soluble solvents, such as ethanol or propylene glycol.

Emulsifier

The liquid topical composition of the invention further comprises the emulsifier. The emulsifier is such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils such as cottonseed, groundnut, corn, germ, olive, castor and sesame oils, glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof; carbomer, hydroxypropyl cellulose, sodium lauryl sulfate; glycerin fatty acid esters (monoglycerides, MG); mono- and di-glycerides (MG & DG) such as Grindsted HV 40™, Poem J-2021™; distilled monoglycerides; citric acid esters of MG (CMG); diacetyl tartaric acid esters of mono- and di-glycerides (DATEMs) such as Panodan AL 10™; polyglycerol esters of fatty acids (PGE); polyglycerol polyricinoleate (PGPR); sorbitan esters of fatty acids suth as Palsgaard 7463™; sucrose esters of fatty acids; calcium stearoyl lactylates; sodium stearoyl lactylates; lecithin including enzyme digested lecithin; caseinates such as sodium caseinates including Alanate 191™; and diacetyl tartaric acid esters of mono- and di-glycerides (DATEMs).

Solubilizing Agent

The liquid topical composition of the invention further comprises the solubilizing agent. The solubilizing agent is such as citric acid, ethylenediamine-tetraacetate, sodium meta-phosphate, succinic acid, urea, cyclodextrin, polyvinylpyrrolidone, diethylammonium-ortho-benzoate, and micelle-forming solubilizers such as TWEEN® and spans such as TWEEN 80®; polyoxyethylene sorbitan fatty acid ester, polyoxyethylene n-alkyl ethers, n-alkyl amine n-oxides, polyoxamers, organic solvents, such as acetone, phospholipids, cyclodextrin, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, sodium lauryl sulfate, sodium doccusate, vitamin E TPGS, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cyclodextrins, ethanol, n-butanol, isopropyl alcohol, cholesterol, bile salts, polyethylene glycol 200 to 600, glycofurol,

transcutol, propylene glycol, and dimethyl isosorbide, miglyol, glycerin and glycerol.

Solvent

The liquid topical composition of the invention further comprises the solvent. The solvent is such as methylene chloride, beta-cyclodextrin, dichloromethane; oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil; aqueous or alcoholic solutions such as water, ethanol, sugar solutions or mixtures thereof; physiological saline solution such as glycerol; alcohols such as methanol, ethanol, propanol, isopropanol; sugar solutions such as glucose or mannitol solutions or mixtures thereof; aromatic hydrocarbon solvents such as benzene, chlorobenzene, toluene and xylene; ether solvents such as diethyl ether, tert-butylmethyl ether, tetrahydrofuran, dimethoxyethane, dioxane and THF; aliphatic hydrocarbon solvents; ester solvents such as ethyl acetate; ketone solvents; chlorinated hydrocarbon solvents dichloromethane, chloroform, and 1,2-dichloroethane, acetonitrile; and an organic solvent such as 1,3-dimethyl-2-imidazolidinone, dimethylformamide, N-dimethylacetamide, N-methylpyrrolidine, dimethylsulfoxide, pyridine, nitromethane, and mixtures thereof.

Base polymer

The liquid topical composition of the invention further comprises the base polymer. The base polymer is such as polysaccharide-based polymers, such as guar, xanthan and/or their derivatives; hydrophobic base polymers such as SIS (styrene/isoprene/styrene)-triblock copolymers, SBS (styrene/butadiene/styrene)-triblock copolymers, SBR (copolymers of styrene and butadiene), synthetic and/or natural polyisoprenes, polyamide, polyester, co-polyester, polyurethane and/or mixtures thereof are also possible as further matrices; water-soluble polymers, plant base polymers such as gum arabic, tragacanth gum, galacian, guar gum, carob gum, karaya gum, carragbeein, pectin, agar, quince seed (Marumero) algae colloid (seaweed extract), starch (rice, corn, potato, wheat), glycyrrhinic acid; microorganism base polymers such as xanthane gum, dextran, succinoglutan, pullulan; animal base polymers such as collagen, caseine, albumin, gelatin; starch base polymers such as carboxymethyl starch, methythydroxypropyl starch; cellulose base polymers such as methyl cellulose nitro cellulose, ethyl cellulose, methythydroxypropyl cellulose, hydroxyethyl cellulose, sodium cellulose

sulfate, hydroxypropyl cellulose, sodium carboxymethyl cellulose (CMC), crystalline cellulose, cellulose powder; alginate base polymers such as sodium alginate, alginate propylene glycol esters; vinyl base polymers such as a polyvinyl alcohol, polyvinylmethyl ether, polyvinylpyrrolidone carboxyvinyl polymer (Carbopol), alkyl modified carboxyvinyl polymer, polyoxyethylene base polymers such as polyethylene glycol 2000, 4000, 6000; acryl base polymers such as polyacrylates or salt thereof, polyoxyethylene polyoxypropylene copolymer brae polymer, sodium polyacrylate, polyethylene acrylate, polyacryl amide, polyethylene imine, and cationic polymer.

Diluent

The liquid topical composition of the invention further comprises the diluent. The diluent is such as water, saline, finger's solutions, dextrose solution; calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as starch gelatin, acacia, microcrystalline cellulose or polyvinyl pyrrolidone; dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar.

Antioxidant

The liquid topical composition of the invention further comprises the antioxidant. The antioxidant is such as sodium bisulfite, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

Film Forming Agent

The liquid topical composition of the invention optionally comprises the film forming agent. The film forming agent is such as polyvinylpyrrolidone, polyvinylpolypyrrolidone, sodium alginate, carboxymethylcellulose, hydroxypropyl methylcellulose, acrylate, acrylamide and methacrylate.

Preservative

The liquid topical composition of the invention further comprises the preservative. The preservative is such as methyl hydroxy benzoate, propyl hydroxy benzoate, chlorocresol, benzoic acid and phenyl mercuric nitrate.

Method of Preparation

The liquid topical composition of the present invention is prepared using the known methods or by adopting specific conditions suitable for the ingredients employed.

Examples of the liquid topical compositions are the amount of the ingredients are listed below, but not limited:

Terbinafine Lacquer Formulation

Ingredients	Ratio (w/w %)
Terbinafine HCl	8.00-12.00
Polyvinylpyrrolidone K 30	0.40-0.60
Isopropyl Myristate	0.00-3.00
Propylene glycol	0.00-3.00
Polysorbate 80	0.00-3.00
Sorbitan Oleate	0.00-3.00
Diethylene Glycol Monoethyl Ether	0.00-6.00
Caprylocaproyl Polyoxylglycerides	0.00-6.00
Propylene Glycol Monolaurate	0.00-6.00
Polyglyceryl Dioleate	0.00-6.00
Medium-Chain Triglycerides	0.00-6.00
Diisopropyl Adipate	0.00-6.00
Benzyl Alcohol	0.40-0.60
Ethyl alcohol, anhydrous	74.00-91.00

Minoxidil Solution Formulation

Ingredients	Ratio (w/w %)
Minoxidil	4.00-6.00
Ethanol, Anhydrous	20.00-35.00
Propylene Glycol	38.00-58.00
Caprylocaproyl Polyoxylglycerides	0.00-3.60
Diethylene Glycol Monoethyl Ether	0.00-8.40
BHT	0.00-0.12
Water	12.00-18.00

EXAMPLES

Selected embodiments of the invention will be described in further detail with reference to the following experimental and comparative examples. These examples are for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1: TERBINAFINE LACQUER FORMULATION

Terbinafine Lacquers were prepared according to the components and amounts shown in Table 1.

Table 1

Formulations	Example (% by weight)						
	1A	1B	1C	1D	1E	1F	1G
Terbinafine HCl	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Polyvinyl-pyrrolidone K 30	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Isopropyl Myristate	--	--	--	--	--	--	--
Propylene glycol	--	--	--	--	--	--	--
Polysorbate 80	--	2.50	--	--	--	--	--

Sorbitan Oleate	--	2.50	--	--	--	--	--
Diethylene Glycol Monoethyl Ether	--	--	5.00	--	--	--	--
Caprylocaproyl Polyoxylglycerides	--	--	--	--	5.00	--	--
Propylene Glycol Monolaurate	--	--	--	5.00	--	--	--
Polyglyceryl Dioleate	--	--	--	--	--	5.00	--
Medium-Chain Triglycerides	--	--	--	--	--	--	5.00
Diisopropyl Adipate	--	--	--	--	--	--	--
Benzyl Alcohol	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Ethyl alcohol, anhydrous	89.00	84.00	84.00	84.00	84.00	84.00	84.00

Table 1 (Continued)

Formulations	**Example (% by weight)**			
	1H	**1I**	**1J**	**1K**
Terbinafine HCl	10.00	10.00	10.00	10.00
Polyvinyl-pyrrolidone K 30	0.50	0.50	0.50	0.50
Isopropyl Myristate	--	2.50	2.50	2.00
Propylene glycol	--	2.50	--	2.00
Polysorbate 80	--	--	--	--
Sorbitan Oleate	--	--	--	--
Diethylene Glycol Monoethyl Ether	--	--	--	--
Caprylocaproyl Polyoxylglycerides	--	--	5.00	5.00

Propylene Glycol Monolaurate	--	--	--	--
Polyglyceryl Dioleate	--	--	--	--
Medium-Chain Triglycerides	--	--	--	--
Diisopropyl Adipate	5.00	--	--	--
Benzyl Alcohol	0.50	0.50	0.50	0.50
Ethyl alcohol, anhydrous	84.00	84.00	81.50	80.00

EXAMPLE 2: MINOXIDIL SOLUTION FORMULATION

Minoxidil solutions were prepared according to the components and amounts shown in Table 2.

Table 2

Ingredients	2A	2B	2C	2D
Minoxidil	5.00	5.00	5.00	5.00
Ethanol, Anhydrous	25.00	30.00	25.00	30.00
Propylene Glycol	45.00	50.00	45.00	50.00
Caprylocaproyl Polyoxylglycerides	3.00	--	3.00	--
Diethylene Glycol Monoethyl Ether	7.00	--	7.00	--
BHT	--	--	--	--
Water	15.00	15.00	15.00	15.00
Total (%w/w)	100.00	100.00	100.00	100.00

Table 2 (Continued)

Ingredients	2E	2F	2G	2H
Minoxidil	5.00	5.00	5.00	5.00
Ethanol, Anhydrous	25.00	30.00	30.00	25.00

Propylene Glycol	45.00	50.00	50.00	45.00
Caprylocaproyl Polyoxylglycerides	3.00	--	--	3.00
Diethylene Glycol Monoethyl Ether	7.00	--	--	7.00
BHT	0.10	0.10	--	--
Water	14.90	14.90	15.00	15.00
Total (%w/w)	100.00	100.00	100.00	100.00

EXAMPLE 3: EFFECT OF PENETRATION ENHANCERS IN TRANSDERMAL PENETRATION OF TERBINAFINE

A Franz diffusion cell system was used to assess the influence of penetration enhancers on the formulation of terbinafine lacquer for penetrating mouse skin. The test drugs shown in Table 1 were applied on mouse skin and allowed to diffuse for 20 hours. The cumulative amount of terbinafine penetrated at the end of 20th hour with regard to various enhancers in the formulations was shown in Table 3. The data in Table 3 showed that all the enhancers promoted the amount of penetrated terbinafine across mouse skin.

Table 3

Penetration Enhancers	**Cumulative Amount of Terbinafine Penetrated (µg/cm2)**
1A	0
1B	343.46
1C	0.04
1D	1541.45
1E	0.44
1F	775.86
1G	449.13
1H	0.16
1I	2904.86

1J	1586.25

EXAMPLE 4: CASE STUDY: FINGERNAIL ONYCHOMYCOSIS TREATED WITH THE INVENTION

A Chinese female onychomycosis patient was treated with the formulation 1K once daily for 10 weeks. Images in Figure 1 show that fungal infections of fingernails were almost completely cured after 10 weeks.

EXAMPLE 5: EFFECT OF PENETRATION ENHANCERS IN TRANSDERMAL PENETRATION OF MINOXIDIL

A Franz diffusion cell system was used to assess the influence of penetration enhancers on the formulation of minoxidil solution for penetrating mouse skin. The test drug containing enhancers (formulation 2H) and no enhancer (formulation 2G) were applied on mouse skin and allowed to diffuse for 20 hours. The cumulative amount of minoxidil penetrated-time curve was shown in Figure 2. It is shown that enhancers promoted the penetration rate of minoxidil and it was increased up to around 3.5 times the maximum at 18th hour.

CLAIMS

We claim:

1. A liquid topical composition comprising:

a matrix comprising an effective amount of a pharmaceutically active agent and one or more penetration enhancer having a combined HLB of about 1 to about 16,

wherein the matrix is a liquid such as solution, suspension, emulsion and lacquer.

2. The liquid topical composition of claim 1,

wherein the pharmaceutical active agent is selected from the group consisting of antifungal agents, hair growth promoting agents, anesthetic agents, nonnarcotic analgesics such as the nonsteroidal anti-inflammatory agent (NSAIDS), erectile dysfunction agents, female sexual dysfunction agents, antihistamine and anti-colds agents, cough suppressant agents, respiratory disorder agents, antiemetic agents, oral hygiene agents, antagonists of CGRP receptors, drugs for hormone replacement, Alzheimer's disease agent, caffeine and caffeine salt compounds and corticosteroid.

3. The liquid topical composition of claim 2, wherein

a. the antifungal agent is terbinafine, terbinafine hydrochloride, butenafine, butenafine hydrochloride, efinaconazole or other pharmaceutically acceptable salts thereof;

b. the hair growth promoting agent is minoxidil or its pharmaceutically acceptable salts thereof;

c. the anesthetic agent is lidocaine (xylocaine), procaine, benzocaine or its pharmaceutically acceptable salts thereof;

d. the nonnarcotic analgesics such as the nonsteroidal anti-inflammatory agents (NSAIDS) is acetaminophen, Ibuprofen, ketoprofen, indomethacin, aspirin (low dose for cardiovascular), naproxen sodium, ketorolac, diclofenac, meloxicam, piroxicam or its pharmaceutically acceptable salts thereof;

e. the erectile dysfunction agent is sildenafil, tadalafil, vardenafil or its pharmaceutically acceptable salts thereof;

f. the female sexual dysfunction agent is sildenafil, tadalafil, vardenafil or its pharmaceutically acceptable salts thereof;

g. the antihistamine and anti-cold agent is cetirizine hydrochloride, loratadine, chlorcyclizine hydrochloride, chlorpheniramine maleate, dextrochlorpheniramine maleate, dexbrompheniramine maleate, diphenhydramine citrate, diphenhydramine hydrochloride, doxylamine succinate, ketotifen fumarate, phenindamine tartrate, pheniramine, pyrilamine maleate, triprolidine hydrochloride, thonzylamine hydrochloride, clemastine fumarate or other pharmaceutically acceptable salts thereof;

h. the cough suppressant agent is menthol, camphor, dextromethorphan hydrobromide, guaifenesin, codeine phosphate, codeine or other pharmaceutically acceptable salts thereof;

i. the respiratory disorder agent is pseudoephedrine hydrochloride, phenylephrine hydrochloride, guaifenesin, dextromethorphan hydrobromide, ephedrine or other pharmaceutically acceptable salts thereof;

j. the antiemetic agent is granisetron, ondansetron, prochloperazine, loxamine, dihydroergotamine, sumatriptan, VR-147, ketorolac tromethamine with lidocaine, lasmiditan, BF-1, diphenhydramine, scopolamine or other pharmaceutically acceptable salts thereof;

k. the drug for hormone replacement is estradiol, testosterone or its pharmaceutically acceptable salts thereof;

l. the Alzheimer's disease agent is donepezil, galantamine, rivastigmine, tacrine, memantine or its pharmaceutically acceptable salts thereof; and

m. the corticosteroid is triamcinolone acetonide or other pharmaceutical acceptable salts.

4. The liquid topical composition of claim 1,

wherein the pharmaceutically active agent is selected from the group consisting of terbinafine hydrochloride, butenafine, butenafine hydrochloride, ketotifen fumarate, triamcinolone acetonide, efinaconzole, minoxidil, sildenafil, tadalafil, vardenafil, cetirizine, donepezil, galantamine, rivastigmine, tacrine, and memantine.

5. The liquid topical composition of claim 1 wherein said enhancers are selected from the group consisting of PEG-8 beeswax, PEG-75 stearate, pegoxol-7 stearate, propylene glycol monocaprylate, propylene glycol monolaurate, propylene glycol monostearate, propylene

glycol dioleate, 2-hydroxypropyl stearate, 2-hydroxypropyl laurate, propylene glycol oleate, propylene glycol distearate, propylene glycol dicaprylate, propylene glycol dilaurate, polypropylene glycol (17) dioleate, propyleneglycol monolaurate, propylene glycol monomyristate, dipropylene glycol dipelargonate, polypropylene glycol monobutyl ether oleate, propylene glycol dipelargonate, propylene glycol didecanoate, dipropylene glycol dipelargonate, propylene glycol bis(9,10-epoxystearate), propylene glycol monoisostearate, propylene glycol diundecanoate, glycol monoethyl ether, diethylene glycol monobutyl ether, oleoyl macrogolglycerides, lauroyl macrogolycerides, stearoyl macrogolgylycerides, caprylocaproyl macrogolglycerides, triglycerides medium-chain, polyglyceryl-3 diisostearate, polyglyceryl oleate, ethylene glycol paimitostearate, dissopropyl adipate, di-n-butyl adipate, dimethyl adipate, dimethyl isosorbide and diethylene glycol monoethyl ether.

6. The liquid topical composition of claim 1, wherein the composition further comprises a surfactant, a humectant, an emulsifier, a solubilizing agent, a solvent, a base polymer, a diluent, an antioxidant, a preservative, a secondary absorption enhancer or a film forming agent.

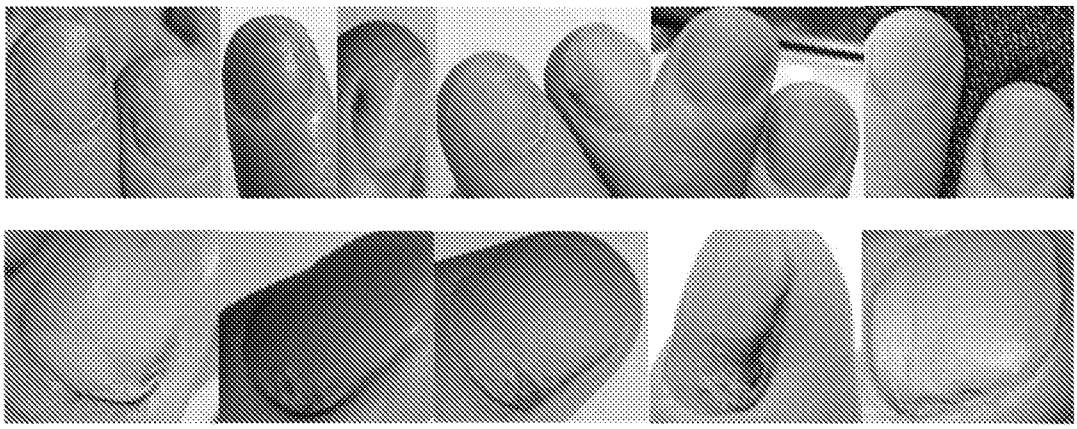
7. The liquid topical composition of claim 1 further comprising a secondary absorption enhancer selected from the group consisting of glycerol and terpenes.

8. The liquid topical composition of claim 1, wherein said liquid contains one or more penetration enhancers in an amount of from about 0.1% by weight to about 20%, about 0.1% by weight to about 15%, or about 1% by weight to about 10% by weight of the liquid dosage form.

9. A method of drug delivery applying the topical composition of claim 1 topically on the skin and nail of a subject in need thereof, wherein at least a fraction of 1% to 80% or greater of the drug is delivered to and absorbed by the skin or nail and absorbed systemically.

1/2

FIGURE 1


Before Treatment
2-Week Post Treatment
4-Week Post Treatment
7-Week Post Treatment
10-Week Post Treatment

2/2

FIGURE 2

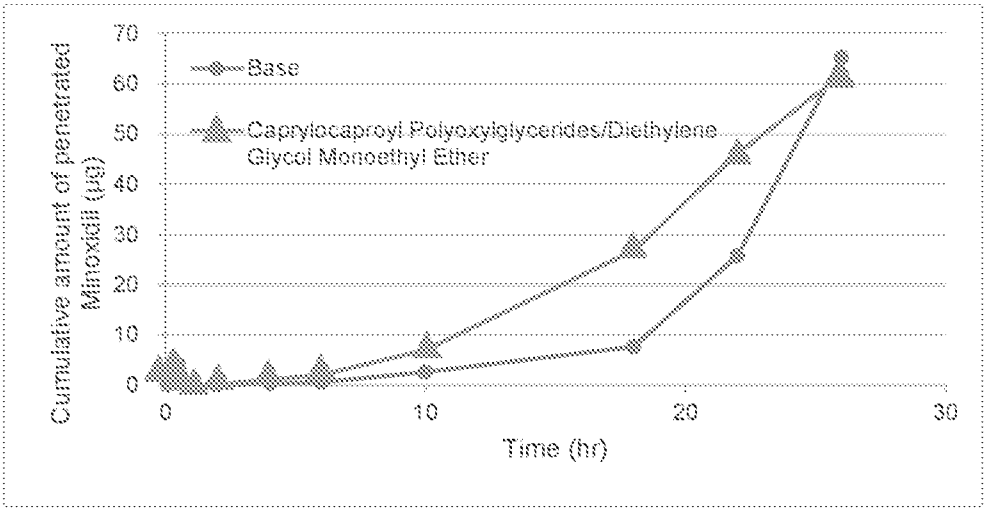
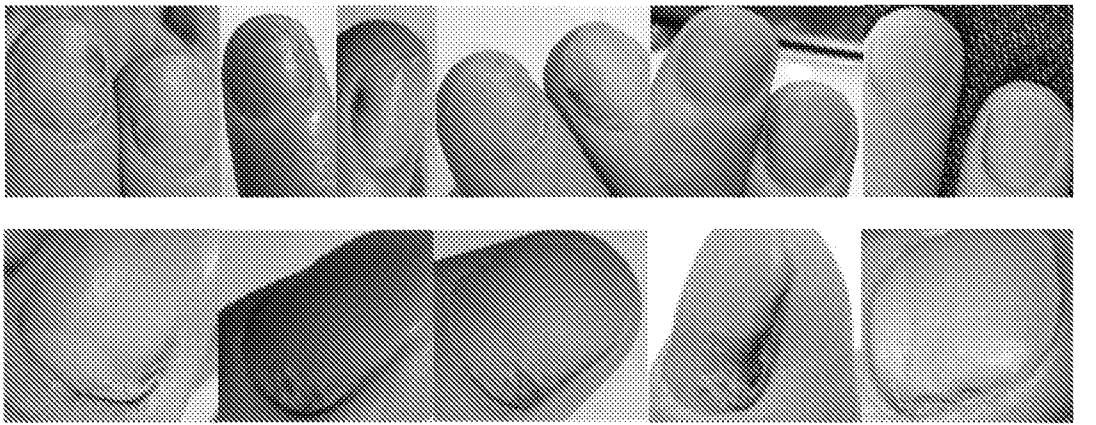

Cumulative amount of penetrated Minoxidil (µg)
70
60
50
40
30
20
10
0
0
10
20
30
Time (hr)
Base
Caprylocaproyl Polyoxylglycerides/Diethylene Glycol Monoethyl Ether

FIGURE 1


Before Treatment
2-Week Post Treatment
4-Week Post Treatment
7-Week Post Treatment
10-Week Post Treatment