AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

WE, FLARER S.A. PHARMACEUTICAL FINE CHEMICALS of Via Cantonale, 28 CH-6855 Stabio, Switzerland, being the applicant in respect of the attached application, state the following:-

The inventor of the invention is as follows:

ALBERTO SALINI of Via Giulia, CH-6855 Stabio, Switzerland.

The person nominated for the grant of the patent: FLARER S.A. PHARMACEUTICAL FINE CHEMICALS is the assignee of GOLGI S.A. in respect of the invention and GOLGI S.A. derived its rights in the invention from the inventor by virtue of a verbal arrangement of March 30 1992; and
FLARER S.A. PHARMACEUTICAL FINE CHEMICALS has the consent of GOLGI S.A. to claim convention priority from the application listed in the declaration under Article 8 of the PCT.

The basic application listed in the declaration made under Article 8 of the PCT is the first application made in a convention country in respect of the invention.

DATED THIS 12TH DAY OF SEPTEMBER 1994.

FLARER S.A. PHARMACEUTICAL FINE CHEMICALS
By their Patent Attorneys
KELVIN LORD AND COMPANY
PERTH, WESTERN AUSTRALIA.

AU9337526

(12) PATENT ABRIDGMENT (11) Document No. AU-B-37526/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 677002

(54) Title
COSMETICAL OR PHARMACEUTICAL COMPOSITIONS COMPRISING DEACYLATED GLYCEROPHOSPHOLIPIDS FOR TOPICAL USE

International Patent Classification(s)
(51)[5] A61K 007/48 A61K 007/06 A61K 031/66 A61K 031/685

(21) Application No. : 37526/93 (22) Application Date : 26.03.93

(87) PCT Publication Number : WO93/19730

(30) Priority Data

(31) Number	(32) Date	(33) Country
1004/92	30.03.92	CH SWITZERLAND

(43) Publication Date : 08.11.93

(44) Publication Date of Accepted Application : 10.04.97

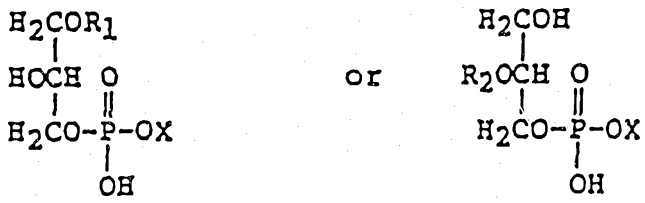
(71) Applicant(s)
FLARER S.A. PHARMACEUTICAL FINE CHEMICALS

(72) Inventor(s)
ALBERTO SALINI

(74) Attorney or Agent
LORD & COMPANY , 4 Douro Place, WEST PERTH WA 6005

(57) Claim

1. Fully deacylated glycerophospholipids and of physiologically acceptable salts thereof, with the exclusion of lysophospholipids of formula.



in which R1, R2 are a fatty acid acyl group;

X is choline, ethanolamine, serine, inositol; together with a pharmaceutically acceptable excipient when used as cosmetic agents for topical application.

2. Fully deacylated glycerophospholipids according to claim 1 when used as cosmetic agents for topical application, selected from L-α-glycerylophosphorylcholine, L-α-glycerylphosphorylethanolamine, L-α-glycerylphosphorylserine, L-α-glycerylphosphoryl-D-myo-inositol.

3. Topical pharmaceutical and cosmetic compositions containing the deacylated glycerophospholipids of claim 1 or 2 together with pharmaceutically or cosmetically acceptable excipients when used as cosmetic agents.

OPI DATE 08/11/93 APPLN. ID 37526/93
AOJP DATE 13/01/94 PCT NUMBER PCT/EP93/00746

AU9337526

ATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 7/48, 7/06, 31/66 A61K 31/685	A1	WO 93/19730
		(43) International Publication Date: 14 October 1993 (14.10.93)

(21) International Application Number: PCT/EP93/00746

(22) International Filing Date: 26 March 1993 (26.03.93)

(30) Priority data:
1004/92-1 30 March 1992 (30.03.92) CH

see folio 3

~~(71) Applicant (for all designated States except US): GOLGI S.A. [CH/CH]; Via Giulia, CH-6855 Stabio (CH).~~

(72) Inventor; and
(75) Inventor/Applicant (for US only) : SALINI, Alberto [IT/CH]; Via Giulia, CH-6855 Stabio (CH).

(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).

(71) FLAMER S.A. PHARMACEUTICAL FINE CHEMICALS
Via Cantonale, 28
CH-6855 Stabio
Switzerland

(81) Designated States: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

677002

(54) Title: COSMETICAL OR PHARMACEUTICAL COMPOSITIONS COMPRISING DEACYLATED GLYCEROPHOSPHOLIPIDS FOR TOPICAL USE

(57) Abstract

Topical use of deacylated glycerophospholipids, such as L-α-glycerylphosphorylcholine, L-α-glycerylphosphorylethanolamine, L-α-glycerylphosphorylserine, L-α-glycerylphosphoryl-D-myo-inositol, pharmaceutical and cosmetic compositions containing them.

COSMETICAL OR PHARMACEUTICAL COMPOSITIONS COMPRISING DEACYLATED GLYCEROPHOSPHOLIPIDS FOR TOPICAL USE

The invention relates to the topical use of deacylated glycerophospholipids and of the physiologically acceptable salts thereof.

Particularly, the invention relates to the use of deacylated glycerophospholipids named L-α-glycerylphosphorylcholine, L-α-glycerylphosphorylethanolamine, L-α-glycerylphosphorylserine, L-α-glycerylphosphoryl-D-myo-inositol, respectively.

Said compounds, in the present invention, can be used alone or in mixtures thereof.

The deacylated glycerophospholipids are mainly obtained by the semisynthetic route, for example those preferred in the present invention are obtained by selective deacylation of the natural phospholipids extracted from soy.

Glycerophospholipids are compounds widely occurring in nature, where they exert important biological functions, for example they are the main lipid components of cell phospholipids.

The administrations thereof by the oral and parenteral routes, for example as diet supplements or as medicaments, proved to be useful in the prevention of the involution processes of the cell membranes, since they can play an important role on the biochemical lesions occurring on the membrane phospholipids.

Now it has surprisingly been found that the deacylated glycerophospholipids of the present invention can be adsorbed by the topical route, if suitably formulated, and this is a valuable alternative to the

exogenous supply to the skin cells.

Deacylated glycerophospholipids, mainly those preferred in the present invention, have interesting properties which can suitably be exploited also in the cosmetic field.

The use of said glycerophospholipids is based on the fact that said compounds can be considered both as basic substances (for the formulation of excipients) and as specializing functional substances.

As basic substances, they can be used, for example, to give wetting, antidehydrating, plasticizing, co-solvent and co preservative properties.

As specializing functional substances, they can be used, for instance, as moisturizers, emollients, elasticizers, restitutives and the like.

Said compounds can usefully be applied also to the hair cosmetic, for example as antistatics, restitutives, voluminizing agents and the like.

The used concentrations of the deacylated glycerophospholipids in the present invention can vary within wide ranges, according to the envisaged uses and the kind of the prepared formulation; for example they can be used in a range from 0.01% up to 50% by weight, preferably from 0.1% to 10%.

The deacylated phospholipids have a very low systemic toxicity as well as a particularly low topical toxicity, as evidenced by the tests carried out in the animal, hereinafter described.

<u>Cutaneous sensitization</u>

350-450 g guinea pigs, depilated on the back, were used.

50 mg of the product were applied on the left side of the depilated area every other day for 15 days. 30-35 days from the beginning of the treatment, 50 mg of the product were applied on the right side of the back, and the observations were recorded during 24 hours.

No cutaneous reactions were observed during the treatment and in the final phase of antigenic induction.

Eye irritation

The eye tolerance was determined on New Zealand rabbits.

0.1 ml of a 1% solution of the product were instilled into the conjunctival sac of the right eye of the rabbit, whereas 0.1 ml of saline solution were instilled into the left eye.

The eyes were carefully checked for a time of 24 hours, recording any anomalies.

Immediately after the administration of the product and of the saline solution, an abundant lachrymation was observed. Subsequently conjunctiva, iris and cornea remained normal during the whole observation time.

Cutaneous irritation

350-450 g guinea pigs were used, which were depilated on the back by means of a razor.

4 Product doses, corresponding to 50 mg - 100 mg - 200 mg - 300 mg, were applied, then observation started, which lasted 24 hours at least.

No cutaneous irritations were observed at the various product doses.

The formulations containing the deacylated pho-

spholipids of the present invention are those known in the art of the dermatological and cosmetic formulations, preferably those containing water as the excipient.

The moisturizing action of L-α-glycerylphosphorylcholine was evidenced carrying out the test described hereinbelow.

Moisturizing activity

18 Albino Sprague-Dawley male rats, weighing 150 g (+/- 20), were used, which were depilated on the back by means of a commercially available depilatory cream, randomly subdivided into 3 groups of 6 animals each and treated for 14 consecutive days, once in the morning and once at night, with:

1st group: 0.2 g/day of white vaseline

2nd group: 0.2 g/day of 0.1% glycerylphosphorylcholine in white vaseline.

When treatment was over, the animals were killed by prolonged ether anaesthesia, cutis was removed from the treated area and carefully laid on a cork board, then 3 small cutis cylinders were taken from the same anatomic area by means of a cork-piercer, dried for 48 hours at 60°C in a dry oven, then weighed again.

The cutis hydration conditions were obtained by the difference between the cutis cylinder weight before and after drying.

The glycerylphosphorylcholine treatment, extended for 2 weeks at a frequency of two daily treatments, could increase the amount of water contained in the cutis of the treated animals, in a statistically significant way compared with white vaseline-treated

controls (Table 1).

TABLE 1

Rat n.	sample n.	Water content (mg) in the cutis: controls	glycerylphosphorylcholine
1	1	230	255
	2	238	247
	3	261	277
2	1	220	249
	2	238	250
	3	248	266
3	1	270	259
	2	263	268
	3	256	265
4	1	233	245
	2	248	262
	3	230	255
5	1	210	274
	2	220	281
	3	230	257
6	1	240	283
	2	235	270
	3	255	295
Mean		240.27	264.33
+/- S.E.		3.86	3.25
P		-	<0.01

The following example further illustrate the invention.

EXAMPLES

MASCARA GEL

A)	1,2-Propanediol	2.0%
	Preservants	q.s.
	Glycerylphosphorylcholine 85° in water	0.2%
	Pearl lustre pigment (E. Merck Darmstadt)	0.004%
	Carbomer 940	0.2%
B)	Triethanolamine	0.2%
	Demineralized water	18.2%
C)	95° Ethanol	10.0%
	Polyvinylpyrrolidone (K 30)	1.0%

Preparation:

1,2-Propanediol, glycerylphosphorylcholine and water were mixed together, then Pearl lustre pigment and subsequently Carbomer 940 were added, stirring strongly. The mixture was neutralized with aqueous triethanolamine.

Ethanol and polyvinylpyrrolidone (K 30) were added under stirring.

EYE POWDER

Pigment	30.0%
Glycerylphosphoryl-inositol calcium salt	0.5%
Talc	49.0%
Potato starch	7.5%
Magnesium stearate	2.5%
Binder	10.5%

(composition of the binder:

cetyl palmitate	5%
petroleum	9%
perfume	q.s.
preservants	q.s.
isopropyl stearate q.s. to	100.0%)

Preparation:

The powder ingredients were mixed thoroughly. The binder, in the molten state, was added in portions under stirring.

Finally the mixture was compressed under 40-60 bars (560-840 psi).

NUTRIENT CREAM

A)	Glycerylphosphorylcholine	2.0%
	Glycerin	2.0%
	Copper pyroglutamate	0.2%
	Zinc pyroglutamate	0.2
B)	Glycerol monostearate emulsified with	
	Polyethylene glycol	5.0%
	Stearic acid	8.0%
	Myristyl ethoxy myristate	6.0%
	Sweet almond oil	9.0%
	Cetyl alcohol	1.0%
	Lauryl pyroglutamate	1.0%
	Silicon	0.5%
	Triethanolamine	q.s.
	Perfume	q.s.
	Demineralized water q.s. to	100.0%

Preparation:

Mix the components of phase A) and water and heat to

70°.

Mix the components of phase B) and heat to 70°.

Add phase A) to phase B) slowly stirring.

Add triethanolamine to the mixture to pH 6.4, then add the perfume and dilute to 100 with water.

Cool to 35° stirring slowly.

SHAMPOO

28% Sodium lauryl ether sulfate	40.0%
Coconut fatty acid diethanolamide	4.0%
85% Glycerylphosphorylcholine in water	1.0%
Sodium chloride	4.0%
Perfumes and preservants	q.s.
Deionized water q.s. to	100.0%

Preparation:

The components are mixed with water in the described order, stirring slowly.

HAIR GEL (WET GEL)

Carbomer 940	1.0%
Triethanolamine (TEA)	1.3%
Glycerylphosphorylserine	0.7%
Pearl lustre pigment (E. Merck, Darmstad)	0.2%
Perfume and preservants	q.s.
Deionized water q.s. to	100.0%

Preparation:

The pigment is dispersed in the water-alcohol mixture, stirring strongly.

Carbomer 940 is added and after complete dissolution, TEA is added to neutralize.

Finally the remaining components are added continuing stirring until homogeneous dispersion.

MAKE-UP CREAM

A) Silicons	10%
(Cyclometicon and Dimeticon Copolyol)	
Silicon (Cyclometicon)	10%
Bee wax	3%
Polyglyceryl-4-oleate	2%
Glycerylphosphorylethanolamine	1%
Pigments	18%
B) Sodium citrate	3%
Preservants	q.s.
Water q.s. to	100%

Preparation:

Silicons, bee wax and polyglyceryl-4-oleate are mixed together and heated to 70°; the remaining components of the phase A) are added, dissolving them in water.

Phase A) is added to phase B) allowing the mixture to cool.

Finally the cream is homogenized.

LIP GLOSS

Castor-oil	70.0%
Miglyol® 812	20.0%
(caprylic/capric triglycerid)	
Bee wax	2.5%
Carnauba wax	2.2%
Glycerylphosphoryl serine calcium salt	0.3%
Pigment	5.0%
Flavours and preservants q.s. to	100.0%

Preparation:

The mixed oils and waxes are heated to melting.

The molten mass is stirred and the deacylated glycerophospholipide, pigment and perfume are added.

The mixture is placed into containers at 50-60°C.

RESTITUTIVE HYDRATANT GEL

Carbomer 940	10.0%
Triethanolamine	12.5%
Glycerylphosphorylcholine	0.1%
Glycerylphosphorylserine	0.1%
Glycerylphosphorylethanolamine	0.1%
Glycerylphosphorylinositol	0.1%
Preservant and perfume	q.s.
Deionized water q.s. to	100.0%

Preparation:

Carbomer 940 is dispersed in water and neutralized with triethanolamine; then the remaining components are added in the indicated order, stirring slowly.

DERMATOLOGIC HYDRATANT LOTION

Glycerylphosphorylcholine	40.0%
Propyl p-oxybenzoate (preservant)	0.3%
Methyl p-oxybenzoate	0.7%
Deionized water q.s. to	100.0%

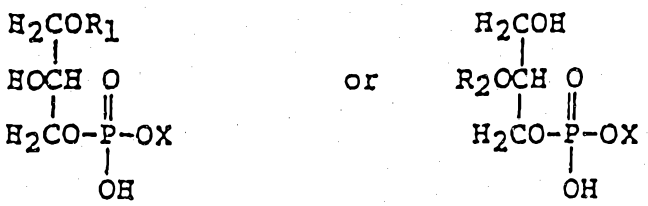
Preparation:

The preservants are warm dissolved in deionized water, then the deacylated glycerophospholipide is added.

Use: apply more times a day on chapped, reddened, dry skin and the like.

The claims defining the invention are as follows:

1. Fully deacylated glycerophospholipids and of physiologically acceptable salts thereof, with the exclusion of lysophospholipids of formula.



in which R1, R2 are a fatty acid acyl group;

X is choline, ethanolamine, serine, inositol; together with a pharmaceutically acceptable excipient when used as cosmetic agents for topical application.

2. Fully deacylated glycerophospholipids according to claim 1 when used as cosmetic agents for topical application, selected from L-α-glycerylophosphorylcholine, L-α-glycerylphosphorylethanolamine, L-α-glycerylphosphorylserine, L-α-glycerylphosphoryl-D-myo-inositol.

3. Topical pharmaceutical and cosmetic compositions containing the deacylated glycerophospholipids of claim 1 or 2 together with pharmaceutically or cosmetically acceptable excipients when used as cosmetic agents.

4. Compositions according to claim 3, in which the deacylated glycerophospholipids are present in an amount from 0.01 to 50% by weight.

5. Compositions according to claim 3 or 4 in form of mascara gel, eye powder, nutritive cream, shampoo, hair gel, make-up cream, lip gloss, restitutive hydrating gel, dermatologic hydrating lotion.

6. Cosmetic compositions when used for topical application substantially as hereinbefore described in any of the foregoing examples.

DATED THIS 31ST DAY OF JANUARY 1997

FLARER S.A. PHARMACEUTICAL FINE CHEMICALS
By Their Patent Attorneys
LORD & COMPANY
PERTH, WESTERN AUSTRALIA

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/00746

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

Int.Cl. 5 A61K7/48; A61K7/06; A61K31/66; A61K31/685

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

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 °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	CHEMICAL ABSTRACTS, vol. 112, no. 4 Columbus, Ohio, US; abstract no. 24365s, K. SENOO 'antioxidants containing glycerol phosphate salts or derivatives' see abstract & JP,A,1 016 890 (SHISEIDO CO. LTD) 20 January 1989	1-5
X	DATABASE WPIL Week 9021, Derwent Publications Ltd., London, GB; AN 90-159797 & JP,A,2 101 086 (NIPPON OILS & FATS KK) 12 April 1990 see abstract	1-5

-/--

° Special categories of cited documents :[10]

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

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

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

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

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

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

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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 JUNE 1993	08.07.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SIERRA GONZALEZ

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0 407 995 (DEPHA TEAM S.R.L.) 16 January 1991 see claims 1-3	1-5
A	EP,A,0 255 937 (KYOWA HAKKO KOGYO CO. LTD) 17 February 1988 see the whole document	1-5

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9300746
SA 72514

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
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 25/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0407995	16-01-91	None	
EP-A-0255937	17-02-88	JP-A- 63041411	22-02-88

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82