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DIRECCION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá, D.C.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Re.: Expediente No. 07 22.740

Fase nacional de Solicitud

de Patente PCT a nombre de

LABORATORIOS LICONSA, S.A.

Código 002 – 001 - 444

En relación con la solicitud contenida en el expediente de la referencia y, en particular, para dar respuesta al Concepto Técnico No. 2618, contenido en su último Oficio proferido dentro del mismo, dentro del término conferido, por medio del presente escrito me permito manifestarle:

1. Con el fin de superar la objeción que por claridad y por reivindicaciones relativas a un uso ha planteado su Despacho, adjunto nuevo pliego reivindicatorio compuesto por doce (12) reivindicaciones en el cual se han eliminado las antiguas reivindicaciones 13 a 24.

Con respecto a los términos no concisos, respetuosamente me permito poner de presente que las reivindicaciones se encuentran enteramente sustentadas en el pliego descriptivo y que a partir de la información allí revelada es posible establecer con exactitud la materia objeto de protección y compararla con el estado del arte.

A saber:

- a. El soporte sólido revelado en el preámbulo de la reivindicación independiente 1 y en la etapa (iv) del método de la reivindicación 5 está definido en el pliego descriptivo en las páginas 8 y 9, párrafos 6 a

8 y 1 a 6 respectivamente. Adicionalmente, las reivindicaciones dependientes 3 y 11 del nuevo pliego reivindicatorio definen dicho soporte con claridad y de conformidad con el pliego descriptivo.

Debido a lo anterior, una persona versada en la materia comprendería a partir de dicha definición, que se hace referencia a entidades terapéuticamente inertes.

- b. Con respecto al término "cantidades mensurables", me permito llamar la atención del Señor Examinador a la página 3, párrafo 2 del pliego descriptivo. Veamos:

*"Tal como se explica en la presente, el solvente volátil cloruro de metileno se utiliza para disolver las drogas. En el posterior paso de la granulación, se seca hasta que se alcanza niveles residuales de solvente muy bajos (véase el Ejemplo 1). Sin embargo, aunque dichos niveles sean bajos, **la persona experta sabe que es aún posible medir pequeñas cantidades del solvente volátil de interés en la composición farmacéutica final. La persona experta sabe que puede hacerse, por ejemplo, mediante el uso de cromatografía gaseosa (GC) y espectrometría de masa (EM)**" (Negrita fuera del texto)*

Así bien, como se explica en el párrafo precedente, las bajas cantidades residuales de cloruro de metileno en el producto final se pueden medir de forma habitual y por la tanto la reivindicación independiente 1 es clara y concisa.

En consecuencia, si se usa cloruro de metileno como solvente según los lineamientos de la presente invención y se obtienen cantidades mensurables de dicho solvente en el producto final, se estaría dentro del alcance de protección de la presente solicitud.

No obstante lo anterior, nótese que el alcance de protección de la invención reivindicada es bastante limitado, toda vez si se usa otro solvente diferente a cloruro de metileno no se estaría infringiendo la patente en cuestión.

En vista de lo anterior, el nuevo pliego reivindicatorio cumple con los requisitos de claridad, concisión y sustento toda vez que permite establecer con exactitud la materia objeto de protección y compararla con el estado del arte de acuerdo con los lineamientos del artículo 30 de la Decisión 486.

2. Ese Despacho afirma que las reivindicaciones 1 a 24 de la presente solicitud no mencionan una característica que conceda un efecto inesperado o especial a la composición farmacéutica, que pueda considerarse como un aporte a la técnica, así que son obvias para una persona versada en la materia a partir de la información revelada en D1 WO01/15701; D2 US2002/128229 y D3 ES2166278.

A este respecto, es importante poner de presente que el examen de nivel inventivo está dirigido a determinar si la invención reivindicada había sido sugerida o enseñada en el estado del arte, de acuerdo con el conocimiento de una persona versada en la materia.

Para los anteriores efectos, el método problema-solución señala que los documentos del estado del arte frente a los cuales se debe efectuar el examen de nivel inventivo son aquellos que **dentro del mismo campo técnico estén dirigidos a solucionar el mismo problema. Así los documentos relacionados con otros campos técnicos o dirigidos a solucionar cualquier otro problema no serían relevantes para estos efectos.**

El Manual para El Examen de Solicitudes de Patentes de la Comunidad Andina¹ en su sección 10.8. referente al nivel inventivo en áreas específicas de la tecnología establece que en el área de la Química un compuesto o **una composición química** (sistema estabilizador) tienen nivel inventivo si se cumple **alguno** de los dos requisitos siguientes:

"- el compuesto tenga una estructura inesperada (caso poco frecuente);

o

*- **presente un efecto inesperado**, (es el caso más frecuente sobre todo si el compuesto es similar a otros del estado de la técnica. El efecto inesperado puede ser completamente diferente de los descritos para los compuestos similares conocidos, **o bien ser igual pero con una mejora en los resultados**)". (Negrita fuera del texto).*

¹ IEPI, BID. "MANUAL PARA EL EXAMEN DE SOLICITUDES DE PATENTES DE INVENCION EN LAS OFICINAS DE PROPIEDAD INDUSTRIAL DE LOS PAISES DE LA COMUNIDAD ANDINA". Quito, Ecuador 2004. Pág.. 82.

✓

Teniendo en cuenta lo anterior, procedo a demostrar que la invención de mi representada no se derivaría de manera obvia y evidente de D1 – D2 y D1 – D3, por cuanto (i) las características técnicas divulgadas en dichos documentos no enseñan ni sugieren la invención reivindicada por mi representada, **la cual tiene un efecto técnico inesperado demostrado** y (ii) el problema técnico que pretenden resolver dichos documentos diverge de aquel propuesto por mi representada.

Así bien, el problema técnico objetivo de la presente invención consiste en proporcionar una composición farmacéutica de drospirenona y etinilestradiol con una **mejor velocidad de disolución** en agua y fluidos corporales y **mayor biodisponibilidad**.

En este sentido, respetuosamente reiteramos que los inventores de la presente solicitud han descubierto que con una composición farmacéutica de drospirenona y etinilestradiol en **forma amorfa**, **sin la presencia de un estado cristalino, partiendo de droga NO micronizada**, pueden mejorar los perfiles de disolución de los dos ingredientes activos, y con ello aumentar la biodisponibilidad (ver página 2 y 3 del pliego descriptivo).

Es por lo tanto el objetivo de la presente invención proveer una composición farmacéutica que contiene drospirenona y etinilestradiol en forma amorfa, partiendo de droga no micronizada y utilizando en su preparación solvente volátil cloruro de metileno solo o en combinación con metanol y posterior adsorción sobre excipientes inertes farmacéuticamente adecuados.

El uso del solvente cloruro de metileno, y en particular el uso de la combinación de una mezcla de los solventes cloruro de metileno y metanol arroja resultados **SIGNIFICATIVAMENTE** mejores de la velocidad de disolución en comparación con el uso del metanol solo.

En este sentido, la página 22, primer párrafo del pliego descriptivo establece:

“Asimismo, en la Tabla 2 puede observarse que el USO DE CLORURO DE METILENO COMO SOLVENTE PROPORCIONA RESULTADOS SIGNIFICATIVAMENTE MEJORES EN COMPARACIÓN CON EL USO DE SÓLO METANOL COMO SOLVENTE”

Lo anterior se evidencia de los datos revelados por la Tabla 2², muestras "LPDIVuru" y "LPDISpray" que emplean cloruro de metileno y muestras "LPDIMet-16mil" y "LPDMet-154 mil" que emplean metanol. Nótese, por ejemplo que el porcentaje de drospirenona disuelta a los 10 minutos en las muestras "LPDIVuru" y "LPDISpray" es de **80.5% y 92%** respectivamente contra un porcentaje de disolución de **22% y 56%** en las muestras "LPDIMet-16mil" y "LPDMet-154 mil".

Por su parte, D1 se relaciona con una composición que comprende un primer agente activo drospirenona **en forma micronizada** y como un segundo agente activo etinilestradiol junto con uno o mas excipientes farmacéuticamente aceptables.

Conforme con los párrafos precedentes, respetuosamente reiteramos que la invención de mi representada:

- (i) Reivindica el uso de cloruro de metileno y en particular una mezcla de cloruro de metileno con metanol como solvente adecuado de disolución/granulación.

A diferencia de lo anterior, D1 **no hace mención alguna al cloruro de metileno ni a la mezcla de cloruro de metileno con metanol** como solvente.

Por el contrario, D1 solo divulga teóricamente el uso de **únicamente metanol** como solvente (sin soporte experimental) en dicha anterioridad. Todos los ejemplos de preparación y las reivindicaciones independientes están referidas a la forma micronizada. Veamos:

"En lugar de proveer lo drospirenona en forma micronizada, es posible disolverla en un solvente adecuado, por ejemplo metanol o acetato de etilo..."

- (ii) Con el fin de obtener los sorprendentes resultados revelados en la presente solicitud, la invención de mi representada requiere partir de droga en forma amorfa **no micronizada** (ver página 3, párrafo 5 y página 8, párrafos 3 y 4).

² Ver Tabla 2, Ejemplo 4 y Tabla 3, Ejemplo 5 de la presente solicitud de patente.

En este sentido, me permito llamar la atención del señor examinador al *Informe de Búsqueda Internacional* (ver Anexos) en donde la anterioridad D1 fue reconocida como documento de categoría "A", es decir, ***"documento que define el estado general de la técnica no considerado como particularmente relevante"***.

Adicional a lo anterior, la Opinión Escrita (ver Anexos) reconoce a D1 como el documento del estado de la técnica más cercano y establece:

"El problema que se pretende solucionar con la presente invención se puede considerar como el suministro de una composición con una mejor velocidad de disolución de drospirenona y etinilestradiol.

Se considera que la solución al problema propuesta en la reivindicación 1 de la presente solicitud involucra un nivel inventivo (Artículo 33(3) PCT) por las siguientes razones:

El Solicitante ha demostrado de forma creíble en la parte experimental de la descripción (página 23, tabla 2; página 25, tabla 3) que el uso de la combinación especial de solventes volátiles, es decir, cloruro de metileno y metanol resulta útil para alcanzar un mejor perfil de disolución en comparación con las composiciones de D1".(Subrayado fuera de texto)

A partir de la información revelada en las Tablas 2 y 3 del pliego descriptivo, es evidente que la composición reivindicada en la presente solicitud tiene un efecto inesperado apreciable en una mejora sorprendente en la velocidad de disolución, la cual se obtiene mediante el uso del solvente volátil cloruro de metileno y particularmente la mezcla de cloruro de metileno con metanol.

Por lo tanto, toda vez que D1 (siendo el documento más cercano del estado de la técnica) no hace mención alguna al uso de cloruro de metileno como disolvente ni mucho menos a la mezcla de cloruro de metileno con metanol, la invención de mi representada goza de nivel inventivo.

Con respecto a D2, pongo de presente que dicho documento equivale al documento EP1216712A, citado en el *Informe de Búsqueda Internacional* (ver

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Anexos) como documento de categoría "A", es decir, ***"documento que define el estado general de la técnica no considerado como particularmente relevante"***.

D2 hace referencia a complejos de inclusión entre ciclodextrina y drospirenona y un método para aumentar la solubilidad en agua de la drospirenona.

El problema técnico que se pretende solucionar en D2, a diferencia del problema técnico de la presente invención, es decir ***una composición con una mejor velocidad de disolución de drospirenona y etinilestradiol***, es una composición con una mejor velocidad de disolución de drospirenona por medio del complejo de inclusión (oligosacárido).

Por lo tanto, D2 es un documento que se encuentra dentro del mismo campo técnico, ***pero NO está dirigido a solucionar el mismo problema*** de la invención de mi representada y por lo tanto no afecta el nivel inventivo de la misma.

En este orden de ideas, D3 tampoco afecta el nivel inventivo de la invención de mi representada toda vez que el problema técnico al cual se refiere es totalmente diferente al resuelto en la presente invención.

3. Para finalizar, respetuosamente pongo de presente que si bien conozco el principio de independencia relacionado con el estudio de patentabilidad de las solicitudes de patente en fase nacional, me permito presentar copia simple de la Patente Europea EP 1848441 B1, en donde se cubre la misma materia objeto de protección de la solicitud de patente colombiana.

Teniendo en cuenta lo anterior y la identidad que existe en los requisitos de patentabilidad entre Colombia y Europa, respetuosamente solicito tener en cuenta el documento acá presentado como prueba de un claro indicio de la patentabilidad de la invención de mi representada.

Lo anterior, por cuanto el principio de independencia no implica que las decisiones que sobre patentabilidad de una invención han sido proferidas por otras oficinas de patentes no puedan ser tenidas en cuenta por la Oficina Colombiana de Patentes.

Prueba de que el principio de independencia no impide a las oficinas de patentes de los países de la Comunidad Andina tener en cuenta los estudios de patentabilidad efectuados por terceros países, es el artículo 46 de la Decisión 486, en el cual se faculta a dichas oficinas no sólo a solicitar copia de dichos estudios sino a adoptar como propias las conclusiones de los mismos, veamos:

"Art.46.- ...

La Oficina nacional competente podrá reconocer los resultados de los exámenes referidos en el literal b) como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención".

Así entonces, teniendo en cuenta que los estudios de patentabilidad efectuados por oficinas foráneas son efectivamente requeridos en algunos casos por la División de Nuevas Creaciones de la Superintendencia de Industria y Comercio para estudiar la patentabilidad de una invención, respetuosamente solicitamos con fundamento en el Artículo 50 del C.C.A. tener en cuenta la Patente Europea EP 1848441 B1, como evidencia de la patentabilidad de la invención de mi representada.

En este sentido el Honorable Consejo de Estado mediante sentencia de 13 de agosto de 2009, ha sostenido lo siguiente:

*"Aunado a lo anterior, se encuentran patentes concedidas en Perú 2727, Venezuela 96-1277 y Ecuador PI 01-169 que corresponden al objeto de la invención denegada, y si bien no obligan a la Administración, las mismas fueron otorgadas bajo los lineamientos de las normas comunitarias, ya que en ese entonces todos eran parte de los Países Miembros del Acuerdo de Cartagena que, por lo tanto, constituyen prueba, que tampoco fue desvirtuada por parte de la entidad demandada"*³

De lo anterior se pone en evidencia que las decisiones sobre patentabilidad de una invención, proferidas por otras oficinas de patentes deben ser tenidas en cuenta como prueba de patentabilidad por la Oficina Colombiana de Patentes cuando sea pertinente.

³ Consejo de Estado, Sala de lo Contencioso Administrativo Sección Primera. Sentencia de 13 de agosto de 2009. Expediente 2003-00256.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho con respecto a la solicitud de patente de la referencia, atentamente solicito se realice el examen de patentabilidad sobre la nueva materia reivindicada.

5. Anexos:

- a. Pliego reivindicatorio compuesto por doce (12) reivindicaciones.
- b. Informe de Búsqueda Internacional PCT/EP2005/053759.
- c. Opinión Escrita PCT/EP2005/053759.
- d. Copia simple de la patente EP 1848 441 B1.

De Usted Atentamente,

GERMAN CASTILLO GRAU

T.P. No. 2.978 del C.S.J.

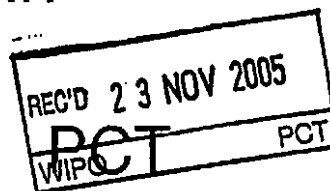
REIVINDICACIONES

1. Una composición farmacéutica que comprende drospirenona y etinilestradiol en forma amorfa, adsorbidos sobre un soporte sólido terapéuticamente inerte, en combinación con excipientes farmacéuticamente aceptables, caracterizada porque la composición comprende cantidades mensurales del solvente volátil cloruro de metileno.
2. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende cantidades mensurables de ambos solventes volátiles: cloruro de metileno y metanol.
3. La composición farmacéutica de conformidad con las reivindicaciones 1 ó 2, en donde el soporte sólido inerte se selecciona de entre partículas del grupo compuesto por almidón de maíz, almidón pregelatinizado, lactosa, croscarmelosa sódica, óxido de hierro amarillo y polivinilpirrolidona o de mezclas de uno o más de ellos, en combinación con excipientes farmacéuticamente aceptados.
4. La composición farmacéutica de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizada porque por lo menos el 80% de la drospirenona y por lo menos el 80% del etinilestradiol se disuelven desde dicha composición dentro de los 20 minutos en un ensayo realizado en un aparato de disolución de acuerdo con la Farmacopea de los Estados Unidos, Edición número 27, Aparato 2, en 900 ml de agua destilada a 37°C y agitados a 50 rpm.
5. Un método para preparar la composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, que comprende las siguientes etapas:
 - (i) disolver drospirenona y etinilestradiol en un solvente volátil o mezcla, de solventes volátiles, en donde por lo menos uno de los solventes

- volátiles es el cloruro de metileno,
 - (ii) opcionalmente agregar un polímero soluble en agua,
 - (iii) mezclar hasta la disolución,
 - (iv) aplicar la solución resultante sobre un soporte de partículas sólidas terapéuticamente inertes y
 - (v) secar el adsorbato granulado obtenido.
6. El método de la reivindicación 5, en donde el solvente volátil es una mezcla de cloruro de metileno y metanol.
 7. El método de la reivindicación 6, en donde la mezcla de cloruro de metileno y metanol es una mezcla de cloruro de metileno/metanol [9 a 4]:[3 a 0,5] v/v.
 8. El método de la reivindicación 7, en donde la mezcla de cloruro de metileno es una mezcla de cloruro de metileno/metanol 6:1 v/v.
 9. El método de cualquiera de las reivindicaciones 5 a 8, en donde en el paso 2 de la reivindicación 5 se agrega un polímero soluble en agua.
 10. El método de la reivindicación 9, en donde el polímero soluble en agua es polivinilpirrolidona.
 11. El método de cualquiera de las reivindicaciones 5 a 10, en donde el soporte sólido, terapéuticamente inerte, se selecciona de entre partículas de almidón de maíz, almidón pregelatinizado, lactosa, croscarmelosa sódica, óxido de hierro amarillo, polivinilpirrolidona o de mezclas de uno o más de ellos.
 12. El método de cualquiera de las reivindicaciones 5 a 11, en donde adicionalmente el adsorbato granulado secado se combina con excipientes farmacéuticamente aceptables para la compresión de los comprimidos.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/EP2005/053759	International filing date (day/month/year) 02.08.2005	Priority date (day/month/year) 09.08.2004	
International Patent Classification (IPC) or both national classification and IPC A61K31/565, A61K31/57, A61P15/18			
Applicant LICONSA, LIBERACION CONTROLADA DE SUSTANCIAS ...			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Beyss-Kahana, E Telephone No. +49 30 25901-344
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/053759

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/053759

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-24
	No: Claims	
Inventive step (IS)	Yes: Claims	1-24
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-24
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2005/053759

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

Reference is made to the following document:

D1: WO-A-0115701

D1 (page 4, line 11-24; page 9, line 17-23; example 2; claims 1, 2), which is considered to represent the most relevant state of the art, discloses a pharmaceutical composition containing drospirenone and ethinylestradiol. Both compounds are micronized or sprayed onto particles of an inert carrier in order to accelerate the dissolution.

The subject-matter of claim 1 differs from this known composition in that it comprises measurable amounts of methylene chloride

The subject-matter of claim 1 is therefore new (Article 33(2) PCT).

The problem to be solved by the present invention may be regarded as the provision of a composition with improved dissolution rate of drospirenone and ethinylestradiol.

The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

The Applicant has credibly demonstrated in the experimental part of the description (page 23, table 2; page 25, table 3) that the use of the special combination of volatile solvents namely methylene chloride and methanol is useful in order to achieve an improved dissolution profile in comparison with the compositions of D1.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 5, 13, 17, 22, 23 which therefore are also considered inventive.

↓

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

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International application No.

PCT/EP2005/053759

Claims 2-4, 6-12, 14-16, 18-21, 24 are dependent on claims 1, 5, 13, 17, 22, 23 and as such also meet the requirements of the PCT with respect to novelty and inventive step. Claims 1-24 meet the requirements of Article 33(4) PCT.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 February 2006 (16.02.2006)

PCT

(10) International Publication Number
WO 2006/015956 A1

(51) International Patent Classification⁷: A61K 31/565,
31/57, A61P 15/18

(21) International Application Number:
PCT/EP2005/053759

(22) International Filing Date: 2 August 2005 (02.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04103837.3 9 August 2004 (09.08.2004) EP

(71) Applicant (for all designated States except US): LI-
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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING DROSPIRENONE AND ETHYNYLESTRADIOL

(57) Abstract: A pharmaceutical composition that comprises drospirenone and ethynylestradiol with an improved dissolution rate.
A method of preparation of a pharmaceutical formulation that comprises drospirenone and ethynylestradiol in order to improve its
dissolution profile. Said formulation can be used to produce an anovulatory effect when administered correctly in humans.

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INTERNATIONAL SEARCH REPORT

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/15701 A (HEITHECKER RENATE ; HEIL WOLFGANG (DE); SCHERING AG (DE); HILMAN JUERG) 8 March 2001 (2001-03-08) cited in the application page 4, lines 11-24; claims 1,2; figure 1; example 2	1-24
A	EP 1 216 712 A (SCHERING AG) 26 June 2002 (2002-06-26) cited in the application claims 1,9,12	1-24
A	US 4 727 064 A (PITHA JOSEF) 23 February 1988 (1988-02-23) column 2, lines 37-40; claim 1	1-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Information on patent family members

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(54) **PHARMACEUTICAL COMPOSITION COMPRISING DROSPIRENONE AND ETHYNYLESTRADIOL**
PHARMAZEUTISCHE ZUSAMMENSETZUNG MIT DROSPIRENON UND ETHINYLÖSTRADIOL
COMPOSITION PHARMACEUTIQUE CONTENANT ÉTHYNYLESTRADIOL ET DROSPIRÉNONE

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Description

FIELD OF THE INVENTION:

5 [0001] The present invention refers to a pharmaceutical composition that comprises drospirenone and ethynylestradiol with an improved dissolution rate. In addition, the invention refers to a method of preparation of a pharmaceutical formulation that comprises drospirenone and ethynylestradiol in order to improve its dissolution profile. Said formulation can be used to produce an anovulatory effect when administered correctly in humans.

10 BACKGROUND OF THE INVENTION:

[0002] It is known that the estrogenic and progestagen sexual hormones are practically insoluble in water or are so slowly dissolved that their biopharmaceutical properties are directly affected by this behavior or characteristic.

15 [0003] In particular, the synthetic progestagen drospirenone, or 6 β ,7 β , 15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone, known from the patents DE3022337 and DE2652761, has a "spatula" form in its crystalline state as can be seen in the microphotographs in Figure 1 herein magnified 200x with a size no less than 50 microns. The dissolution rate of this crystal in oral pharmaceutical formulations such as tablets shows a very slow dissolution rate as shown in Figure 17 herein (see batches LP01, LP02 and LP03).

20 [0004] The published application EP1216712A1 discloses the preparation of inclusion complexes between cyclodextrin and drospirenone with the aim of increasing the solubility of drospirenone in water.

[0005] The bioavailability of a drug can be limited by a poor dissolution of the same in corporal aqueous fluids, particularly gastric fluids, immediately after administration. The dissolution rate can therefore be critical to rapidly reach therapeutically effective drug levels or in addition, as is the case for drospirenone, it can be influenced by the degradation of the active ingredient due to prolonged contact with gastric fluids with a very low pH, as described in the application

25 WO01/15701 (in patent family with EP1214076B1).
[0006] This behavior is seen *in vitro*, in an acidic medium (HCl 0.1 N), for samples of drospirenone with different particle sizes (see Figure 16 herein). It can be observed that the presence of the drug in the acidic medium decreases rapidly, after an initial dissolution, regardless of the size of the particles. Drospirenone's bioavailability is therefore doubly affected by the low dissolution rate in aqueous medium and by rapid degradation due to prolonged contact with gastric

30 fluids with a very low pH.
[0007] The published patent EP1214076B1 discloses a pharmaceutical composition containing drospirenone and ethynylestradiol where the drospirenone is in a micronized form so that the particles of the active substance have a superficial area of more than 10.000 cm²/g, and a distribution of the size of the particles determined under a microscope where no more than two particles in a given batch have a diameter of more than 30 μ m and preferably 20 particles or

35 less have a diameter between 10 μ m and 30 μ m, thus increasing its dissolution rate particularly for use in oral contraception.
[0008] Further the final part of section [0017] of EP1214076B1 reads "Instead of providing the drospirenone in micronized form, it is possible to dissolve it in a suitable solvent, e.g. methanol or ethyl acetate, and spray it onto the surface of inert carrier particles followed by incorporation of the particles containing drospirenone on their surface in the composition." However, this section stands alone in the description of EP1214076B1. All working examples plus independent

40 SUMMARY OF THE INVENTION:

45 [0009] The problem to be solved by the present invention is to provide a pharmaceutical composition of drospirenone and ethynylestradiol with an improved dissolution rate in water and bodily fluids and improved bioavailability.

[0010] The present inventors have discovered that with a pharmaceutical composition of drospirenone and ethynylestradiol in an amorphous form, without the presence of a crystalline state, they can improve the dissolution profiles of both active ingredients, thus increasing their bioavailability.

50 [0011] Further, the present inventors have demonstrated that use of the volatile solvent methylene chloride and in particular use of the combination of a mixture of the solvents methylene chloride and methanol gives SIGNIFICANT improved dissolution rate results over the use of methanol alone. For further details see e.g. Table 2 of Example 4 and Table 3 of Example 5 herein. Use of methanol alone is theoretically suggested in the prior art document EP1214076B1 (see above).

55 [0012] As explained herein, the volatile solvent methylene chloride is used to dissolve the drugs. In the subsequent granulation step there is dried until the residual levels of solvent is very low (see Example 1). However, even though it is low it is known to the skilled person that it is still possible to measure small amounts of the volatile solvent of interest in the final pharmaceutical composition. As known to the skilled person this may e.g. be done by use of gas chromatog-

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raphy (GC) and mass spectrometry (MS).

[0013] Therefore, the first aspect of the present invention refers to a pharmaceutical composition that comprises drospirenone and ethynylestradiol in an amorphous form, adsorbed on a therapeutically inert solid support, in combination with pharmaceutically acceptable excipients, characterized by that the composition comprises measurable amounts of the volatile solvent methylene chloride.

[0014] As said above, it is herein preferred to use a mixture of the solvents methylene chloride and methanol. Accordingly, in a preferred embodiment the composition of the first aspect is characterized by that the composition comprises measurable amounts of both of the volatile solvents methylene chloride and methanol.

[0015] The dissolution rate of drospirenone and ethynylestradiol is increased by introducing changes in their crystalline structure, so that the energy needed to dissolve the drug is much lower. In this case, the dissolution rate will increase considerably, thus achieving an increase in the drugs absorption rate. This way, the time the drugs are in contact with the gastric medium where the pH is too low is reduced, thus avoiding the eventual degradation reactions of the sensitive drugs by hydrolysis, as described above.

[0016] It is therefore an aim of the present invention to provide a pharmaceutical composition that contains drospirenone and ethynylestradiol in an amorphous form, without the presence of the crystalline state, preferably beginning with a non-micronized drug and using adequate dissolution/granulation solvents in its preparation.

[0017] Surprisingly, it has been discovered that the greatest dissolution rate is obtained by solubilization of drospirenone and ethynylestradiol in the appropriate combination of a mixture of the solvents methylene chloride and methanol and subsequent adsorption on adequate pharmaceutically inert excipients.

It has been observed that the use of another solvent, such as ethanol, even with heat, despite dissolving the drug, does not allow the application on pharmaceutically adequate excipients.

Further, use of methylene chloride and in particular use of the combination of a mixture of the solvents methylene chloride and methanol gives improved results over the use of methanol alone.

[0018] The new pharmaceutical composition of the invention is designed to provide a rapid dissolution of drospirenone and ethynylestradiol in water as the reference solvent.

[0019] More particularly, the invention provides a solid particulate composition that comprises drospirenone and ethynylestradiol in an amorphous state and adsorbed on a therapeutically inert support, with some components being soluble in water and others being insoluble in water, characteristics which facilitate a rapid disintegration of the pharmaceutical formulation.

[0020] Even more particular is an additional aim of the invention of a pharmaceutical composition that offers an improved dissolution of drospirenone and ethynylestradiol, which comprises a solid particulate formulation of an adsorbate consisting of drospirenone and ethynylestradiol in an amorphous state adsorbed on a solid, therapeutically inert, support, in combination with pharmaceutically acceptable excipients.

[0021] In a preferred embodiment, the solid particulate composition consists of particles selected from the following group of materials or adequate mixtures thereof: corn starch, pregelatinized starch, lactose, Croscarmellose sodic, yellow iron oxide and povidone covered with drospirenone and ethynylestradiol in an amorphous state.

[0022] Furthermore, another aim of the present invention is the preparation process of a pharmaceutical composition of drospirenone and ethynylestradiol, where said active compounds are found in an amorphous state and free of crystalline shapes.

[0023] Consequently, a second aspect of the present invention relates to a method for the preparation of a new pharmaceutical composition of drospirenone and ethynylestradiol, of the first aspect, that comprises following steps: i) dissolving drospirenone and ethynylestradiol in a volatile solvent or mixture of volatile solvents, ii) optionally adding a water-soluble polymer, iii) mixing until dissolution, iv) applying the resulting solution onto the solid, therapeutically inert support of particles, and v) drying the resulting adsorbate.

Preferably, at least one of the volatile solvent(s) of step (i) is methylene chloride. Preferably, there is added a water-soluble polymer in step (ii).

[0024] The active compounds drospirenone and ethynylestradiol, used in the preparation of the pharmaceutical composition of the invention are preferably in the form of non-micronized particles, more preferably with an average diameter no less than 50 μm and a specific surface area of less than approximately 5000 cm^2/g measured by the BET technique.

[0025] Advantageously, the use of non-micronized forms reduces the environmental inconveniences associated with an additional stage in the manipulation of hormones, such as the process of micronization.

[0026] A third aspect of the invention relates to a pharmaceutical preparation that comprises a number of dose units for daily oral administration for a period of at least 21 consecutive days, where said dose units comprises approximately from 1 to 4 mg of drospirenone and approximately from 0,01 to 0,05 mg of ethynylestradiol, characterized in that said drospirenone and ethynylestradiol are in an amorphous form, adsorbed on a therapeutically inert solid support, of the first aspect of the invention or embodiments thereof as described herein, in combination with pharmaceutically acceptable excipients.

[0027] A fourth aspect of the invention relates to use of drospirenone combined with ethynylestradiol for preparing a

pharmaceutical composition, of the first aspect of the invention or embodiments thereof as described herein, for the anovulation of a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 1 mg to 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the composition, of from about 0.01 to 0.05 mg.

[0028] This fourth aspect may alternatively be formulated as a method for the anovulation of a mammal, in particular a human, that consists of administering a pharmaceutical composition, of the first aspect of the invention or embodiments thereof as described herein, made up of a number of dose units for daily oral administration, where said dose units consist of approximately 1 mg to 4 mg drospirenone and approximately 0.01 to 0.05 mg of ethinylestradiol, in which the drospirenone and ethinylestradiol are in an amorphous shape, adsorbed onto a solid therapeutically inert support, in combination with acceptable pharmaceutical excipients.

BRIEF DESCRIPTION OF THE FIGURES:

[0029]

Figure 1 shows the microphotographs of drospirenone in its crystalline state (magnified 200x)

Figure 2A shows a microphotograph of a lactose particle;

Figure 2B shows a microphotograph of a group of lactose particles;

Figure 2C shows a microphotograph of a particle of corn starch;

Figure 2D shows a microphotograph of a group of corn starch particles;

Figure 2E shows a microphotograph of a particle of pregelatinized starch;

Figure 2F shows a microphotograph of a group of pregelatinized starch particles;

Figure 2G shows a microphotograph of a particle of sodic Croscarmellose;

Figure 2H shows a microphotograph of a group of sodic Croscarmellose particles;

Figure 2I shows a microphotograph of a particle of yellow iron oxide;

Figure 2J shows a microphotograph of a group of yellow iron oxide particles;

Figure 2K shows a microphotograph of a particle of Povidone;

Figure 2L shows a microphotograph of a group of Povidone particles;

Figure 3 shows a microphotograph of a physical mixture of the two distinct components of the adsorbate;

Figures 4A and 4B show microphotographs of the adsorbate of drospirenone and ethinylestradiol on the components that are adequate for obtaining the tablets.

Figure 5 shows a graph of the DSC of lactose alone;

Figure 6 shows a graph of the DSC of drospirenone;

Figure 7 shows a graph of the DSC of magnesium stearate;

Figure 8 shows a graph of the DSC of corn starch;

Figure 9 shows a graph of the DSC of pregelatinized starch;

Figure 10 shows a graph of the DSC of yellow iron oxide;

Figure 11 shows a graph of the DSC of sodic Croscarmellose (Ac-Di-SoD)

Figure 12 shows a graph of the DSC of Povidone;

Figure 13 shows a graph of the DSC of placebo (mixture of the excipient components with the absence of ethinylestradiol and drospirenone)

Figure 14 shows a graph of the DSC of a simple mixture of the components of the adsorbate.

Figure 15 shows a graph of the DSC of the granules of Example 1 which contains drospirenone and ethinylestradiol adsorbed on the inert excipients.

Figure 16 shows the dissolution profiles for the tablets of drospirenone in a strongly acidic aqueous medium HCl 0.1 N.

Figure 17 shows the dissolution profiles for the tablets of the invention containing amorphous drospirenone adsorbed on inert excipients, compared to those of compositions containing crystalline drospirenone of various-sized particles.

Figure 18 shows the dissolution profiles for the tablets of the invention containing amorphous ethinylestradiol adsorbed on inert excipients, compared to those of compositions containing crystalline ethinylestradiol of various-sized particles.

DETAILED DESCRIPTION OF THE INVENTION:

A pharmaceutical composition comprising drospirenone and ethinylestradiol and a method for preparing it:

[0030] In agreement with the first aspect, the present invention provides a solid particulate formulation that consists of drospirenone and ethinylestradiol in an amorphous state adsorbed on a pharmaceutically acceptable and therapeutically inert support.

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[0031] The term "adsorbed on a therapeutically inert solid support" may herein also be termed "adsorbed on a therapeutically inert solid base" and the terms may herein be used interchangeably.

[0032] Preferably, the solid particulate formulation contains particles of pharmaceutically acceptable excipients covered with drospirenone and ethynylestradiol in an amorphous state and ready to be compressed into their definitive pharmaceutical formulation.

[0033] The composition of the invention can be obtained according to the following steps:

i) dissolving drospirenone and ethynylestradiol in a mixture of volatile solvents, ii) adding a polymer that is water-soluble and/or soluble in the volatile solvent or mixture of volatile solvents, iii) mixing until dissolution, iv) applying the resulting solution onto a support of pharmaceutically acceptable and therapeutically inert solid particles, v) drying the resulting adsorbate.

[0034] The volatile solvent may be methanol. However, preferably, the volatile solvent is methylene chloride and even more preferable is a mixture of methylene chloride and methanol, which is acceptable to use in drug manufacturing processes.

[0035] Preferably the volatile solvent is a [9 to 4]:[3 to 0.5] v/v mixture of methylene chloride/methanol. Within the range of mixtures it is preferred that the volatile solvent is a 6:1 v/v mixture of methylene chloride/methanol or a 5:2 v/v mixture of methylene chloride/methanol.

[0036] The drospirenone can be prepared as described, in for example, US 4.129.564. The drug drospirenone used in the preparation of the pharmaceutical composition of the invention is preferably in the form of non-micronized particles with an average diameter of no less than 50 μm and a specific surface area of less than approximately 5000 cm^2/g obtained by the BET technique.

[0037] The estrogen ethynylestradiol can be prepared according to the methods described in GB 516.444, US 2.243.887, US 2.251.939, US 2.265.976 and US 2.267.257. The drug ethynylestradiol used in the preparation of the pharmaceutical composition of the invention is preferably in the form of non-micronized particles with an average diameter no less than 50 μm and a specific superficial area obtained by the BET Technique of less than approximately 5000 cm^2/g .

[0038] Water-soluble polymers that are acceptable for the preparation of the binder solution are preferably chosen from the polyvinylpyrrolidones as preferred in the method of the invention, more preferably polyvinylpyrrolidone Povidone K 30 (such as that provided by BASF or ISP).

[0039] Examples of other suitable water-soluble polymers include a polymer selected from the group consisting of: Alginic acid, Carbomer, Carboxymethylcellulose Sodium, Carrageenan, Dextrin, Hydroxypropyl Methylcellulose, Polyethylene Glycol, Polymethacrylates, Polyvinil Alcohol and Povidone K90.

[0040] The resulting solution is applied onto a base of solid particles, which are pharmaceutically acceptable and therapeutically inert. The application is preferably done using a mixer/granulator like a Pony mixer. However, it may also be done by other techniques such as fluid bed based spraying.

[0041] The adequate particle materials used to make the base of the invention are preferably chosen from either starch, pregelatinized starch, lactose, sodic Croscarmellose, or yellow iron oxide and mixtures of the same.

[0042] The lactose used is preferably monohydrate lactose, which is commonly used as an excipient and diluent in the pharmaceutical industry. This lactose can be provided by manufacturers such as MEGGLE, QUEST International, or BORCULO Whey Products.

[0043] The starch can be from corn or potatoes, and is commonly used as a diluent in the pharmaceutical industry. The starch can be provided by: ORCON, OAVEBE, CERESTAR INT. SALES, GRAIN PROCESSING CORP., PARTICLE DYNAMICS INC., GLUTAL, etc.

[0044] The pregelatinized starch can be from corn or potatoes, and is commonly used as a diluent and agglutinant in the pharmaceutical industry. The pregelatinized starch can be provided by: COLORCON, OAVEBE, CERESTAR INT. SALES, GRAIN PROCESSING CORP., PARTICLE DYNAMICS INC., GLUTAL, etc.

[0045] The sodic croscarmellose, commonly used as a superdisintegrants in the pharmaceutical industry, can be provided by COLORCON, ALLCHEM INTERNATIONAL, METSA SPECIALITY CHEMICAL LTD, AVEBE, etc.

[0046] The yellow iron oxide, commonly used as a coloring material in the pharmaceutical industry, can be provided by COLORCON.

[0047] The magnesium stearate, commonly used as a lubricant in the pharmaceutical industry, can be provided by LE STAR QUIMICA.

[0048] The granules obtained can be dried using any known drying method within the art, preferably the drying may be done in a static bed dryer.

[0049] The drying is carried out until obtaining a granule with residual levels of solvent that are 100 times below that permitted by the International Harmonization Conference on technical requirements for the registration of pharmaceutical products for human use, in its guide Q3C.

[0050] By subjecting the granule to drying, the presence of polyvinylpyrrolidone in the drospirenone and ethynylestradiol

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solution acts by the formation of a tridimensional polymer structure, preventing the crystalline growth of drospirenone and ethynylestradiol, in such a way that the drugs are deposited onto the excipient particles in an amorphous state. Subsequently, this mixture should only be lubricated in order to compress it and obtain a pharmaceutical formulation that gives the dose unit.

[0051] A separate aspect of the invention relates to a pharmaceutical composition that comprises drospirenone and ethynylestradiol in amorphous form, adsorbed on a therapeutically inert solid support, in combination with pharmaceutically acceptable excipients obtained by a method for the preparation of a pharmaceutical composition of the second aspect of the invention and embodiments thereof as described herein.

[0052] Particular examples of preparation are given below. The purposes of these are merely illustrative and are not intended to limit the scope of the invention, which is determined by the claims.

Pharmaceutical preparation:

[0053] Preferably, the pharmaceutical preparation of the third aspect of the invention is characterized because it comprises of drospirenone and ethynylestradiol in amorphous form, adsorbed on a solid basis chosen from among particles selected from the group consisting of corn starch, pregelatinized starch, lactose, sodic croscarmellose, yellow iron oxide, polyvinylpyrrolidone or mixtures of one or more of the same, in combination with pharmaceutically acceptable excipients.

[0054] Further, the pharmaceutical preparation is preferably characterized because at least 80% of drospirenone dissolves from said dose units within 20 minutes, in a test carried out in a dissolution apparatus according to the U.S. Pharmacopoeia, Edition number 27, Apparatus 2, in 900 ml of distilled water at 37°C and stirred at 50 rpm.

[0055] In a further embodiment the pharmaceutical preparation is preferably characterized because at least 80% of ethynylestradiol dissolves from said dose units within 20 minutes, in a test carried out in a dissolution apparatus according to the U.S. Pharmacopoeia, Edition number 27, Apparatus 2, in 900 ml of distilled water at 37°C and stirred at 50 rpm.

[0056] Compositions particularly adequate for oral administration are unitary dose formulations such as tablets, capsules, pills, powder in packets, etc. These dose units will normally contain an amount of drospirenone in the range from approximately 1 mg to approximately 4 mg, with 3 mg being preferable, and an amount of ethynylestradiol in the range from approximately 0,01 to approximately 0,05 mg, with 0,02 to 0,03 mg being preferable.

A method for the anovulation a mammal:

[0057] This fourth aspect may alternatively be formulated as a method for the anovulation of a mammal, in particular a human, that consists of administering a pharmaceutical composition, of the first aspect of the invention or embodiments thereof as described herein, made up of a number of dose units for daily oral administration, where said dose units consist of approximately 1 mg to 4 mg drospirenone and approximately 0,01 to 0,05 mg of ethynylestradiol, in which the drospirenone and ethynylestradiol are in an amorphous shape, adsorbed onto a solid therapeutically inert support, in combination with acceptable pharmaceutical excipients.

[0058] With respect to the method for the anovulation of a mammal, in particular a human, of the fourth aspect of the invention, the daily oral administration is preferably for a period of at least 21 consecutive days.

[0059] Further, there may be 7 or less said daily dosage units containing no active agent.

[0060] Alternatively, it is possible to include, in the dosage regimen, a period of 7 days or less during which no dosage units are ingested.

[0061] In suitable embodiments, the number of daily dosage units comprising the combination of drospirenone and ethynylestradiol may be 21, 22, 23 or 24, and the number of daily dosage units containing no active agent may then be 7, 6, 5 or 4, as the case may be.

[0062] Alternatively, the a pharmaceutical composition, of the first aspect of the invention or embodiments thereof as described herein, may be used for hormone replacement therapy (HRT). The skilled person knows how to optimise doses and administration with respect to hormone replacement therapy.

Pharmaceutically acceptable excipient

[0063] By "pharmaceutically acceptable excipient" it should be understood as any pharmaceutically acceptable conventional vehicle including binders, tablet disintegrants, diluents, lubricants, tablet glidants, opacifiers of tablets and capsules, colorings, sweeteners, flavoring, antioxidants, buffer agents, etc.

[0064] As used here, the expression "binders" designates substances used to provoke the adhesion of the dust particles in the granules of the tablets, and include as examples and without being limiting, sodic carboxymethylcellulose, polyvinylpyrrolidone, sugars, ethylcellulose, gelatin, guar gum, polyethylene glycol, polyethylene oxide or combinations of the same and similar ones known to those with common knowledge of the art.

[0065] As used here, the expression "tablet desintegrants" designates a compound used in solid dosing formulations to promote the rupture of the solid mass into small particles. Examples of desintegrants include, without being limiting, starches, pregelatinized starches, bentonite, microcrystalline cellulose and its esters and salts, calcium or sodium carboxymethylcellulose and its modifications, alginates, reticulated povidone, gums such as guar, agar, pectin and the like that are known to those with common knowledge of the art.

[0066] As used here, the expression "tablet diluents or filler" designates inert substances used as filling materials to create the desired mass, in the preparation of tablets and capsules, and include, as examples and without being limiting, dibasic calcium phosphate, kaolin, lactose, saccharose, mannitol, microcrystalline cellulose, sorbitol, starch and sugars (mono and polysaccharides) and the like known to those with common knowledge in the art.

As used here, the expression "lubricant" designates substances used in the formulations of tablets to reduce friction during the compression of the tablets, that include, as examples and without being limiting, calcium stearate, magnesium stearate, mineral oil, stearic acid, 1-Leucine, zinc stearate, talc and the like that are known by those with common knowledge in the art.

[0067] As used here, the expression "tablet glidants" or "flow promoters" designates agents used in the formulations of capsules and tablets to promote the fluidity of the granulation, that include, as examples and without being limiting, colloidal silica, corn starch, talc calcium silicate, magnesium silicate, and the like that are known by those with common knowledge in the art.

As is used here, the expression "opacifiers of tablets and capsules" designates a compound used to coat a tablet or capsule with an opaque covering combined or not with a coloring, and include, as examples and without being limiting, titanium dioxide, magnesium carbonate, calcium carbonate and the like that are known by those with common knowledge of the art.

[0068] As is used here, the expression "coloring" designates a compound used to give color to the pharmaceutical compositions, as for example and without being limiting, caramel, ferric oxide, beta carotene, carmine, curcumin, coloring bases and their sprays and other materials known by those with common knowledge in the art.

[0069] As used here, the expression "sweetening agent" designates a compound used to give a preparation a sweet flavor, and include as examples without being limiting, saccharose, dextrose, aspartame, mannitol, sodium saccharin, sorbitol and the like known by those with common knowledge of the art.

[0070] As is used here, the expression "flavoring" designates a compound used to give flavor and/or a pleasant aroma to a pharmaceutical preparation. Examples of flavoring agents include, without being limiting, flavoring and aromatic oils, synthetic flavorings and/or natural oils, and plant extracts, leaves, flowers, fruits and other combinations of the same.

[0071] As is used here, the expression "antioxidant" designates an agent that prevents the oxidation and therefore the deterioration of the active agent and other components by oxidative processes, and include as examples without being limiting ascorbic acid, ascorbyl palmitate, sodium bisulfate and the like known by those with common knowledge of the art.

[0072] As used here, the expression "buffer agent" designates a compound used to resist the change in pH when there is dissolving or the addition of acids or alkalines in the composition, and include as examples without being limiting, potassium metaphosphate, potassium phosphate, monobasic sodium acetate, sodium citrate and the like known by those with common knowledge of the art.

[0073] It should be understood that the compounds used in the art of pharmaceutical formulations generally serve a variety of functions and objectives, meaning that the agents mentioned are therefore not for a specific function or limited to that function.

Separate independent aspects of the invention

[0074] As explained herein and demonstrated in working examples herein (see e.g. Table 2 of Example 4 and Table 3 of Example 5) a pharmaceutical composition as described herein may be characterized by a very good dissolution profile. More specifically, it may be characterized by that at least 80% of drospirenone and ethynylestradiol dissolves from said composition within 20 minutes in a test carried out in a recognized standard dissolution apparatus.

[0075] This is the first time that a pharmaceutical composition has been described with such a preferred dissolution profile and it is a significant contribution to the art. As explained herein, such a pharmaceutical composition is preferably obtained by use of methylene chloride as one of the volatile solvents. However once the skilled person now knows that one may be able to obtain such a pharmaceutical composition he could further investigate the issue and probably identify other solvents than methylene chloride that could be used to make adequate pharmaceutical compositions.

[0076] Accordingly, a separate independent aspect of the invention relates to a pharmaceutical composition that comprises drospirenone and ethynylestradiol in amorphous form, adsorbed on a therapeutically inert solid support, in combination with pharmaceutically acceptable excipients, **characterized in that** at least 80% of drospirenone and at least 80% of the ethynylestradiol dissolve from said composition within 20 minutes in a test carried out in a dissolution apparatus according to the U.S. Pharmacopoeia, Edition number 27, Apparatus 2, in 900 ml of distilled water at 37°C

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and stirred at 50 rpm.

[0077] As discussed above, the pharmaceutical composition of this separate independent aspect of the invention may be made by use of methylene chloride as volatile solvent. However, it may also be made by use of other volatile solvent (s) not involving methylene chloride.

[0078] In line of this, another separate independent aspect of the invention relates to a method for the preparation of a pharmaceutical composition, of above mentioned separate independent aspect of the invention that comprises following steps:

- i) dissolving drospirenone and ethynylestradiol in a volatile solvent or mixture of volatile solvents,
- ii) optionally, adding a water-soluble polymer,
- iii) mixing until dissolution,
- iv) applying the resulting solution onto a base of solid particles that are therapeutically inert,
- v) drying the obtained granulated adsorbate.

[0079] Preferably, there is in step ii) added a water-soluble polymer.

[0080] The working examples herein provide guidance in order to identify other (not methylene chloride) adequate volatile solvents. For instance, in comparative example 2B is shown that 16 ml of methanol alone is not enough to completely dissolve 3.06g of drospirenone. This may be used as basis for identifying suitable solvents. One may repeat the dissolution protocol, as described in working example 1 herein, but using a panel of other suitable solvent candidates. The ones that are capable of completely dissolving drospirenone are herein preferred solvents.

[0081] Accordingly, a preferred embodiments of the method of the separate independent aspect above, is wherein the volatile solvent or mixture of volatile solvents of step i) is/are solvent(s) that are capable of completely dissolving drospirenone in the following dissolution assay:

16.0 ml of the volatile solvent or mixture of volatile solvents are placed in a stainless steel stirring apparatus, next, 0.0306 g of ethynylestradiol (non-micronized with a particle size no less than 50 µm) are added under constant stirring, the mixture is shaken/stirred until completely dissolved, next 3.06 g of drospirenone (non-micronized with a particle size no less than 50 µm) are added under constant stirring until the drospirenone is completely dissolved.

[0082] All embodiments described above in relation to the aspects of the invention described above are also preferred embodiments in relation to the separate independent aspects of the invention as described in this section.

EXAMPLES:

Examples for Reference

Dissolution profiles of crystalline drospirenone in acidic medium

[0083] The dissolution profiles were obtained from tablets containing drospirenone in a crystalline state with different sized particles, using a dissolution apparatus designated in the U.S. Pharmacopoeia, Edition 27, apparatus 2, at 50 rpm and 900 ml of lauryl sulfate 0,07% in a strongly acidic medium, HCl 0,1 N, thermostated at 37°C. The results of the amounts of dissolved drug at different time-points are summarized in the following table:

Table 1

	% of drospirenone dissolved					
Time (minutes)	0	10	20	30	45	60
LP01	0	50,1%	47,9%	37,6%	33,8%	26,7%
LP02	0	38,1%	33,5%	29,7%	23,8%	20,5%
LP04	0	85,3%	76,5%	64,6%	51,1%	42,2%

Samples:

[0084]

- LP01: Batch of tablets with non-micronized, crystalline drospirenone with an average particle size of > 100 µm
- LP02: Batch of tablets with non-micronized, crystalline drospirenone with an average particle size = 100 µm
- LP04: Batch of tablets with micronized, crystalline drospirenone with an average particle size = 10 µm

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[0085] For a better interpretation of the results shown in Table 1, the results are also shown in Figure 16. From this figure one can see the instability of the drospirenone in an acidic medium, regardless of the size of the particle.

EXAMPLE 1

[0086] Amount required for producing 1000 tablets:

Granule:

[0087]

Drospirenone (+ 2% excess for losses during the process)	3,0600 g
Ethinylestradiol(+ 2% excess for losses during the process)	0,0306 g
Corn starch	12,7800 g
Pregelatinized starch	15,4400 g
Monohydrate lactose	44,0000 g
Sodic croscarmellose	0,4000 g
Yellow iron oxide	0,0900 g
Povidone	3,4000 g
Methylene chloride / methanol (6:1)	16,0000 ml

Lubrication and final mixture:

Sodic Croscarmellose	0,4000 g
Magnesium stearate	0,4000 g

Covering/coating:

Aqueous clear lake 5% (OPADRY YS-1-7006 at 5%)	0,0060 g
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II. PREPARATION TECHNIQUE

II.1. Dissolution of the active ingredients and binder

[0088] 16,00 ml of the dichloromethane/methanol solution at a 6:1 ratio were placed in a stainless steel stirring apparatus . Next, 0.0306 g of ethinylestradiol, non-micronized with a particle size no less than 50 µm (addition of an excess of 2% was foreseen to make up for losses during the process), were added under constant stirring. The mixture was shaken/stirred until completely dissolved. 3.0600 g of drospirenone, non-micronized with a particle size no less than 50 µm (addition of an excess of 2% was foreseen to make up for losses during the process), were added under constant stirring until completely dissolved. Once dissolved, 3.4000 g of polyvinylpyrrolidone K-30 were added with stirring until completely dissolved.

II.2. Granulation - Drying

[0089] In a planetary-type mixer, the following, which were previously adequately sized by a 30 mesh net, were added: 44.0000 g of monohydrate lactose, 12.7800 g of corn starch, 15.4400 g of pregelatinized starch, 0.4000 g of sodic croscarmellose and 0.0900 g of yellow iron oxide. These were mixed for 15 to 20 minutes.

[0090] Next, the previously prepared binder solution that contains the active ingredients was added, and they were kneaded until reaching an adequate consistency for granulating. If necessary, it is possible to add additional solvent (mixture 6:1 of dichloromethane/methanol).

[0091] The wet mass was granulated by making it pass through a 10 mesh net. It was dried in a heater at 40°C for 24 hours, until reaching residual levels of solvent that were 100 times less than that allowed by the International Conference of Harmonization of technical requirements for the registration of pharmaceutical products for human use, its guide Q3C.

[0092] In a separate experiment, the binder solution was applied onto the base of solid particles via spraying. It was done in the following way. In a fluid bed dryer / granulator, previously sized by a 30 mesh, were added: 44.0 g of monohydrate lactose, 12.780 g of corn starch, 15.44 g of pregelatinized starch, 0.400 g of sodic croscarmellose and

0.0900 g of yellow iron oxide. These were mixed for 15 to 20 minutes. Then, the previously prepared binder solution that contains the active ingredients was sprayed. The wet mass was dried at 40°C.

II.3. Final Mixture - Compression - Covering

[0093] The dried granulate was passed through net 18, followed by the addition of 0.4000 g of sodic croscarmellose and 0.4000 g of magnesium stearate. These were mixed for 15 minutes. The resulting granules were compressed into tablets using a rotating machine equipped with a set of flat biconcave punchers of 13/64" in diameter at a weight of 80 mg/tablet and a force of 6-12 Stron Cobb units.

The compressed tablets were coated with an aqueous clear lake 5%. Name of the batch granulated in the planetary-type mixer: LPDIVuru and name of the batch granulated in the fluid bed dryer: LPDISpray.

The morphology of the components in each step of the process has been analyzed under an electronic microscope. The microphotographs in Figure 1, magnified 200x, show crystals of drospirenone, with its characteristic "spatula" shape at sizes greater than 50 µm. Figures 2A to 2L show microphotographs of the therapeutically inert materials used as a base for the active agents. In particular, Figures 2A and 2B show microphotographs of a lactose particle and of a group of lactose particles, respectively; Figures 2C and 2D show microphotographs of a corn starch particle and a group of corn starch particles, respectively; Figures 2E and 2F show microphotographs of a particle of pregelatinized starch and a group of pregelatinized starch particles, respectively; Figures 2G and 2H show microphotographs of a particle of sodic croscarmellose and a group of sodic croscarmellose particles, respectively; Figures 2I and 2J show microphotographs of a particle of yellow iron oxide and a group of yellow iron oxide particles, respectively; Figures 2K and 2L show microphotographs of a particle of Povidone and of a group of Povidone particles, respectively. Figure 3 is a microphotograph of a physical mixture of the different components. Figures 4A and 4B are microphotographs of particles of the adsorbate of drospirenone and ethynylestradiol on the inert components, in two views.

EXAMPLE 2

[0094] A batch of 1000 tablets were prepared using a process similar to that described in Example 1, where the mixture of volatile solvents methylene chloride / methanol were applied at a proportion of 5:2. Results similar to those described in Example 1 were obtained.

EXAMPLE 2B

[0095] This is a comparative example, where only methanol was used as solvent. Only the differences compared to example 1 is given below. The rest was done identical to example 1.

[0096] In the first example was used 16 ml methanol only. The 16 ml is the same volume as the 16 ml methylene chloride / methanol (6:1) used in example 1. When made the step "II.1. Dissolution of the active ingredients and binder", it is important to note that this 16 ml quantity of methanol was not enough for the total dissolution of drospirenone because the methanol solubility was too low. Recall that in example 1 drospirenone was completely dissolved. However, even though the process was continued in accordance with example 1, where there in step "II.2. Granulation - Drying" was used a planetary-type mixer and kneaded. The name the final batch granulated: LPDIMet-16ml.

[0097] In view of above was made an extra experiment, where there in step "II.1. Dissolution of the active ingredients and binder" was added methanol until complete dissolution. The required amount was 154.3 ml methanol. Such a high necessary amount of methanol is generally excessive for a relevant industrial granulation process. The process was continued in accordance with example 1, where there in step "II.2. Granulation - Drying" was used a fluid bed dryer and sprayed. The name the final batch granulated: LPDIMet-154ml.

EXAMPLE 3

Differential Scanning Calorimetry (DSC)

[0098] DSC - using a Shimadzu DSC-60 at 10 °C/min, with a flow of nitrogen at 30 ml/min as the purge gas - demonstrates the absence of the endothermic signal of fusion characteristic of the crystalline state of the drospirenone in the adsorbate obtained in accordance with Example 1.

The different inert components and drospirenone were analyzed by DSC before preparing the adsorbate of drospirenone and ethynylestradiol, in accordance with Example 1. Figure 5 shows a graph of the DSC of lactose monohydrate alone; Figure 6 shows a graph of the DSC of drospirenone in the crystalline state (temperature of the beginning of the endotherm $T_0 = 198,9 \pm 0,8^\circ\text{C}$). Figure 7 shows a graph of the DSC of magnesium stearate; Figure 8 shows a graph of the DSC of corn starch; Figure 9 shows a graph of the DSC of pregelatinized starch; Figure 10 shows a graph of the DSC of

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yellow iron oxide; Figure 11 shows a graph of the DSC of sodic croscarmellose (AC-Di-Sol); Figure 12 shows a graph of the DSC of Povidone K30.

Figure 13 shows a graph of the DSC of the mixture of inert excipient components or placebo with the absence of drospirenone and ethynylestradiol.

Figure 14 shows a graph of the DSC of the mixture of the components of the adsorbate in the state of simple mixture, where the signal of fusion of drospirenone in the crystalline state (endotherm of fusion at 197°C) has been particularly marked.

Figure 15 shows a graph of the DSC of the granulate obtained in Example 1 which contains drospirenone and ethynylestradiol adsorbed on inert excipients where one notes the lack of the peak of fusion of the drospirenone in the crystalline state. The lack of the peak indicates the loss of the crystalline state of drospirenone as a result of the process applied in Example 1, where by subjecting the granulate to drying, the presence of the polyvinylpyrrolidone in the drospirenone and ethynylestradiol solution acts through the formation of a tridimensional polymer structure, preventing the crystalline growth of both active compounds, so that the drugs are deposited on the excipient particles in an amorphous state.

EXAMPLE 4

Comparative dissolution profiles of drospirenone

[0099] Drospirenone dissolution profiles were obtained from compressed tablets obtained according to Example 1 and "methanol only" comparative example 2B using a dissolution apparatus designated in the U.S. Pharmacopoeia, Edition number 27, Apparatus 2, at 50 rpm and 900 ml of distilled water at 37°C. Similarly, the dissolution profiles of drospirenone were obtained from tablets containing drospirenone in a crystalline state with different sized particles. The results of the amount of drug dissolved at different times are summarized in the following table:

Table 2

	% of drospirenone dissolved					
Time (minutes)	0	10	20	30	45	60
LP01	0	31,2%	48,0%	59,9%	69,9%	77,8%
LP02	0	26,7%	48,6%	61,0%	72,7%	71,7%
LP03	0	32,6%	56,2%	70,7%	74,3%	80,5%
LPDIVuru	0	80,5%	97,0%	101,0%	102,0%	102,0%
LPDISpray	0	92%	96%	95%	95%	95%
LPDIMet-16ml	0	22%	29%	33%	38%	42%
LPDIMet-154ml	0	56%	73%	80%	86%	88%

Samples:

[0100]

LP01: Batch of tablets with non-micronized, crystalline drospirenone with an average particle size of > 100 µm
LP02: Batch of tablets with non-micronized, crystalline drospirenone with an average particle size = 100 µm
LP03: Batch of tablets with non-micronized, crystalline drospirenone with an average particle size = 70 µm
LPDIVuru and LPDISpray: Batch of tablets with adsorbates of drospirenone and ethynylestradiol in amorphous form obtained according to Example 1 (i.e. use of mixture of methylene chloride and methanol). For LPDIVuru the granulation was done in a planetary-type mixer and kneaded and for LPDISpray the granulation was done in a fluid bed dryer and sprayed.
LPDIMet-16ml and LPDIMet-154ml: Batch of tablets with adsorbates of drospirenone and ethynylestradiol in amorphous form obtained according to comparative Example 2B (i.e. use methanol alone). The first is where 16 ml methanol was used (same amount as in example 1. Drospirenone was not completely dissolved. See example 2B) and the latter is where 154 ml methanol was used in order to completely dissolve drospirenone.

[0101] For a better interpretation of the results shown in Table 2, the results are also shown in Figure 17. From this

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figure, one can observe that the batches of tablets of drospirenone in crystalline state, with different sizes of particles, show a very slow dissolution rate. However the LPDIVuru batch, in accordance with the present invention, shows a dissolution rate for drospirenone of at least 80% within the 20 minutes.

[0102] Further, from Table 2 it can be seen that USE OF METHYLENE CHLORIDE AS SOLVENT GIVES SIGNIFICANT BETTER RESULTS COMPARED TO USE OF ONLY METHANOL AS SOLVENT.

EXAMPLE 5

Comparative dissolution profiles of ethynylestradiol

[0103] Ethynylestradiol dissolution profiles were obtained from compressed tablets obtained according to Example 1 and "methanol only" comparative example 2B using a dissolution apparatus designated in the U.S. Pharmacopoeia, Edition number 27, Apparatus 2, at 50 rpm and 900 ml of distilled water at 37°C. Similarly, the dissolution profiles of ethynylestradiol were obtained from tablets containing ethynylestradiol in a crystalline state with different sizes of particles. The results of the amount of drug dissolved at different times are summarized in the following table:

Table 3

	% of ethynylest radiol dissolved					
Time (minutes)	0	10	20	30	45	60
LP01	0	10,0%	14,5%	21,0%	32,0%	45,0%
LP02	0	25,0%	35,4%	45,6%	52,0%	60,5%
LP03	0	33,1%	42,0%	55,5%	63,0%	72,5%
LPDIVuru	0	75,9%	86,0%	92,0%	100,1%	101,8%
LPDISpray	0	85%	89,5%	92,3%	95,3%	102,3%
LPDIMet-16ml	0	70%	75,3%	81%	95%	99%
LPDIMet-154ml	0	65%	72,3%	80,5%	90,1%	100,3%

Samples:

[0104]

LP01: Batch of tablets with non-micronized, crystalline ethynylestradiol with an average particle size of > 100 µm
LP02: Batch of tablets with non-micronized, crystalline ethynylestradiol with an average particle size = 90 µm
LP03: Batch of tablets with non-micronized, crystalline ethynylestradiol with an average particle size = 80 µm
LPDIVuru and LPDISpray: Batch of tablets with adsorbates of drospirenone and ethynylestradiol in amorphous form obtained according to Example 1 (i.e. use of mixture of methylene chloride and methanol). For LPDIVuru the granulation was done in a planetary-type mixer and kneaded and for LPDISpray the granulation was done in a fluid bed dryer and sprayed.
LPDIMet-16ml and LPDIMet-154ml: Batch of tablets with adsorbates of drospirenone and ethynylestradiol in amorphous form obtained according to comparative Example 2B (i.e. use methanol alone). The first is where 16 ml methanol was used (same amount as in example 1 - drospirenone not completely dissolved) and the latter is where 154 ml methanol was used in order to completely dissolve drospirenone.

[0105] For a better interpretation of the results shown in Table 3, the results are also shown in Figure 18. From this figure, it can be observed that the batches of tablets of ethynylestradiol in crystalline state, with different sizes of particles, show a very slow dissolution rate. However, the LPDIVuru batch, in accordance with the present invention, shows a dissolution rate for ethynylestradiol of at least 80% within the 20 minutes.

[0106] Further, from Table 3 it can be seen that USE OF METHYLENE CHLORIDE AS SOLVENT GIVES BETTER RESULTS COMPARED TO USE OF ONLY METHANOL AS SOLVENT.

EXAMPLE 6

[0107] Due to its low aqueous solubility, Drospirenone and Ethynylestradiol often shows low dissolution rate. The

enhancement of rate of dissolution of poorly water-soluble drugs remains one of the most challenging aspects of drug product development. The solid dispersion of poorly water-soluble drugs in water-soluble surface-active carriers enhances drug dissolution and bioavailability.

The nature of Drospirenone and Ethinylestradiol dispersed in the matrix of polyvinylpyrrolidone K-30 was studied.

[0108] In this comparative example was example 1 repeated but made without use of Povidone (polyvinylpyrrolidone K-30) in the dissolution step. Microphotography by electronic microscopy was obtained. An Electronic Microscopic property of UNLP (Universidad Nacional de La Plata- Argentina) was used in order to obtain the microphotographs.

[0109] The microphotograph images of Drospirenone and Ethinylestradiol crystals obtained by the same manner as in Example 1 but without polyvinylpyrrolidone K-30 showed that there were micro-crystals precipitate on the excipients. On the contrary, for microphotograph of granules with Drospirenone and Ethinylestradiol obtained by wet granulation as in Example 1 (with polyvinylpyrrolidone K-30: matrix of solid dispersion), the image did not exhibit micro-crystals precipitate on the excipients.

[0110] Further, making the Dissolution Test with the USP's apparatus as aforementioned, the results indicated that the Drospirenone and Ethinylestradiol solid dispersion is released faster from the solid dispersion (with polyvinylpyrrolidone K-30) than from the pure crystalline drug (without polyvinylpyrrolidone K-30).

[0111] Accordingly, an improved product is obtained by adding a water soluble polymer such as polyvinylpyrrolidone K-30 (Povidone) in a manner as described herein.

Claims

1. A pharmaceutical composition that comprises drospirenone and ethinylestradiol in amorphous form, adsorbed on a therapeutically inert solid support, in combination with pharmaceutically acceptable excipients, **characterized by** that the composition comprises measurable amounts of the volatile solvent methylene chloride.
2. The pharmaceutical composition in accordance with claim 1, **characterized by** that the composition comprises measurable amounts of both of the volatile solvents methylene chloride and methanol.
3. The pharmaceutical composition in accordance with claims 1 or 2, wherein the inert solid support is chosen from among particles of selected from the group consisting of corn starch, pregelatinized starch, lactose, sodic croscarmellose, yellow iron oxide and polyvinylpyrrolidone or mixtures of one or more of these, in combination with pharmaceutically acceptable excipients.
4. The pharmaceutical composition in accordance with any of the claims 1 to 3, **characterized in that** at least 80% of drospirenone and at least 80% of the ethinylestradiol dissolve from said composition within 20 minutes in a test carried out in a dissolution apparatus according to the U.S. Pharmacopoeia, Edition number 27, Apparatus 2, in 900 ml of distilled water at 37°C and stirred at 50 rpm.
5. A method for the preparation of a pharmaceutical composition, of any of the preceding claims, that comprises following steps:
 - i) dissolving drospirenone and ethinylestradiol in a volatile solvent or mixture of volatile solvents, wherein at least one of the volatile solvent is methylene chloride,
 - ii) optionally, adding a water-soluble polymer,
 - iii) mixing until dissolution,
 - iv) applying the resulting solution onto a base of solid particles that are therapeutically inert,
 - v) drying the obtained granulated adsorbate.
6. The method of claim 5, wherein the volatile solvent is a mixture of methylene chloride and methanol.
7. The method of claim 6, wherein the mixture of methylene chloride and methanol is a [9 to 4]:[3 to 0.5] v/v mixture of methylene chloride/methanol.
8. The method of claim 7, wherein the mixture of methylene chloride is a 6:1 v/v mixture of methylene chloride/methanol.
9. The method of any of claims 5 to 8, wherein there is step two of claim 5 is added a water-soluble polymer.
10. The method of claim 9, wherein the water-soluble polymer is polyvinylpyrrolidone.

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11. The method of any of claims 5 to 10, wherein the solid support, that is therapeutically inert, is chosen from among particles of corn starch, pregelatinized starch, lactose, sodic croscarmellose, yellow iron oxide, polyvinylpyrrolidone or mixtures of one or more of the same.

12. The method of any of claims 5 to 11, wherein in addition, the dried granulated adsorbate is combined with pharmaceutically acceptable excipients for the compression of the tablets.

Patentansprüche

1. Pharmazeutische Zusammensetzung, die auf einem therapeutisch inerten festen Trägermaterial adsorbiertes Drospirenon und Ethinylöstradiol in amorpher Form in Kombination mit pharmazeutisch verträglichen Hilfsstoffen enthält, **dadurch gekennzeichnet, dass** die Zusammensetzung messbare Mengen des flüchtigen Lösungsmittels Methylenchlorid enthält.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Zusammensetzung messbare Mengen der beiden flüchtigen Lösungsmittel Methylenchlorid und Methanol enthält.

3. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, worin das inerte feste Trägermaterial aus Partikeln aus der Gruppe, die aus Speisestärke, Quellstärke, Laktose, Croscarmellose-Natrium, Eisen(III)-oxidhydroxid und Polyvinylpyrrolidon besteht, oder Mischungen eines oder mehrerer davon ausgewählt wird, kombiniert mit pharmazeutisch verträglichen Hilfsstoffen.

4. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, dass** in einem Test, der in einem Lösungsprüfgerät nach der U.S. Pharmacopoeia, Ausgabe Nummer 27, Gerät 2, in 900 ml destilliertem Wasser bei 37°C und mit einer Umrührgeschwindigkeit von 50 Umdrehungen pro Minute ausgeführt wird, mindestens 80% des Drospirenon und mindestens 80% des Ethinylöstradiols aus der besagten Zusammensetzung innerhalb von 20 Minuten in Lösung übergehen.

5. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, nach einem der vorstehenden Ansprüche, das folgende Verfahrensschritte umfasst:

- i) Lösen des Drospirenon und Ethinylöstradiols in einem flüchtigen Lösungsmittel oder einer Mischung aus flüchtigen Lösungsmitteln, worin mindestens eines der flüchtigen Lösungsmittel Methylenchlorid ist,
- ii) wahlweise Zugabe eines wasserlöslichen Polymers
- iii) Mischen bis zur Auflösung,
- iv) Auftragen der entstandenen Lösung auf ein Trägermaterial aus festen Partikeln, die therapeutisch inert sind,
- v) Trocknen des erhaltenen gekörnten Adsorbats.

6. Verfahren nach Anspruch 5, bei dem das flüchtige Lösungsmittel eine Mischung aus Methylenchlorid und Methanol ist.

7. Verfahren nach Anspruch 6, bei dem die Mischung aus Methylenchlorid und Methanol eine [9 bis 14]:[3 bis 0,5] V/V Methylenchlorid/Methanol-Mischung ist.

8. Verfahren nach Anspruch 7, bei dem die Methylenchloridmischung eine 6:1 V/V Methylenchlorid/Methanol-Mischung ist.

9. Verfahren nach einem der Ansprüche 5 bis 8, bei dem in Verfahrensschritt zwei des Anspruchs 5 ein wasserlösliches Polymer zugegeben wird.

10. Verfahren nach Anspruch 9, bei dem das wasserlösliche Polymer Polyvinylpyrrolidon ist.

11. Verfahren nach einem der Ansprüche 5 bis 10, bei dem das feste Trägermaterial, das therapeutisch inert ist, aus Partikeln der Speisestärke, Quellstärke, Laktose, Croscarmellose-Natrium, Eisen(III)-oxidhydroxid, Polyvinylpyrrolidon oder Mischungen aus einem oder mehreren davon ausgewählt wird.

12. Verfahren nach einem der Ansprüche 5 bis 11, bei dem zusätzlich das getrocknete gekörnte Adsorbat mit pharmazeutisch verträglichen Hilfsstoffen kombiniert wird.

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zeutisch verträglichen Hilfsstoffen für die Tablettierung kombiniert wird.

Revendications

1. Composition pharmaceutique qui comprend de la drospirénone et de l'éthynylestradiol sous forme amorphe, adsorbés sur un support solide inerte du point de vue thérapeutique, en combinaison avec des excipients acceptables sur le plan pharmaceutique, **caractérisée en ce que** la composition comprend des quantités mesurables du solvant volatil chlorure de méthylène.
2. Composition pharmaceutique selon la revendication 1, **caractérisée en ce que** la composition comprend des quantités mesurables de l'un et l'autre solvants volatils chlorure de méthylène et méthanol.
3. Composition pharmaceutique selon la revendication 1 ou 2, dans laquelle le support solide inerte est choisi parmi des particules sélectionnées dans le groupe constitué de l'amidon de maïs, l'amidon prégélatinisé, le lactose, la croscarmellose sodique, l'oxyde de fer jaune et la polyvinylpyrrolidone ou des mélanges d'un ou plusieurs de ceux-ci, en combinaison avec des excipients acceptables sur le plan pharmaceutique.
4. Composition pharmaceutique selon l'une quelconque des revendications 1 à 3, **caractérisée en ce qu'au moins** 80 % de la drospirénone et au moins 80 % de l'éthynylestradiol se dissolvent de ladite composition dans les 20 minutes dans un essai effectué dans un appareil de dissolution selon la Pharmacopée U.S., Numéro d'édition 27, Appareil 2, dans 900 mL d'eau distillée à 37 °C et sous agitation à 50 tr/min,
5. Procédé pour la préparation d'une composition pharmaceutique, selon l'une quelconque des revendications précédentes, lequel comprend les étapes suivantes :
 - i) une dissolution de drospirénone et d'éthynylestradiol dans un solvant volatil ou un mélange de solvants volatils, dans lequel au moins l'un des solvants volatils est du chlorure de méthylène,
 - ii) un ajout éventuel d'un polymère hydrosoluble,
 - iii) un mélange jusqu'à dissolution,
 - iv) une application de la solution résultante sur une base de particules solides qui sont inertes du point de vue thérapeutique,
 - v) un séchage de l'adsorbat granulé obtenu.
6. Procédé selon la revendication 5, dans lequel le solvant volatil est un mélange de chlorure de méthylène et de méthanol.
7. Procédé selon la revendication 6, dans lequel le mélange de chlorure de méthylène et de méthanol est un mélange [9 à 4]:[3 à 0,5] volume/volume de chlorure de méthylène/méthanol.
8. Procédé selon la revendication 7, dans lequel le mélange de chlorure de méthylène est un mélange 6:1 volume/volume de chlorure de méthylène/méthanol.
9. Procédé selon l'une quelconque des revendications 5 à 8, dans lequel on ajoute à l'étape deux de la revendication 5 un polymère hydrosoluble.
10. Procédé selon la revendication 9, dans lequel le polymère hydrosoluble est de la polyvinylpyrrolidone.
11. Procédé selon l'une quelconque des revendications 5 à 10, dans lequel le support solide, qui est inerte du point de vue thérapeutique, est choisi parmi des particules d'amidon de maïs, d'amidon prégélatinisé, de lactose, de croscarmellose sodique, d'oxyde de fer jaune, de polyvinylpyrrolidone ou des mélanges d'un ou plusieurs de ceux-ci.
12. Procédé selon l'une quelconque des revendications 5 à 11, dans lequel en outre, l'adsorbat granulé séché est combiné avec des excipients acceptables sur le plan pharmaceutique en vue de la compression des comprimés.

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FIGURE 1

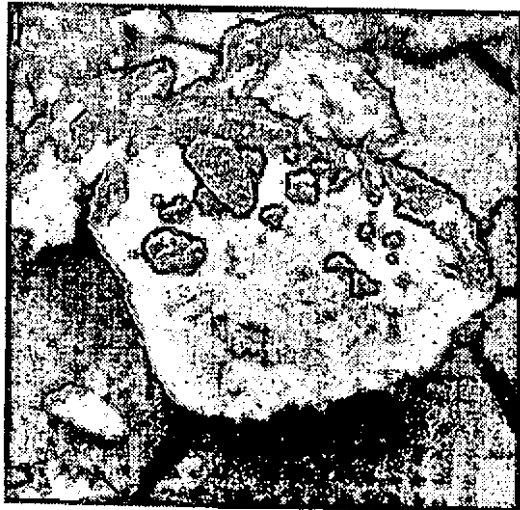


FIGURE 2A



FIGURE 2B

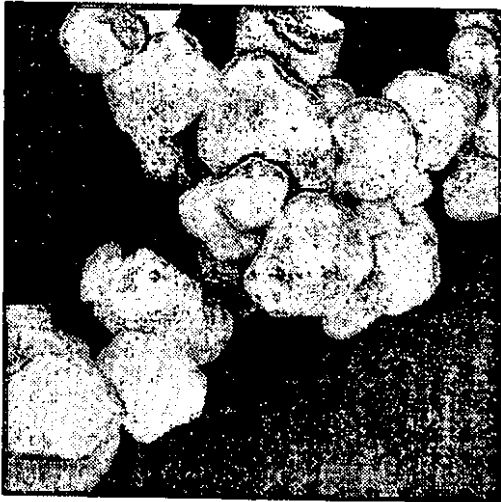


FIGURE 2C



FIGURE 2D



FIGURE 2E

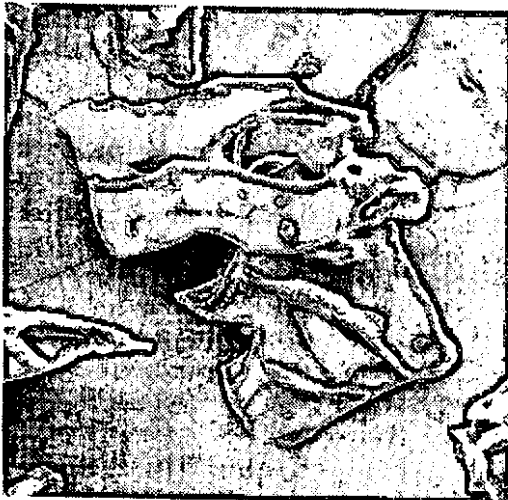


FIGURE 2F

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FIGURE 2G



FIGURE 2H



FIGURE 2I

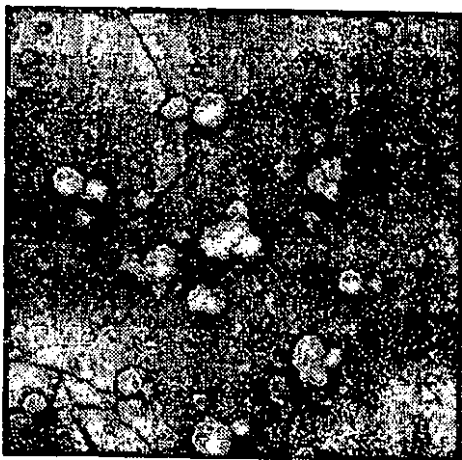


FIGURE 2J

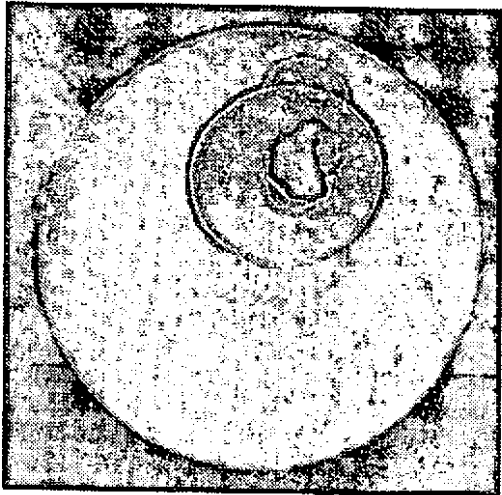


FIGURE 2K

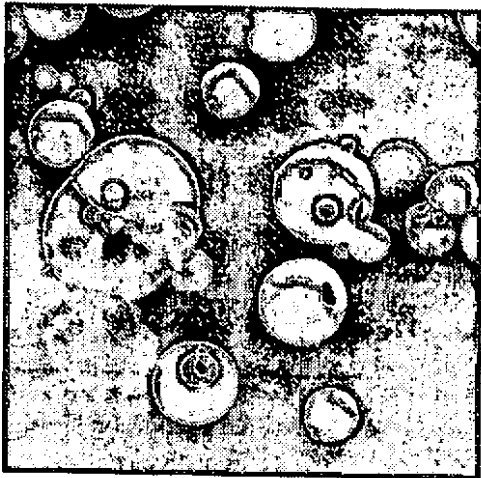


FIGURE 2L

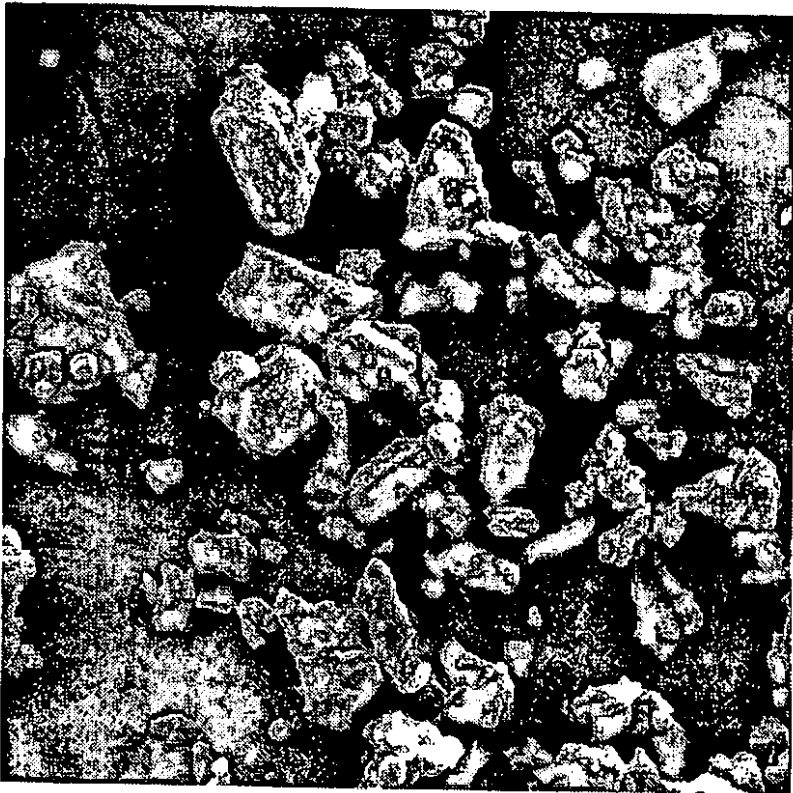


FIGURE 3

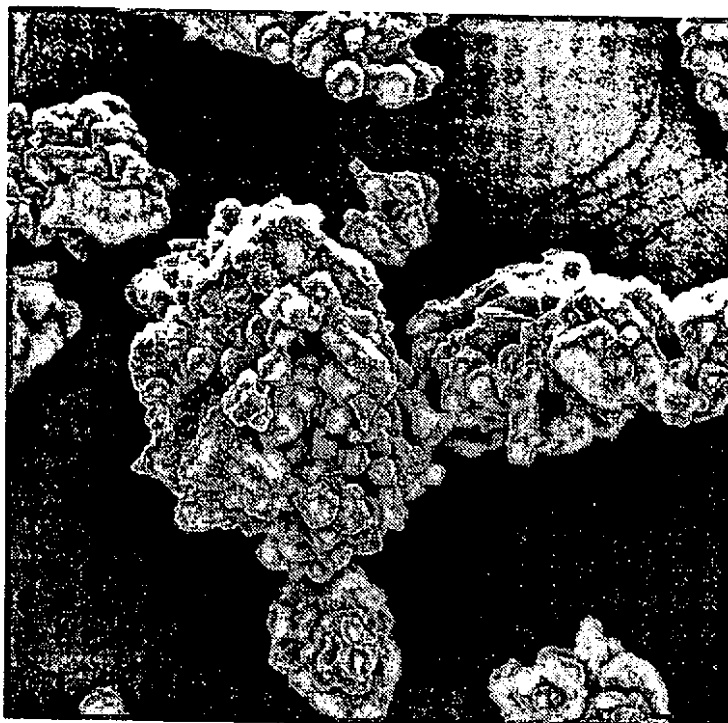


FIGURE 4A



FIGURE 4B

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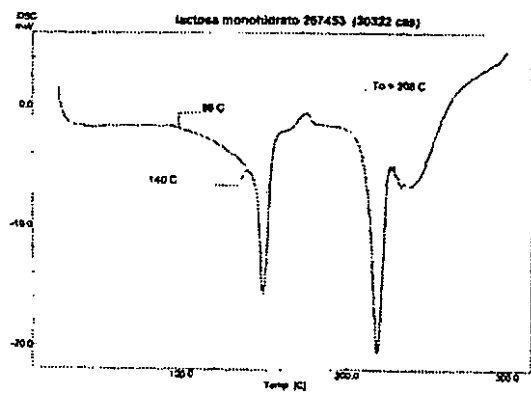


FIGURE 5

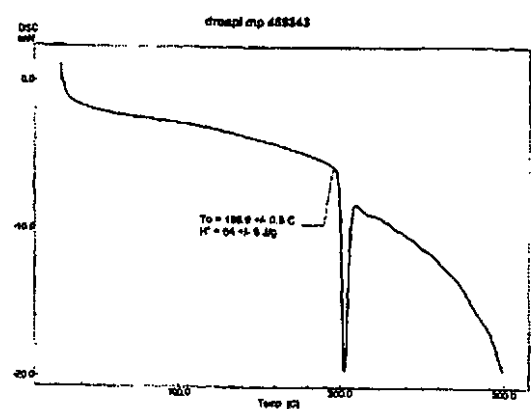


FIGURE 6

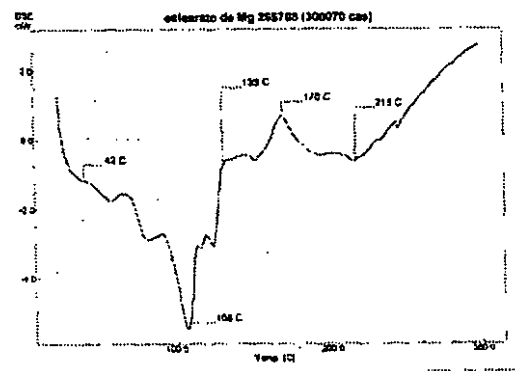


FIGURE 7

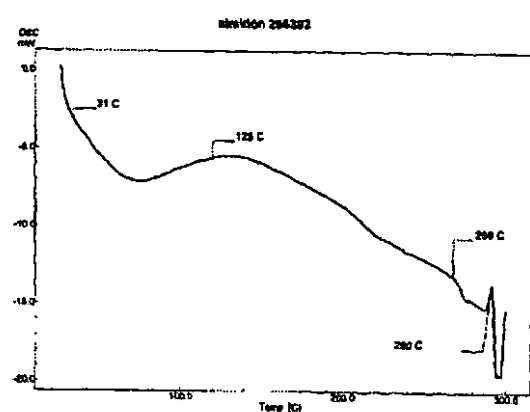


FIGURE 8

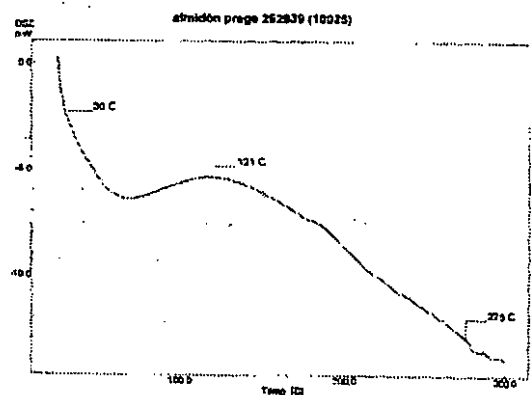


FIGURE 9

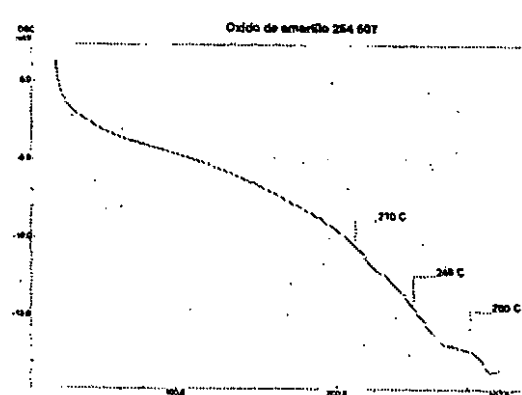


FIGURE 10

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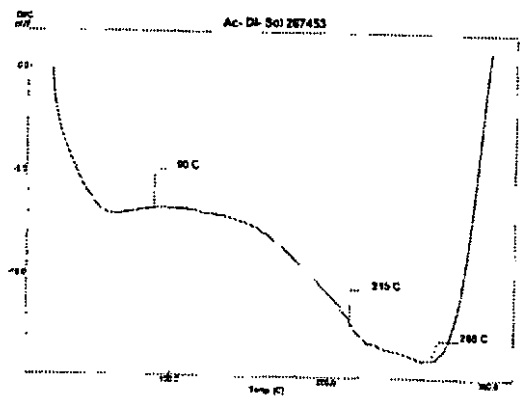


FIGURE 11

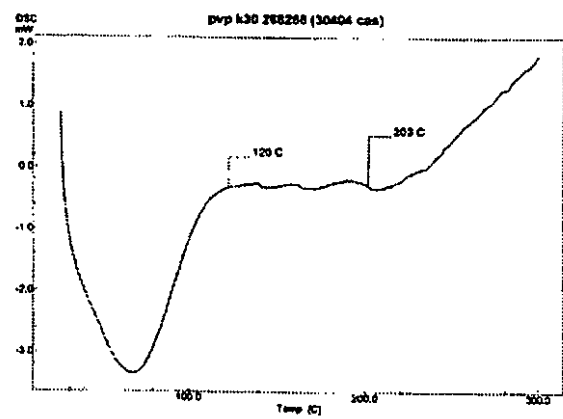


FIGURE 12

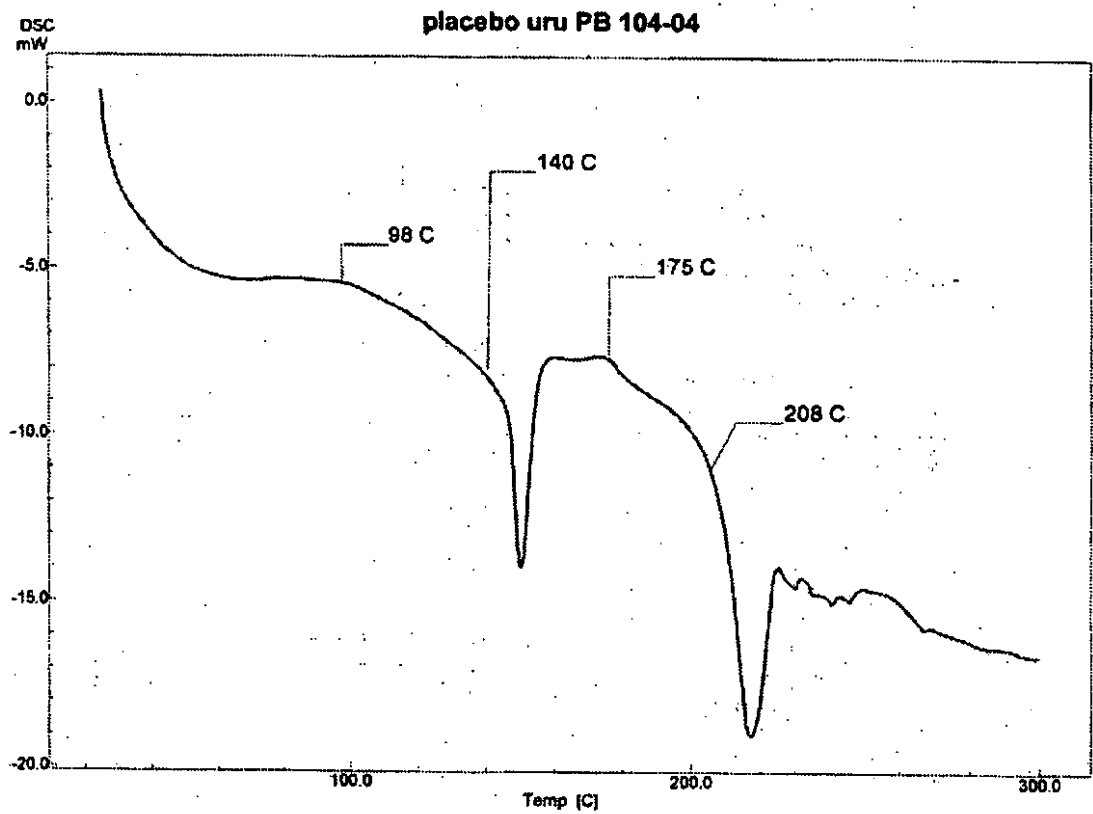


FIGURE 13

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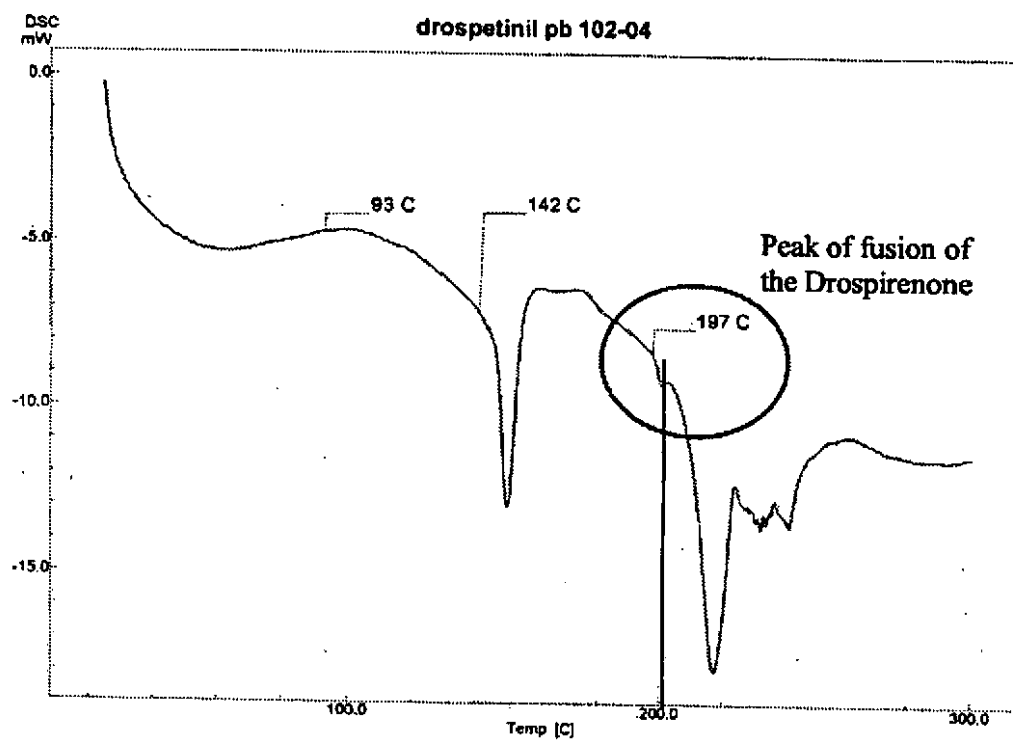


FIGURE 14

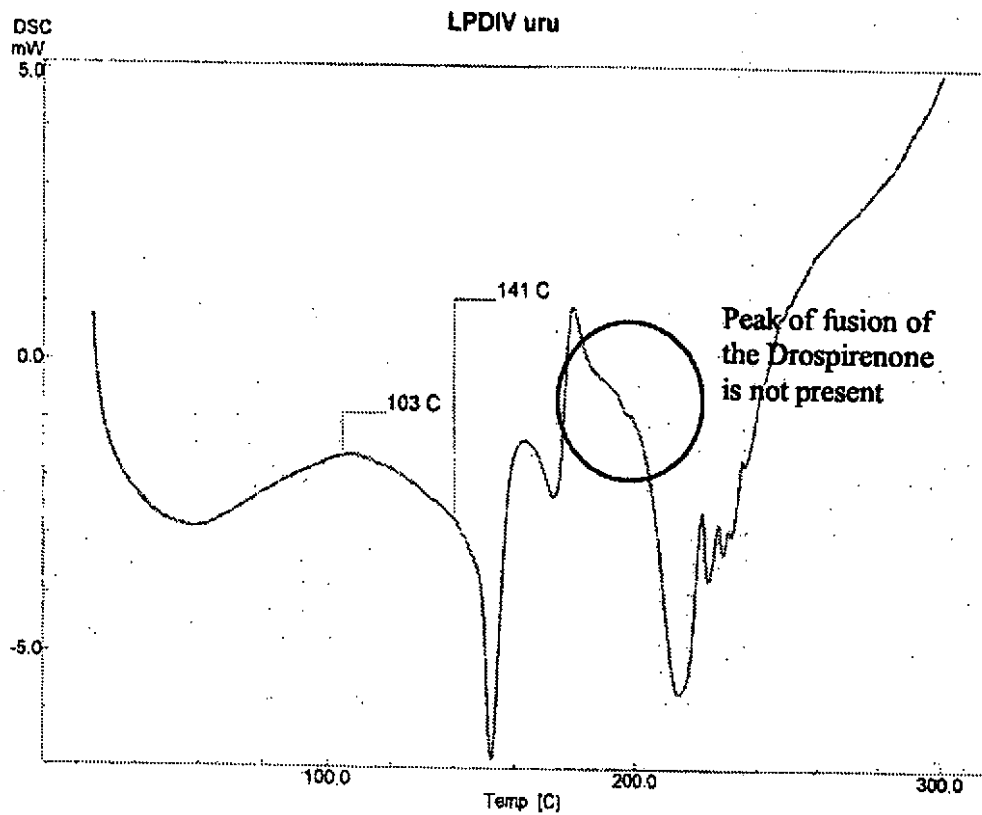


FIGURE 15

H/3

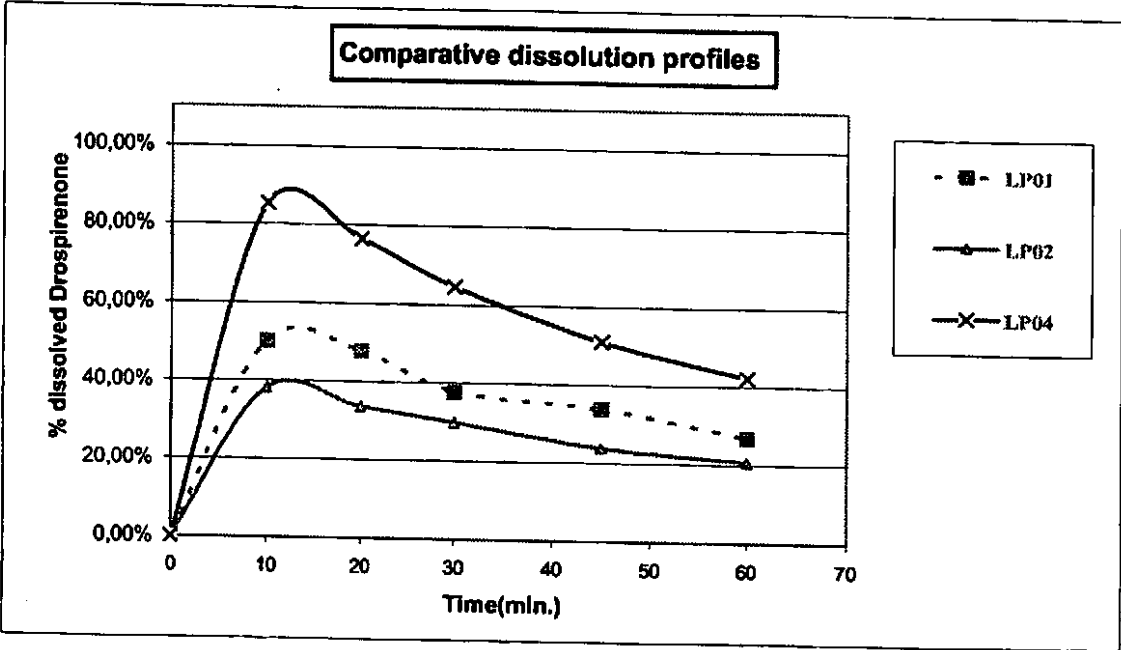


FIGURE 16

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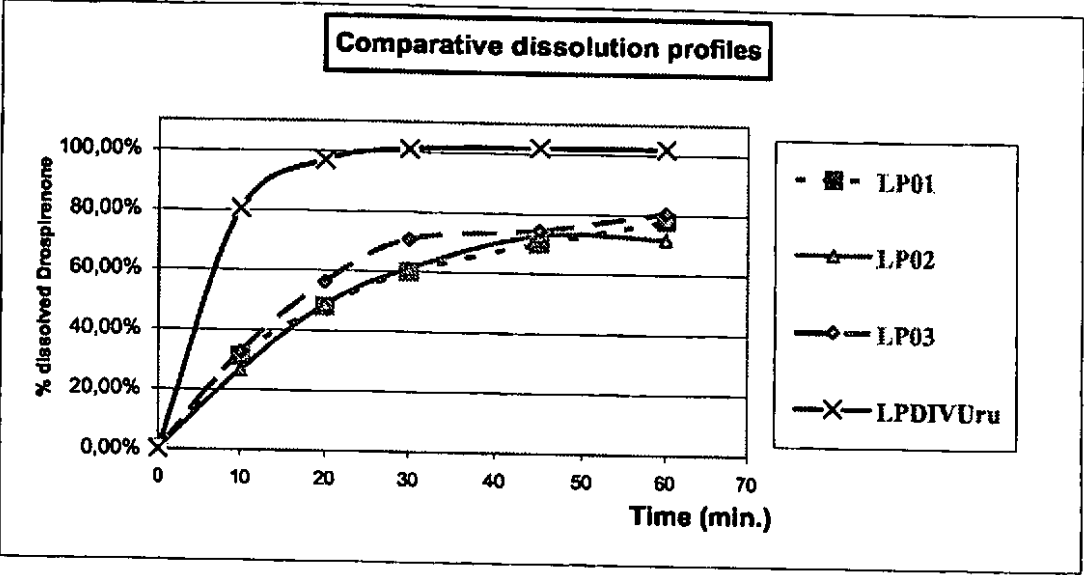


FIGURE 17

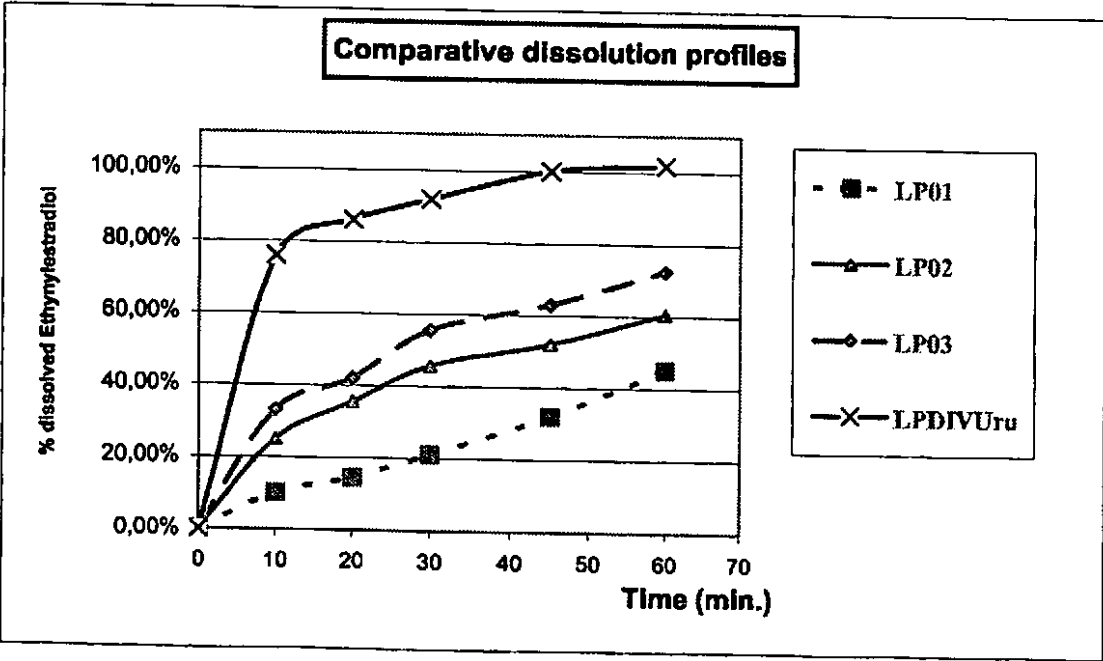


FIGURE 18

REFERENCES CITED IN THE DESCRIPTION

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