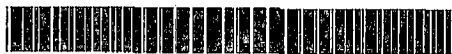


AS: 102.451

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-111945- -00003-0000

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Act. 538 PETICION Folios: 2

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

REF.: Expediente No. 06 111.945 - Solicitud de Patente FASE NACIONAL

Corresp. a la Solicitud Internacional PCT/MX2004/000025

a nombre de: **LABORATORIOS LIOMONT, S.A. DE C.V.**

Titulada: **NUEVA PRESENTACIÓN DE UNA COMPOSICIÓN FARMACÉUTICA ANTIVIRAL**

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la sociedad **LABORATORIOS LIOMONT, S.A. DE C.V.**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 08-23.597 por valor de \$420.000.

De la Señora Jefe atentamente,

JUAN PABLO CADENA SARMIENTO

C.C. No. 80.410.337 de Usaquén

T.P. No. 57492 del C.S.J.

Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 14 de abril de 2008

MEV/JCN/aac

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-111945

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **582** DE

FECHA **30 DE NOVIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **27 DE FEBRERO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X



US005585379A

United States Patent [19]

Sintov et al.

[11] **Patent Number:** 5,585,379[45] **Date of Patent:** Dec. 17, 1996[54] **ACYCLOVIR ANTIVIRAL GEL
COMPOSITION**[75] **Inventors:** Amnon Sintov, Omer; Rina Uzan,
Beer Sheva, both of Israel[73] **Assignee:** AGIS Industries (1983) Ltd.,
Yerucham, Israel[21] **Appl. No.:** 186,259[22] **Filed:** Dec. 28, 1993[30] **Foreign Application Priority Data**

Dec. 30, 1992 [IL] Israel 104283

[51] **Int. Cl.⁵** A61K 31/52[52] **U.S. Cl.** 514/262; 514/944; 514/946;
514/947; 424/677[58] **Field of Search** 514/49, 50, 256,
514/261, 944, 946; 424/677[56] **References Cited****U.S. PATENT DOCUMENTS**4,537,776 8/1985 Cooper 514/825
4,956,184 9/1990 Kross 514/931**FOREIGN PATENT DOCUMENTS**0135312A2 3/1985 European Pat. Off. 514/50
0397211A2 11/1990 European Pat. Off. 514/50**OTHER PUBLICATIONS**Toshinobu Seki et al., *Enhanced Transdermal Delivery of
Zidovudine in Rats and Human Skin*, *Chem. Pharm. Bull.*,
vol. 38, No. 11, 1990 (pp. 3086-3089).Toshinobu Seki et al., *Percutaneous Absorption of Azido-
thymidine in Rats*, *International Journal of Pharmaceutics*,
vol. 57, 1989 (pp. 73-75).*Primary Examiner*—James O. Wilson
Attorney, Agent, or Firm—Darby & Darby[57] **ABSTRACT**

An antiviral topical pharmaceutical composition for treating viral diseases of the skin or mucosa comprises a poorly soluble antiviral nucleoside derivative, dispersed in an aqueous gel carrier containing a gelling agent and a water-soluble carboxylic or dicarboxylic acid salt.

1 Claim, 6 Drawing Sheets

5,585,379

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ACYCLOVIR ANTIVIRAL GEL COMPOSITION

The present invention relates to an antiviral topical pharmaceutical composition.

More particularly, the present invention relates to a topical pharmaceutical composition containing a water-insoluble, antiviral nucleoside derivative dispersed in an aqueous gel carrier.

Many antiviral nucleoside derivatives are known, which suffer from the problem of low solubility in water and almost total insolubility in hydrophobic systems. The antiviral nucleoside derivatives that are sparingly soluble in water include:

1. Acyclovir [9-(2-hydroxyethoxymethyl)guanine]
2. Vidarabine (adenine arabinoside)
3. Azidothymidine (AZT, Retrovir, Zidovudine, 3(-azido-3'-deoxythymidine
4. Ganciclovir [9-(1,3-dihydroxy-2-propoxy)methylguanine, DHPG]

An especially important antiviral nucleoside derivative is acyclovir.

As described and explained in Israel Patent 63351:

"Acyclovir and pharmaceutically acceptable salts and esters thereof are known to have antiviral activity against various classes of DNA and RNA viruses, both in vitro and in vivo, see UK Patent No. 1,523,865 (corresponding to Israel Patent 48035). In particular, the compound is active against herpes simplex virus, which causes herpetic keratitis in rabbits, herpetic encephalitis in mice, and cutaneous herpes in guinea pigs.

"Acyclovir suffers from the disadvantage that it has a low solubility in water and is almost totally insoluble in hydrophobic solvent systems. It is accordingly difficult to produce a topical formulation containing a sufficiently dissolved concentration of active ingredient for it to exert its full effect and also to optimise the flux of the compound into the skin. In addition to ease of release, it is also important that any formulation of a pharmaceutically active compound should be stable for long periods of time; should not lose its potency; should not discolour or form insoluble substances or complexes; and also should not be unduly irritating to the skin or mucosa."

Said patent teaches solving the above stated problem by providing an oil-in-water topical pharmaceutical formulation for treating virus diseases of the skin or mucosa, of 9-(2-hydroxyethoxymethyl)guanine (hereinafter referred to as acyclovir) or a pharmaceutically acceptable salt and ester thereof, having a dispersed oil phase and a continuous aqueous phase, characterised in that the aqueous phase comprises water, at least 30% w/w of a water-miscible polyhydric alcohol and solubilized acyclovir or salt or ester thereof.

The present invention comes to challenge the accepted practice relating to penetration of acyclovir and other nucleoside analogues through biological membranes, using a different drug vehicle/dosage form.

As stated, acyclovir is a guanosine analogue with potent antiviral activity against herpes simplex virus. This agent is a prescription antiviral agent, currently marketed by Burroughs-Wellcome under the trade name ZOVIRAX®, and is available for topical use as 5% (w/w) ointment or cream in a polyethylene glycol base.

The ability to deliver acyclovir to herpes simplex virus infections is a prerequisite of any dosage form developed. There are a considerable amount of reports pointing out that topical acyclovir therapy lacks efficacy as compared to oral or parenteral administrations. The lack of efficacy can most likely be related to the poor water-solubility and lipophilic-

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ity of acyclovir, resulting in its inadequate skin or mucous membrane partitioning ability.

The present invention relates to a novel composition consisting of poorly water-soluble active ingredients in a gel formulation. Although this composition is an aqueous gel, it enhances the absorption of acyclovir and its related lipophilic compounds to the skin and through the skin, as well as mucous membranes of the nasal, buccal, sublingual and vaginal cavities. It is noteworthy that the delivery of drugs through the skin or mucous membranes offers a targeting of the drugs in a local manner to the affected area, accompanying a significant reduction in side effects and drug biodegradation.

Thus, according to the present invention there is now provided an antiviral, topical pharmaceutical composition for treating viral diseases of the skin or mucosa, comprising a poorly water-soluble, antiviral nucleoside derivative dispersed in an aqueous gel carrier containing a gelling agent and a carboxylic or dicarboxylic acid salt, such as a water solubilized C₁₆-C₁₈ carboxylic acid salt, e.g., a linoleate, elaidate, palmitate, myristate or oleate, or a dicarboxylic acid salt, e.g., a malonate, succinate, adipate, pimelate, maleate, fumarate or azelate.

Said compositions can further comprise a carboxylic or dicarboxylic acid in combination with said acid salt.

In contradistinction to the approaches suggested in the prior art of utilizing water-in-oil or oil-in-water emulsions in an ointment or cream topical delivery system, it has now been found, according to the present invention, that a gel formulation containing a soluble salt of a carboxylic or dicarboxylic acid, such as sodium or potassium oleate, enhances the permeation of a poorly absorbed drug (e.g., acyclovir) through skin. A composition consisting of potassium oleate is superior over an o/w or w/o cream. As shown in the examples hereinafter, ZOVIRAX (o/w) cream delivers more drug than w/o cream. However, a continuous aqueous phase gel functions as an even more effective drug delivery system when water-soluble carboxylic or dicarboxylic acid salt is included therein. Therefore, the present invention in its preferred embodiment provides an enhanced bioavailability of acyclovir and its poorly absorbed derivatives, and provides an unexpected improved delivery of acyclovir from an aqueous dosage form to and through the skin and other mucous membranes, thus increasing the blood level of the active agent.

Thus the present invention, in especially preferred embodiments, provides a topical pharmaceutical composition comprising an antiviral topical aqueous gel pharmaceutical composition according to the present invention, comprising 0.1-30% of an alkali oleate, 0.5-20% acyclovir, 0-70% propylene glycol, 0-50% glycerine and 0.1-5% of a gelling agent.

Preferably, said antiviral topical aqueous gel pharmaceutical composition will also comprise a polyhydroxy compound of the type known in the art such as glycerine, propylene glycol and polyethylene glycol.

While the invention will now be described in connection with certain preferred embodiments in the following examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for

purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

In the following examples and comparative examples, tradenames and/or trademarks will be used to indicate components of compositions instead of the chemical names, according to the following key:

1. NIPAGIN™—ethylparaben, 4-hydroxybenzoic acid ethyl ester
2. NAPASOL™—propylparaben, 4-hydroxybenzoic acid propyl ester
3. CARBOPOL™ 940—carbomer, carboxyvinyl polymer, carboxypolymethylene
4. LUTROL™ F-127—poloxamer 407, polyethylenepolypropylene glycols
5. METHOCEL K 15M—Hydroxypropyl methylcellulose
6. TRANSCUTOL™—ethoxy di-glycol
7. DRAGOSAN™ W/O—a mixture of sorbitan isostearate, hydrogenated castor oil, ceresin, beeswax and mineral oil
8. VESTAN™ 50—mineral oil
9. MYGLOIL™ 812—caprylic/capric acids
10. DRAGOXAT™ EH—octyldodecyl octanoate

COMPARATIVE EXAMPLE 1

- a) The objective of the present study was to compare several acyclovir gels and one w/o cream that were formulated in our laboratory with 5% ZOVIRAX (o/w) cream (Burroughs-Wellcome, North Carolina), in their ability to deliver the drug transdermally. The gels and the w/o cream were physically acceptable as topical preparations and could challenge the present patents, if they would deliver the drug effectively. That was, basically, the goal of the present study.
- b) The formulations were prepared and sent to an independent laboratory for transdermal assessment in two separate experiments. The first experiment was performed with formulations designated AGD2110, AGD2210, AGD21T10, AGD22T10 and a commercial ZOVIRAX cream (D8289). All these formulations were radiolabeled under gentle heating with 0.04 mCi of tritiated acyclovir per 5g of the gel. The second experiment was conducted with formulations designated AGD37, AGD38A, ZOVIRAX and ACD03. All preparations were tested for acyclovir permeation through hairless rat skin in a diffusion cell system. The permeated acyclovir was analyzed in the first experiment by measuring the radioactivity (in dpm/mg), and in the second experiment by HPLC. Only product ACD03, from which a 5 g specimen was taken and radiolabeled (without heating), was analyzed by the two methods.
- c. Formulations:

Ingredients	Conc., %					
	AGD 21A (2110)	V 22A (2210)	21A-3 (21T10)	22A-3 (22T10)	37	38A
Acyclovir mic.**	5	5	5	5	5.3*	5.3*
Purified Water	60	66.6	55	61.6	35	45.3
Propyl Glycol	25	—	20	—	39.5	38
Nipagin	0.2	0.2	0.2	0.2	0.2	0.1
Nipazol	—	—	—	—	0.0	0.0
Glycerine	6.6	6.6	6.6	6.6	—	—

—continued—

Conc., %					
Cyclodextrine	1.6	—	1.6	—	—
Carbopol 940	0.8	0.8	0.8	0.8	—
Lutrol F-127	—	—	—	—	20
Pot. oleate 40%	—	—	—	—	7
Methocel-K 15M	—	—	—	—	1.5
citric acid 20%	—	—	—	—	2.7
NaOH 20%	0.8	0.8	0.8	0.8	—
Transcutol	—	—	10	10	—
Alcohol (ethanol)	—	20	—	15	—

Ingredients	ACD 03
Phase A:	
Dragosan w/o	8
Vestan-50	6
Mygloil-812	10
Dragoxat EH	4
Nipazol	0.0
Phase B:	
Acyclovir mic.	0.5
Purified water	63
MgSO ₄ ·7H ₂ O	0.7
Propyl glycol	3
Nipagin	0.1
Phase C:	
Acyclovir mic	4.7

*A correction was made in accordance to the material's assay.

**Resfar R-51209-021

d) Manufacturing Procedure:

Formulations containing glycerine were prepared by dispersing acyclovir in the glycerine, and mixing this paste with an aqueous solution of the other ingredients. Small portions of acyclovir (16%) were dissolved in the aqueous solution by using an appropriate amount of sodium hydroxide. The last step was an addition of carbopol and mixing until an homogeneous gel was obtained.

Formulation AGD37 and AGD38A were prepared by dispersing the acyclovir in propylene glycol (and potassium oleate as in AGD38A). Then, the aqueous solution containing the preservative was added and mixed followed by a subsequent addition of the gelling agent. The pH was adjusted, if necessary, to 7–8.

The w/o cream (ACD03) was prepared as follows:

1. Phase A was heated while stirring at 80° C.
2. Phase B was prepared by dissolving nipagin and magnesium sulphate in the 80° C. preheated water. While stirring, propylene glycol and the small portion of acyclovir were added and dissolved.
3. At 80° C. phase B was emulsified in phase A.
4. On cooling to 50° C., the acyclovir (phase C) was added, mixed and the cream was homogenized.

e) In-vitro Skin Permeability of Acyclovir:

Diffusion cells: The permeability of hairless rat skin to acyclovir was measured in vitro using diffusion cells. The diffusion area was 2.54 cm², and the donor compartment volume was 8 ml. The solutions in the donor side were stirred by externally driven, teflon-coated magnetic bars. Half of the cells were immersed in a 37° C. water bath for the whole experiment. In the first experiment, 6 diffusion cells were used for each formulation, while in the second experiment only 3 were employed.

Skin preparation: Full-thickness hairless rat (5–6 wks nude rats, Hyfac Credo, Orleans, France) skin was excised from the fresh carcasses of animals (abdominal side only) sacrificed with chloroform. Subcutaneous fat was removed with a scalpel and the skin was mounted in diffusion cells. The abdominal skin of each animal was



US005331012A

United States Patent [19]

Riddick et al.

[11] Patent Number: **5,331,012**[45] Date of Patent: **Jul. 19, 1994**

[54] **TOPICAL PHARMACEUTICAL
PREPARATION FOR FEVER BLISTERS AND
OTHER VIRAL INFECTIONS AND METHOD
OF USE**

[76] Inventors: **Kenneth B. Riddick**, 918 Liberty St.;
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175, all of Ahoskie, N.C. 27910

[21] Appl. No.: **846,734**

[22] Filed: **Mar. 5, 1992**

Related U.S. Application Data

[63] Continuation of Ser. No. 559,617, Jul. 30, 1990, abandoned.

[51] Int. Cl.⁵ **A61K 31/16**

[52] U.S. Cl. **514/626; 514/692**

[58] Field of Search **514/626, 692**

[56] **References Cited**

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Primary Examiner—Frederick E. Waddell

Assistant Examiner—Russell Travers

Attorney, Agent, or Firm—Richard E. Jenkins

[57] **ABSTRACT**

The present invention relates to a method and pharmaceutical composition for treating fever blisters or cold sores in mammals, and particularly in humans, by topically administering a pharmaceutical composition comprising ethyl alcohol in a concentration of at least 85% W/V and lidocaine in a concentration of 0.5–10% W/V at a periodicity of at least 10 to 12 times daily.

1 Claim, No Drawings

**TOPICAL PHARMACEUTICAL PREPARATION
FOR FEVER BLISTERS AND OTHER VIRAL
INFECTIONS AND METHOD OF USE**

This is a continuation of co-pending application Ser.
No. 07/559,617 filed on Jul. 30, 1990, now abandoned.

TECHNICAL FIELD

This invention relates to a method and pharmaceuti-
cal composition for topically treating fever blisters or
cold sores and other vital infections in mammals, and in
particular in humans.

BACKGROUND ART

"Fever blisters" or "cold sores" have long been a
very unpleasant manifestation of vital Herpes-type in-
fections. Typically, the lesions form on the lips and/or
genital area of a human and are very uncomfortable as
well as unsightly during the several week healing peri-
od. Since these lesions are normally of a recurring
nature, a remedy which will serve to relieve the discom-
fort and expedite the healing process has long been
sought after.

In an effort to address the discomfort of fever blisters,
cold sores and other lesions caused by Herpes-type
viruses, many home remedies have been used over the
years without any significant success. Also, commercial
products have been developed in recent years to at-
tempt to treat the vital infections. Representative of
such products are the following: CAMPHO-
PHENIQUE manufactured by Winthrop Consumer
Products of New York, N.Y.; HERPECIN-L manufac-
tured by Campbell Labs of New York, N.Y.; and BLIS-
TEX manufactured by Blistex Incorporated of Oak-
brook, Ill. Unfortunately, none of the commercial for-
mulations have been found to be entirely satisfactory
when used as topical preparations for treating humans
for fever blisters or cold sores and other vital infections
of both the single occurrence as well as recurrent type.

Of interest, U.S. Pat. No. 4,628,063 to Haynes et al.
discloses that the use of lidocaine, and particularly lido-
caine in combination with a pantothenic acid, is an
effective anti-vital agent in use to treat Herpes virus
infections in mammals and is particularly effective in
the treatment of HSV oral and genital lesions on hu-
mans. Haynes et al. discloses that lidocaine, a local
anesthetic agent, and pantothenic acid (Vitamin B5)
have an anti-vital effect on mammals, including human
beings. It is further disclosed that lidocaine adminis-
tered in the form of a pharmaceutical formulation com-
prising lidocaine and pantothenic acid together with a
pharmaceutically acceptable carrier is particularly ef-
fective when injected in a single daily dosage or topi-
cally applied in an ointment or solution form 3 to 4
times daily. Unfortunately, this formulation is not en-
tirely satisfactory due to the inconvenience of injections
and the lengthy time of therapy required for topical
treatment.

DISCLOSURE OF THE INVENTION

In accordance with the present invention, applicants
provide a pharmaceutical composition for topically
treating fever blisters or cold sores, Herpes virus infec-
tions, and other vital infections in mammals, and particu-
larly in humans. The pharmaceutical composition
comprises ethyl alcohol in a concentration of at least
85% W/V and lidocaine or a pharmaceutically accept-

able salt thereof in a concentration of 0.5 to 10% W/V,
preferably about 1-2% W/V. Optionally, the formula-
tion may also include camphor in a concentration of 0.5
to 5% W/V, and preferably about 1.5% W/V. In use,
the pharmaceutical composition is topically applied to
the infected area in an effective anti-vital amount at
least 10 to 12 times daily until the lesions heal.

It is therefore the object of this invention to provide
an improved pharmaceutical composition for topically
treating fever blisters or cold blisters on mammal s.

It is another object of the present invention to pro-
vide a pharmaceutical composition for topically treat-
ing fever blisters or cold blisters, Herpes virus infec-
tions, and other vital infections which manifest them-
selves in a sore or lesion on the human body.

It is yet another object of the present invention to
provide a pharmaceutical composition for topically
treating fever blisters or cold sores, Herpes virus infec-
tions, and other vital infections which expeditiously
relieves the discomfort of the lesion and results in the
healing or remission of the lesion within only several
days.

It is still another object of the present invention to
provide a pharmaceutical composition in a gel or liquid
form for topical treatment of fever or cold blisters
which results in the curing or remission thereof within
3 or 4 days when applied directly to the lesion at least 10
to 12 times daily.

Some of the objects of the invention having been
stated, other objects will become evident as the descrip-
tion of the invention proceeds.

**BEST MODE FOR CARRYING OUT THE
INVENTION**

Applicants have discovered that ethyl alcohol (typi-
cally 95% V/V, although other concentrations may be
used, and all concentrations hereinafter being referred
to as "ethyl alcohol") is an effective anti-vital agent for
use in treating fever blisters or cold sores and other
Herpes-type virus infections on mammals, and in particu-
lar on humans, when applied directly to the lesions at
least 10 to 12 times daily. Furthermore, applicants have
discovered that the addition of lidocaine or a pharma-
ceutically acceptable salt thereof to the ethyl alcohol
significantly enhances the effectiveness of the drug.
Optionally, camphor may also be added to the formula-
tion.

Applicants are believed to be the first to discover that
ethyl alcohol can very successfully treat fever blisters
or cold sores on humans when applied directly to the
lesions at least 10 to 12 times daily, and preferably 2 to
3 times per hour during the first day of application of
the formulation. Although applicants believe the ethyl
alcohol to be effective without the addition of other
agents to treat fever blisters or cold sores, the preferred
formulation also includes lidocaine. Lidocaine (2-di-
ethylaminoacetyl-2 6-xylydide) is known for its prop-
erties as a topical local anesthetic and serves to reduce the
pain associated with the fever blister or cold sore lesions
while the ethyl alcohol acts to cause the lesions to heal
or go into remission. Also, camphor may be added to
the formulation and is an enhancement thereto due to its
known properties as a counter-irritant.

While a pharmaceutical formulation in accordance
with the present invention can vary, applicants pres-
ently contemplate that the formulation will comprise at
least 85% W/V (by weight per unit volume) of ethyl
alcohol, and lidocaine or a pharmaceutically acceptable

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salt thereof in a concentration of 0.5 to 10% W/V, and preferably about 1-2% W/V. Optionally, a concentration of 0.5 to 5% W/V, preferably about 1.5% W/V, of camphor may be added to the pharmaceutical formulation to enhance its counterirritant characteristics.

Although many formulations are possible of the pharmaceutical composition contemplated by the applicants, three preferred formulations are set forth below. All formulations are for 100 ml of topical treatment composition, and the weight per unit volume (W/V) of each element thereof is as follows:

Formulation 1	
Ethyl Alcohol	97.5%
Lidocaine	1.0%
Camphor	1.5%
Formulation 2	
Ethyl Alcohol	99.0%
Lidocaine	1.0%
Formulation 3	
Ethyl Alcohol	87.5%
Lidocaine	1.0%
Camphor	1.5%
Methylcellulose	10.0%

As will be noted above, Formulation 3 contains a thickening agent, methylcellulose, in order to render the pharmaceutical composition more gel-like than the liquid solutions of Formulations 1 and 2. As a matter of choice, the pharmaceutical formulation may be a liquid solution or, if desired, 5-15% W/V of a suitable thickening agent (such as methylcellulose) may be added to render the composition more gel-like. Whether the pharmaceutical composition of the invention is in liquid or gel form is a matter of choice, and the use of a thickening agent is conventional and known to those skilled in the art.

In use, the topical pharmaceutical formulation of the invention should be applied directly to the fever blister or cold sore lesion at least 10 to 12 times daily, and applications as often as every 20 minutes have yielded very good results with no reported adverse side effects. Normally topical application of the formulation should begin at the first signs of a lesion and continue at the rate of 1 to 3 applications per hour during waking hours until the lesion is completely eradicated. Although therapy should begin as early as possible, applicants have found that topical treatment of fully erupted fever blisters results in enhanced healing and thus believe that the formulation is effective when applied at any stage of lesion development.

After extensive testing on human subjects with varying types of vital lesions, applicants have found the pharmaceutical formulation of the invention to provide unexpected and surprisingly effective results in reducing pain and facilitating healing of lesions. Although intended primarily for fever blisters or cold sores, applicants have found the pharmaceutical formulation to be effective with Herpes virus infections and believe that the formulation would also be effective in healing lesions from other related vital-type infections.

Applicants have treated a number of human subjects with the pharmaceutical formulation and had surprisingly successful results in over 90% of the cases. In the study, the patients were initially seen at varying times after the appearance of fever blisters or cold sores and were advised to apply the pharmaceutical treatment of the invention directly to the lesion as often as possible in the morning, in the afternoon, and at night before going

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to bed. The results of the human case studies indicate that the pharmaceutical formulation, topically applied to lesions, is able to successfully treat fever blisters or cold sores and other vital infections in humans. Representative case studies are set forth below:

Human Case Studies

EXAMPLE 1

A 68 year old male started treatment with Formulation 1 at the first signs of an oral fever blister. The formulation was applied topically about 6 to 7 times per day and resulted in a complete remission of the lesion in 3 days.

EXAMPLE 2

A 38 year old male had Herpes Genitalis lesions on his penis. The pharmaceutical formulation (Formulation 2) was applied directly to the lesions 5 times daily, and complete remission was achieved in 4 days.

EXAMPLE 3

A 34 year old female who frequently experienced oral fever blisters was using a prescription formulation sold under the tradename ACYCLOVIR. The patient applied the pharmaceutical formulation of the invention (Formulation 1) as directed and reported complete remission of the lesions.

EXAMPLE 4

A 34 year old male had multiple lesions around the mouth wherein one or two of the lesions were fully erupted. The pharmaceutical formulation of the invention (Formulation 2) was applied as directed. At the end of day 1 the patient reported considerable comfort improvement, and at the end of day 3 a complete remission occurred.

EXAMPLE 5

A 55 year old female had two to three day old oral lesions. The pharmaceutical formulation (Formulation 1) was applied as directed, and complete remission occurred in two to three days.

EXAMPLE 6

A 60 year old male had chronic lesions and cracking of his lips for a period of 1 year, and his lips were reported to crack and bleed periodically. The pharmaceutical formulation (Formulation 2) was applied several times daily and relief was felt within several days and complete healing occurred in 30 days. Due to the severity of the case, the patient experienced burning from the ethyl alcohol in the formulation, but he continued to use the formulation with no adverse side effects and reported the formulation to be excellent.

EXAMPLE 7

An 84 year old male had Herpes Zoster ("shingles") condition for several months. The pharmaceutical formulation (Formulation 2) was applied 12-15 times daily, and the patient reported that the burning had stopped and the soreness and pain had been relieved over a period of 2.5 days. The patient reported spending about \$800.00 in the previous months in an unsuccessful effort to obtain relief for his condition.

It will be understood that various details of the invention may be changed without departing from the scope of the invention. Furthermore, the foregoing descrip-

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado: JUAN PABLO CADENA SARMIENTO

ASUNTO: Radicación No. 06-111945
Trámite 002
Evento 001
Actuación 430
Folios 10896

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Documentos estudiados:

Descripción: Folios 5 a 7 como se radicó inicialmente.
Reivindicaciones: Folios 8 a 9 como se radicó inicialmente.
Dibujos: Folios 6 a 6 como se radicó inicialmente.

Objeto de la Invención

Título de la invención:

Nueva presentación de una composición farmacéutica antiviral

Problema Técnico Planteado:

Formulación de un producto farmacéutico que contenga aciclovir como principio activo, que sea estable por periodos de tiempo prolongados, sin que pierda su actividad farmacéutica y que evite en lo posible la irritación de la piel del paciente a quien se aplica.

Solución:

Formulación farmacéutica en solución con atomizador para la aplicación tópica de aciclovir.

IPC: A61K 31/522

Análisis de la Solicitud de Patente

Descripción (Art 28 D 486)

Suficiencia:

La descripción no contiene la información suficiente para establecer la forma como se desarrolla la invención en cuanto a orden de adición de los componentes y metodología, de igual manera como esto se diferencia de otras composiciones presentes en el estado del arte.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Concisión

Los términos "aproximadamente", "alrededor de", utilizados para definir la composición de la Reivindicación 1 (Renglones 9 al 14) hacen que esta no sea

precisa, lo cual no permite realizar una comparación real con el estado de la técnica.

Es necesario que el solicitante defina los rangos de la composición a reivindicar pues sugiere de forma imprecisa muchas posibles variaciones o modificaciones.

De igual manera, los términos utilizados en la reivindicación 1 no definen la materia que se desea proteger ya que no involucran la característica esencial presente en la descripción la cual se corresponde a una solución con **atomizador** la cual esta descrita en la pagina 2 renglón 6. Es necesario que se introduzca esta característica en las reivindicaciones.

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de solicitud PCT 2004-04-05 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	US585379	Acyclovir antiviral gel composition	1996-12-17
D2	US5331012	Topical pharmaceutical preparation for fever blisters and other viral infections and method of use	1994-07-19
D3	EP0044543	Topical formulations of 9-(2-hydroxyethoxymethyl) guanine.	1980-10-15

Nivel Inventivo (Art18 D486)

La reivindicación 1 dice: "Nueva presentación de una composición farmacéutica antiviral en solución, que comprende como principio activo el **aciclovir** en una cantidad de aproximadamente el 5% en peso; un **solvente** en una cantidad de aproximadamente del 10 al 20% en peso; un agente **solubilizante** en una cantidad de aproximadamente 1.5 al 5.0% en peso; un agente **humectante** en una cantidad de aproximadamente del 2 al 10% en peso; un agente **antiprurítico** en una cantidad. de aproximadamente 0.05 al 1.0% en peso; un agente **antioxidante** en una cantidad de alrededor del 0.1 al 0.5% en peso; y, **agua** desmineralizada en una cantidad de alrededor del 20 al 80% en peso"

D1 es el estado de la técnica más cercano, porque describe establece una composición tópica que contiene **aciclovir** para el tratamiento de herpes simple, esta composición contiene 5% en peso del activo y una serie de componentes que le dan estabilidad a la formulación la cual es de tipo gel acuoso (columna 2-línea 45 -55).

Dentro de los componentes de la formulación se describen etanol (**solvente** o vehículo) en una cantidad de 20% en peso, NaOH (**agente solubilizante**) en una cantidad de 0.8%, glicerina (**humectante**) en una cantidad de 6.6%, Nipagin (preservante) en una cantidad de 0.2% y **agua** purificada en una cantidad de 66.6 % (Columna 3 – líneas 11-12 y 55, Columna 4-línea 10).

La composición objeto de esta reivindicación, se diferencia de la composición de D1, en que se encuentra en solución y que tiene como componente un agente antiprurítico.

El efecto logrado por la invención por esta diferencia es la composición en solución que tiene un efecto antiprurítico.

Así, el problema técnico objetivo a resolver es "¿Cómo generar una composición tópica de aciclovir en solución, con efecto antiprurítico?"

Por su parte, D2 establece una composición antiviral en solución para el tratamiento de los síntomas del herpes simple en donde uno de los componentes es alcanfor a una concentración de 0.5 a 5.0% (columna 3, línea 2 a 6, formulaciones 1 y 3) que ejerce una acción antiirritante (antiprurítica), junto con la acción conjunta de componente como analgésico (lidocaína) y etanol (Columna 2, línea 53 a 64).

Por lo tanto, para un experto medio en la materia, que tenga que generar una composición tipo solución de aciclovir como la propuesta en esta solicitud, que tenga los componentes presentes en D1 y busque una forma de generar un efecto antiprurítico, propuesto en D2, llegaría de manera obvia al contenido de las reivindicaciones objeto de la presente invención. Por lo anterior se concluye que las reivindicaciones 1 a 7 no tienen nivel inventivo.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

Item	Documento	Reivindicaciones Afectadas	Requisito que afecta
D1	<i>Acyclovir antiviral gel composition</i>	1-7	Nivel inventivo
D2	<i>Topical pharmaceutical preparation for fever blisters and other viral infections and method of use</i>	1-7	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

27 AGO. 2010

CONCEPTO TECNICO: 1622	EXAMINADOR TÉCNICO: Código:202093
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OK