

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

2020
Bogotá, D.C.,

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-033824- -00003-0000

Fecha: 2010-09-16 13:08:00 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 519 TRASLADOINFORME Folios: 1

Abogado
✓ **EMILIO FERRERO**

ASUNTO	Radicación	07-33824
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	2005
	Folios	006

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (Fase Nacional)	☒	Cap. I	☒ Cap. II ☐

No. Sol. Internacional	<u>PCT/EP2005/010026</u>
Fecha de Presentación Internacional	<u>16/09/2005</u>

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 le comunica:

1. Documentos estudiados

Descripción: Folios 52 a 61 modificado.

Reivindicaciones: Folios 62 y 63 modificado.

Prioridad: Folio 1 DE 102004049008.2 del 05/10/2004.

2. Objeto de la invención

Título: COMPOSICION FARMACEUTICA DE SIMPATOMIMETICOS ALFA CON ESTRUCTURA 2-IMIDAZOLINA.

Objeto: La invención consiste en una composición farmacéutica de simpaticomimético alfa con estructura de 2 imidazolina.

El problema planteado en la solicitud es proveer nuevas composiciones farmacéuticas de derivados de 2-imidazolina para el tratamiento de enfermedades víricas.

Para solucionar este problema técnico la solicitud proporciona nuevas composiciones farmacéuticas de compuestos de 2-imidazolina entre ellos oximetazolina.

EXP 2007 033824

Reivindicaciones 1 a 10: Composición farmacéutica de simpatomiméticos alfa con estructura de 2-imidazolina.

Se catalogó la invención según la IPC así: A61K 31/4174 y A61P 11/02

3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

En la reivindicación 1 la expresión "*simpatomimético alfa con estructura de 2-imidazolina*" es muy general y no es concisa.

Las reivindicaciones 2 a 7 caracterizan la composición farmacéutica por su uso, lo cual no le otorga ninguna característica adicional.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 05/10/2004, se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de publicación
D1	US 5854269	Nasal spray compositions	29/12/1998

5. Análisis de patentabilidad (artículo 14 D 486)

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial para establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Novedad: (artículo 16 D 486)

La reivindicación independiente (1) de la solicitud reclama una composición farmacéutica de simpatomiméticos alfa con estructura de 2-imidazolina.

La reivindicación 2 menciona la oximetazolina como un compuesto preferido con estructura de 2-imidazolina y las reivindicaciones 8 a 10 mencionan que el principio activo se encuentra en una solución acuosa con un tampón fosfato y cloruro de benalconio como conservante.

Las características **esenciales** de la composición de la reivindicación 1 y sus dependientes habían sido divulgadas previamente por D1, es decir composiciones acuosas de oximetazolina con tampón fosfato y cloruro de benalconio (ejemplos 1 a 5), por lo tanto las composiciones reclamadas en la presente solicitud no son novedosas.

6. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	US 5854269	1 a 10	Novedad

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 sesenta 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 SEP, 2010

CONCEPTO TECNICO No. 2940	EXAMINADOR TECNICO Código No. 202077
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de



US005854269A

United States Patent [19]
Haslwanter et al.

[11] **Patent Number:** **5,854,269**
[45] **Date of Patent:** **Dec. 29, 1998**

[54] **NASAL SPRAY COMPOSITIONS**
[75] **Inventors:** **Joseph A. Haslwanter**, Germantown;
William Rencher, Cordova, both of
Tenn.
[73] **Assignee:** **Schering-Plough Healthcare Products,**
Inc., Kenilworth, N.J.
[21] **Appl. No.:** **640,767**
[22] **PCT Filed:** **Nov. 17, 1994**
[86] **PCT No.:** **PCT/US94/12945**
§ 371 Date: **Aug. 5, 1996**
§ 102(e) Date: **Aug. 5, 1996**
[87] **PCT Pub. No.:** **WO95/13810**
PCT Pub. Date: **May 26, 1995**

[51] **Int. Cl.[°]** **A61K 31/355**
[52] **U.S. Cl.** **514/385**
[58] **Field of Search** **514/385**

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,114,979 5/1992 Kielley 514/783

Primary Examiner—Zohreh Fay
Attorney, Agent, or Firm—Arthur Mann; John J. Maitner

[57] **ABSTRACT**

An aqueous nasal decongestant composition containing oxy-
matazoline is disclosed which does not contain mercurial
preservatives.

8 Claims, No Drawings

NASAL SPRAY COMPOSITIONS

BACKGROUND OF THE INVENTION

This invention relates to an aqueous, topical, nasal decongestant composition containing oxymetazoline or a pharmaceutically acceptable salt thereof, an aqueous carrier which does not require undesirable mercurial anti-microbial agents.

Aqueous, topical, nasal decongestant compositions containing oxymetazoline hydrochloride, the longest acting nasal decongestant currently available, are applied to the nasal passages of mammals especially human beings to effect temporary relief of nasal congestion associated with colds, hay fever and sinusitis.

It is known that one of the most common complaints of patients and consumers that use nasal spray products is the drying and associated stinging within the nasal cavity. Other common nasal product negative attributes include odor and product taste. Additionally, due to the propensity of nasal products to become microbially contaminated, the use of a two preservative ingredient formulation is preferred.

It is also well known that aromatic ingredients, such as menthol, camphor and eucalyptol are used to promote the opening, draining and subsequent relief of sinus pressure in nasal spray products. Unfortunately, such ingredients are not soluble in water and require the addition of solubilizers to the formulation. It is also unfortunate that the required amount and solubilizers, such as Polysorbate 80 and alcohol solvents significantly adds to the associated unpleasant odor and stinging within the nasal cavity. It is also well known that the addition of surfactants, such as Polysorbate 80 greatly reduces the antimicrobial activity of benzalkonium chloride. As a result of this microbial activity reduction in benzalkonium chloride, other well known mercurial preservatives, such as thimerosal and phenyl mercuric acetate are reluctantly used.

A menthol flavored composition containing vapors of menthol, eucalyptol and camphor in addition to oxymetazoline hydrochloride and an aqueous carrier is currently available as an OTC product under the tradename AFRIN® Menthol Nasal Spray from Schering-Plough HealthCare Products, Liberty Corner, N.J. The aqueous carrier of this product contains benzalkonium chloride, glycerine, phenylmercuric acetate, sorbitol, polysorbate 80 and water.

The use of mercurial preservatives, e.g. phenylmercuric acetate, in nasal compositions, has been questioned and elimination of mercurial preservatives is desirable.

We have surprisingly discovered that incorporation of an aromatic alcohol, e.g. benzyl alcohol and phenyl ethyl alcohol, in menthol type nasal sprays containing oxymetazoline allows removal of the undesirable mercurial preservatives from the nasal spray compositions.

It has been discovered that the incorporation of benzyl alcohol in menthol type aromatic nasal sprays has generated benefits beyond what would be normally expected as "well known" within the formulation arts. It has been found that the characteristic odor of the aromatic alcohols is effectively covered by the menthol type odor. This resulted in the development of a product with a pleasant aromatic odor. It has also been discovered that the addition of aromatic alcohols allowed for the unexpected and desired reduction, and or elimination of required surfactants. As surfactants are also characterized as having an unpleasant odor this reduction contributed to a pleasant product odor. Furthermore, it has been unexpectedly discovered that the lower surfactant usage levels did not affect the microbial activity of benza-

lkonium chloride, allowing removal of mercurial preservatives and still maintain a preservative system based on two ingredients.

SUMMARY OF THE INVENTION

The present invention provides an aqueous, topical nasal, decongestant composition comprising an amount of oxymetazoline or a pharmaceutically acceptable salt thereof sufficient to effect nasal decongestion and an aqueous carrier which is free of mercurial preservatives.

The present invention also provides an aqueous, flavored, topical nasal decongestant composition comprising an amount of oxymetazoline or a pharmaceutically acceptable salt thereof sufficient to effect nasal decongestion and an aqueous carrier comprising:

- 70 to 90% by weight/volume of water;
- 0.10 to 5.00% by weight/volume of an aromatic alcohol;
- 0 to 0.3% by weight/volume of a non-mercurial anti-microbial preservative
- 0 to 10% by weight/volume of a moisturizing agent;
- 0 to 0.10% by weight/volume of an antioxidant;
- 0 to 2.00% by weight/volume of a surfactant;
- 0 to 0.75% by weight/volume of menthol;
- 0 to 0.15% by weight/volume of camphor;
- 0 to 0.15% by weight/volume of eucalyptol; and
- a sufficient amount of a pharmaceutically acceptable buffer to maintain the pH of the composition within the range of about 4.00-8.00;
- and QS water.

The present invention further provides a method of treating nasal congestion by administering to a nasal passage of a patient with nasal congestion an aqueous, topical nasal decongestant composition of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The novel nasal compositions of the present invention contain oxymetazoline and an aqueous carrier.

The amount of oxymetazoline or pharmaceutically acceptable salt thereof found sufficient to effect nasal decongestion is in the range of about 0.01% to about 0.1% by weight/volume of the topical nasal decongestant composition. Typically, 0.05% by weight/volume of oxymetazoline (as the HCl salt) is suitable for adults and children above five years of age. Oxymetazoline HCl is commercially available from Schering Labs, Kenilworth, N.J. See also The Merck Index, Tenth Edition, 1983 p. 6838. By the term "pharmaceutically acceptable salt" as used herein is meant the acid addition salt formed by admixing oxymetazoline with a pharmaceutically acceptable acid such as HCl, HF, H₂SO₄, HNO₃, malonic, succinic, trifluoroacetic acids and the like.

The compositions of the present invention contain an aromatic alcohol selected from the group consisting of benzyl alcohol and phenyl ethyl alcohol. The amount of aromatic alcohol present in the composition is from about 0.10 to 5.00% by weight/volume of the total composition. Ranges of 0.20-3.00% by weight/volume of the total composition are particularly suitable, and a range of 0.25 to 1.00% by weight/volume of the total composition being most preferable.

The compositions of the present invention may contain a surfactant, e.g. polysorbate 80. The amount of surfactant present in the composition is from about 0 to 2.00% by

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weight/volume of the total composition. Ranges of 0 to 1.50% by weight/volume of the total composition are particularly suitable, and a range of 0 to 1.25% by weight/volume of the total composition being most preferable.

The compositions of the present invention may contain moisturizing agents, e.g. propylene glycol. The amount of moisturizing agent present in the composition is from about 0 to 10.00% by weight/volume of the total composition. Ranges of 1.00 to 4.00% by weight/volume of the total composition are particularly suitable, and a range of 1.5 to 3.50% by weight/volume of the total composition being most preferable.

The compositions of the present invention may contain an antioxidant, e.g. disodium EDTA. The amount of antioxidant present in the composition is from about 0 to 0.10% by weight/volume of the total composition. Ranges of 0.01 to 0.05% by weight/volume of the total composition are particularly suitable, and a range of 0.015 to 0.030% by weight/volume of the total composition being most preferable.

The compositions of the present invention contains at least one antimicrobial preservative in the range of 0.01% to about 0.3% by weight/volume of the composition. Typical suitable preservatives function as antimicrobial agents and include the commercially available preservatives, e.g. benzalkonium chloride in the range of about 0.02 to about 0.025% by weight/volume.

The compositions of the present invention also include pharmaceutically acceptable buffers sufficient to adjust and maintain the pH of the compositions of the present invention in the range of about 4.0 to about 8.0, preferably about 5.5 to about 7.0 and 6.25 to 6.75 being most preferable. Typically suitable buffers include citrate, phosphate and glycine.

The nasal spray compositions of the present invention is manufactured in a conventional manner by thoroughly mixing the ingredients at ambient or elevated temperatures in order to achieve solubility of ingredients where appropriate.

All percentages are by weight/volume. The definitions of components whose chemical composition is not immediately clear from the name used, such as "Polysorbate 80", may be found in the CTEA Cosmetic Ingredients Dictionary, 4th Edition, 1991, published by Cosmetic Toiletry and Fragrance Association, Inc., Washington, DC.

The following examples describe in detail the invention. It will be apparent to those skilled in the art that modifications may be practiced without departing from the purpose and intent of this disclosure.

EXAMPLE 1

An aromatic nasal spray formulated with 2.2% solubilizing agent requiring a preservative system based on mercurial compounds to yield satisfactory microbial activity.

Ingredients	% Wt/Vol
Water USP purified	80.0000
Sorbitol (70% solution)	5.7100
Glycine USP (aminoacetic acid)	0.3747
Benzalkonium chloride (17% solution)	0.1169
Polysorbate 80 NF (Tween 80)	2.2000
L-Menthol USP	0.2000
Camphor USP (synthetic)	0.0400
Eucalyptol	0.0400
Phenylmercuric Acetate	0.0024
Oxymetazoline Hydrochloride USP	0.0500
Water USP purified	QS

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EXAMPLE 2

A satisfactorily preserved mercurial free aromatic nasal spray is formulated with 1.0% Benzyl alcohol enabling a 43.2% reduction in solubilizing agent.

Ingredients	% Wt/Vol
Water USP purified	80.0000
Sodium phosphate monobasic	0.5525
Sodium phosphate dibasic	0.0975
Disodium EDTA	0.0200
Benzyl alcohol	1.0000
Benzalkonium chloride (17% solution)	0.1177
Propylene glycol USP	3.5000
Polysorbate 80 NF (Tween 80)	1.2500
L-Menthol USP	0.1750
Camphor USP (Synthetic)	0.0300
Eucalyptol	0.0300
Oxymetazoline hydrochloride USP	0.0500
Water USP purified	QS

Method of Preparation

1. To any appropriate reaction container, add the following: sodium phosphate monobasic, sodium phosphate dibasic, disodium EDTA, benzyl alcohol and oxymetazoline hydrochloride to 70% of the water at a temperature of 50° C. Continue mixing the aqueous mixture while cooling to 30° C.
2. In a separate container, add with mixing the following: menthol, camphor, eucalyptol and Polysorbate 80 and continue to mix until all is in solution.
3. In a separate container, add 10% of the water and the propylene glycol and mix the solution at 30° C. for at least 5 minutes.
4. Transfer the solution of step 2 to the solution of step 3 and mix for at least 5 minutes.
5. Transfer the contents of step 4 into the aqueous mixture of step 1.
6. While mixing, add the benzalkonium chloride 17% solution to the aqueous mixture of step 5 and mix for at least 5 minutes.
7. Adjust the final batch volume with water, mix until uniform and then filter.

EXAMPLE 3

A satisfactorily preserved mercurial free aromatic nasal spray is formulated with 0.25% Benzyl alcohol enabling a 90.9% reduction in solubilizing agent.

Ingredients	% Wt/Vol
Water USP purified	80.0000
Sodium phosphate monobasic	0.5525
Sodium phosphate dibasic	0.0975
Disodium EDTA	0.0200
Benzyl alcohol	0.2500
Benzalkonium chloride (17% solution)	0.1177
Propylene glycol USP	1.5000
Polysorbate 80 (Tween 80)	0.1500
L-Menthol USP	0.0900
Camphor USP (Synthetic)	0.0300
Eucalyptol	0.0300
Oxymetazoline hydrochloride	0.0500
Water USP purified	QS

The procedure for preparation of this composition is as described in Example 2.