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<p>(21) International Application Number: PCT/US87/02168 (22) International Filing Date: 2 September 1987 (02.09.87) (31) Priority Application Number: 904,146 (32) Priority Date: 5 September 1986 (05.09.86) (33) Priority Country: US (60) Parent Application or Grant (63) Related by Continuation US 904,146 (CIP) Filed on 5 September 1986 (05.09.86) (71) Applicant (for all designated States except US): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).</p>		<p>(72) Inventors; and (75) Inventors/Applicants (for US only) : HATZENBUHLER, Douglas, A. [US/US]; 2726 Bronson Circle, Kalamazoo, MI 49008 (US). BROWNE, Jeffrey, Edward [US/US]; 7504 Thrasher Lane, Kalamazoo, MI 49002 (US). PENA, Lorraine, Elisabeth [US/US]; 1804 Cambridge Drive, Kalamazoo, MI 49001 (US). (74) Common Representative: THE UPJOHN COMPANY; Patent Law Department, Kalamazoo, MI 49001 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US. Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: SEBUM-DISSOLVING NONAQUEOUS MINOXIDIL FORMULATION</p>		
<p>(57) Abstract</p> <p>Novel topical formulations of minoxidil comprising minoxidil; a solvent for minoxidil; a non-polar solvent which renders the formulation approximately the same polarity as human sebum; and a cosolvent which enhances the delivery of minoxidil through the stratum corneum.</p>		

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SEBUM-DISSOLVING NONAQUEOUS MINOXIDIL FORMULATION

DESCRIPTION

The present application provides a novel composition of matter. More particularly, the present application provides a new formulation
5 for known pharmaceutical products. Most particularly, the present application provides a topical composition containing minoxidil which dissolves sebum, the oil surrounding the hair follicle, and provides a means for penetrating the outer skin layer, the stratum corneum.

Minoxidil is a well-known pharmaceutical compound. It is
10 marketed by The Upjohn Company as the active ingredient in LONITEN® Tablets for the treatment of hypertension. It is also useful in topical compositions for the treatment of baldness. The structure and use of this compound for this purpose is described in U.S. Patents 4,139,619 and 4,596,812. This compound has varying degrees
15 of efficacy for hair growth purposes, depending on the patient, the degree of baldness, the dose, and the nature of the topical composition. Currently, topical minoxidil is administered in a composition containing propylene glycol, ethanol and water.

INFORMATION DISCLOSURE

20 U.S. Patent 4,139,619 discloses topical minoxidil compositions containing carriers selected from ointments, lotions, pastes, jellies, sprays, and aerosols. U.S. patent 4,596,812 also discloses topical compositions of minoxidil. Cooper, J. Pharm. Sci. 73:1153 (1984) describes means for increasing skin transport of certain
25 pharmaceutical compounds.

SUMMARY OF THE INVENTION

The present invention particularly provides:

- (1) A topical hair growth composition comprising:
- (a) minoxidil;
 - 30 (b) a solvent capable of dissolving minoxidil;
 - (c) a non-polar solvent which renders the formulation approximately the same polarity as human sebum; and
 - (d) a cosolvent having a polarity between that of the solvent capable of dissolving minoxidil and the non-polar solvent,
35 which enhances the delivery of minoxidil through the stratum corneum, said cosolvent in an amount less than that which causes skin irritation.

The present invention thus provides a non-aqueous topical

minoxidil formulations having improved efficacy.

By minoxidil is meant the 2,4-pyrimidinediamine, 6-(1-piperidinyl)-3-oxide, analogs as well as salts thereof, as described in U.S. Patents 4,139,619, and 4,596,812, which patents are expressly
5 incorporated by reference herein.

Suitable solvents for minoxidil include propylene glycol, 1,3-butylene diol, polyethylene glycol 200 (PEG 200), polyethylene glycol 400 (PEG 400), isopropanol, ethanol, methanol, 1,5 pentane diol, 1,2,6-trihydroxyhexane, 1,7-heptanediol, 1,4 butane diol and N-
10 methylpyrrolidone and related compounds (see, e.g., J. Pharm. Pharmacol. 37:298-304 (1985)).

Suitable non-polar solvents include silicone oils such as the following volatile silicone oils: Dow Corning - 344 fluid; Dow Corning - 345 fluid; Union Carbide - V.S. 7207; Union Carbide - V.S. 7158; and Union Carbide - V.S. 7349, and the following nonvolatile
15 (or less volatile) silicone oils: Dow Corning - 200 fluids of various viscosities; and Union Carbide - L-45 fluids of various viscosities.

Suitable cosolvent/penetration enhancers include alcohols such as butanol, hexanol, octanol, decanol, dodecanol and oleyl alcohol; amines, such as isopropyl amine, diisopropyl amine, triethyl amine, triethanol amine and ethylene diamine; carboxylic acids, such as oleic acid, linoleic acid and linolenic acid; esters, such as dibutyl sebacate, dibutyl phthalate, butyl benzoate and ethyl caprate; and
20 others, such as AZONE®, N methyl pyrrolidone, bile salts and urea. Oleyl alcohol is the preferred cosolvent.

To aid in the miscibility of the components, preferably an additional cosolvent is added to the cosolvent having a polarity between the minoxidil solvent and the non-polar solvent oleyl alcohol. Thus, for oleyl alcohol, the preferred penetration-enhancer and cosolvent, isopropanol is the preferred additional cosolvent making a miscible solution with volatile silicones (e.g. Dow Corning 344 fluid). The isopropanol is used in the range of from 16 to 27% and makes single phase solutions of all mixtures of interest. The
30 volatility of the isopropanol reduces some of the oiliness caused by the oleyl alcohol, since lesser amounts of oleyl alcohol need be used in these formulations to make a miscible solution than were used prior to the addition of isopropanol. Ethanol can also be used as a
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less chemically "smelling" cosolvent for these vehicles, but ethanol must be present at concentrations 5-10% greater than isopropanol and the resulting vehicle is not as effective in solubilizing sebum.

5 Sebum is the relatively non-polar material excreted from the sebaceous glands located in the hair follicle. In order to stimulate hair growth, it is desirable to target topical minoxidil formulations to the sebaceous glands. The present composition, which is miscible with human sebum, accomplishes this purpose.

10 Hildebrand solubility coefficients (HSC) (see Vaughn, J. Soc. Cosmet. Chem. 36:319-333 (Sept/Oct 1985)) are used to characterize a miscible vehicle using a sebum solubilizing agent of low (i.e. non-polar) Hildebrand solubility coefficient in combination with a skin penetration aid with a Hildebrand solubility coefficient intermediate between that of the non-polar sebum solvent and the more polar
15 minoxidil solvent. The resulting vehicle has Hildebrand solubility coefficient close to that of human sebum and can completely solubilize the amount of sebum on the scalp. The currently used more polar vehicles for minoxidil cannot solubilize this amount of sebum.

20 Based upon the composition of synthetic (or artificial) sebum, the Hildebrand (HSC) solubility coefficient for sebum is about 7 or 8 cal $^{1/2}$ cm $^{-3/2}$. Minoxidil shows its best solubility in propylene glycol which has an HSC of 14. Miscibility (the ability of two or more liquids to mix in all proportions) is shown on this scale typically when there is a difference of 2 units. Therefore, in order
25 to lower the HSC of the vehicle from that of pure propylene glycol down to 2 of sebum, a solvent with HSC below that of sebum must be chosen. One of the most suitable solvents is volatile silicone oil with a HSC of about 5.8-5.9. Since the silicone oils are totally immiscible with the propylene glycol, it is necessary to add a
30 cosolvent to render the two more miscible.

This cosolvent could have only HSC between 6 and 14, however, the midpoint (about 10) should require the smallest amount of cosolvent and is thus preferred.

35 Minoxidil is not well absorbed through the skin in the prior art formulations (e.g., propylene glycol/ethanol/water). Thus, addition of a vehicle component that enhances skin penetration as well as renders the silicone oils and propylene glycol miscible is desired. Most preferable is oleyl alcohol, having an HSC of 9.8. A single

phase (i.e. solution) formulation can be prepared from these materials. This vehicle can completely solubilize the sebum levels on the skin whereas previous minoxidil formulations do not dissolve the amounts of sebum reported to be on the scalp.

5 For purposes of skin penetration, it is desirable to have less oleyl alcohol in the formulation (e.g., approximately 1:1 ratio of oleyl alcohol to propylene glycol). However, the formulation is not miscible at the 1:1 ratio. A single phase system (at 1:1 oleyl alcohol:propylene glycol) can be prepared by adding some nonvolatile
10 silicone oil (e.g., Dow Corning 200 fluid) and a surfactant (e.g., Union Carbide SILWET L-77).

Further, high concentrations of oleyl alcohol are dermally irritating. Thus, concentrations of oleyl alcohol of from about 10 to about 40% of the total solution are preferred. It is more
15 preferred for cosmetic acceptability to use less than about 20% oleyl alcohol, so that the composition has a less oily "feel".

Preferred proportions of the components are as follows:

Based upon in vitro transdermal data, the concentration of minoxidil should be from about 1.0% to 2.5%; the concentration of
20 propylene glycol from about 12% to 25%; and the concentration of oleyl alcohol from about 6% to 20%. These vehicles give in vitro human skin transport levels of minoxidil that range from about equal to the current 2% minoxidil formulation (20% propylene glycol/60% ethanol/20% water) to approximately 10 fold greater transport, as
25 seen by Example 2.

The use of topical minoxidil compositions is well known to the ordinarily skilled physician or dermatologist. This use is also set forth in U.S. Patents 4,139,619 and 4,596,812, incorporated by reference herein.

30 DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is seen more fully by the Examples below.

Example 1

The following formulations are prepared according to the procedure below:

35 Procedure

(Step 1) Propylene glycol is measured and added to a suitable container. (Step 2) Propylene glycol is heated to 52°-58° using a water bath, and heated for 10-15 min once the temperature has reached

the required range. (Step 3) Minoxidil is weighed and added slowly to the heated propylene glycol with rapid mixing. Mixing continues until the minoxidil is completely dissolved (approx. 30-40 min). Temperature is maintained at 52°-58°C using the water bath. (Step 4)
 5 The minoxidil-propylene glycol solution is cooled to room temperature (approx. 25°C). (Step 5) Oleyl alcohol is measured and added to the cooled step 4 solution and mixed for 1 min. (Step 6) If procetyl-10 is added, it is added to the step 5 mixture and mixed for 1 min at this point. (Step 7) Dow Corning 344 is added to the above mixture
 10 and mixed for 5-10 min until a uniform mixture is obtained.

Formulation 1 Minoxidil USP milled (~90 mg/ml propylene glycol to give saturated solution)

	Propylene Glycol	15%
	Oleyl Alcohol USP	15%
15	Dow Corning 344 (volatile silicone oil)	70%

Formulation 2 Minoxidil USP milled (~90 mg/ml propylene glycol)

	Propylene Glycol USP	15%
	Oleyl Alcohol USP	30%
	Procetyl-10(PEG 10 cetyl ether)	10%
20	PGE 10 cetyl ether	
	Dow Corning 344	45%

Formulation 3 Minoxidil USP milled (~90 mg/ml propylene glycol)

	Propylene Glycol USP	12.5%
	Oleyl Alcohol USP	25%
25	Procetyl-10	10%
	Dow Corning 344	52.5%

Example 2

Based on the foregoing specification, and on techniques known in the art, all of the compositions of the invention are prepared.
 30 Three representative nonaqueous formulations of minoxidil were prepared and are characterized by their dermal characteristics as follows:

Vehicle	Composition (Vol%)			
<u>Transport*</u>	<u>Propylene Glycol</u>	<u>Oleyl Alc.</u>	<u>IPA</u>	<u>Vol. Silicone</u>
35 High (~12X)	25	15	27	33
Medium (~4X)	15	7.5	25	52.5
Low (~1.5X)	12	6	25	57

* Vehicle transport is defined as the ratio of the peak (1 hr)

transport flux measured for minoxidil through human cadaver skin for the vehicle listed divided by the "standard" reference vehicle (20% propylene glycol/60% ethanol/20% water) peak minoxidil transport measured on a portion of the same piece of skin.

5 The weight percent of minoxidil in each of these formulations is: 2.3% for the high transport; 1.3% for the medium transport; and 1.1% for the low transport vehicle, while the reference vehicle contains 2.0% minoxidil.

10 Autoradiographic examination of drug distribution in Macaque monkeys indicates that a formulation containing 20% propylene glycol, 20% oleyl alcohol, 16% isopropanol, and 44% volatile silicone had an approximately sixfold increase in drug delivery into the sebaceous gland in the hair follicle relative to the drug content away from the hair follicle at an equal distance into the skin. The standard
15 formulation had essentially no difference between the amounts in the follicle and outside the follicle. Human in vivo dermal irritation tests show minimal unoccluded dermal irritation for this composition.

Example 3

20 Using the procedures of the preceding Examples, and techniques known in the art, the following compositions are prepared. (All concentrations are in volume percentages (volume %)).

TABLE 1

Nonaqueous Minoxidil Formulations

5	<u>Formulation</u>	Conc.	Conc.	Conc. DC 344	Other
		Propylene Glycol	Oleyl Alcohol	Silicone Oils	Composition
	1	25%	25%	50%	0
	2	20%	30%	50%	0
	3	20%	20%	60%	0
	4	20%	25%	55%	0
10	5	22.5%	22.5%	55%	0
	6	15%	25%	60%	0
	7	30%	20%	50%	0
	8	25%	15%	60%	0
	9	25%	20%	55%	0
15	10	15%	30%	45%	10% Pro-10*
	11	12.5%	25%	57.5%	5% Pro-10*
	12	25%	10%	65%	0
	13	15%	7.5%	77.5%	0

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35 *Pro-10 = Procetyl-10 (propylene cetyl ether) surfactant added to initial emulsions to improve stability.

CLAIMS

1. A topical hair growth composition comprising:

- (a) minoxidil;
- (b) a solvent, capable of dissolving minoxidil;

5 (c) a non-polar solvent, which renders the polarity of the total formulation approximately the same as human sebum; and

(d) a cosolvent having a polarity between that of the solvent capable of dissolving the minoxidil and the non-polar solvent, which enhances the delivery of minoxidil through the stratum corneum, said
 10 cosolvent in an amount less than that which cause skin irritation.

2. A composition of Claim 1, wherein the solvent capable of dissolving minoxidil is propylene glycol, the cosolvent is a mixture of oleyl alcohol and isopropanol, and the non-polar cosolvent is a
 15 volatile silicone oil.

3. A composition of Claim 2, wherein the minoxidil concentration is from about 1.0 to about 2.5% volume %, propylene glycol is from about 12 to about 25% volume %, oleyl alcohol is from about 6 to about 20
 20 volume % w/w, and the isopropanol is from about 16 to about 27 volume %.

4. A composition of Claim 3, selected from the group consisting of formulations having the following proportions:

25		Propylene	Oleyl		Volatile
	<u>Composition</u>	<u>Glycol</u>	<u>Alcohol</u>	<u>Isopropanol</u>	<u>Silicone</u>
	(a)	25	15	27	33
	(b)	15	7.5	25	52.3
	(c)	12	6	25	57

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5. A composition of Claim 2, selected from the group consisting of formulations having the following proportions:

		Conc.	Conc.		
		Propylene	Oleyl	Conc. DC 344	Other
35	<u>Formulation</u>	<u>Glycol</u>	<u>Alcohol</u>	<u>Silicone Oils</u>	<u>Composition</u>
	1	25%	25%	50%	0
	2	20%	30%	50%	0
	3	20%	20%	60%	0

	<u>Formulation</u>	Conc. Propylene <u>Glycol</u>	Conc. Oleyl <u>Alcohol</u>	Conc. DC 344 <u>Silicone Oils</u>	Other <u>Composition</u>
	4	20%	25%	55%	0
5	5	22.5%	22.5%	55%	0
	6	15%	25%	60%	0
	7	30%	20%	50%	0
	8	25%	15%	60%	0
	9	25%	20%	55%	0
10	10	15%	30%	45%	10% Pro-10*
	11	12.5%	25%	57.5%	5% Pro-10*
	12	25%	10%	65%	0
	13	15%	7.5%	77.5%	0

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*Pro-10 = Procetyl-10 (propylene cetyl ether) surfactant added to initial emulsions to improve stability.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 87/02168

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶				
According to International Patent Classification (IPC) or to both National Classification and IPC				
IPC ⁴ : A 61 K 7/06				
II. FIELDS SEARCHED				
Minimum Documentation Searched ⁷				
Classification System	Classification Symbols			
IPC ⁴	A 61 K			
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸				
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹				
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³		
A	WO, A, 85/04577 (G. BAZZANO) 24 October 1985 see page 4, lines 12-35; examples	1-5		
A	US, A, 4596812 (CHIDSEY, III et al.) 24 June 1986 see the whole document cited in the application	1-5		
A	US, A, 2643375 (V.A. GANT) 23 June 1953 see the whole document	1-5		

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IV. CERTIFICATION				
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report			
3rd December 1987	14 JAN 1988			
International Searching Authority	Signature of Authorized Officer			
EUROPEAN PATENT OFFICE	 P.C.G. VAN DER PUTTEN			

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 8702168
SA 18604

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/12/87. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8504577	24-10-85	EP-A- 0177581	16-04-86
US-A- 4596812	24-06-86	US-A- 4139619	13-02-79
US-A- 2643375		None	