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2337/P

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00041828 00000001

Folios: 27

Fecha (AMD): 2000-08-23 13:48:06

Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 00041828

Solicitud de Patente en nombre de
McNEIL-PPC, Inc.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Santafé de Bogotá, en la carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad McNeil-PPC, Inc., solicitante de la patente de la referencia, anexo al presente memorial el siguiente documento:

Copia certificada de la solicitud de Patente Número 09/329,900 presentada en los Estados Unidos de América el día 10 de junio de 1999, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.

Señor Superintendente,



JIMENA ESCOBAR URIBE

C.C.39.779.452 de usaquén

T.P. 68228

Cód. 5376

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ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

Junio 08, 2000

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 09/329,900

Fecha de Presentación: Junio 10, 1999

Por la autoridad del
Comisionado de Patentes y Marcas

(fdo) P. SWAIN
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América.

REIVINDICACIONES

1.- Un método para proveer absorción incrementada de una amina farmacéuticamente aceptable en la sangre de un humano, caracterizado porque comprende proveer una dosificación farmacológicamente efectiva de una amina farmacéuticamente aceptable y una cantidad efectiva de un fármaco ácido antiinflamatorio no esteroidal en forma líquida estable.

2.- El método de conformidad con la reivindicación 1, caracterizado además porque la absorción incrementada es indicada por AUC_{1H} (exposición temprana de fármaco) que es por lo menos aproximadamente 10% mayor que la exposición temprana de fármaco de la misma amina a partir de un líquido de un solo ingrediente.

3.- El método de conformidad con la reivindicación 1, caracterizado además porque la absorción incrementada es indicada por AUC_{2H} (exposición temprana de fármaco) que es por lo menos aproximadamente 10% mayor que la exposición temprana de fármaco de la misma amina a partir de un líquido de un solo ingrediente.

4.- El método de conformidad con la reivindicación 1, caracterizado además porque la absorción incrementada es indicada por una C_{MAX} (concentración máxima) que es por lo menos aproximadamente 10%

mayor que la C_{MAX} de la misma amina a partir de un líquido de un solo ingrediente.

5.- El método de conformidad con la reivindicación 1, caracterizado además porque la forma líquida estable es una suspensión.

6.- El método de conformidad con la reivindicación 1, caracterizado además porque la amina es pseudoefedrina.

7.- El método de conformidad con la reivindicación 1, caracterizado además porque el fármaco antiinflamatorio no esterooidal es ibuprofeno.

8.- El método de conformidad con la reivindicación 6, caracterizado además porque la pseudoefedrina es provista en una escala de aproximadamente 15 mg a aproximadamente 60 mg por unidad de dosificación.

9.- El método de conformidad con la reivindicación 6, caracterizado además porque la pseudoefedrina es provista en una escala de aproximadamente 15 mg a aproximadamente 45 mg por unidad de dosificación.

10.- El método de conformidad con la reivindicación 7, caracterizado además porque el ibuprofeno es provisto en una cantidad de aproximadamente 40 mg a aproximadamente 800 mg por unidad de dosificación.

11.- El método de conformidad con la reivindicación 7, caracterizado además porque el ibuprofeno es provisto en una cantidad de

aproximadamente 40 mg a aproximadamente 300 mg por unidad de dosificación.

12.- El método de conformidad con la reivindicación 1, caracterizado además porque la amina es pseudoefedrina a aproximadamente 15 miligramos, y el antiinflamatorio no esterooidal es ibuprofeno provisto a un nivel de aproximadamente 100 miligramos por 6 ml.

13.- El método de conformidad con la reivindicación 1, caracterizado además porque el humano es un infante.

14.- Una composición que comprende una cantidad farmacológicamente efectiva de una amina farmacéuticamente aceptable y una cantidad farmacológicamente efectiva de un fármaco antiinflamatorio no esterooidal, dicha amina y dicho fármaco antiinflamatorio no esterooidal siendo provistos en una forma líquida estable.

15.- La composición de conformidad con la reivindicación 14, caracterizada además porque la forma líquida estable es una suspensión.

16.- La composición de conformidad con la reivindicación 14, caracterizada además porque el fármaco antiinflamatorio no esterooidal es ibuprofeno, y la amina farmacéuticamente aceptable es pseudoefedrina.

17.- La composición de conformidad con la reivindicación 16, caracterizada además porque el ibuprofeno es provisto a una dosificación de aproximadamente 100 miligramos, y la pseudoefedrina es provista a una dosificación de aproximadamente 15 miligramos por 6 ml.



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 08, 2000

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.**

APPLICATION NUMBER: 09/329,900

FILING DATE: June 10, 1999

**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**




P. SWAIN

Certifying Officer

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Please type a plus sign (+) inside this box → ☐

**UTILITY
PATENT APPLICATION
TRANSMITTAL**

(Form for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. MCP-226

First Named Inventor or Application Identifier
Cathy Klech Gelotte

Express Mail Label No. EL190925980US

U.S. PRO
09/329900
06/10/99

APPLICATION ELEMENTS
See MPEP Chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner
Box Patent Applications
Washington, DC 20231

1. ☒ Fee Transmittal Form (attached hereto in duplicate)

2. ☒ Specification [Total Pages 14]
(Preferred arrangement set forth below)

- Descriptive Title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R&D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

3. ☒ Drawing(s) (35 USC 113) [Total Sheets 3]

4. Oath or Declaration

- a. ☐ Newly executed (original or copy)
- b. ☒ Unexecuted original
- c. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional check boxes 5 and 16)
- i. ☐ Deletion of Inventor(s)
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).

5. ☐ Incorporation by Reference
(useable if Box 4c is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4c, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Microfiche Computer Program (Appendix)

7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)

- a. ☐ Computer Readable Copy
- b. ☐ Paper Copy (identical to computer copy)
- c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))

9. ☐ 37 CFR 3.73(b) Statement
(when there is an assignee) ☐ Power of Attorney

10. ☐ English Translation Document (if applicable)

11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations

12. ☐ Preliminary Amendment

13. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)

14. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)

15. ☐ Other:

16. ☐ If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:
Amend the specification by inserting before the first line: -- This is a ☐ Continuation ☐ Divisional
☐ Continuation-in-Part (CIP) of prior application No.: , filed -

17. For this divisional application, please cancel original Claims of the prior application before calculating the filing fee.

18. CORRESPONDENCE ADDRESS

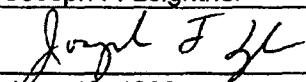
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19. TELEPHONE CONTACT

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Telephone: (732) 524-1214 Fax: (732) 524-2808

19. SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

NAME	Joseph F. Leightner	Reg. No. 34209
SIGNATURE		
DATE	June 10, 1999	

VIA EXPRESS MAIL NO. EL190924980
- MAILED JUNE 10, 1999

RAPIDLY ABSORBED LIQUID COMPOSITIONS

Field of the Invention

This invention relates to medicaments that contain a combination of an analgesic/anti-inflammatory acidic compound and a pharmacologically active amine. In a preferred embodiment the present invention is related to the combination of materials in a liquid dosage form.

Background of the Invention

Products which combine multiple pharmaceutically active ingredients are available commercially throughout the world. Consumers purchase these medicaments because they relieve several symptoms at the same time. For example, ibuprofen and pseudoephedrine are sold in combination in solid forms, such as tablets, capsules, and powders for re-constitution. Ibuprofen is an effective analgesic/antipyretic agent, whereas pseudoephedrine is an effective decongestant. The combination of these two active ingredients is particularly effective for relieving sinus headache, and symptoms of cold and flu. Ibuprofen and pseudoephedrine combinations are disclosed in US Patent 4,552,899.

While these products are known to be effective, consumers who use them are seeking faster symptom relief. Consequently, there continues to be a long felt need to develop products which bring rapid relief to the consumer.

Attempts have been made to improve the rate of onset of activity of various drugs by increasing their rates of absorption into the bloodstream following oral administration. For example, PCT application WO98/38983 discloses a method of improving the absorption rate of the analgesic, paracetamol, by combining it with sodium bicarbonate in a tablet or capsule formulation in a specific weight ratio. Irwin et. al. [J. Pharm. Sci. 58(3), March 1969] demonstrated enhanced absorption of the quaternary ammonium compound, isopropamide, when it was

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administered in combination with a large molar excess of trichloroacetate in solution. Meyer and Manning [Pharm. Res. 15(2), 1998] discuss the use of hydrophobic ion pairing to enhance the bioavailability of poorly lipid-soluble protein and peptide drugs.

5 It has now been found, unexpectedly, that the absorption rate of a pharmaceutically active amine (such as pseudoephedrine) is improved when the amine is formulated together with an acidic non-steroidal anti-inflammatory drug (such as ibuprofen) in a liquid medium.

Summary of the Invention

10 The present invention provides a method for enhancing the absorption of a pharmacologically active amine which comprises providing a pharmaceutically effective dose of the amine, and an effective dose of a non-steroidal anti-inflammatory agent together in a liquid medium to provide enhanced bio-absorption of the amine.

Description of the Drawings

15 Figure 1 shows the pharmacokinetic profiles for ibuprofen from liquid dosage forms.

20 Figure 2 shows the pharmacokinetic profiles for pseudoephedrine from liquid dosage forms.

25 Figure 3 shows the pharmacokinetic profiles for pseudoephedrine from solid dosage forms.

Detailed Description of the Invention

The nonsteroidal anti-inflammatory drugs, commonly referred to as NSAIDs, for use in the present invention are well known in the art. They may be selected from propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, and biphenylcarboxylic acid derivatives. Accordingly, the term NSAID as used herein is understood to mean any non-narcotic analgesic nonsteroidal anti-inflammatory compound, including pharmaceutically acceptable salts thereof which fall within the classes of compounds set forth above. The acceptable salts include sodium, potassium, arginine, lysine, and the like.

Specific examples of the propionic acid derivatives include ibuprofen, naproxen, naproxen sodium, fenoprefen, ketoprofen and the like. Suitable acetic acid derivatives include indomethacin, zomepirac, sulindac and the like. Suitable fenamic acid derivatives include mefenamic acid and meclofenamate sodium. Suitable biphenylcarboxylic acid derivatives include diflunisal and flufenisal. The preferred NSAIDs are ibuprofen, ketoprofen and naproxen. It is understood that aspirin is not included in the definition of NSAID as used in this invention.

The dosage of the NSAID will vary according to the potency of the specific compound. Therapeutic doses for these analgesics are well known in the art and can be found in the Physician's Desk Reference (Medical Economics Company, Montvale, NJ). The preferred dosage of NSAID is 40 - 800 milligrams of ibuprofen every 4 to 6 hours.

The pharmaceutically acceptable amines include primary, secondary and tertiary amines. Suitable pharmaceutically acceptable amines include pseudoephedrine, phenylpropanolamine, dextromethorphan, chlorpheniramine, diphenhydramine, loratadine, fexofenadine, and citirazine, famotidine, ranitidine, cimetidine and their pharmaceutically acceptable salts.

The dosage of the amine will vary according to the potency of the specific compound. Therapeutic doses for these analgesics are well known in the art and can

be found in the Physician's Desk Reference (Medical Economics Company, Montvale, NJ). The preferred dosage of amine is 15 to 60 milligrams of pseudoephedrine every 4 to 6 hours, with the preferred combination being 100 milligrams of ibuprofen and 15 milligrams of pseudoephedrine per 5 milliliter dosage.

5 The present invention contemplates the NSAID and the amine to be in any stable liquid form, which includes but is not limited to solutions, emulsions, dispersions, colloidal dispersions, suspensions, liquid-filled soft gelatin capsules, and the like. The liquids will employ suitable emulsifying, suspending, dispersing, stabilizing, or solubilizing agents and diluents that are well known in the art. As used herein, stable liquid forms are understood to be systems that maintain acceptable physical, chemical, and microbial properties for at least 30 days, preferably at least 12 months, and most preferably at least 24 months in ordinary pharmaceutical packaging under conditions encountered during normal distribution and storage of the liquid product.

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The NSAID will be dissolved or suspended, but preferably suspended, whereas the amine will be substantially dissolved in the liquid medium. As used herein, suspensions are understood to be a system in which small particles are more or less uniformly dispersed in a liquid medium. The suspensions will employ suitable suspending and dispersing agents that are well known in the art, see for example US Pat. No. 5,375,659 the contents of which are hereby incorporated by reference. Examples of such suspending materials include, but are not limited to, polycarbohydrates such as cellulose derivatives, starch and starch derivatives, xanthan gum, carageenan, locust bean gum, and the like, wetting agents such as sodium laurel sulfate and alkyl polyoxyethylene sulfates; sulfonates such as quaternary ammonium compounds; nonionic materials such as polyoxyethylene fatty alcohol ethers, sorbitan fatty esters and polyoxyethylene sorbitan fatty acid esters. A preferred system as disclosed in US Pat. No. 5,374,659, is comprised of xanthan gum, pregelatinized starch and polyoxyethylene monooleate. Further agents are set

forth in Remington's Pharmaceutical Sciences, 15th Edition, Osal and Hoover Editors, 1975.

5 The suspending agents are employed at levels of from about 0.1 to about 5 weight percent, preferably from about 0.25 to about 3 and most preferably from about 0.5 to about 2 weight percent. Water is the preferred solvent system, although any pharmaceutically acceptable solvent may be employed.

10 The compositions of the present invention may also contain, in addition to the NSAID and amine components, other pharmaceutically active ingredients including antihistamines, decongestants, antitussives, and expectorants. Typically these pharmaceutically active ingredients are provided in their effective dosages which are known, see for example US Pat. 4,552,889.

15 The compositions of the present invention have an increased drug exposure of the amine to humans at early times after dosing, when compared with other amine compositions. Early drug exposure is measured by the area under the blood, plasma, or serum concentration curve from when the drug is swallowed until 1 or 2 hours later (AUC 1H or AUC 2H). Total drug exposure is the area under the curve that is extrapolated to infinite time (AUC INFINITY). A comparative study has demonstrated an increased early amine exposure (AUC 1H and AUC 2H) with respect to that obtained in absence of an effective amount of an NSAID in the liquid form.

20 The compositions of the present invention give an early amine exposure in the consumer's bloodstream for the first hour (AUC 1H) that is about 10% higher, preferably more than about 40% higher, and most preferably more than about 80% higher than the early drug exposure of the same amine from a single-ingredient liquid product. Furthermore, compositions of the present invention give an early amine exposure in the consumer's bloodstream for the first 2 hours (AUC 2H) that is about 10% higher, preferably more than about 20% higher, and most preferably more than about 40% higher than the early drug exposure of the same amine from a single-ingredient liquid product.

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Furthermore, compositions according to the present invention have an increased CMAX, where CMAX is the maximum concentration of the amine in blood, plasma, or serum, that occurs sooner when compared with other amine liquid compositions. This change also indicates the increased rate or enhancement of absorption of the pharmaceutically acceptable amine, as compared with amines in the absence of the NSAID. The compositions of the present invention give a maximum concentration of amine in the consumer's bloodstream about 10% higher, preferably more than about 12.5% higher, and most preferably more than about 15% higher than the maximum concentration of the same amine from a single-ingredient liquid product.

Furthermore, the compositions according to the present invention provide total amine exposure (AUC INFINITY) that is equal to that provided by amines in the absence of the NSAID, indicating that there is no decrease in the overall extent of absorption of the pharmaceutically acceptable amine.

Without wishing to be bound by any theory, the present invention is believed to function due to the formation of an ion pair in the liquid medium. This ion pairing apparently does not form with solid dosage forms. The ion pair enables the amine drugs to be delivered more efficiently and rapidly to the bloodstream, thus providing higher early drug exposure and higher maximum concentrations sooner compared with the amine in the absence of the NSAID in the liquid form or with the amine in the presence of the NSAID in a solid form. The present invention, therefore, will provide the consumer with a faster onset of activity for the pharmacologically active amine.

The following examples are provided to further illustrate the claimed invention, but not limit the invention to the examples provided below. As used herein mg is understood to mean milligrams, ng is understood to mean nanograms, kg is understood to be kilograms and ml is understood to be milliliters.

Example 1

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Twenty-four healthy subjects, 10 men and 14 women, ages 18 through 55 years, were included in a study. Subjects crossed over three treatments, and the study periods were separated by a minimum of one week for drug washout. They reported to the clinical site the evening before each study period, and remained cloistered until after the last blood sample was collected 14 hours after dosing.

Treatment A was one dose of test suspension, consisting of 7.5 mg/kg ibuprofen and 1.125 mg/kg pseudoephedrine HCl (ingredients provided in Table 1) prepared as disclosed in US Patent 5,621,005, example 1, additionally with pseudoephedrine HCl added after the ibuprofen addition step. Treatment B was one dose of Children's Motrin® Ibuprofen Suspension, (McNeil Consumer Healthcare) consisting of 7.5 mg/kg ibuprofen. Treatment C was one dose of Children's Sudafed® Nasal Decongestant Liquid (Warner Lambert), consisting of 1.125 mg/kg pseudoephedrine.

Table 1

Treatment A Suspension Formula

<u>Ingredients</u>	<u>(% w/v)</u>
Glycerin USP	10.0
Xanthan Gum NF	0.18
Pregelatinized Starch	1.5
Sucrose NF	35.0
Colors	0.0038
Polysorbate 80 NF	0.05
Artificial Flavors	0.893
Ibuprofen USP	2.0
Pseudoephedrine HCL USP	0.30
Sodium Benzoate NF	0.20
Citric Acid USP	0.18
Purified Water USP	64.2

After an overnight fast, subjects swallowed the product and drank six fluid ounces of water immediately. Seven milliliters of blood were before dosing and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 14 hours after dosing. Plasma was removed from the blood samples, and was quantified for ibuprofen and pseudoephedrine separately using two specific high-performance liquid chromatography (HPLC) methods.

The following single-dose pharmacokinetic parameters for ibuprofen and pseudoephedrine in plasma were determined using noncompartmental methods: early drug exposure up to 1 hour (AUC 1H), early drug exposure up to 2 hours (AUC 2H), area under the plasma concentration-time curve extrapolated to infinity (AUC INFINITY), and peak plasma concentration (C_{MAX}). The speed or rate of drug absorption are reflected by AUC 1H, AUC 2H, and C_{MAX}.

Ibuprofen and pseudoephedrine parameter means were analyzed separately creating a three-period, two-treatment crossover. Means for the combination product and either ibuprofen or pseudoephedrine alone were compared by analysis of variance (ANOVA). From the ANOVA, statistically significant differences in means are detected for p values less than 0.05.

Mean profiles of ibuprofen plasma concentrations over time for the ibuprofen-pseudoephedrine combination suspension and the Motrin[®] suspension are shown in Figure 1. They are similarly shaped and virtually superimposable, indicating no change in ibuprofen absorption rate when combined with an amine. Mean profiles of pseudoephedrine for the ibuprofen-pseudoephedrine combination suspension and the Sudafed[®] liquid are shown in Figure 2. The amine was absorbed at a faster rate from the combination suspension than from the marketed liquid, which is reflected by a steeper slope and higher peak concentration. This observation was unexpected, because pseudoephedrine is dissolved as the hydrochloride salt in the liquid vehicle of both products.

Results from the data analysis for pseudoephedrine are summarized in Table 2, which clearly demonstrate that the amine's absorption rate was enhanced by ibuprofen in the liquid dosage form. The example composition of the present invention increased the early amine exposure in humans by 93% over the first hour (AUC 1H) and by 54% over the first two hours (AUC 2H) when compared with the single-ingredient, amine liquid product. This difference was highly statistically significant, as both p values were equal to 0.0001. In addition, the average pseudoephedrine concentration in plasma from the combination liquid product peaked 18% higher and occurred one hour earlier when compared with Sudafed[®] liquid. Both of the latter differences were statistically significant.

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TABLE 2. Pseudoephedrine (PSE) Study Results

Parameters	SUDAFED® Liquid	IBU-PSE Suspension	Percent Difference	ANOVA p value
AUC up to 1 hour (ng·h/mL)	83.6	161.6	+ 93 %	0.0001
AUC up to 2 hours (ng·h/mL)	299	461	+ 54 %	0.0001
AUC INFINITY (ng·h/mL)	2633	2614	- 1 %	NS
C _{MAX} (ng/mL)	273	322	+ 18 %	0.0001

NS = not statistically significant

Comparative Example 2

Twenty-four healthy men, ages 18 through 50 years, were included in a study. Subjects crossed over four treatments, and the study periods were separated by a minimum of one week for drug washout. They reported to the clinical site the evening before each study period, and remained cloistered until after the last blood sample was collected 24 hours after dosing.

Treatment A was one combination tablet containing 200 mg ibuprofen and 30 mg pseudoephedrine. Treatment B was one Nuprin® tablet (Bristol-Meyers), containing 200 mg ibuprofen, plus one Sudafed® tablet (Warner Lambert), containing 30 mg pseudoephedrine. Treatment C was one Nuprin® tablet (Bristol-Meyers), containing 200 mg ibuprofen. Treatment D was one Sudafed® tablet (Warner Lambert), containing 30 mg pseudoephedrine.

After an overnight fast, subjects swallowed the product and drank 200 ml of water immediately. Eight milliliters of blood were collected before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours after dosing. Plasma was removed from the blood samples and was quantified for ibuprofen and pseudoephedrine separately using high-performance liquid chromatography and gas chromatography methods, respectively.

The following single-dose pharmacokinetic parameters for ibuprofen and pseudoephedrine in plasma were determined using noncompartmental methods: early drug exposure up to 1 hour (AUC 1H), early drug exposure up to 2 hours
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(AUC 2H), area under the plasma concentration-time curve extrapolated to infinity (AUC INFINITY), and peak plasma concentration (C_{MAX}). The speed or rate of drug absorption is reflected by AUC 1H , AUC 2H, and C_{MAX}.

Ibuprofen and pseudoephedrine parameter means were analyzed separately creating a four-period, three-treatment crossover. Means for the combination product and either ibuprofen or pseudoephedrine alone were compared by analysis of variance (ANOVA). From the ANOVA, statistically significant differences in means are detected for p values less than 0.05.

Mean profiles of pseudoephedrine for the ibuprofen-pseudoephedrine combination tablet and for the Sudafed[®] tablet dosed alone and with a NUPRIN[®] tablet are shown in Figure 3. They are similarly shaped and virtually superimposable, indicating that ibuprofen did not change the absorption rate of pseudoephedrine when formulated in a solid dosage form.

Results from the data analysis for pseudoephedrine are summarized in Tables 3 and 4, which clearly demonstrate that the amine's absorption rate was not affected by ibuprofen when formulated as a tablet. There were no statistically significant differences between any of the following means: AUC 1H , AUC 2H, AUC INFINITY, and C_{MAX}.

TABLE 3. Pseudoephedrine (PSE) Study Results Comparing Treatments A and B

Parameters	SUDAFED [®] Tablet (NUPRIN)	IBU-PSE Tablet	Percent Difference	ANOVA p value
AUC up to 1 hour (ng·h/mL)	43.8	43.2	- 1 %	NS
AUC up to 2 hours (ng·h/mL)	136	140	+ 4 %	NS
AUC INFINITY (ng·h/mL)	1111	1203	+ 8 %	NS
C _{MAX} (ng/mL)	102	107	+ 5 %	NS

NS = not statistically significant

SECRET

NS = not statistically significant

We claim:

1. A method for providing enhanced absorption of a pharmaceutically acceptable amine into the blood of a human comprising providing a pharmacologically effective dosage of a pharmaceutically acceptable amine and an effective amount of a nonsteroidal anti-inflammatory acidic drug in a stable liquid form.
2. The method of claim 1 wherein the enhanced absorption is indicated by AUC_{1H} (early drug exposure) that is at least about 10% higher than the early drug exposure of the same amine from a single-ingredient liquid.
3. The method of claim 1 wherein the enhanced absorption is indicated by AUC_{2H} (early drug exposure) that is at least about 10% higher than the early drug exposure of the same amine from a single-ingredient liquid.
4. The method of claim 1 wherein the enhanced absorption is indicated by a C_{MAX} (maximum or peak concentration) that is at least about 10% greater than the C_{MAX} of the same amine from a single-ingredient liquid.
5. The method of claim 1 wherein the stable liquid form is a suspension.
6. The method of claim 1 wherein the amine is pseudoephedrine.
7. The method of claim 1 wherein the nonsteroidal anti-inflammatory drug is ibuprofen.
8. The method of claim 6 wherein the pseudoephedrine is provided in a range from about 15 mg to about 60 mg per dosage unit.
9. The method of claim 6 wherein the pseudoephedrine is provided in a range from about 15 mg to about 45 mg per dosage unit.
10. The method of claim 7 wherein the ibuprofen is provided in an amount of from about 40 mg to about 800 mg per dosage unit.

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11. The method of claim 7 wherein the ibuprofen is provided in an amount of from about 40 mg to about 300 mg per dosage unit.
12. The method of claim 1 wherein the amine is pseudoephedrine at about 15 milligrams and the nonsteroidal anti-inflammatory is ibuprofen provided at a level at about 100 milligrams per 5 mL.
13. The method of claim 1 wherein the human is a child.
14. A composition comprising a pharmacologically effective amount of a pharmaceutically acceptable amine and a pharmacologically effective amount of a nonsteroidal anti-inflammatory drug, said amine and nonsteroidal anti-inflammatory drug are provided in a stable liquid form.
15. The composition of claim 14 wherein the stable liquid form is a suspension.
16. The composition of claim 14 wherein the nonsteroidal anti-inflammatory drug is ibuprofen and the pharmaceutically acceptable amine is pseudoephedrine.
17. The composition of claim 16 wherein the ibuprofen is provided at dosage of about 100 milligrams and the pseudoephedrine is provided at a dosage of about 15 milligrams per 5 mL.

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[illegible]

VIA EXPRESS MAIL NO. EL190924980
MAILED JUNE 10, 1999

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Prior Foreign Application(s):

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No. Filing Date Status

Application Serial No. Filing Date Status

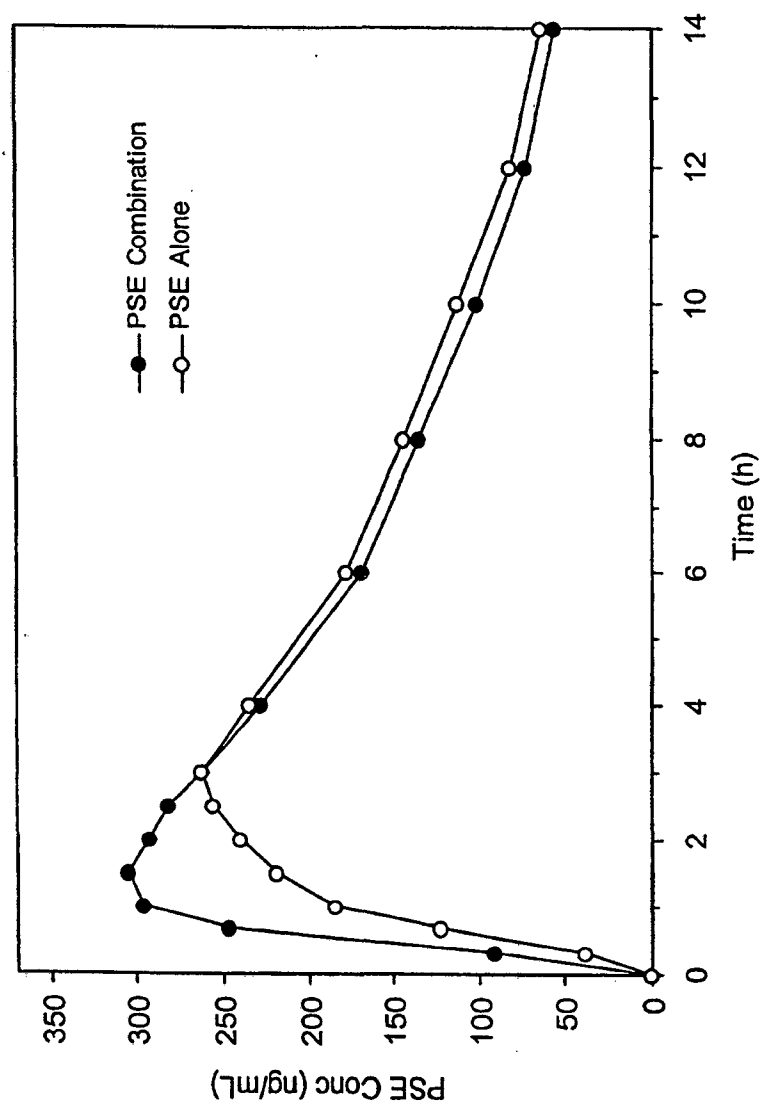
I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith as well as to file equivalent patent applications in countries foreign to the United States including the filing of international patent applications in accordance with the Patent Cooperation Treaty: Audley A. Ciamporcero, Jr. (Reg. #26,051), Steven P. Berman (Reg. #24,772), Andrea L. Colby (Reg. #30,194), Michael Stark (Reg. #32,495), and Joseph F. Leightner (Reg. #34,209), One Johnson & Johnson Plaza, New Brunswick, NJ 08933.

Address all telephone calls to Joseph F. Leightner at telephone no. (732) 524-1214.

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FIGURE 2



Espero con esto haber dado cabal cumplimiento a lo solicitado por ese despacho. De no ser así me acojo al plazo de prórroga establecido en el artículo 22 de la Decisión 344 de la Comisión de Acuerdo de Cartagena y atentamente solicito que se me indique cuáles son los requisitos faltantes. En caso de que la anterior respuesta no se adecue técnica o jurídicamente al requerimiento, solicito atentamente que ese despacho proceda de

REIVINDICACIONES

1. Un método para proveer absorción incrementada de una amina farmacéuticamente aceptable en la sangre de un humano, caracterizado porque comprende proveer una dosificación farmacológicamente efectiva de una amina farmacéuticamente aceptable y una cantidad efectiva de un fármaco ácido antiinflamatorio no esteroidal en forma líquida estable.
2. El método de conformidad con la reivindicación 1, caracterizado además porque la absorción incrementada es indicada por AUC 1H (exposición temprana de fármaco) que es 10% mayor que la exposición temprana de fármaco de la misma amina a partir de un líquido de un solo ingrediente.
3. El método de conformidad con la reivindicación 1, caracterizado además porque la absorción incrementada es indicada por AUC 2H (exposición temprana de fármaco) que es 10% mayor que la exposición temprana de fármaco de la misma amina a partir de un líquido de un solo ingrediente.
4. El método de conformidad con la reivindicación 1, caracterizado además porque la absorción incrementada es indicada por una CMAX (concentración máxima) que es 10% mayor que la CMAX de la misma amina a partir de un líquido de un solo ingrediente.
5. El método de conformidad con la reivindicación 1, caracterizado además porque la forma líquida estable es una suspensión.
6. El método de conformidad con la reivindicación 1, caracterizado además porque la amina es pseudoefedrina.

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7. El método de conformidad con la reivindicación 1 caracterizado además porque el fármaco antiinflamatorio no esterooidal es ibuprofeno.
 8. El método de conformidad con la reivindicación 6, caracterizado además porque la pseudoefedrina es provista en una escala de 15 mg a 60 mg por unidad de dosificación.
 9. El método de conformidad con la reivindicación 6, caracterizado además porque la pseudoefedrina es provista en una escala de 15 mg a 45 mg por unidad de dosificación.
 10. El método de conformidad con la reivindicación 7, caracterizado además porque el ibuprofeno es provisto en una cantidad de 40 mg a 800 mg por unidad de dosificación.
 11. El método de conformidad con la reivindicación 7, caracterizado además porque el ibuprofeno es provisto en una cantidad de 40 mg a 300 mg por unidad de dosificación.
 12. El método de conformidad con la reivindicación 1, caracterizado además porque la amina es pseudoefedrina a 15 miligramos, y el antiinflamatorio no esterooidal es ibuprofeno provisto a un nivel de 100 miligramos por 6 ml.
 13. El método de conformidad con la reivindicación 1, caracterizado además porque el humano es un infante.
 14. Una composición que comprende una cantidad farmacológicamente efectiva de una amina farmacéuticamente aceptable y una cantidad farmacológicamente efectiva de un fármaco antiinflamatorio no esterooidal, dicha amina y dicho fármaco antiinflamatorio no esterooidal siendo provistos en una forma líquida estable.
 15. La composición de conformidad con la reivindicación 14, caracterizada además porque la forma líquida estable es una suspensión.

16. La composición de conformidad con la reivindicación 14, caracterizada además porque el fármaco antiinflamatorio no esteroidal es ibuprofeno, y la amina farmacéuticamente aceptable es pseudoefedrina.
17. La composición de conformidad con la reivindicación 16, caracterizada además porque el ibuprofeno es provisto a una dosificación de 100 miligramos, y la pseudoefedrina es provista a una dosificación de 15 miligramos por 6 ml.

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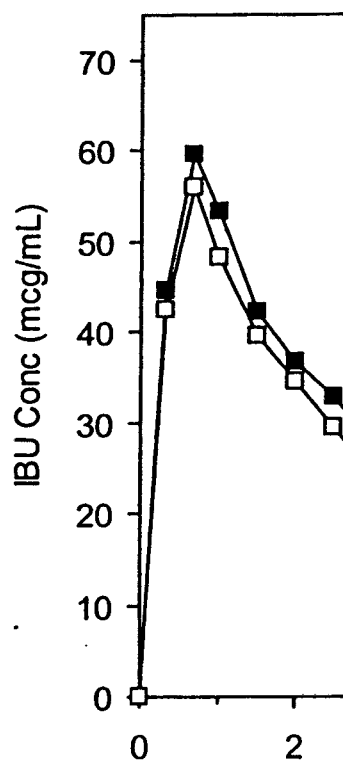
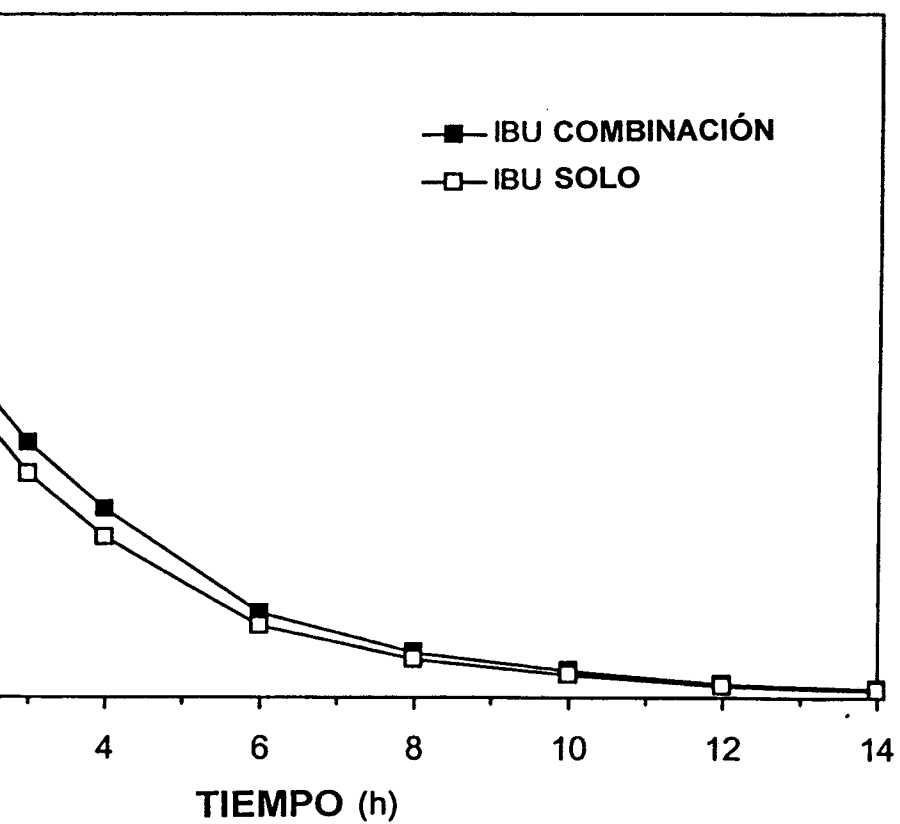


FIGURA 1



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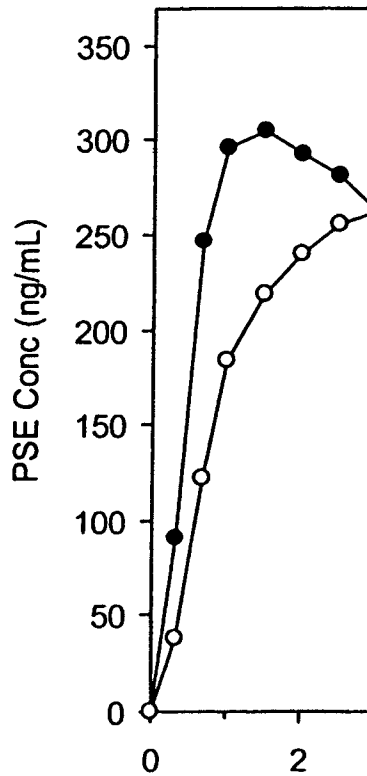
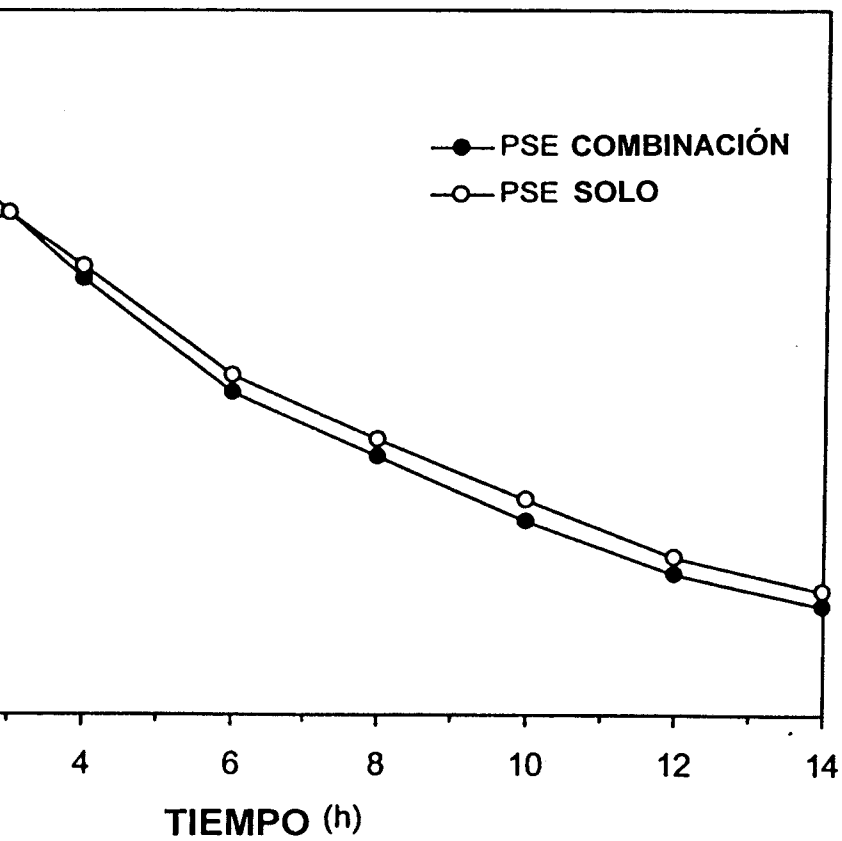


FIGURA 2



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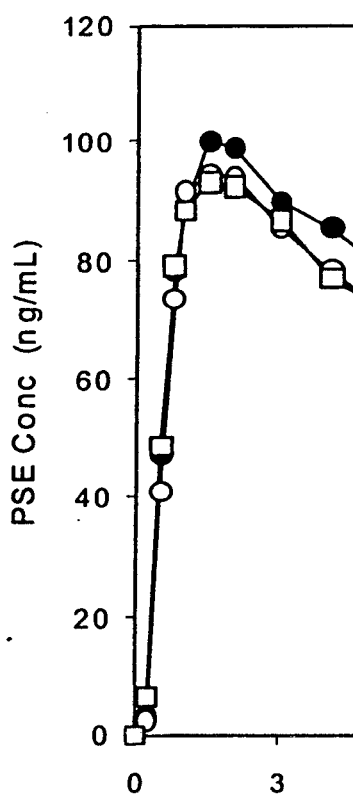
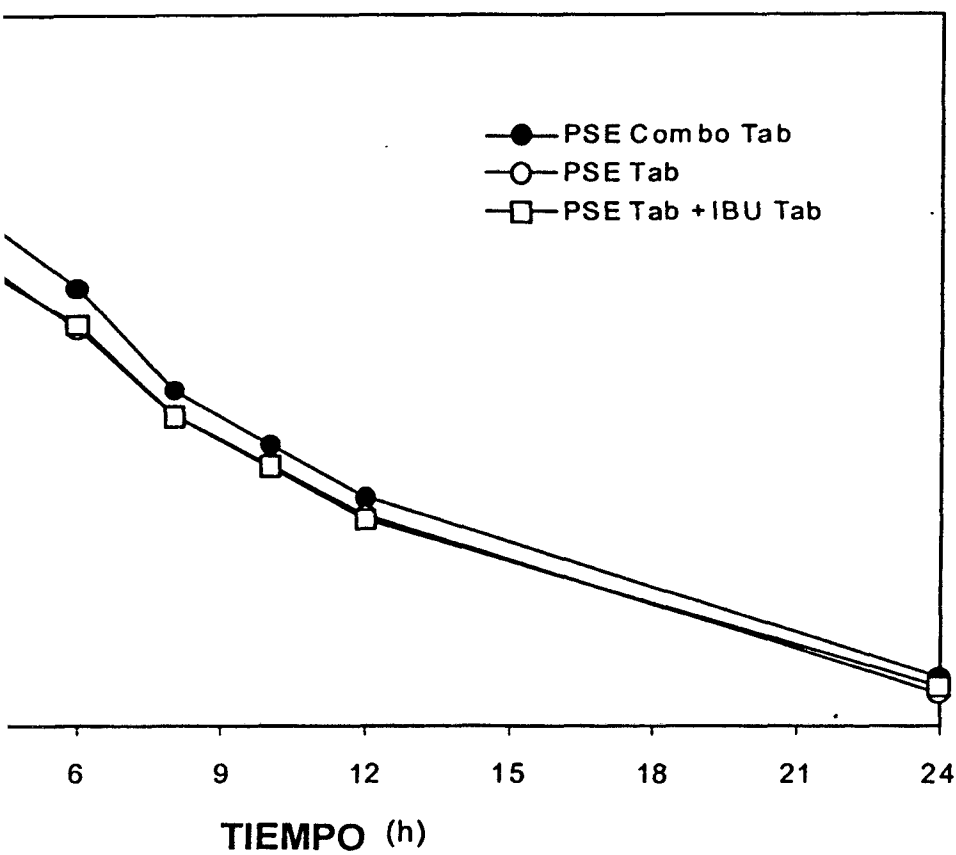


FIGURA 3



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**EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCION**

**Industria y Comercio
SUPERINTENDENCIA**

(21) No. SOLICITUD:

(51) INT. CL.: A 61

(22) FECHA DE
PRESENTACIÓN:

(71) SOLICITANTE: MCNEIL - PPC, INC.
domiciliado en Skillman, New Jersey, E.U.A.

(30) PRIORIDAD: SÍ

(31) No. DE SOLICITUD: 09/329900

(72) INVENTORES: CATHY CLECH GELOTTE (North
Wales, Pennsylvania, E.U.A.); JOANNA F. HILLS
(Glenside, Pennsylvania, E.U.A.); CHARLES E.
PENDLEY, II (Abington, Pennsylvania, E.U.A.);
MANOJ N. SHAH (Norristown, Pennsylvania, E.U.A.).

(32) FECHA DE
PRESENTACIÓN: Junio 10, 1999

(33) PAÍS: ESTADOS UNIDOS DE AMÉRICA.

(74) APODERADO: JIMENA ESCOBAR URIBE

(54) TÍTULO: MÉTODO PARA PROVEER ABSORCIÓN INCREMENTADA DE UNA AMINA FARMA-
CÉUTICAMENTE ACEPTABLE EN LA SANGRE DE UN HUMANO Y COMPOSICIÓN
QUE COMPRENDE UNA AMINA FARMACÉUTICAMENTE ACEPTABLE Y UN FÁR-
MACO ANTIINFLAMATORIO NO ESTEROIDAL.

(57) RESUMEN:

La presente invención se refiere a un método para proveer absorción incrementada de una amina farmacéuticamente aceptable en la sangre de un humano, caracterizado por que comprende suministrar una dosis farmacológicamente efectiva de una amina farmacéuticamente aceptable y una cantidad efectiva de un fármaco ácido antiinflamatorio no esterooidal en forma líquida estable.

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(21)		Resumen (57) <i>La presente invención se relaciona con un método para proveer absorción incrementada de una amina farmacéuticamente aceptable en la sangre de un humano, caracterizado por que comprende suministrar una dosis farmacológicamente efectiva de una amina farmacéuticamente</i>
(22)		
(31) 09/329900		
(32) Junio 10, 1999		
(33) ESTADOS UNIDOS DE AMÉRICA		
(51) A 61		
(74) JIMENA ESCOBAR URIBE		
(72) CATHY CLECH GELOTTE //		
JOANNA F. HILLS // CHARLES E. PENDLEY III // MANOJ N. SHAH.		te efectiva de una amina farmacéuticamente
(71) McNEIL - PPC, INC. (Skillman, New Jersey, Estados Unidos de América).		
(54) TITULO: MÉTODO PARA PROVEER ABSORCIÓN INCREMENTADA DE UNA AMINA FARMACÉUTICAMENTE ACEPTABLE EN LA SANGRE DE UN HUMANO Y COMPOSICIÓN QUE COMPRENDE UNA AMINA FARMACÉUTICAMENTE ACEPTABLE Y UN FÁRMACO ANTIINFLAMATORIO NO ESTEROIDAL.		

te aceptable y una cantidad efectiva de un fármaco ácido antiinflamatorio no esterooidal en forma líquida estable.