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DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



Fecha: ... CREACIONES
NACIONALES

Trámite : 011 Evento : 379 Actuación : 444

Referencia : Expediente No. 04010954

Asunto : Solicitud de patente para: **FORMULACION DE MEDICAMENTO QUE CONTIENE UN AGONISTA DE LTB4**

Solicitante : **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG**

Fecha de Solicitud : 10 de febrero de 2004

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. **10205** notificado por fijación en lista del 24 de agosto de 2007.

2. Mediante mi memorial de fecha 16 de noviembre de 2007 solicité un plazo de 30 días para atender el Oficio No. **10205**.

3. Mediante el Oficio No. **10205** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente.

Atiendo a las observaciones de la manera siguiente:

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3.1 CLARIDAD DE LA SOLICITUD Y REIVINDICACIONES DE USO.

Para subsanar las objeciones que sobre claridad y por incluir reivindicaciones de uso hizo su Despacho, presento nuevo pliego reivindicatorio con 17 reivindicaciones en el cual se han hecho cambios que permiten apreciar claramente el objeto reivindicado en la presente solicitud de patente. Las modificaciones al capítulo reivindicatorio fueron las siguientes:

- El número de compuestos, es decir, el listado de posibles sustituyentes en los compuestos reivindicados se ha limitado de acuerdo con el sustento descriptivo.
- Las nuevas reivindicaciones 2 a 15 se han redactado de tal forma que especifican y delimitan características particulares de la formulación farmacéutica de la reivindicación independiente 1.
- Las reivindicaciones 18 y 19 que reclamaba el uso de las tabletas han sido eliminadas de éste pliego reivindicatorio.
- Por otra parte, respetuosamente ponemos de presente que el objeto de la presente invención son formulaciones farmacéuticas de un comprimido que tienen el mismo núcleo. Por lo tanto, toda vez que el título **"FORMULACIÓN DE MEDICAMENTO QUE CONTIENE UN AGONISTA DE LTB4"** indica con claridad el producto objeto de la invención, el mismo cumple con los requisitos de claridad.
- Finalmente, respetuosamente ponemos de presente al Despacho que si bien comprendemos que el mismo es autónomo en cuanto al estudio de patentabilidad se refiere, el pliego reivindicatorio de la presente invención ha sido motivo de patente en Europa (Nº concesión: EP-1408943-B1), país que comparte las normas de patentabilidad.

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De esta manera es claro que con las anteriores modificaciones del capítulo reivindicatorio quedan subsanadas las objeciones que por claridad y por incluir reivindicaciones de uso hizo su Despacho, ya que ahora, dicho pliego reivindica un producto en los términos sugeridos por su Despacho y permite determinar el alcance de la protección reivindicada y compararla frente al estado del arte, de acuerdo con las disposiciones de los artículos 14 y 30 de la Decisión 486.

3.2 NOVEDAD

Ese Despacho afirma que el documento **D1** afecta la novedad de la presente solicitud, con lo cual estamos en desacuerdo, toda vez que las características técnicas de la invención de mi representada no estaban previamente descritas en dicho documento, tal y como lo demuestra el Informe de Examen Preliminar Internacional elaborado por la Oficina Europea de Patentes (Anexo. 6.2), en donde si bien dicho documento es citado como anterioridad, la novedad y el nivel inventivo de la presente solicitud es reconocida gracias a que el uso de un surfactante no se encontraba revelado en dicho documento ni sugerido en el mismo de tal manera que el mismo pudiera resultar obvio y/o evidente para un técnico medio en la materia.

4. Por lo tanto, le solicito se sirva continuar con el trámite de la presente solicitud pues las reivindicaciones se presentan de una forma clara. A pesar que las objeciones que sobre claridad planteó ese Despacho en el Oficio No. **10205** se deben tener por superadas, en el evento que el Despacho considere que sea necesario, respetuosamente le solicito hacer uso de la facultad que le otorga el artículo 45 inciso 2. de la Decisión 486 de la Comisión de la Comunidad Andina a efecto de requerir nuevamente de nuestra parte cualquier complementación o aclaración que considere necesaria.

5. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

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6. Anexos:

- 6.1 Nuevo pliego reivindicatorio con 17 reivindicaciones;
- 6.2 Copia del Informe de Examen Preliminar Internacional en español;
- 6.3 Formulario para modificaciones;
- 6.4 Recibo por valor de \$99.000 por concepto de modificaciones en solicitud pendiente.

Bogotá,
Señora Jefe,



EMILIO FERRERO

T.P.A. No. 31.929

COLO-13736-841-023-9
NNJ\NNJ\ID-115676\WPC13736
No. M-2007-115676\NNJ

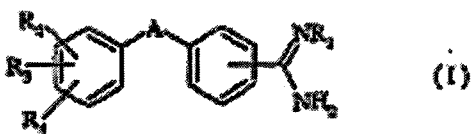
FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG. Sociedad constituida y existente bajo las leyes de Alemania. Dirección: Binger Strasse 173, 55216 Ingelheim, Alemania Domicilio: Ingelheim, Alemania Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019</u> TP <u>31.929</u>
4	Número de expediente: <u>04.010.954</u>	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 17 reivindicaciones con el fin de subsanar las objeciones hechas por Su Despacho a la presente solicitud de Patente y solicito respetuosamente que el examen de patentabilidad sea realizado sobre este nuevo pliego reivindicatorio.	
6	Comprobante de pago No. <u>07,100,283</u> Fecha: <u>10 de diciembre de 2007</u>	
7	Anexos ☒ Comprobante de pago de la tasa por \$99.000.00 por concepto de modificaciones. ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO FIRMA:  C.C. 438.019 de Usaquén T.P.A. 31.929	

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REIVINDICACIONES

1. Una formulación farmacéutica en la forma de un comprimido que contiene un antagonista de LTB₄ de la fórmula I:

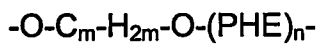


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En donde

A denota un grupo de fórmula

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En donde

m es un entero de 2 0 6

n es 0 o 1

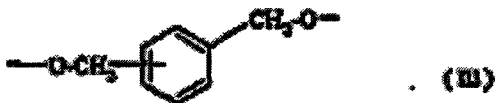
15

PHE denota un grupo 1,4-fenileno opcionalmente sustituido con uno o dos grupos alquilo C₁-C₆.

o

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A denota un grupo de fórmula



R₁ denota H, OH, CN, COR₁₀ o CHO

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R_2 denota H, Br, Cl, F, CF_3 , CHF_2 , OH, HSO_3-O , alquilo C_1-C_6 , alcoxi C_1-C_6 , cicloalquilo C_5-C_7 , $CONR_8R_9$, arilo, O-arilo, CH_2 -arilo, CR_5R_6 -arilo, o $C(CH_3)_2-R_7$,

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R_3 denota H, alquilo C_1-C_6 , alcoxi C_1-C_6 , OH, Cl o F,

R_4 denota H o alquilo C_1-C_6 ;

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R_5 denota alquilo C_1-C_6 , CF_3 , CH_2OH , $COOH$ o COO (alquilo C_1-C_4);

R_6 denota H, alquilo C_1-C_4 o CF_3 ;

R_7 denota CH_2OH , $COOH$ o COO (alquilo C_1-C_4), $CONR_8R_9$ o $CH_2NR_8R_9$;

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R_8 denota H, alquilo C_1-C_6 , fenilo, fenil-(alquilo C_1-C_6), COR_{10} , $COOR_{10}$, CHO , $CONH_2$, $CONHR_{10}$, SO_2 -(alquilo C_1-C_6), SO_2 -fenilo, mientras el grupo fenilo puede ser mono o disustituido por Cl, F, CF_3 , alquilo C_1-C_4 , OH y/o alcoxi C_1-C_4 ;

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R_9 denota H o alquilo C_1-C_6 ; o

R_8 y R_9 juntos representan un grupo alquilenos C_4-C_6 ;

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R_{10} denota alquilo C_1-C_6 , cicloalquilo C_5-C_7 , arilo, heteroarilo, aralquilo o heteroarilo-(alquilo C_1-C_6)

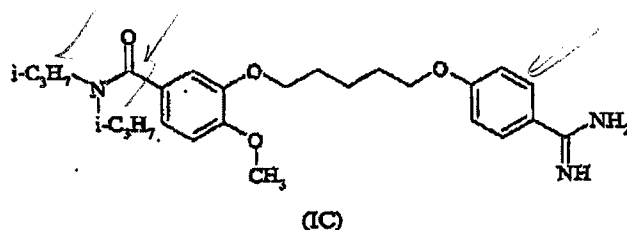
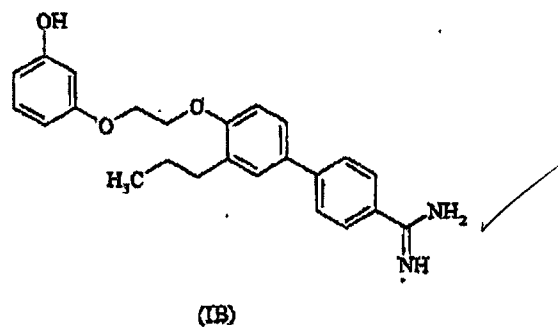
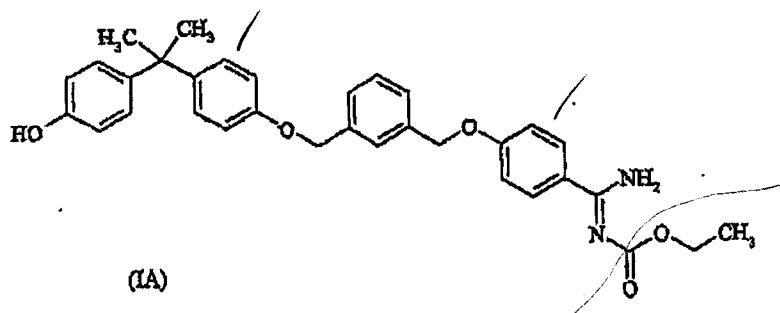
mientras los grupos arilo mencionados en los grupos R_2 y R_{10} denotan fenilo o naftilo, los grupos heteroarilo denotan pirol, pirazol, imidazol, furanilo, tienilo, pirdino o pirimidino y cada uno pueden ser mono- o polisustituidos por Cl, F, CF_3 , alquilo C_1-C_4 , OH, HSO_3-O , o alcoxi C_1-C_4 ,

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así como también las sales de adición ácida farmacológicamente aceptables y glicósidos y O-sulfatos de esta; y por lo menos un excipiente farmacológicamente aceptable, caracterizado porque el comprimido contiene por lo menos un agente humectante.

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2. El comprimido de acuerdo con la reivindicación 1, caracterizado porque el antagonista LTB_4 es un compuesto selecciona entre las fórmulas IA, IB, e IC.



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3. El comprimido de acuerdo con una de las reivindicaciones 1 o 2, caracterizado porque el agente humectante es una sustancia de superficie activa aniónica.

5 4. El comprimido de acuerdo con las reivindicaciones 1 a 3, caracterizado porque el agente humectante es lauril sulfato de sodio.

5. El comprimido de acuerdo con las reivindicaciones 1 a 4, caracterizado porque este contiene lactosa o manitol como excipiente.

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6. El comprimido de acuerdo con las reivindicaciones 1 a 5, caracterizado porque este contiene adicionalmente por lo menos un ligador seco, por lo menos un lubricante, por lo menos un desintegrante y/o por lo menos un agente de separación y opcionalmente un colorante.

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7. El comprimido de acuerdo con la reivindicación 6, caracterizado porque el ligador seco se selecciona entre celulosa en polvo, celulosa microcristalina, almidón, polivinilpirrolidona, copolímeros de vinilpirrolidona con otros derivados vinilo, derivados de celulosa y mezclas de estos compuestos.

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8. El comprimido de acuerdo con las reivindicaciones 6 o 7, caracterizado porque este ligador seco es celulosa microcristalina o una mezcla de celulosa microcristalina y un copolímero de vinilpirrolidona y acetato de vinilo.

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9. El comprimido de acuerdo con las reivindicaciones 1 a 8, caracterizado porque este contiene 0.2 a 80% en peso, preferiblemente 0.7 a 40% en peso de un compuesto de la fórmula I.

5 10. El comprimido de acuerdo con una de las reivindicaciones 1 a 9, caracterizado porque la proporción en peso entre el agente humectante y la sustancia activa de la fórmula I está en un rango de aproximadamente 1:200 a aproximadamente 1:5, preferiblemente entre aproximadamente 1:150 a aproximadamente 1:10.

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11. El comprimido de acuerdo con una de las reivindicaciones 5 a 10, caracterizado porque la proporción en peso entre lactosa o manitol y la sustancia activa de la fórmula I está en el rango de aproximadamente 20:1, a aproximadamente 1:4, preferiblemente aproximadamente 12:1 a aproximadamente 1:1.2.

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12. El comprimido de acuerdo con una de las reivindicaciones 5 a 11, caracterizado porque la proporción en peso entre lactosa y la sustancia activa de la fórmula I está en el rango de 4:1 a aproximadamente 1:4, preferiblemente aproximadamente 1.8:1 a aproximadamente 1: 1.2.

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13. El comprimido de acuerdo con una de las reivindicaciones 5 a 11, caracterizado porque la proporción en peso entre manitol y la sustancia activa de la fórmula I está en el rango de aproximadamente 20:1 a aproximadamente 1:2, más preferiblemente en el rango de aproximadamente 15:1 a 3:1.

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14. El comprimido de acuerdo con una de las reivindicaciones 6 a 13, caracterizado porque la cantidad en peso del desintegrante basado sobre el total de masa del comprimido, está en un rango de aproximadamente 0.5 a 10% en peso.

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15. El comprimido de acuerdo con una de las reivindicaciones 5 a 14, caracterizado porque la cantidad por peso del agente de flujo, agente lubricante y agente de separación basado sobre el total de masa del comprimido está en el rango de aproximadamente 0.1 a 5% en peso.

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16. El comprimido de acuerdo con una de las reivindicaciones 1 a 15, caracterizado porque este consiste esencialmente de los siguientes ingredientes:

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- Un compuesto de la fórmula I;
- Celulosa microcristalina;
- Lactosa o manitol;
- Opcionalmente un copolímero de vinilpirrolidona y acetato de vinilo;
- Lauril sulfato de sodio;

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- Polivinilpirrolidona o una sal de celulosa carboximetiléter sódica reticulada, particularmente sal croscarmelosa sódica;
- Estearato de magnesio; y
- opcionalmente un colorante farmacéuticamente aceptable.

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17. Proceso para preparar un comprimido de acuerdo con las reivindicaciones 1 a 16 al:

- (a) mezclar un compuesto de la fórmula I con un agente humectante y opcionalmente otros excipientes farmacéuticamente aceptables, opcionalmente en la presencia de un diluyente volátil;
- (b) seleccionar la mezcla obtenida;
- 5 (c) agregar opcionalmente un lubricante, y
- (d) comprimir con una prensa para comprimidos adecuada.

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1-1228-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2002/007618	International filing date (day/month/year) 09 July 2002 (09.07.2002)	Priority date (day/month/year) 14 July 2001 (14.07.2001)
International Patent Classification (IPC) or national classification and IPC A61K 31/155		
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of <u>4</u> sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of <u> </u> sheets.
3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application

Date of submission of the demand 12 February 2003 (12.02.2003)	Date of completion of this report 22 September 2003 (22.09.2003)
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP2002/007618

I. Basis of the report

1. With regard to the elements of the international application:*

- ☐ the international application as originally filed
- ☒ the description:
 pages _____ 1-17 _____, as originally filed
 pages _____, filed with the demand
 pages _____, filed with the letter of _____
- ☒ the claims:
 pages _____ 1-19 _____, as originally filed
 pages _____, as amended (together with any statement under Article 19
 pages _____, filed with the demand
 pages _____, filed with the letter of _____
- ☒ the drawings:
 pages _____ 1/2-2/2 _____, as originally filed
 pages _____, filed with the demand
 pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
 pages _____, as originally filed
 pages _____, filed with the demand
 pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequences listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(e)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP 02/07618

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-19	YES
	Claims		NO
Inventive step (IS)	Claims	1-19	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims		NO

2. Citations and explanations

1. This report makes reference to the following documents:

- D1: WO 96 02497 A (BOEHRINGER INGELHEIM KG; ANDERSKEWITZ RALF (DE); SCHROMM KURT (DE)) 1 February 1996 (1996-02-01), cited in the application
- D2: WO 93 16036 A (BOEHRINGER INGELHEIM INT; BOEHRINGER INGELHEIM KG (DE)) 19 August 1993 (1993-08-19), cited in the application
- D3: WO 97 21670 A (BOEHRINGER INGELHEIM KG; ANDERSKEWITZ RALF (DE); SCHROMM KURT (DE)) 19 June 1997 (1997-06-19), cited in the application
- D4: WO 98 11119 A (ANDERSKEWITZ RALF; BOEHRINGER INGELHEIM PHARMA (DE); BIRKE FRANZ) 19 March 1998 (1998-03-19), cited in the application
- D5: WO 98 11062 A (ANDERSKEWITZ RALF; BOEHRINGER INGELHEIM PHARMA (DE); BIRKE FRANZ) 19 March 1998 (1998-03-19), cited in the application
- D6: WO 01 25186 A (ANDERSKEWITZ RALF; BOEHRINGER INGELHEIM PHARMA (DE)) 12 April 2001 (2001-04-12), cited in the application
- D7: WO 94 11341 A (CIBA GEIGY AG; MORRISSEY MICHAEL M (US); SUH HONGSUK (KR)) 26 May 1994 (1994-05-26), cited in the application

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP 02/07618

D8: HUNNIUS: 'PHARMAZEUTISCHES WÖRTERBUCH' 1993 DE
GRUYTER, BERLIN/NEW YORK XP002228284

D9: ARTHUR H KIBBE: 'HANDBOOK OF PHARMACEUTICAL
EXCIPIENTS' 2000, AMERICAN PHARMACEUTICAL
ASSOCIATION, WASHINGTON, USA XP002228285

2. All of the substances used are known from D1 to D7 as LTB₄ antagonists. Tablets containing these substances are also known.

However, a person skilled in the art would not expect, in light of the teachings of D8 and D9, that wetting agents could significantly improve the bioavailability of an LTB₄ antagonist of formula (I).

Novelty and inventive step can therefore be recognized (PCT Article 33(2) and (3)).

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 80017

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-010954- -00008-0000

RECIBO OFICIAL DE CAJA : 07 - 100,283
FECHA : DICIEMBRE 10 DE 2007

Fecha: 2007-12-28 17:14:11 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 17

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	49377610	10/12/2007	44,065,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LEMAS COMERCIALES	99,000.00
		TOTAL :	\$ 99,000.00

SON: NOVENTA Y NUEVE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

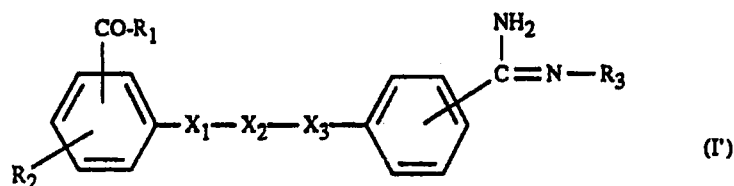
216 13736-846-023-9

D1 194
194

- 3 -

antagonizing LTB-4 and of treating diseases in mammals which are responsive to LTB-4 antagonism using said compounds or pharmaceutical compositions comprising said compounds of the invention.

The compounds of the invention wherein the C(=NH)-NHR₃ group is in tautomeric or isomeric form are represented by formula I'



wherein R₁, R₂, R₃, X₁, X₂ and X₃ have the meanings as defined for formula I.

As compounds according to the invention have a basic centre, they can thus form acid addition salts, especially pharmaceutically acceptable salts. These are formed, for example, with inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric or hydrohalic acid, or with organic carboxylic acids, such as (C₁-C₄-)alkanecarboxylic acids which, for example, are unsubstituted or substituted by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, benzoic acid or with organic sulfonic acids, such as (C₁-C₄-)alkane- or arylsulfonic acids which are unsubstituted or substituted, for example, by halogen, for example methane- or toluenesulfonic acid. Preferred are salts formed with hydrochloric acid, methanesulfonic acid and maleic acid.

The general definitions used below have, if not defined differently, the following meanings:

An aliphatic hydrocarbon radical is, for example, lower alkyl, lower alkenyl and secondarily lower alkynyl.

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or mono- or polysubstituted by C_1 - C_7 -alkyl, or is amino which is disubstituted by C_3 - C_6 -alkylene;

R_2 is C_1 - C_7 -alkoxy substituted by carboxy or lower alkoxycarbonyl;

R_3 is hydrogen, C_1 - C_{12} -alkoxy-carbonyl, C_2 - C_5 -alkanoyl, phenyl- C_2 - C_5 -alkanoyl, benzoyl which is unsubstituted or substituted by halogen, trifluoromethyl, C_1 - C_7 -alkyl, or C_1 - C_7 -alkoxy, C_3 - C_6 -cycloalkylcarbonyl which is unsubstituted or substituted by C_1 - C_7 -alkyl, or is benzoyl, naphthoyl, indanoyl or fluorenyl, or is C_1 - C_7 -alkanesulfonyl, phenyl- C_1 - C_7 -alkanesulfonyl, C_3 - C_7 -cycloalkanesulfonyl, or phenylsulfonyl, or is aminocarbonyl which is substituted by C_1 - C_7 -alkyl, phenyl- C_1 - C_7 -alkyl or phenyl;

X_1 and X_3 each are -O-, or furthermore are, independently of one another, -O- or -S-;

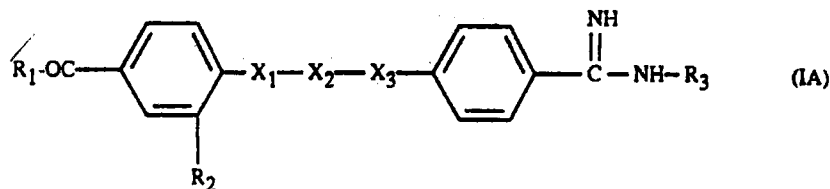
X_2 is C_2 - C_7 -alkylene or C_2 - C_4 -alkylene-phenylene- C_2 - C_4 -alkylene;

wherein the phenyl rings of formula I may be unsubstituted or, furthermore, independently of one another, substituted by one or more substituents selected from halogen, trifluoromethyl, C_1 - C_7 -alkyl, and C_1 - C_7 -alkoxy;

wherein phenyl in the above definitions is unsubstituted or, furthermore, independently of one another, substituted by one or more substituents selected from halogen, trifluoromethyl, C_1 - C_7 -alkyl, and C_1 - C_7 -alkoxy.

The invention especially relates to compounds of formula I and pharmaceutically acceptable salts thereof, in which -CO- R_1 is located in position 4 (para) or 3 or 5 (meta) of the corresponding phenyl ring with respect to - X_1 -; R_2 - is located in position 2 (ortho) or 3 (meta) of the corresponding phenyl ring with respect to - X_1 -; and -C(=NH)-NHR₃ is located in position 4 (para) of the corresponding phenyl ring with respect to - X_3 -.

The invention especially relates to compounds of formula IA *compounds of formula I, IIA, IIC, IIC.*



wherein the C(=NH)-NHR₃ group may be in tautomeric or isomeric form, and pharmaceutically acceptable salts thereof, in which:

R_1 is di- C_1 - C_4 -alkylamino, such as di-ethylamino or di-isopropylamino,

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C₁-C₄alkyl-(phenyl)amino, such as phenyl-isopropyl-amino,

C₁-C₄alkyl-(phenyl-C₁-C₄alkyl)-amino, such as methyl-benzyl-amino,

di-C₃-C₆-cycloalkylamino, such as di-cyclohexylamino, which is unsubstituted or substituted by C₁-C₄alkyl, or 1-piperidino substituted by C₁-C₄alkyl, such as 2-methyl-1-piperidino;

R₂ is C₁-C₄-alkoxy which is substituted by carboxy, lower alkoxycarbonyl, aminocarbonyl or by mono- or di-lower alkylaminocarbonyl;

R₃ is hydrogen, C₁-C₁₂-alkoxycarbonyl, such as methoxycarbonyl or octyloxycarbonyl, phenyl-C₁-C₄-alkoxycarbonyl, such as benzyloxycarbonyl, C₂-C₅-alkanoyl, such as acetyl, benzoyl which is unsubstituted or substituted by halogen, trifluoromethyl, C₁-C₄alkyl or by C₁-C₄-alkoxy, such as 3,4-dimethoxybenzoyl, C₃-C₆-cycloalkylcarbonyl which is unsubstituted or substituted by C₁-C₄alkyl, such as 2-isopropyl-5-methyl-cyclohexylcarbonyl;

✓ X₁ and X₃ are -O-;

✓ X₂ is C₄-C₇-alkylene, such as pentylene;

wherein the phenyl rings of formula IA may be unsubstituted or, furthermore, independently of one another, substituted by one or more substituents selected from halogen, trifluoromethyl, C₁-C₄alkyl, and C₁-C₄-alkoxy.

The invention especially relates to compounds of formula IA and pharmaceutically acceptable salts thereof, in which:

R₁ is di-C₁-C₄-alkylamino, such as di-ethylamino or di-isopropylamino,

C₁-C₄alkyl-(phenyl)-amino, such as phenyl-isopropyl-amino,

C₁-C₄alkyl-(phenyl-C₁-C₄alkyl)-amino, such as methyl-benzyl-amino,

di-C₃-C₆-cycloalkylamino, such as di-cyclohexylamino which is unsubstituted or substituted by C₁-C₄alkyl, or 1-piperidino substituted by C₁-C₄alkyl, such as 2-methyl-1-piperidino;

R₂ is C₁-C₄-alkoxy which is substituted by carboxy, lower alkoxycarbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl;

R₃ is C₁-C₄alkanesulfonyl, such as methane-, ethane- or isopropanesulfonyl, phenyl-C₁-C₄-alkanesulfonyl, such as benzy lsulfonyl, C₃-C₇-cycloalkane-sulfonyl, such as cyclohexanesulfonyl, or phenylsulfonyl, or is aminocarbonyl which is substituted by

C₁-C₄alkyl, phenyl-C₁-C₄alkyl or phenyl;

X₁ and X₃ are -O-;

X₂ is C₄-C₇-alkylene, such as pentylene.

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Any resulting mixtures of isomers can be separated on the basis of the physico-chemical differences of the constituents, into the pure geometric or optical isomers, diastereoisomers, racemates, for example by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g. by separation of the diastereoisomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. Racemic amidines (wherein R_3 represents hydrogen) can thus be resolved into their optical antipodes e.g. by fractional crystallization of a salt formed with an optically active acid.

Finally, the compounds of the invention are either obtained in the free form, or as a salt thereof.

In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, to antagonize LTB_4 receptors, and for the treatment of a condition or syndrome responsive to the selective antagonism of LTB_4 receptors, comprising an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable carriers.

The novel pharmaceutical products contain, for example, from about 10 % to about 80 %, preferably from about 20 % to about 60 %, of the active compound. Examples of pharmaceutical products according to the invention for enteral or parenteral administration are those in dose-unit forms such as coated tablets, tablets, capsules or suppositories, as well as ampoules. These are prepared in a manner known per se, for example using conventional mixing, granulating, coating, dissolving or freeze-drying processes. Thus, pharmaceutical products for oral use can be obtained by combining the active compound

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aminocarbonyl]phenoxy-4-butanoic acid monohydrochloride, as a colorless solid; CHN calculated for $C_{29}H_{42}ClN_3O_6 \cdot H_2O$:

Theory: %C: 59.82; %H: 7.62; %N: 7.22;

Found: %C: 60.06; %H: 7.66; %N: 6.64.

(f) Ethyl 5-[5-[4-[(3-pyridylcarbonylimino)aminomethyl]phenoxy]pentyloxy]-2-[N,N-bis(1-methylethyl)aminocarbonyl]phenoxy-4-butanoate, as an oil; CHN calculated for $C_{37}H_{48}N_4O_7$:

Theory: %C: 67.26; %H: 7.32; %N: 8.48;

Found: %C: 66.93; %H: 7.40; %N: 8.37;

IR(cm^{-1}): 1727, 1606.

(g) Ethyl 5-[5-[4-[(3-pyridylcarbonylimino)aminomethyl]phenoxy]pentyloxy]-2-[N,N-bis(1-methylethyl)aminocarbonyl]phenoxydimethylacetate as a colorless foam; CHN calculated for $C_{37}H_{48}N_4O_7$:

Theory: %C: 67.26; %H: 7.32; %N: 8.48;

Found: %C: 66.93; %H: 7.23; %N: 8.31;

IR(cm^{-1}): 1728, 1608; MS: 528(M+1).

Example 10

a) Preparation of 10,000 tablets each containing 20 mg of the active ingredient, for example, the compound of example 6:

✓ active ingredient	200.00 g
✓ Lactose	2,535.00 g
✓ Corn starch	125.00 g
Polyethylene glycol 6,000	150.00 g
Magnesium stearate	40.00 g
Purified water	q.s.

Procedure: All the powders are passed through a screen with openings of 0.6 mm. The drug substance, lactose, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the suspension added to the boiling solution of the polyethylene glycol in 250 ml of water. The paste formed is added to the powders, which are granulated, if necessary, with an additional

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amount of water. The granulate is dried overnight at 35°C broken on a screen with 1.2 mm openings and compressed into tablets, using concave punches uppers bisected.

Analogously tablets are prepared, containing about 10-100 mg of one of the other compounds disclosed and exemplified herein.

b) Preparation of 1,000 capsules each containing 40 mg of the active ingredient, for example, the compound of example 6:

active ingredient	40.00 g
Lactose	177.00 g
Modified starch	80.00 g
Magnesium stearate	3.00 g

Procedure: All the powders are passed through a screen with openings of 0.6 mm. The drug substance is placed in a suitable mixer and mixed first with the magnesium stearate, then with the lactose and starch until homogenous. No. 2 hard gelatin capsules are filled with 300 mg of said mixture each, using a capsule filling machine.

Analogously capsules are prepared, containing about 10-100 mg of the other compounds disclosed and exemplified herein.

(c) Preparation of 3000 capsules each containing 25 mg of the active ingredient, for example, the compound of example 6:

Active ingredient	75.00 g
Lactose	750.00 g
Avicel PH 102 (microcrystalline cellulose)	300.00 g
Polyplasdone XL (polyvinylpyrrolidone)	30.00 g
Purified water	q.s.
Magnesium stearate	9.0 g

The active ingredient is passed through a No. 30 hand screen.

PCT
WELTORGANISATION
IN
INTERNATIONALE ANMELDUNG VON
INTERNATIONALE ZUSAMMENARBEIT



WO 9402497A1

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(21) Internationales Aktenzeichen: PCT/EP95/02112		(81) Bestimmungsorten: AU, BG, BR, BY, CA, CN, CZ, DE, FI, HU, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, UA, US, VN, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
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(71) Anmelder (für alle Bestimmungsorten außer US): BOEHRINGER INGELHEIM KG (DE/DE); D-55216 Ingelheim (DE).		Veröffentlicht Mit internationalem Recherchenbericht.	
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(54) Title: SUBSTITUTED BENZAMIDINES, THEIR PRODUCTION AND THEIR USE AS MEDICAMENTS			
(54) Bezeichnung: SUBSTITUIERTE BENZAMIDINE, IHRE HERSTELLUNG UND VERWENDUNG ALS ARZNEIMITTEL			
(57) Abstract		(I)	
The novel compounds of formula (I) (the meanings of A and R₁ to R₄ are given in the description) may be produced by conventional methods and therapeutically used as, for example, LTB₄ antagonists.			
(57) Zusammenfassung			
Die neuen Verbindungen der Formel (I) (die Bedeutung von A und R₁ bis R₄ ist in der Beschreibung erläutert) lassen sich nach konventionellen Methoden herstellen und können u.a. als LTB₄-Antagonisten therapeutisch verwendet werden.			

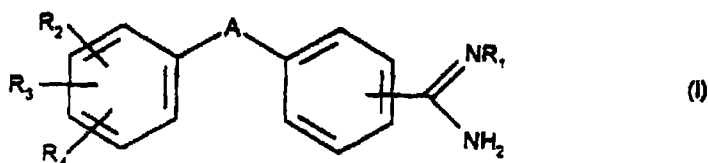
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Benzamidinas sustituidas, su preparación y empleo como
sustancias medicamentosas

DESCRIPCION DE LA INVENCION

La invención se refiere a nuevas benzamidinas sustituidas, a su preparación según métodos convencionales y a su empleo como sustancias medicamentosas, en particular con un efecto antagonista del receptor de LTB_4 .

Las nuevas benzamidinas sustituidas corresponden a la fórmula



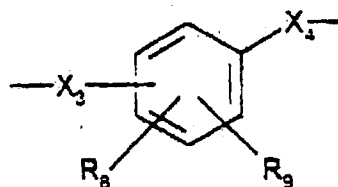
en que

A representa el grupo



(m igual 2 a 6)

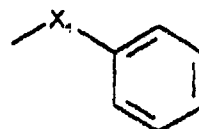
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(III)

X_1 representa O, NH ó NCH_3 .

X_2 representa O, NH, NCH_3 ó



(IV)

X_3 representa $-X-C_nH_{2n}-$;

X_4 representa $-C_nH_{2n}-X-$ ($n = 1$ ó 2 , $X = O$, NH ó NCH_3);

R_1 representa OH, CN, COR_{12} , $COOR_{12}$ y CHO;

R_2 representa Br, Cl, F, CF_3 , OH, alquilo C_1-C_6 , cicloalquilo C_3-C_7 , arilo, O-arilo, CH_2 -arilo, CR_5R_6 -arilo, $C(CH_3)_2-R_7$;

además, representa H cuando A es un radical de la fórmula III ó cuando X_1 es un radical de la fórmula IV;

además, representa alcoxi C_1-C_6 cuando A es el grupo II,

X_1 y m tienen los significados anteriores y X_2 representa NH, NCH_3 ó el grupo IV,

ó cuando A significa el grupo III, X_3 tiene el significado anterior, y en X_4 , X representa NH ó NCH_3 ;

R_3 representa H, alquilo C_1-C_6 , OH, Cl, F, además representa alcoxi C_1-C_6 cuando R_2 es arilo, O-arilo, CH_2 -arilo, CR_5R_6 -arilo ó $C(CH_3)_2-R_7$, ó cuando X_1 significa el grupo

IV:

R_2 y R_3 pueden significar juntos también un anillo aromático o heteroaromático condensado;

- R_4 representa H o alquilo C_1-C_6 ;
- 5 R_5 representa alquilo C_1-C_4 , CF_3 , CH_2OH , $COOH$ o COO (alquilo C_1-C_4);
- R_6 representa H, alquilo C_1-C_4 ó CF_3 ;
- R_7 y R_8 pueden formar juntos también un grupo alquileno C_4-C_6 ;
- 10 R_7 representa CH_2OH , $COOH$, COO (alquilo C_1-C_4), $CONR_{10}R_{11}$ ó $CH_2NR_{10}R_{11}$;
- R_8 , R_9 representan H, Br, Cl, F, OH, alquilo C_1-C_6 o alcoxi C_1-C_6 ;
- 15 R_{10} representa H, alquilo C_1-C_6 , fenilo, fenil-(alquilo C_1-C_6), COR_{12} , $COOR_{12}$, CHO , $CONH_2$, $CONHR_{12}$, SO_2 -(alquilo C_1-C_6), SO_2 -fenilo, pudiendo estar el radical fenilo sustituido una o varias veces con Cl, F, CF_3 , alquilo C_1-C_4 , OH, alcoxi C_1-C_4 ;
- R_{11} significa H ó alquilo C_1-C_6 ;
- 20 R_{10} y R_{11} pueden representar juntos también un grupo alquileno C_4-C_6 ;
- R_{12} representa alquilo C_1-C_6 , cicloalquilo C_3-C_7 , arilo, heteroarilo, aralquilo o heteroaril-(alquilo C_1-C_6), pudiendo estar sustituidos los grupos arilo o heteroarilo una o varias veces con Cl, F, CF_3 , alquilo C_1-C_4 , OH
- 25

o alcoxi C_1-C_6 .

Los nuevos compuestos pueden presentarse en cada caso en forma de bases libres o como sales con ácidos, preferiblemente con ácidos fisiológicamente compatibles; en la medida en que contengan uno o varios centros quirales, se reivindican en forma de racematos, en forma pura en cuanto a los enantiómeros o enriquecida, eventualmente en forma de pares de diastereoisómeros. Están incluidos también posibles tautómeros (con $-C(NH)-NHR_1$).

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Se prefieren compuestos de la fórmula I,

en donde

A, m, n, X_1 , X_2 y R_1 tienen los significados anteriores;

X_1 representa O;

X_2 representa O o un grupo IV (en donde X_1 es igual a O);

15

R_1 representa Cl, F, CF_3 , OH, alquilo C_1-C_6 , arilo, O-arilo,

CH_2 -arilo ó CR_3R_6 -arilo y, cuando X_2 es el grupo IV,

representa además alcoxi C_1-C_6 ;

R_3 representa H, alquilo C_1-C_6 u OH, y

cundo R_3 es CR_3R_6 -arilo, representa además alcoxi C_1-C_6 ;

20

R_4 representa H;

R_5 representa alquilo C_1-C_3 , CF_3 ó CH_2OH ;

R_6 representa H, alquilo C_1-C_3 ó CF_3 ,

R_5 y R_6 pueden formar juntos también un grupo alquileno

C_4-C_5 ;

25

R_1 , R_2 representan H, F u OH.

Se han de destacar en particular los compuestos en los que en el marco de las precedentes definiciones

X_1 representa O;

X_2 representa el grupo IV (en donde X_1 es igual a O);

5

X representa O;

R_1 representa COOR_{12} ;

R_2 representa alquilo $\text{C}_1\text{-C}_6$, arilo, O-arilo, CH_2 -arilo ó CR_3R_6 -arilo;

10

R_3 representa H, OH o alquilo $\text{C}_1\text{-C}_6$ y, cuando R_1 es CR_3R_6 -arilo, representa también alcoxi $\text{C}_1\text{-C}_6$;

R_4 representa H;

R_5, R_6 representan alquilo $\text{C}_1\text{-C}_3$ ó CF_3 ;

R_7, R_8 representan H;

15

R_{12} representa alquilo $\text{C}_1\text{-C}_6$, aralquilo o cicloalquilo $\text{C}_1\text{-C}_7$.

En la medida en que los símbolos según las definiciones anteriores pueden tener significados iguales o diferentes, han de estar incluidas ambas posibilidades. Cadenas alifáticas que presentan un número suficiente de átomos de C pueden ser de cadena lineal o ramificadas.

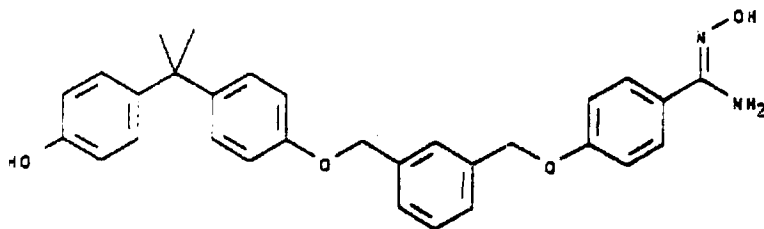
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"Arilo" significa un radical arilo eventualmente sustituido (una o varias veces), por ejemplo naftilo, pero preferiblemente un radical fenilo eventualmente sustituido (una o varias veces). Se prefieren como sustituyentes: Cl, F, Br, OH, alquilo $\text{C}_1\text{-C}_6$, alcoxi $\text{C}_1\text{-C}_6$, CF_3 ; además, son posibles los grupos que, por norma general, sólo están presentes una

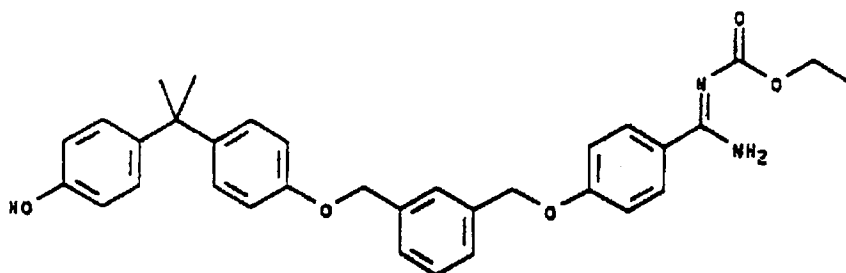
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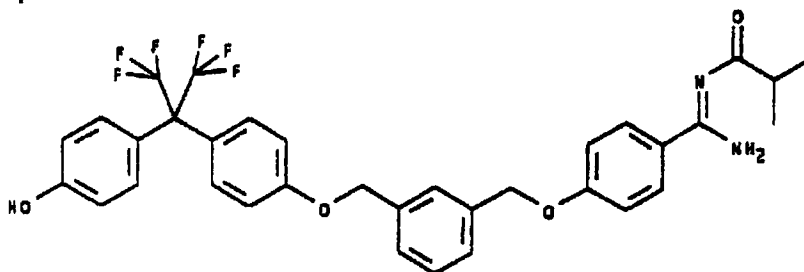


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IA.

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Se hace constar que con relación a esta fecha, el mejor método conocido por la solicitante para llevar a la práctica la citada invención, es el que resulta claro de la presente descripción de la invención.

25

Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes:

D3 207

United States Patent [19]

Martin et al.

[11] 4,344,934

[45] Aug. 17, 1982

[54] THERAPEUTIC COMPOSITIONS WITH ENHANCED BIOAVAILABILITY

[75] Inventors: Frederick H. Martin, West Chazy; Andrew G. Tsuk, Plattsburgh, both of N.Y.

[73] Assignee: American Home Products Corporation, New York, N.Y.

[21] Appl. No.: 123,143

[22] Filed: Feb. 21, 1980

Related U.S. Application Data

[63] Continuation of Ser. No. 962,435, Nov. 20, 1978, abandoned.

[51] Int. Cl.³ A61K 31/79; A61K 37/00; A61K 31/74; A61K 9/24; A61K 31/245

[52] U.S. Cl. 424/80; 424/177; 424/78; 424/310; 424/22

[58] Field of Search 424/80, 285, 177

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Primary Examiner—Delbert R. Phillips

Attorney, Agent, or Firm—Adley F. Mandel

[57] ABSTRACT

Novel compositions comprising wetted mixtures of poorly soluble drugs with water soluble polymers useful in increasing bioavailability are disclosed.

23 Claims, No Drawings

**THERAPEUTIC COMPOSITIONS WITH
ENHANCED BIOAVAILABILITY**

This is a continuation, of application Ser. No. 5
962,435, filed Nov. 20, 1978, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to compositions of poorly solu- 10
ble or water soluble drugs which provide poor bioavail-
ability or are irregularly absorbed following oral admin-
istration of their solid dosage forms. More specifically,
the herein disclosed invention relates to new composi- 15
tions of matter containing poorly soluble or water insol-
uble drugs, a nontoxic water soluble polymer and a
wetting agent. The invention further relates to a process
for preparing and a method for using the disclosed com-
positions which compositions provide a high order of 20
drug bioavailability. In the main, the invention will be
illustrated with the known antifungal griseofulvin.

2. Description of the Prior Art

Many drugs give an incomplete and irregular absorp-
tion when taken orally, particularly poorly water solu- 25
ble or water insoluble compounds such as griseofulvin
and many steroids. One of the earlier attempts to en-
hance the availability or bioavailability of such drugs
relied on mechanical micronization of the pure com-
pounds in order to decrease their particle size. While 30
micronization did enhance absorption over the use of
unmicronized material, absorption of the drug was still
incomplete. Further the degree of micronization which
can be achieved is limited and the micronized particles
tend to agglomerate, thus diminishing both the solubil- 35
ity of the drug and its bioavailability. U.S. Pat. No.
2,900,304 is an illustration of griseofulvin compositions
for oral or parenteral administration employing micron-
ized drug particles.

Another approach for attempting to enhance the
bioavailability of griseofulvin was studied by Marvel et 40
al and reported in *The J'l of Investigative Dermatology*,
42, 197-203 (1964). Their studies related to the effect
of a surfactant and particle size on the bioavailability
of griseofulvin when orally administered. Results of their 45
studies indicated that bioavailability of the drug was
enhanced when administered in very dilute solutions or
aqueous suspensions. Their results further tended to
confirm that enhanced bioavailability was obtained
with griseofulvin having a higher specific surface area,
at least when administered in full daily divided doses. 50
With respect to the effect of the surfactant sodium lau-
ryl sulfate incorporated into griseofulvin tablets, their
results demonstrated some initial enhancement of bi-
oavailability with regularly particle sized drug and very
little enhancement with micronized drug in comparison 55
to surfactant-free tablets. These investigators further
reported that when the daily dose was divided, the
surfactant had no enhancing effect.

Still another approach for the enhancement of drug
bioavailability is represented by the work of Tachibana 60
and Nakamura in *Kolloid-Zeitschrift und Zeitschrift Für
Polymere*, 203, pgs. 130-133 (1965) and Mayersohn et
al in the *Journal of Pharmaceutical Science*, 55, pgs.
1323-4 (1966). Both publications deal with the use of
polyvinylpyrrolidone (PVP) for forming dispersions of 65
a drug. Tachibana discusses the role of PVP in forming
very dilute colloidal dispersions of β -carotene in PVP.
Mayersohn further prepared solid dispersions or solid

solutions of griseofulvin in PVP and the reported results
show dissolution rates for the drug increasing with
increasing proportions of PVP. This last publication
further reported that in the absence of wetting agent in
the dissolution medium, the enhancement of the dissolu-
tion rate is still greater.

Canadian Pat. No. 987,588 of Riegelman et al, simi-
larly discloses the use and process for making solid
dispersions of a drug for enhancing its dissolution rate
and bioavailability. In this case the solvents employed
were polyethylene glycol (PEG) having molecular
weights ranging from 4,000 to 20,000, pentaerythritol,
pentaerythritol tetraacetate and monohydrous citric
acid. Riegelman postulated that these solvents provided
a matrice for griseofulvin which retards crystallization
during the solidification process resulting in an ultrami-
crocrystalline form of the drug with correspondingly
faster dissolution. Riegelman's results tend to support
this finding of faster dissolution rates for solid solutions
of griseofulvin over those of unmicronized, non-wetted
micronized and wetted micronized griseofulvin. But his
findings were limited to those solid solutions which
contain less than 50 percent by weight of the drug since
the results demonstrated a slowing of the dissolution
rate with higher concentrations of griseofulvin. Riegel-
man further concluded that the rate of dissolution for a
composition having the same ratio of drug to solvent
varies significantly depending on the method of prepa-
ration, with melt mixing at elevated temperatures in a
volatile solvent providing the preferred mode or pro-
cess.

Another process for preparing ultramicrocrystalline
drug particles to increase dissolution of a drug is dis-
closed by Melliger in Belgian Pat. No. 772,594. That
process is characterized by preparing a solution of the
drug, PVP and urethane and subsequently removing the
urethane. It was reported that, in general, satisfactory
results were obtained using solutions in which the quan-
tity of drug represented up to 50 percent by weight of
the quantity of PVP present.

U.S. Pat. Nos. 3,673,163 and 4,024,240 respectively
are further illustrations relating to the use of PVP in
solid dispersions. In the first-cited patent, coprecipitates
of acronycine with polyvinylpyrrolidone were pre-
pared in proportions weighted to the polymer to in-
crease the solubility of the coprecipitated acronycine.
In the second-cited patent solid antibiotic dispersions
containing the antibiotic designated A-32390, in propor-
tions again weighted toward the PVP co-dispersant,
were disclosed. Further examples of antibiotic combina-
tions containing PVP are disclosed in U.S. Pat. No.
3,577,514 wherein the PVP is used as a binding agent;
and in U.S. Pat. Nos. 3,485,914 and 3,499,959, wherein
the PVP is used to sustain the release of the antibiotic.
PVP has also been used as a stabilizer with nitroglycerin
to retard migration between nitroglycerin tablets as
disclosed in U.S. Pat. No. 4,091,091.

With respect to processes employed in preparing
certain PVP-griseofulvin compositions, Junginger in
Pharm. Ind. 39, Nr. 4 at pgs. 384-388 and Nr. 5 at pgs.
498-501 (1977), reported that spray-dried products pro-
vided systems with higher energy levels in comparison
with those of simple mixtures and coprecipitates, and
correspondingly greater dissolution rates. Junginger
further disclosed that the dissolution rates of the simple
mixtures were higher when the PVP contents were in-
creased.

In a further attempt to increase the bioavailability of griseofulvin, the drug was treated with small amounts of hydroxypropyl cellulose and formulated into capsules, see Fell et al, J. Pharm. Pharmac., 30, 479-482 (1978). While the formulation produced by this treatment increases the rate and extent of availability of micronized griseofulvin, and authors reported that the treated formulation does not always lead to complete absorption from the upper intestine as was reported for the Riegelman solid disperse system with polyethylene glycol 6000.

SUMMARY OF THE INVENTION

This invention provides compositions of poorly soluble or water insoluble drugs which provide higher dissolution rates in vitro and increased bioavailability of said drugs in vivo. The composition of this invention comprises a mixture or solution of the drug with a non-toxic, pharmacologically acceptable water soluble polymer wherein said mixture or solution has been treated with a minor amount of a wetting agent selected from anionic and cationic surfactants. The term mixture means the product of a melt mix or that of a dried solution.

Examples of suitable polymers are those selected from at least one of the group comprising polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, block copolymers of ethylene oxide and propylene oxide, and polyethylene glycol. Suitable surfactants include those of the anionic variety such as sodium lauryl sulfate, sodium laurate or dioctylsodium sulphosuccinate, and those of the cationic variety such as benzalkonium chloride, bis-2-hydroxyethyl oleyl amine or the like.

In another embodiment, the invention includes a method for treating mammals with said drugs by increasing the bioavailability of the drug following its administration using the composition of this invention.

Still a further embodiment of this invention is a method of preparing compositions with increased bioavailability in mammals from a poorly soluble or water insoluble drug. The method includes the steps of:

- (a) Forming a mixture or solution of a drug with a non-toxic, pharmacologically acceptable water-soluble polymer;
- (b) drying the drug-polymer solution;
- (c) mixing the dried drug-polymer mixture or solution with a surface wetting amount of wetting agent solution wherein said agent is selected from anionic and cationic surfactants; and
- (d) drying the mixture of step (c).

The method for preparing these compositions is also useful as a method for preparing ultramicrocrystalline griseofulvin.

While the invention is illustrated with poorly soluble or water soluble drugs, and particularly griseofulvin, it will become apparent to those skilled in the art that the compositions and method of this invention are also suitable for other drugs which while relatively soluble have a tendency to agglomerate or crystallize in storage, or after formulation into pharmaceutical dosage forms.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compositions of a drug with a water soluble polymer which has been treated with a wetting sufficient amount of a wetting agent selected

from anionic and cationic surfactants. In preferred embodiments the composition is a solid, usually a powder, which is then compounded into suitable solid dosage forms for oral administration.

Griseofulvin is a known antibiotic which has been found useful in the treatment of certain fungus diseases of plants, man and animals. Griseofulvin as discussed in the background of this invention is also known as a poorly soluble or water soluble drug, which in vivo provides a low order of bioavailability when administered orally. Thus the composition of the instant invention is particularly useful for griseofulvin and drugs of a similar nature such as certain steroids and antibiotics which due to their low aqueous solubility and/or high melting point are poorly absorbed. Illustrative of such drugs are medrogestone; progesterone; estradiol; 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-carboxamide; 5H-dibenzo[a,d]cycloheptene-5-carboxamide and the like. The compositions of this invention, as will soon be appreciated, further permit the formulation of solid dosage forms which may contain high concentrations of the particular drug, such as griseofulvin, with no concomitant loss of bioavailability usually associated with such high concentrations. These compositions thus allow the preparation of elegant solid dosage forms. The compositions of this invention are also resistant to agglomeration of the drug particles or the tendency of the drug in storage to produce undesirable crystal formation which adversely affects bioavailability of the drug.

Polymers useful in this invention include water soluble polymers which are nontoxic and pharmacologically acceptable, particularly for oral administration. Illustrative of polymers, found suitable in this invention include polyvinylpyrrolidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, block co-polymers of ethylene oxide and propylene oxide, and polyethylene glycol.

Generally these polymers are commercially available over a broad range of average molecular weights. For example, polyvinylpyrrolidone (PVP) is a well known product produced commercially as a series of products having mean molecular weights ranging from about 10,000 to 700,000. Prepared by Reppe's process: 1,4-butanediol obtained in the Reppe butadiene synthesis is dehydrogenated over copper at 200° forming γ -butyrolactone; reaction with ammonia yields pyrrolidone. Subsequent treatment with acetylene gives the vinyl pyrrolidone monomer. Polymerization is carried out by heating in the presence of H_2O_2 and NH_3 . DeBell et al., German Plastics Practice (Springfield, 1946); Hecth, Weese, Munch. Med. Wochenschr. 1 943, 11; Weese, Naturforschung & Medizin 62, 224 (Wiesbaden 1948), and the corresp. vol. of FIAT Review of German Science. Monographs: General Aniline and Film Corp., PVP (New York, 1951); W. Reppe, Polyvinylpyrrolidone (Monographie zu "Angewandte Chemie" no. 66, Weinheim/Bergstr., 1954). Generally available commercial grades have average molecular weights in the range of 10,000 to 360,000, for example, General Aniline and Film Corporation (GAF) markets at least four viscosity grades available as K-15, K-30, K-60, and K-90 which have average molecular weights of about 10,000, 40,000, 160,000 and 360,000, respectively. The K- values are derived from viscosity measurements and calculated according to Fikentscher's formula (Kline, G. M., Modern Plastics 137 No. 1945). Similar commercial products are available from BASF-Wyandotte.

Selection of a particular polymer with its characteristic molecular weight will in part depend on its ability to form suitable dosage forms with the particular drug. Thus, in preparing solid dosages, whether in powder, tablet or capsule units, the composition of this invention should be readily grindable or pulverizable, or in the form of free-flowing powders. A second consideration in the selection of a particular polymer derives from the limitations inherent in the use of specific equipment with polymers of increasingly higher viscosity. For example in forming the drug-polymer solution or mixture, complete dissolution or mixing could be inhibited utilizing blenders, mixer or the like, which are inadequate by reason of low shear or proper baffles to form a uniform and homogeneous drug-polymer solution or mixture. Depending on the process employed for forming of the drug-polymer mixture, another consideration in the selection of a particular polymer is that the polymer be mutually soluble in solvents for the particular drug.

The wetting agents found most suitable for the present invention are those selected from anionic or cationic surfactants. In addition, to those cited in the summary of this disclosure, other suitable surfactants of the anionic variety are illustrated by sodium stearate, potassium stearate, sodium oleate and the like.

The compositions of this invention are prepared in a step by step process.

In the first step, a mixture or solution of the drug with the water soluble polymer is formed. The mixture can be formed in a solvent or solvent mixture which is a mutual solvent for both the drug and the polymer. Alternatively, the drug-polymer, solvent mixture can, at this stage, be coated onto lactose. Where the drug and the polymer are not subject to degradation at elevated temperatures, the drug-polymer mixture may also be formed by melt mixing. Any volatile solvent in which the drug is soluble is suitable for forming the drug-polymer mixture. For griseofulvin, suitable solvents would include methylene chloride, methylene chloride-ethanol, chloroform, acetone, methyl ethyl ketone and combinations thereof. The most suitable polymer for forming the melt mixture with a drug such as griseofulvin is hydroxypropyl cellulose.

After the drug-polymer mixture or solution has been formed in a solvent it is dried by spray-drying, flash evaporation or air drying. Commercially, spray-drying is most practical since the dried mixture is already in powder form. In the case of the melt mixture drying the drug-polymer mixture is defined as cooling. The melt-mix product is then ground or milled into powder form in preparation for the next step; grinding or milling may also be necessary for dried solvent formed mixtures.

The powdered drug-polymer mixture is then treated with a wetting sufficient amount of a primarily aqueous wetting solution containing a wetting agent selected from anionic and cationic surfactants. This wetting treatment is accomplished by forming a slurry, wet granulation or paste mixture of the powdered drug-polymer with the wetting solution. The wetting solution treatment can be achieved with small incremental additions of the wetting solution or a larger single-shot treatment. The wetting solution treatment apparently fulfills two roles: crystallization of any amorphous regions into ultramicrosize crystals, and the breakup of clusters of such crystals so that they disperse spontaneously when exposed to water. Also, the role of the primarily aqueous solution for the wetting agent treat-

ment is to distribute the wetting agent to surfaces of the drug, whether or not the drug is amorphous or crystalline.

When the employment of more than one polymer is desired, separate drug-polymer mixtures for each polymer are usually prepared which are then intimately blended with each other either in dry form prior to or after the wetting solution treatment.

The treated mixture is then dried as earlier described and, if necessary, it is milled, screened or ground prior to formulating into suitable dosage forms with pharmaceutically acceptable excipients.

It will be again appreciated by those skilled in the art that while the invention is illustrated with particularly water insoluble drugs, the composition and method of this invention is also applicable to more soluble drugs in need of enhanced bioavailability. In such instances a broader range of solvents and polymers including the natural gums may be employed to form the drug-polymer mixture.

The concentrations of drug found useful in the drug-polymer mixture of this invention range from the lowest therapeutically effective amount of the drug up to about 90 to 95% of the drug. Thus, in griseofulvin-polymer mixtures, the concentration of griseofulvin ranges from about 0.1% by weight to about 90-95% by weight. In order to form pharmaceutically elegant dosage forms for high dose drugs, the concentration of the drug should be at least 50% by weight of the drug-polymer mixture. In especially preferred embodiments the concentration of drug in the drug polymer mixture will range from about 50% to about 80% by weight.

The required concentration for the wetting agent (or surfactant) in the primarily aqueous wetting solution is a wetting sufficient amount. This amount further depends on whether incremental or single-shot wetting treatments are employed and on whether a slurry or paste treatment is contemplated. Generally, small incremental treatments will require less wetting agent than a larger single shot treatment and a paste treatment will require more wetting agent than a slurry. In any case, it has been found that satisfactory results are obtained when the amount of wetting agent comprises from about 0.025% to about 2.0% by weight of the dried drug polymer mixture and preferably from about 0.1% or 0.2% to about 1.0% by weight. While higher concentrations of the wetting agent may be satisfactorily employed, no additional advantages in terms of dissolution and/or bioavailability are obtained. It has also been found that when a griseofulvin-polymer, melt mixture has been wetted and crystallized from an aqueous sorbitol solution, enhanced dissolution rates was obtained, however the rate of dissolution was still less than those mixtures treated with a wetting agent.

The invention is further illustrated by the following examples.

EXAMPLE 1

The rate of dissolution of the powdered materials was determined by one of three methods. All three methods gave equivalent results and only the results of method 1 outlined below are used herein unless otherwise noted. Method (1) A sample containing 20 mg of griseofulvin was dissolved into 1 liter of a 0.02% polysorbate 80 aqueous solution at 37° C. The solution was monitored by a flow cell in a spectrophotometer set at 295 nm.

Method (2) A sample containing 500 mg griseofulvin was dissolved in 10 liters of 0.15% sodium lauryl sulfate in water at 37° C.

Method (3) A sample containing 125 mg griseofulvin was dissolved in 24 liters of water at 37° C.

For examples 2-5 the wetting agent solution employed was as follows: 2.5 g of sodium lauryl sulfate (SLS) were dissolved into 500 ml of a mixture of 100 ml of water and 400 ml of ethyl alcohol or 0.25 g of sodium lauryl sulfate were dissolved into 50 ml of a mixture of 10 ml of water and 40 ml of ethyl alcohol.

EXAMPLE 2

This example describes the preparation of ultramicrocrystalline griseofulvin. The method consists of flash evaporation of a solution containing 10 g of griseofulvin and 10 g of polyvinylpyrrolidone (POVIDONE® K-30, U.S.P.-from GAF Corp.) dissolved in 200 ml of methylene chloride. The evaporation was done on a rotating evaporator at 35°-45° C. in a closed system (Vacuum). About 4-5 ml of the solution to be evaporated was placed in a 100 ml round bottom flask, then placed on the evaporator. Upon evaporation of solvent, the material was deposited onto the wall of the flask. The dried material was found to be amorphous by X-ray diffraction. Next, this amorphous material was treated with the SLS solution. To 2 g of powder, 0.125 ml of the solution was added with constant mixing and the solvent was allowed to dry. This was repeated six more times until a total of 0.875 ml of solution had been added. Microscopic observation and dissolution data showed that ultramicrocrystalline griseofulvin was formed by this method and has a much faster dissolution rate into water at 37° C., than micro-sized griseofulvin or untreated amorphous material.

TABLE 1

Dissolution profile of griseofulvin into water at 37° C. The dissolved griseofulvin, unless otherwise specified, is expressed in mg/liter over an elapsed time period in minutes.							
Sample	1 min.	2 min.	3 min.	5 min.	10 min.	14 min.	
1	11.2	11.7	11.9	12.0	12.2	12.5	
2	2.5	3.8	4.8	6.5	8.7	9.8	
3	1.6	2.7	3.4	4.7	7.0	8.2	

1-Flash evaporated griseofulvin: PVP (50% griseofulvin) treated with SLS solution.
2-Flash evaporated griseofulvin: PVP(50% griseofulvin)
3-Microsized griseofulvin

EXAMPLE 3

Table 1—This example describes the preparation of ultramicrocrystalline griseofulvin by coating a solution of griseofulvin and polyvinylpyrrolidone onto lactose then treating the powder with a solution of sodium lauryl sulfate.

A solution was prepared by dissolving 1 g of griseofulvin and 1 g of polyvinylpyrrolidone into 8 ml of methylene chloride. All this solution was coated successively in 1 ml portions onto 2 g of lactose and allowed to dry. The material formed by this method was crystalline by X-ray diffraction. Next 1 ml of the SLS solution was added to the 4 g of powder and allowed to dry. Microscopic observation and dissolution data showed that the griseofulvin formed by this method was ultramicrocrystalline and had a much faster dissolution rate into water at 37° C., than micro-sized griseofulvin.

TABLE 2

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	14 min.
1	10.8	11.6	11.8	11.9	12.0	12.0
2	7.0	8.7	9.7	10.5	11.5	11.5
3	1.6	2.7	3.4	4.7	7.0	8.2

1-griseofulvin: PVP (50:50) coated onto lactose and treated with SLS solution.
2-griseofulvin: PVP (50:50) coated onto lactose.
3-Microsized griseofulvin

EXAMPLE 4

This example describes the preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and polyvinylpyrrolidone then treating with powder with a solution of sodium lauryl sulfate. A solution of 50 g of griseofulvin and 50 g of polyvinylpyrrolidone dissolved in 2 liters of methylene chloride was spray dried at room temperature. A mixture of 1 ml of the SLS solution and 2 g of the powder was dried. Microscopic observation and dissolution data showed the griseofulvin formed by this method to be ultramicrocrystalline and has a much faster dissolution rate into water at 37° C. than micro-sized griseofulvin.

TABLE 3

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	14 min.
1	10.5	10.7	10.8	11.0	11.0	11.0
2	3.2	4.4	5.6	8.1	9.9	10.4
3	1.6	2.7	3.4	4.7	7.0	8.2

1-Spray dried griseofulvin: PVP (1:1) treated with SLS solution.
2-Spray dried griseofulvin: PVP(1:1)
3-Microsized griseofulvin

EXAMPLE 5

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and polyvinylpyrrolidone and then treating the powder with a solution of sodium lauryl sulfate. A solution containing 70 g of griseofulvin and 30 g of polyvinylpyrrolidone dissolved into 2 liters of methylene chloride was spray dried at room temperature. To 2 g of the powder, $\frac{1}{2}$ ml of the SLS solution was added in six 0.125 ml increments and dried between additions. Microscopic observation and dissolution data showed that the griseofulvin formed by this method was ultramicrocrystalline and had a much faster dissolution rate into water at 37° C. than micro-sized griseofulvin.

TABLE 4

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	14 min.	15 min.
1	10.0	10.9	11.5	12.0	12.5	12.7	—
2	2.5	3.9	4.9	6.5	9.0	10.4	—
3	1.6	2.7	3.4	4.7	7.0	8.2	—
4	1.9	3.5	4.6	6.3	8.6	—	9.7
5	1.8	3.0	4.0	5.8	8.1	—	9.3
6	1.9	3.1	4.3	6.0	8.6	—	9.7

1-Spray dried griseofulvin: PVP(70:30) treated with SLS solution.
2-Spray dried griseofulvin: PVP(70:30).
3-Microsized griseofulvin
4-Spray-dried griseofulvin: PVP treated with the non-ionic polysorbate 80. griseofulvin: PVP: non-ionic(69.7:29.7:0.5)
5-Spray dried griseofulvin: PVP treated with the non-ionic block co-polymer of ethylene oxide and propylene oxide (Pluronic® F77) griseofulvin:PVP: non-ionic (69.7:29.7:0.5)
6-Spray dried griseofulvin: PVP treated with the non-ionic isooctyl phenoxy polyethoxy ethanol.griseofulvin PVP: non-ionic (69.7:29.7:0.5)

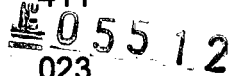
212 212

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

2020
Bogotá, D.C.

Abogado
✓ **EMILIO FERRERO**

ASUNTO

Radicación 0410954
Trámite 011
Evento 379
Actuación 411
Oficio 
Folios 023

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒
No. Sol. Internacional PCT/EP/02/07618
Fecha de Presentación Internal. Julio 9 de 2002.

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

- 1.1. Descripción: Folios: 68 a 90 como se radicó inicialmente.
- 1.2. Reivindicaciones: Folios: 91 a 96 como se radicó inicialmente.
Folios: 182 a 188 modificado.
- 1.3. Prioridad: Julio 14 de 2001, DE, 101 34 377.9
- 1.4 Respuesta del solicitante Folios: 177 a 192

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2. Objeto de la invención

Título de la invención: FORMULACION QUE CONTIENE UN AGONISTA DE LTB4.

Problema Técnico Planteado: Es la necesidad de una formulación del compuesto de formula (I), con elevada biodisponibilidad (folio 70, pg 3)

Solución: Una formulación sólida por vía oral, en forma de un comprimido, del compuesto de fórmula (I) conforme a las reivindicaciones 1-16 y su proceso de obtención.

IPC: A61K31/00.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

En la reivindicación 1, se mencionan glicósidos y O-sulfatos del compuesto de formula (I), de los cuales no existe sustento en la descripción.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria: Julio 14 de 2001.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	WO9411341	Substituted amidino compounds, their manufacture and methods of treatment	Mayo 26 de 1994
D2	WO9602497	Substituted benzamidines, their production and their use as medicaments	Febrero 1 de 1996
D3	US4344934	Therapeutic compositions with enhanced bioavailability	Agosto 17 de 1982

D1 (folios: 168-170, 194-199); D2 (folios: 200-206); D3 (folios: 207-211)

5. Análisis de patentabilidad (artículo 14 D486)

5.1 Novedad (artículo 16 D486)

La reivindicación 1, reclama una formulación farmacéutica en la forma de un comprimido que contiene:

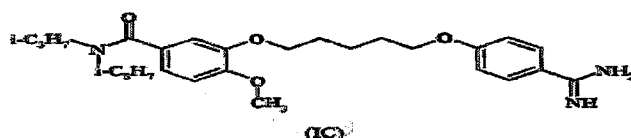
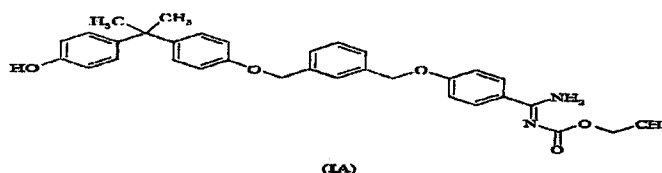
-Un antagonista de LTB4 de la forma (I), así como sus sales de adición ácida,

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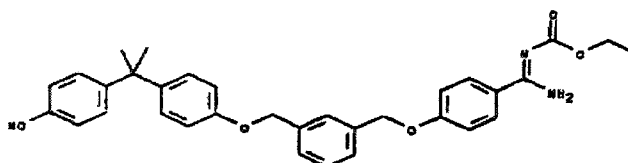
- y por lo menos un excipiente farmacológicamente aceptable,
- y por lo menos un agente humectante.

Comparando elemento por elemento, la materia solicitada, con **D1**; esta anterioridad ya divulga: Un antagonista de LTB4 de la forma (I), así como sus sales de adición ácida, (folios: 168 (abstract); folio: 169,pg 2; folio:194 pg 3 y folio:195, pg 13 (formula IA); por lo menos un excipiente farmacológicamente aceptable, y por lo menos un agente humectante (folio 170, pg 27 , líneas 1-17); por lo tanto se concluye que la presente reivindicación, no es nueva.

La reivindicación 2, que se refiere a un comprimido de acuerdo con la reivindicación 1, caracterizado porque el antagonista de LTB4, es un compuesto que se selecciona entre las formulas:

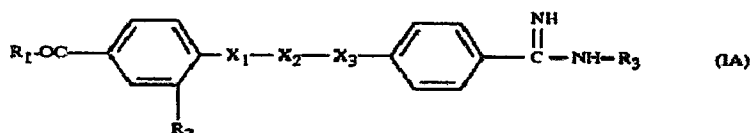


Comparando elemento por elemento, la materia solicitada, con **D2**; esta anterioridad ya divulga: Un antagonista de LTB4 de la forma (I), de formula IA, (folio 203, pg 25):



;por lo tanto se concluye que la presente reivindicación, no se considera nueva.

Además, comparando elemento por elemento, la materia solicitada, con **D1**; esta anterioridad ya divulga: Un antagonista de LTB4 de la forma (I), de formula IC (folio: 195-196, pg 13-14)



Cuando: R1 es un diisopropilamino, R2 es un alcoxi C₁₋₄, R3 es H, X1 y X3 son -O- y X2 es un pentilene; por lo tanto se concluye que la presente reivindicación, no se considera nueva.

La reivindicación 17, se refiere al proceso de fabricación del comprimido que consiste en:

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- a) mezclar un compuesto de la formula (I) con un agente humectante y opcionalmente otros excipientes farmacéuticamente aceptables, opcionalmente con la presencia de un diluyente volátil;
- b) seleccionar la mezcla obtenida;
- c) agregar opcionalmente un lubricante, y
- d) comprimir en una prensa para comprimidos adecuada.

D1, divulga la manera de obtener tabletas con los compuestos de formula (I), que consiste en mezclar el compuesto activo con los excipientes, como por ejemplo un agente humectante y si es necesario después adicionar auxiliares a tabletas ó los núcleos y comprimir a tabletas (folios 197 y 170, pgs 26 y 27 respectivamente y ejemplo 10 (folio 198, pg 38, folio 199, pg 39 líneas 1-2).

Por lo tanto, tal como esta reivindicado el proceso, de la presente reivindicación por las etapas de: mezclar, seleccionar y comprimir, la mezcla del compuesto de formula (I) con un humectante no es nuevo comparado con el proceso mencionado por D1, para obtener las tabletas ó los núcleos respectivos.

5.2 Nivel inventivo (artículo 18 D486)

Las reivindicaciones 3-16 que consisten en: Un comprimido de acuerdo con las reivindicaciones 1 y 2, caracterizado porque el agente humectante de superficie activa aniónica, es el lauril sulfato de sodio; que además contiene lactosa ó manitol, un ligante, un lubricante, un desintegrante, opcionalmente un colorante, y porque el porcentaje de principio activo esta en el rango de 0.7 a 40% preferiblemente.

El Estado de la Técnica más cercano es D1 (WO9411341) que da a conocer composiciones (tabletas) en donde el principio activo esta en proporción del 20%-60% (folio 197, pg 26, ultimo párrafo), que contiene: lactosa, manitol, ligantes, lubricantes, desintegrantes, colorantes almidón de maíz, celulosa, polivinilpirrolidona (folio 170, pg 27, líneas 7-28) y (folio 198, pg 38, ej:10).

La composición objeto de esta solicitud se diferencia de las composiciones de D1, en que esta menciona específicamente el lauril sulfato de sodio como humectante.

El hecho de incluir el lauril sulfato de sodio como humectante, causa que el comprimido tenga buena biodisponibilidad.

El Problema Técnico Objetivo era "cómo obtener comprimidos con buena disponibilidad", como alternativa, a los ya divulgados en D1.

D3 (US4344934) describe una manera de solucionar el problema técnico, mediante una composición con biodisponibilidad aumentada porque utiliza el lauril sulfato de sodio (humectante).

Entonces, la solicitud, tal como se reivindica, es obvia, porque el Experto en la Materia enfrentado al problema de "cómo obtener comprimidos con buena disponibilidad", incluiría el lauril sulfato de sodio que se revela en D3, dentro de las composiciones que se enseñan en D1, logrando de esta forma la composición objeto de esta solicitud.

Por lo tanto las reivindicaciones 3-16 no tienen nivel inventivo.

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6.Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO9411341	1-2 17 3-16	Novedad Novedad Nivel Inventivo
D2	WO9602497	2	Novedad
D3	US4344934	3-16	Nivel Inventivo

7. Respuesta a los argumentos del solicitante:

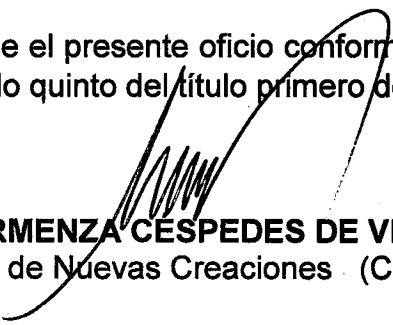
El solicitante allega un nuevo capítulo reivindicatorio donde se excluye las reivindicaciones de uso.

El solicitante afirma que D1, no afecta la novedad ya que este no revela el uso de un surfactante.

Se aclara que dicho documento revela humectantes en general y que los surfactantes, pueden tener la función de humectantes como en la presente solicitud (folio 170, pg 27, líneas 7-28).

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.


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El anterior requerimiento fue notificado por fijación en lista, de fecha
30 ABR, 2010

CONCEPTO TÉCNICO No. 1308	EXAMINADOR TÉCNICO Código No.202078
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EXAMEN TÉCNICO DE FONDO			
Nº Radicación	04-10954	Fecha de presentación	2007-08-13
Nº Solicitud Internacional	_____	Fecha Solicitud Internacional	_____
Nº Prioridad	EP 02/07618	Fecha de Prioridad	2002.08.09

Palabras clave	

CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
A61K31/00

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES	
WO 96/02497 WO 94/11341	
Patente Original	

BASES DE DATOS CONSULTADAS
Espacenet

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Oficina	Fecha	Reiv. afectadas
Oficina Europea de patentes	Enero 22 de 2003	1-6

ANTERIORIDADES ENCONTRADAS		
Documento	Relevancia	Reiv. afectadas
WO96/02497	X (Alta)	1-15
WO94/11341	X (Alta)	1
Wo93/16036	X (Alta)	1-15

LITERATURA NO PATENTES		

Observaciones	

Fecha del examen	2007-08-13
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