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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E S D

Re **Expediente No. 03 059764**
Solicitud de patente **PCT** fase nacional
Solicitud internacional No PCT/IB01/02605
Solicitante SCHERING AKTIENGESELLSCHAFT

Yo, GUSTAVO HOLLMANN RESTREPO, vecino de Bogotá D C , portador de la tarjeta profesional No 5903, obrando como apoderado en este negocio, manifiesto a usted que acompaño al presente memorial los siguientes documentos, para que sean agregados al expediente de la referencia

- Con carácter de anexión voluntaria, copia certificada de la solicitud de patente No 00610135 6, presentada en Europa el 20 de diciembre de 2000, con su correspondiente traducción al español de la carátula y Reivindicaciones

- Con caracter de anexión voluntaria, copia certificada de la solicitud de patente No 60/256,484, presentada en Estados Unidos el 20 de diciembre de 2000, con su correspondiente traduccion al español de la carátula y Reivindicaciones

- El documento en el cual consta la cesión del derecho a la patente de los inventores al solicitante, debidamente traducido y legalizado

Señor Superintendente,

GUSTAVO HOLLMANN RESTREPO
C C No 2 878 023 de Bogota
T P No 5903
mm

LOS ESTADOS UNIDOS DE AMERICA

A TODOS CUANTOS LAS PRESENTES VIEREN

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

Julio 25 del 2003

SE CERTIFICA QUE ADJUNTO SE ENCUENTRA UNA COPIA FIEL Y EXACTA DE LOS REGISTROS EXISTENTES EN LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS RESPECTO A LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO, LA CUAL CUMPLIO CON LOS REQUISITOS PARA QUE SE LE OTORGARA UNA FECHA DE PRESENTACIÓN DE CONFORMIDAD CON 35 USC 111

NUMERO DE SOLICITUD *60/256,484*
FECHA DE PRESENTACIÓN *Diciembre 20 del 2000*

Por Autoridad del
COMISIONADO DE PATENTES Y MARCAS

M K HAWKINS, Funcionario de Certificaciones
(Firma y Sello Oficial)

51799 54859. (C 01

COLOMBIA

155

DOCUMENTO DE CESIÓN
ASSIGNMENT DOCUMENT

Los suscritos
(We, the undersigned)

THOMAS BACKENSFELD
con domicilio en Berlin, Alemania
(domiciled in)

WOLFGANG HEIL
con domicilio en Stelle, Alemania
(domiciled in)

RALPH LIPP
con domicilio en Berlin, Alemania
(domiciled in)

declaramos que somos los inventores de la invencion que lleva el título
(declare that we are the inventors of the invention titled)

COMPOSITIONS OF ESTROGEN-CYCLODEXTRIN COMPLEXES

y que hemos cedido el derecho sobre esta invención en Colombia, junto con los privilegios
(and that we have assigned our rights over this invention in Colombia, together with its privileges)
y anexidades a favor de SCHERING AKTIENGESELLSCHAFT
(and attachments to) Berlin, Alemania

1) 2) Wolfgang Heil

3) Ralph Lipp

Urkundenrolle-Nr R 432/2003

Ich habe das Mitwirkungsverbot nach § 3 Abs 1 Nr 7 BeurkG erläutert. Meine Frage, ob eine Vorbefassung im Sinne der Vorschrift vorliege, wurde verneint

Die vor mir geleisteten Unterschriften

des Herrn Dr Wolfgang H e i l,
geboren am 3 April 1962,
geschaftsansassig in 13353 Berlin, Mullerstraße 178,

- von Person bekannt -

beglaubige ich

Berlin, 15 September 2003

Notar

Kostenberechnung gem §§ 141, 154 KostO

Geschaftswert 12 000,00 €

Beglaubigungsgebühr §§ 32, 45 I	15,00 €
Wegegebuhr gem § 58	15,00 €
Schreibauslagen §§ 136, 152	1,00 €
Postauslagen §§ 137, 152	1,44 €
	32,44 €
16 % Mehrwertsteuer	5,19 €
	37,63 €

Berlin, 15 September 2003

Notar

Urkundenrolle-Nr R 441/2003

Ich habe das Mitwirkungsverbot nach § 3 Abs 1 Nr 7 BeurkG erlautert Meine Frage, ob eine Vorbefassung im Sinne der Vorschrift vorliege, wurde verneint

Die vor mir geleistete Unterschrift

des Herrn Dr Thomas **B a c k e n s f e l d**,
geboren am 22 Dezember 1959,

und des Herrn Dr Ralph **L i p p**,
geboren am 12 Mai 1960,

- beide von Person bekannt -

beide geschaftsansassig in 13353 Berlin, Mullerstraße 178,

beglaubige ich

Berlin, 18 September 2003

Notar

Kostenberechnung gem. §§ 141, 154 KostO

Geschäftswert 12.000,00 €

Beglaubigungsgebuhr §§ 32, 45 I	15,00 €
Wegegebühr gem § 58	15,00 €
Schreibauslagen §§ 136, 152	1,00 €
Postauslagen §§ 137, 152	1,44 €
	32,44 €
16 % Mehrwertsteuer	5,19 €
	37,63 €

Berlin, 18 September 2003

Notar

9101 a E - F

158

Apostille
(Convention de La Haye du 5 octobre 1961)

1 Land Bundesrepublik Deutschland
Diese öffentliche Urkunde

2 ist unterschrieben von Dimitri R e m p e n

3 in seiner Eigenschaft als Notar

4 sie ist versehen mit den Siegeln
des Notars

Bestätigt

5 in Berlin 6 am 24 September 2003

7 durch den Prasidenten des Landgerichts in Berlin

8 unter Nr 9101 a E - F 3535/2003

9 Siegel

10 Unterschrift
Im Auftrage

(H o l l d o r f)
Richter am Landgericht

Traducción Oficial del Alemán de las autenticaciones de firmas y la apostilla adjuntas al documento de cesión suscrito entre los inventores Thomas Backensfeld, Wolfgang Heil y Ralph Lipp y la compañía Schering Aktiengesellschaft

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Registro Notarial No R 432/2003

Yo leí la prohibición de participación según el Artículo 3 inciso 1 No 7 de la Ley de Notarización Mi pregunta acerca de si existía algún impedimento conforme a esa disposición fue contestada negativamente

Autentico la firma que aparece anteriormente, la cual fue ejecutada en mi presencia por el

Señor Dr Wolfgang Heil,
nacido el 3 de Abril de 1962,
domicilio comercial en 13353 Berlín, Müllerstraße 178,

quien es conocido personalmente por el suscrito Notario

Berlín, 15 de Septiembre del 2003

Dimitri Rempen, Notario en Berlín
(Firma y Sello Oficial)

Nota de gastos Artículos 141, 154 Disposición de Impuestos

Valor del negocio 12 000,-- EUROS		
Impuesto Artículos 32, 45I		15,00 EUROS
Impuesto Artículo 58		15,00 EUROS
Impuesto Artículos 136, 152		1,00 EUROS
Impuesto Artículos 137, 152		1,44 EUROS
16% I V A		5,19 EUROS
	Total	37,63 EUROS

Berlín 15, de Septiembre del 2003

Dimitri Rempen, Notario (firma)

Registro Notarial No R 441/2003

Yo leí la prohibición de participación según el Artículo 3 inciso 1 No 7 de la Ley de Notarización Mi pregunta acerca de si existía algún impedimento conforme a esa disposición fue contestada negativamente

Autentico las firma que aparecen anteriormente, las cuales fueron ejecutadas en mi presencia por

Señor Dr Thomas Backensfeld,
nacido el 22 de Diciembre de 1959,

Señor Dr Ralph Lipp,
nacido el 12 de Mayo de 1960,

ambos conocidos personalmente por el suscrito Notario y ambos con domicilio comercial en 13353 Berlín, Müllerstraße 178

Berlín, 18 de Septiembre del 2003

Dimitri Rempen, Notario en Berlín
(Firma y Sello Oficial)

Nota de gastos Artículos 141, 154 Disposición de Impuestos

Valor del negocio 12 000,-- EUROS		
Impuesto Artículos 32, 45I		15,00 EUROS
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Impuesto Artículos 136, 152		1,00 EUROS
Impuesto Artículos 137, 152		1,44 EUROS
16% I V A		5,19 EUROS
	Total	37,63 EUROS

Berlín 18, de Septiembre del 2003

Dimitri Rempen, Notario (firma)

8
161

Apostilla

(Convención de La Haya del 5 de Octubre de 1961)

1 País República Federal de Alemania

Este documento público

2 Ha sido firmado por Dimitri Rempen

3 En su calidad de Notario

4. Y lleva el sello Del Notario

Confirmado

5 En Berlín

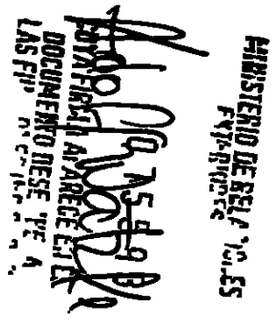
6 El 24 de Septiembre del 2003

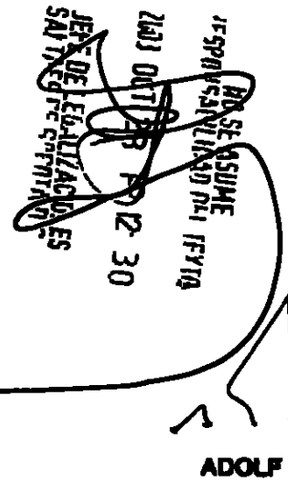
7 Por El Presidente del Tribunal Regional en Berlín

8 Bajo el No 9101 a E-F 3535/2003

9 Sello EL PRESIDENTE DEL TRIBUNAL REGIONAL EN BERLÍN

10 Firma Holldorf, Juez en el Tribunal





ADOLF WATZKE
Traductor Oficial
Res 8433 Minjusticia

PTO 1043952

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

July 25, 2003

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

APPLICATION NUMBER ***60/256,484***
FILING DATE ***December 20, 2000***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. K. HAWKINS
Certifying Officer

TO 163

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1 53(c)

Docket Number PLOVIN-5V1

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Backensfeld	Thomas		Berlin, Germany
Heil	Wolfgang		Berlin, Germany

☐ Additional inventors are named on separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 CHARACTERS MAX

COMPOSITIONS OF ESTROGEN-CYCLODEXTRIN COMPLEXES

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ENCLOSED APPLICATION PARTS

☐	Abstract			☐	Small Entity Statement
☑	Specification	*Number of Pages*	32		Language ENGLISH
☑	Claims	*Number of Pages*	7	☐	Other (specify)
☐	Drawing(s)	*Number of Sheets*			

METHOD OF PAYMENT

☑ A check or money order is enclosed to cover the Provisional Filing Fees

☑ The Commissioner is hereby authorized to charge filing fees and credit any overpayment to Deposit Account Number 13-3402

PROVISIONAL FILING FEE AMOUNT **$150.00**

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the name of the U S Government agency and the Government contract number are

Respectfully Submitted,

December 20, 2000

Anthony J. Zelano
Registration Number 27,969

PROVISIONAL APPLICATION FILING ONLY

COMPOSITIONS OF ESTROGEN-CYCLODEXTRIN COMPLEXES

FIELD OF INVENTION

The present invention relates to pharmaceutical composition comprising a cyclodextrin-estrogen inclusion complex that confers very high chemical stability to the estrogen. The composition according to the present invention allows for an increased stability of ethinyl estradiol upon storage.

BACKGROUND OF THE INVENTION

Degradation of estrogens, such as ethinyl estradiol, in conventional formulations is one of the most critical issues with regard to product shelf life. The stabilisation of the estrogen may be achieved by either product packaging in hermetic containers or more effectively as in the present invention by actual stabilisation of the formulation.

Formulations comprising naturally or synthetically derived sex hormones often consist of low dosages of these active ingredients. Given the small amounts of active ingredient required per single dosage often ranging between 0.1 µg and 500 µg content uniformity of the preparation is a significant contributor to fluctuations in actual doses of these active ingredients.

Similarly the oxidative degradation of these small amounts of active ingredient is a further contributor to the strong fluctuations of the active ingredient in low dosage formulations. In low dosage formulations these fluctuations are critical to quality assurance.

In general these low dose formulations are problematic in terms of their preparation storage and use.

US 4 596 795 discloses a complex between α- β- and γ-cyclodextrins and derivatives thereof with testosterone progesterone and estradiol and the solubility of said complexes.

US 4 727 064 discloses a method of producing a stabilizing amorphous complex of a drug and a mixture of cyclodextrin derivatives

US 4 383 992 discloses a water soluble inclusion compound formed by complexing beta-cyclodextrin with a steroid compound such an estogen

US 5 798,338 discloses a composition of a clathrate between β-cyclodextrin and 17-α-ethinyl estradiol for reducing the oxidative degradation of 17-α-ethinyl estradiol

SUMMARY OF THE INVENTION

An object of the present invention is to provide a pharmaceutical composition comprising an estrogen wherein the stability of said estrogen is significantly improved over that of conventional formulations without complexed estrogens Degradation of estrogens such as ethinyl estradiol, in conventional formulations is one of the most critical issue with regard to product shelf life The stabilisation of the estrogen may be achieved by either product packaging in hermetic containers (e g pouch) or more effectively by actual stabilisation of the formulation

It has surprisingly been found that a complex of cyclodextrin and estrogen significantly improves the stability of the estrogen and consequently the shelf-life of an estrogen-containing composition Accordingly, the present invention relates to a pharmaceutical composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and an estrogen, wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w such as at the most 5 4 3 or 2% w/w based on the total content of said estrogen together with one or more pharmaceutically acceptable carriers or excipients

Moreover, an alternative embodiment of the present invention relates to a pharmaceutical composition comprising an inclusion complex between cyclodextrin or derivative thereof and an estrogen wherein the composition is such that said estrogen has a 12-month stability at 25°C and 60% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w such as at the most 5 4 3 or 2% w/w

based on the total content of said estrogen together with one or more pharmaceutically acceptable carriers or excipients

The present invention further relates to a pharmaceutical composition comprising an inclusion complex between cyclodextrin or derivative thereof, and estrogen wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% such as at the most 5 4, 3 or 2% based on the total content of estrogen and a therapeutically active compound, such as a gestagen, such as drospirenone, together with one or more pharmaceutically acceptable carriers or excipients.

Furthermore, the invention relates to a pharmaceutical composition comprising an inclusion complex between a cyclodextrin or derivative thereof and an estrogen suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w such as at the most 5 4, or 3% w/w based on the total content of said estrogen together with one or more pharmaceutically acceptable carriers or excipients

Compositions of the present invention may be used as medicaments Accordingly, the use of a composition described infra for the preparation of a pharmaceutical for female contraception for hormone replacement therapy for the treatment of menopausal, pre-menopausal, and/or post-menopausal symptoms for the treatment of acne or for the treatment of PMDD is a further aspect of the present invetion

As the formulation of the complex is another important aspect to achieve the improved effects the present invention further relates to a pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin or derivative thereof, wherein the total amount of oxidant in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen

Alternatively measured the present invention provides a pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between

a cyclodextrin or derivative thereof wherein the total amount of oxidant in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w such as at the most 10 9, 8, 7 or 6% w/w based on the total content of said estrogen

Still further the present invention relates to pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin or derivative thereof wherein the total amount of oxidant in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol 6-keto- ethinyl estradiol and Δ9 11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 6%, such as at the most 0 7% and 0 6% based on the total content of estrogen

In a broad sense, the present invention relates a method of improving the stability of ethinyl estradiol in a pharmaceutical formulation comprising the step of a) complexing said ethinyl estradiol with cyclodextrin, and optionally of b) limiting the polyvinylpyrrolidone content to less than 5% such as less than 4%, such as less than 3%, such as less than 2% such as less than 1% such as providing a substantially polyvinylpyrrolidone-free formulation

Generally an object of the present invention is to provide a pharmaceutical composition comprising an estrogen wherein the stability of said estrogen is significantly improved over that of conventional formulations

DETAILED DESCIPTION OF THE INVENTION

The term "complex" is intended to mean an inclusion complex between estrogen and cyclodextrin wherein a molecule of said estrogen is at least partially inserted into the cavity of one or more cyclodextrin molecules, wherein for example two moieties of a single estrogen molecule are each inserted into one cyclodextrin molecule to give 2 1 ratio between cyclodextrin and estrogen Similarly the complex may comprise of more than one molecule of estrogen at least partially inserted into one or more cyclodextrin

molecules wherein for example 2 estrogen molecules are at least partially inserted into a single cyclodextrin molecule to give a 1 2 ratio between cyclodextrin and estrogen Complexes wherein one estrogen molecule is complexed with one or more cyclodextrin molecules are certainly anticipated such as 1 estrogen molecule complexed with 2 cyclodextrin molecules or 3 cyclodextrin molecules Typically, the ethinyl estradiol-β-cyclodextrin inclusion complex as prepared by the present invention is preferably a complex between one molecule of ethinyl estradiol and two molecules of β-Cyclodextrin

The term "ethinyl estradiol-β-Cyclodextrin inclusion complex" or "EE-β-CD" is intended to mean a complex, of any ratio, between ethinyl estradiol and β-cyclodextrin

The term "oxidant-free" relates to formulations substantially devoid of all agents having substantial oxidizing capacity whereas the term "oxidant-restricted" relates to formulations substantially devoid of at least one agent having substantial oxidizing capacity For example, a polyvinylpyrrolidone-free formulation is an oxidant-restricted formulation.

The present investigators have developed formulations wherein a remarkable improvement of the stability of the estrogen ethinyl estradiol (EE) has been achieved by individual or combined means One such means is the protection of EE by forming a β-cyclodextrin complex Another such means is by the judicious selection of additives and excipients to the formulation such that oxidants are minimised or excluded from the formulation Individually, or acting in concert, these means have resulted in formulations wherein said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of between 3 and 10 % w/w compared to conventional formulations wherein estrogen degrades by up to 25% under identical conditions (see Table 1 3 Example 1) Thus a preferred embodiment of the invention is that of a pharmaceutical composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and an estrogen wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen together with one or more pharmaceutically acceptable carriers or excipients

It is evident that the stability test may be performed under alternative conditions such as higher temperatures Thus an alternative embodiment wherein the composition is such

that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w such as at the most 10 9 8 7 6 or 5% w/w based on the total content of said estrogen

As stated the formulation of the estrogen-cyclodextrin complex is critical to achieve the desired effect of improved stability of a composition comprising said complex. The present inventors have developed a pharmaceutical composition comprising an inclusion complex between a cyclodextrin or derivative thereof, and an estrogen suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5 4, or 3% w/w, based on the total content of said estrogen, together with one or more pharmaceutically acceptable carriers or excipients

An embodiment of an oxidant-restricted formulation (see Table 1 3, Example 1) comprising EE complexed with βCD compares surprisingly well with known formulations in 3-month stability studies at 60°C and 75% relative humidity (RH), wherein a less than 4% decrease in EE content was observed in said embodiment compared to an almost 30% decrease was observed in known formulations or free-estrogen formulations

As the person skilled in the art will appreciate, the estrogen may be selected from the group consisting of ethinyl estradiol (EE) estradiol estradiol sulfamates estradiol valerate estradiol benzoate estrone, estriol estriol succinate and conjugated estrogens including conjugated equine estrogens such as estrone sulfate, 17β-estradiol sulfate, 17α-estradiol sulfate, equilin sulfate 17β-dihydroequilin sulfate 17α-dihydroequilin sulfate equilenin sulfate, 17β-dihydroequilenin sulfate and17α-dihydroequilenin sulfate or mixtures thereof Particularly interesting estrogens are selected from the group consisting of ethinyl estradiol (EE), estradiol, estradiol sulfamates estradiol valerate estradiol benzoate estrone and estrone sulfate or mixtures thereof notably ethinyl estradiol (EE) estradiol estradiol valerate estradiol benzoate and estradiol sulfamates Most preferred is ethinyl estradiol (EE)

In the preferred embodiment wherein the estrogen is ethinyl estradiol (EE), some of the degradation products are well known Thus it is possible to express the stability of the formulation in terms of the amount of these degradation products Accordingly, the

composition according to one embodiment of the present invention comprises an inclusion complex between cyclodextrin or derivative thereof and ethinyl estradiol, wherein the composition is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol 6-keto-ethinyl estradiol, Δ9 11-ethinyl estradiol and Δ6 7-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8% such as at the most 0 7% and 0 6%, based on the total content of estrogen, together with one or more pharmaceutically acceptable carriers or excipients

A pharmaceutical composition comprising an inclusion complex between a cyclodextrin, or derivative thereof and ethinyl estradiol suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol, Δ6,7-ethinyl estradiol and Δ-9 11-ethinyl estradiol of said ethinyl estradiol totals at the most 3% such as at the most 2% based on the total content of estrogen, together with one or more pharmaceutically acceptable carriers or excipients

When exposed to an alternative stability test the composition comprises an inclusion complex between cyclodextrin, or derivative thereof, and ethinyl estradiol, wherein the composition is such that said ethinyl estradiol has a 12-month stability at 40°C and 75% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol 6-β-hydroxy-ethinyl estradiol 6-keto- ethinyl estradiol and Δ-9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 3%, such as at the most 2 % based on the total content of estrogen together with one or more pharmaceutically acceptable carriers or excipients

The cyclodextrin may be selected from α- cyclodextrin, β- cyclodextrin γ- cyclodextrin and derivatives thereof The cyclodextrin may be modified such that some or all of the primary or secondary hydroxyls of the macrocycle or both may be alkylated or acylated Methods of modifying these alcohols are well known to the person skilled in the art and many are commercially available Thus, some or all of the hydroxyls of cyclodextrin may modified cyclodextrins have be substituted with an O-R group or an O-C(O)-R wherein R is an optionally substituted C_{1-6} alkyl an optionally substituted C_{2-6} alkenyl, an optionally

substituted C_{2-6} alkynyl an optionally substituted aryl or heteroaryl group Thus R may be methyl ethyl propyl butyl pentyl or hexyl group Consequently O-C(O)-R may be an acetate Furthermore, with the commonly employed 2-hydroxyethyl group, or 2-hydroxypropyl group R may be used to derivatize cyclodextrin Moreover, the cyclodextrin alcohols may be per-benzylated per-benzoylated or benzylated or benzoylated on just one face of the macrocycle, or wherein only 1, 2, 3, 4, 5, or 6 hydroxyls are benzylated or benzoylated. Naturally the cyclodextrin alcohols may be per-alkylated or per-acylated such as per-methylated or per-acetylated, or alkylated or acylated, such as methylated or acetylated, on just one face of the macrocycle, or wherein only 1 2 3 4 5 or 6 hydroxyls are alkylated or acylated such as methylated or acetylated

Preferably, the complex comprises of β-cyclodextrin or a derivative thereof most preferably β-cyclodextrin

Thus, in a particularly preferred embodiment which is a combination of preferred embodiments, the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin

The estrogen-cyclodextrin complex may be obtained by methods known to the person skilled in the art (e g US 5 798 338)

The ethinyl estradiol-β-cyclodextrin complex may also be obtained by co-precipitation as follows Ethinyl estradiol is dissolved in ethanol β-cyclodextrin is dissolved at 45°C in water the ethinyl estradiol solution is added to the beta-cyclodextrin solution, the obtained suspension is stirred for some hours at 20 to 25°C and afterwards at 2°C the crystallisation product is isolated and dried

Alternatively, the ethinyl estradiol-β-cyclodextrin complex may be obtained as follows Ethinyl estradiol is dissolved in acetone, β-cyclodextrin is dissolved at 45°C in water; the ethinyl estradiol solution is added to the β-cyclodextrin solution, the obtained suspension is stirred for some hours at temperatures below 25°C, afterwards, the crystallisation product is isolated and dried

In an alternative embodiment of the invention the composition further comprises a therapeutically active compound Thus in this embodiment the composition comprises an inclusion complex between cyclodextrin, or derivative thereof and estrogen

wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10%, such as at the most 5, 4 3 or 2% based on the total content of estrogen, and a therapeutically active compound such as a gestagen, preferably drospirenone together with one or more pharmaceutically acceptable carriers or excipients

In the preferred embodiment wherein the therapeutically active substance is drospirenone said drospirenone is preferably micronised Micronization of drospirenone provides for improved dissolution in aqueous media, potentially improving bioavailability of the gestagen

In the preferred embodiment where the therapeutically active substance is drospirenone, all or substantially all of said drospirenone may be present as an inclusion complex with cyclodextrin As the person skilled in the art will appreciate the dissociation constant of the drospirenone cyclodextrin complex may result in a mixture of cyclodextrin-complexed drospirenone and uncomplexed (free) drospirenone As was the case for uncomplexed drospirenone the complexed drospirenone may also be micronized

The complex of EE and cyclodextrin also has a more rapid dissolution in water than EE itself putatively improving bioavailability of the estrogen

An object of the invention is to provide a stable composition wherein said composition comprises an inclusion complex between cyclodextrin preferably β-cyclodextrin, and ethinyl estradiol wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% such as at the most 5, 4 3 or 2% based on the total content of estrogen and a therapeutically active compound, such as a gestagen, preferably drospirenone together with one or more pharmaceutically acceptable carriers or excipients

It can be easily appreciated that in embodiments where the estrogen is ethinyl estradiol said ethinyl estradiol may be micronized Similarly complexes between ethinyl estradiol and cyclodextrins may be micronized

In embodiments wherein the composition comprises the estrogen ethinyl estradiol the dose of the ethinyl estradiol may correspond to a daily release of the said estrogen of from 0 002 to 1 mg, such as from 0 005 to 0 5 mg such as from 0 01 to 0 25 mg, preferably from 0 01 to 0.1 mg such as from 0 01 to 0 05 mg, from 0 01 to 0 03 mg, such as 0 02 mg

Thus one embodiment of the invention is a composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and ethinyl estradiol having a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said ethinyl estradiol of at the most 10%, such as at the most 5 4, 3 or 2% based on the total content of ethinyl estradiol, wherein the dose of ethinyl estradiol corresponds to a daily release of estrogen of from 0 002 to 1 mg, such as from 0 005 to 0 5 mg such as from 0 01 to 0 25 mg, preferably from 0 01 to 0 1 mg, such as from 0 01 to 0 05 mg from 0 01 to 0 03 mg such as 0 02 mg together with one or more pharmaceutically acceptable carriers or excipients,

In embodiments wherein the composition further comprises a therapeutically active compound and that said compound is drospirenone, the dose of drospirenone may correspond to a daily release of said gestagen of from 0 1 to 10 mg, preferably from 0 2 to 8 mg such as from 0.25 to 6 mg preferably from 0 5 to 5 mg such as from 1 5 to 4 mg, such as 1 2 3, 4 mg

One embodiment of the invention relates to composition comprising an inclusion complex between cyclodextrin or derivative thereof and ethinyl estradiol having a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said ethinyl estradiol of at the most 10% such as at the most 5, 4 3 or 2%, based on the total content of ethinyl estradiol and drospirenone wherein the dose of drospirenone corresponds to a daily release of said gestagen between 1 and 5 mg, such as 3 mg, together with one or more pharmaceutically acceptable carriers or excipients.

A particularly preferred embodiment comprises of a composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and ethinyl estradiol having a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said ethinyl estradiol of at the most 10%, such as at the most 5 4 3, or 2% based on the total content of ethinyl estradiol wherein the dose of ethinyl estradiol

corresponds to a daily release of estrogen of from 0 002 to 1 mg such as from 0 005 to 0 5 mg such as from 0 01 to 0 25 mg preferably from 0 01 to 0 1 mg such as from 0 01 to 0 05 mg from 0 01 to 0 03 mg, such as 0 02 mg and drospirenone and wherein the dose of drospirenone corresponds to a daily release of said gestagen between 1 and 5 mg, such as 3 mg together with one or more pharmaceutically acceptable carriers or excipients

As stated an object of the present invention is to provide a pharmaceutical composition comprising an estrogen wherein the stability of said estrogen is significantly improved over that of conventional formulations Degradation of estrogens such as ethinyl estradiol, in conventional formulations is the most critical issue with regard to product shelf life One means of increasing the stability of an estrogen such as ethinyl estradiol (EE) in a composition is by the judicious selection of additives and excipients to the formulation such that oxidants are minimised or excluded from the formulation

Thus the formulation of the compositions of the present invention is also critical The gain stability of the estrogen by means of complexation with cyclodextrin must be maintained in the formulation A vigilant control of the amount of oxidant used in formulation is critical to maintaining the stability of the estrogen Consequently the present invention relates to a pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof wherein the total amount of oxidant in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w such as at the most 5, 4 or 3% w/w, based on the total content of said estrogen

Again alternatively measured, the present invention relates to a pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof wherein the total amount of oxidant in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10, 9, 8, 7, or 6% w/w, based on the total content of said estrogen

Furthermore the present invention relates to a pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin or derivative thereof, wherein the total amount of oxidant in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol 6-β-hydroxy-ethinyl estradiol 6-keto- ethinyl estradiol and Δ9 11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8% such as at the most 0 7% and 0 6% based on the total content of estrogen

Consequently, in one embodiment of the invention, the amount of oxidants is such that the decrease in estrogen content is a further 0 1% less such as at least 0 2 0 3 0.4 or 0 5% less than the decrease in estrogen content in pharmaceutical formulations of compositions not comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen, as measured at the same time mark under the same conditions

The EE-cyclodextrin complex has been found by the present investigators to be sensitive to polyvinylpyrrolidone, which is typically used as a binder for fluid bed granulations Polyvinylpyrrolidone has a deleterious effect on the stability of estrogen whether complexed or uncomplexed and hence on the formulations comprising estrogens

Thus, another aspect of the invention relates to a pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof wherein the amount of polyvinylpyrrolidone in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w such as at the most 5, 4 or 3% w/w based on the total content of said estrogen

Again alternatively measured the invention relates to a pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof,
wherein the amount of polyvinylpyrrolidone in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w such as at the most 10 9, 8, 7 or 6% w/w based on the total content of said estrogen

The invention further provides a pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof wherein the amount of polyvinylpyrrolidone in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol 6-β-hydroxy-ethinyl estradiol 6-keto- ethinyl estradiol and Δ9 11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8% such as at the most 0 7% and 0 6%, based on the total content of estrogen

Most preferably, a formulation of the present invention may be characterised in that it is a polyvinylpyrrolidone-free formulation

The investigators have prepared formulations possessing remarkable stability of the estrogen ethinyl estradiol wherein the amount of polyvinylpyrrolidone has been strictly restricted Thus a preferred formulation is one wherein the amount of polyvinylpyrrolidone is such that the said decrease in estrogen content is at least 0 1% less, such as at least 0 2 0 3, 0 4 or 0 5% less than the decrease in estrogen content in pharmaceutical formulations of compositions not comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen, as measured at the same time mark under the same conditions

As can be seen from the Example 1 3 the stability of EE in formulations wherein EE is present as an inclusion complex with cyclodextrin is greater than wherein EE is present as a free steroid The present invention thus relates to the compositions comprising EE as an inclusion complex with cyclodextrin Furthermore, the Examples illustrates that formulations of the inclusion complex not comprising polyvinylpyrrolidone have increased stability of EE Thus the present invention further relates to the formulations comprising EE as an inclusion complex with cyclodextrin, preferably formulated to be polyvinylpyrrolidone-free Example 2 demonstrates that the total amount of degradation products in formulations according to the present invention is dramatically reduced in comparison to conventional formulations.

The Examples teach that oxidation of EE by oxidants is significant in reducing the stability of EE Consequently it is anticipated that a formulation according to the present invention may further comprise an anti-oxidant.

A further object of the invention is to provide a composition as described *infra* adapted to be formulated for conventional granulation pelletation dry powder blend fluid bed granulation encapsulation or compactation

A preferred embodiment of the invention provides a particulate formulation comprising a composition as described *infra* The particulate formulation may be prepared by a method involving a fluid bed granulation procedure or conventional granulation pelletation dry powder blend, encapsulation, or compactation

The formulations comprising a composition as described *infra* may be in unit dosage form and may be adapted for the preparation of solid dosage forms or dispersion forms as well as adapted to the preparation of tablets capsules or sachets.

A further aspect of the invention is to provide a composition as described *infra* adapted to be administered by oral parenteral mucosal nasal vaginal or topical administration

Formulations comprising either EE or EE-cyclodextrin complex either with or without polyvinylpyrrolidone and either with or without drospirenone and with varying common excipients were prepared to establish features or combination of features which improve the stability of EE

A typical formulation may comprise (wt/wt)

i) 0 002-1% ethinyl estradiol (micronised)
ii) 10-98% such as 45-60% lactose monohydrate
iii) 1-80% such as 1-35% corn starch
iv) 0-90% such as 0-35% cellulose (microcrystalised)
v) 0 05-5% magnesium stearate
vi) 0-5% colloidal silicon dioxide

In the embodiment wherein the composition further comprises a therapeutically active compound such as a gestagen, preferably drospirenone a typical formulation may comprise (wt/wt)

i) 0 1-15% drospirenone (micronised)
ii) 0 002-1% ethinyl estradiol (micronised)
iii) 10-98% such as 45-80% lactose monohydrate
iv) 1-80%, such as 1-35% corn starch
v) 0-90% such as 0-35% cellulose (microcrystallised)
vi) 0 05-5% magnesium stearate
vii) 0-5% colloidal silicon dioxide

A preferred formulation of a tablet core consists of 1 5 to 4 mg most preferably 3 mg of drospirenone 0 01 to 0 03 mg, most preferably 0 02 mg of EE as an EE-βCD complex lactose monohydrate corn starch magnesium stearate

A further object of the invention is to provide a process for preparing a formulation as described *infra* the process comprising suspending maize starch in purified water, adding lactose monohydrate, ethinyl estradiol-cyclodextrin complex, optionally adding drospirenone granulating and drying in a fluid bed granulator

Formulations and compositions described *infra* and in the Examples are anticipated for use in the preparation of a pharmaceutical for female contraception, for hormone replacement therapy, for the treatment of menopausal, pre-menopausal, and/or post-menopausal symptoms for the treatment of acne or for the treatment of PMDD

A still further object of the invention is to provide a method of improving the stability of ethinyl estradiol in a pharmaceutical composition comprising the step of complexing said ethinyl estradiol with cyclodextrin Moreover an object of the present invention is to provide a method of improving the stability of ethinyl estradiol in a pharmaceutical formulation comprising the step of a) complexing said ethinyl estradiol with cyclodextrin and optionally of b) limiting the polyvinylpyrrolidone content to less than 5% such as less than 4% such as less than 3% such as less than 2% such as less than 1% such as providing a substantially polyvinylpyrrolidone-free formulation

The present invention is further defined by the Examples herein which are not intended to be limiting in any way

BRIEF DESCRIPTION OF THE EXAMPLES

Example 1 discloses a composition and a formulation according to some embodiments of the present invention The content of formulations known to the person skilled in the art are outlined in comparison with the contents of embodiments of the present invention and in comparison to a formulation which is oxidant-restricted I e free of povidone Table 1 3 illustrates the performance in terms of stability in comparison to known formulations after a fixed period of time under controlled environmental conditions Direct compression of the powder blend resulted in a dramatic improvement in the stability of EE in comparison to blends which comprise the free steroid The Formulation E was prepared to be povidone-free This also results in increased stability of the active ingredient. By comparison the fluid-bed formulation, which is also povidone-free, does not perform as well as those formulations wherein EE is complexed with cyclodextrin Complexation of EE with cyclodextrin improves the stability of EE

Example 2 illustrates the stability of EE in Formulations D and E in comparison to other formulations in terms of the breakdown products isolated from samples upon storage after a fixed period of time under controlled environmental conditions

Example 3 discloses the contents of one embodiment of the present invention, wherein the composition further comprises drospirenone

Example 4 describes the morphology or some physical characteristics of a typical dosage form of a formulation according to the present invention

Example 5 discloses a typical process for the preparation of a tablet.

Example 6 describes the method in which certain physical properties namely the rate constant of the dissociation constant of the inclusion complex between EE and CD, was studied The half-life of the 1 1 complex was determined to be 155 8 s and the dissociation constant was determined to be 4 45 x 10^{-3} s^{-1}

Example 7 describes the method in which the equilibrium stability constant (formation constant) of the inclusion complex between EE and CD was studied The stability constant of the 1 1 complex was found to be 9 5 x 10^{-4} M^{1} The solubility of complexed ethinyl estradiol was found to improve in comparison to the free steroid

Example 8 describes the method in which the equilibrium stability constant (formation constant) of the inclusion complex between EE and CD in acidic medium was studied The stability constant of the 1 1 and 1 2 complex in acidic medium is disclosed The solubility of complexed ethinyl estradiol was found to improve in comparison to the free steroid in acidic medium

Example 9 discloses the method in which the acid dissociation constant (pK_a) of the EE-CD complex in aqueous media was determined to be approx. 10 51 in comparison to the pK_a of approx 10 25 of the free-steroid

Example 10 describes the method in which the n-octanol/water partition coefficient of the EE-CD inclusion complex was determined and its dependence on pH Its log P value ranges from 3 20 to 3 53

Example 11 discussed whether the ethinyl estradiol-β-cyclodextrin inclusion complex can exist in multiple solid state forms and to provide test methods which can detect and distinguish between such forms

Example 12 describes typical preparations of an EE-CD complex

EXAMPLES

Example 1

Comparative of EE Content After Storage of Test Formulations

1. Summary of Contents of Film-Coated Tablets

a) **Formulation A**
EE-β-CD complex fluid bed granulation with polyvinylpyrrolidone (povidone)

b) **Formulation B (a standard formulation)**
EE as free steroid fluid bed granulation with polyvinylpyrrolidone

c) **Formulation C**
EE as free steroid, fluid bed granulation without polyvinylpyrrolidone

d) **Formulation D**
EE-β-CD complex direct compression of powder blend (without povidone)

e) **Formulation E**
EE-β-CD complex fluid bed granulation, without polyvinylpyrrolidone

2. Composition of Test Formulations

Table 1 2

formulation	Formulation A	Formulation B	Formulation C	Formulation D	Formulation E
EE	-	✓	✓	-	-
EE-β-CD	✓	-	-	✓	✓
DRSP	-	✓	✓	✓	✓
lactose	✓	✓	✓	✓	✓
maize starch	✓	✓	✓	✓	✓
micro cellulose	-	-	-	✓	-
starch 1500	✓	✓	-	-	-
povidone 25 000	✓	✓	-	-	-
Mg Stearate	✓	✓	✓	✓	✓

3 EE-Content After Storage

Table 1 3

formulation	start	3 months		12 months	
		40°C 75% RH	60°C 75% RH	25°C 60% RH	40°C 75% RH
Formulation A	93.1	86.3	77 8	93 8	75 9
Formulation B	98 9	94 9	70 7	95 6	85 7
Formulation C	100 1	95 8	86 1	100 1	92 1
	99 1	96 2	86 1	99 1	92 1
Formulation D	101 6	98 8	96 4	101 4	99 9
	102 7	100 7	98 6	101 8	100 0
Formulation E	103.2	101 3	96.4	100 5	98.9
	103 3	102 0	96.6	101.8	99 3

5 Example 2

Comparative of Known Degradation Products After Storage

Table 2 1 *After 12 months, 25°C, 60% RH*

formulation	6-α-OH-EE	6-β-OH-EE	6-Keto-EE	Δ9 11-EE	total known
EE	0 004	0 005	n d	0 38	0 389
EE-β-CD	0 002	0 003	n d	0 38	0 385
Formulation B	0 04	0 07	0 32	0 74	1 20
Formulation C	0 05	0 09	0 11	0 73	1 00
	0 04	0 07	0 06	0 70	0 91
Formulation D	0 01	0 02	n d	0 49	0 52
	0 01	0 01	n d	0 45	0 47
Formulation E	0.03	0 01	n d	0.46	0 50
	0.02	0.01	n d	0.40	0 43
specification	≤ 0 5	≤ 0 5	≤ 2 0	≤ 1 0	-

n d = not detectable, 6-α-OH-EE = 6-α-hydroxy-ethinyl estradiol, 6-β-OH-EE = 6-β-hydroxy-ethinyl estradiol 6-Keto-EE = 6-keto- ethinyl estradiol Δ9,11-EE = Δ9 11-ethinyl estradiol

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Table 2.2 *After 12 months 40°C, 75% RH*

formulation	6-α-OH-EE	6-β-OH-EE	6-Keto-EE	Δ9 11-EE	total known
EE	0 004	0 005	n d	0 38	0 389
EE-β-CD	0 002	0 003	n d	0 38	0 385
Formulation B	0 16	0 25	1.92	3.14	5.47
Formulation C	0 33 0 28	0 61 0 54	1 03 0 67	1 86 1 59	3 83 3 28
Formulation D	0 03 0 03	0 09 0 10	0.10 0.09	0.79 0 79	1 01 0 98
Formulation E	0 08 0 08	0 19 0 19	0.30 0.41	0.93 0.89	1 60 1 59
specification	≤ 0 5	≤ 0 5	≤ 2 0	≤ 1 0	-

n d = not detectable 6-α-OH-EE = 6-α-hydroxy-ethinyl estradiol, 6-β-OH-EE = 6-β-hydroxy-ethinyl estradiol 6-Keto-EE = 6-keto- ethinyl estradiol Δ9,11-EE = Δ9,11-ethinyl estradiol

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Example 3

Typical composition

The drug product consists of the components listed below The batch size is determined by 200 000 - 550 000 tablets (development site) and 2 5 Mio tablets (production site) respectively Water is used as a processing aid for the manufacture of the tablet mass (fluid bed granulation) and film-coating

Component	mg per tablet	kg per batch (pilot site), batch size = 550 000 tablets	kg per batch (production site), batch size = 2 5 mio. tablets
drospirenone, micro 15	3 0	1 650	7 500
ethinyl estradiol-ß-cyclodextrine complex, micro	0 020 *	0 011 *	0 050 *
lactose monohydrate	48 18	26 499	120 450
maize starch	28 0	15 400	70 000
magnesium stearate	0 8 **	0 440 **	2 000 **
tablet mass weight	80 0 mg	44.000 kg	200 000 kg
hydroxypropylmethyl cellulose	1 5168	0 83424	3 792
talc	0.3036	0 16698	0 759
titanium dioxide	1 1748	0 64614	2 937
ferric oxide pigment red	0 0048	0 00264	0 012
weight of film-coat	3 0 mg	1 650 kg	7 500 kg
total weight	83.0 mg	45.650 kg	207 500 kg

* quantities given state the amount of ethinyl estradiol

BT
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Example 4

Description of the dosage form

Core	Shape	round biconvex
	Diameter	8 mm
	Curvature radius	8 mm
	Height	2 95 mm
	Weight	80 0 mg
	Hardness	40 N
	Friability (Ph Eur / USP)	≤ 0 5 %
	Disintegration time	≤ 10 min
Coated tablet	Color	light pink
	Weight	83 0 mg

Example 5

Description of manufacturing process

- Weigh all ingredients.
- Prepare the granulation liquid

  -Suspend maize starch in purified water and add this suspension to purified water while stirring
- Prepare the tablet mass.

  -Introduce lactose drospirenone micro 15, ethinyl estradiol-ß-cyclodextrine complex micro and maize starch (portion) into the fluid bed granulator Activate a continuous fluid bed Dry Check relative humidity of the tablet mass Dry the tablet mass if necessary until the desired range of relative humidity is reached
- Check yield
- Compress the tablet mass

  -Perform on a rotary tableting machine to tablet cores Pass the cores through a tablet deduster

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- Prepare the film-coating suspension

  -Suspend talc, ferric oxide pigment red and titanium dioxide in purified water and homogenise the suspension Dissolve hydroxypropylmethyl cellulose in purified water while stirring Combine and homogenise the mixture and check yield

- Film-coating

  -Introduce the tablet cores into a suitable coater and warm them up

  -Spray the appropriate amount of film-coating suspension continuously on the rotating cores while drying with warm air Polish and check weight uniformity disintegration time and yield

  -Equilibrate the film-coated tablets

  Check the disintegration time of at least 6 tablets

Example 6

Determination of Rate Constant of the Dissociation Constant of EE-β-CD complex in aqueous solution

Background

The ethinyl estradiol-β-Cyclodextrin inclusion complex as prepared by the present invention is preferably a clathrate complex containing one molecule ethinyl estradiol and two molecules of β-Cyclodextrin

When dissolved in water the ethinyl estradiol-β-Cyclodextrin inclusion complex dissociates into its components ethinyl estradiol (EE) and the ligand β-Cyclodextrin (CD) following law of mass action equilibria

1 $EE + CD \Leftrightarrow EE\,CD \qquad K_{11} = \frac{c_{EECD}}{c_{EE}\ c_{CD}}$

2 $EE\text{-}CD + CD \Leftrightarrow EE\,CD_2 \qquad K_{12} = \frac{c_{EECD_2}}{c_{EECD}\ c_{CD}}$

In this study, the dissociation rate of the 1 1 complex was determined using a stopped flow relaxation method with conductometric detection

Ethinyl estradiol is practically undissociated at pH = 7 (pKa = 10 25) For this reason it remains uncharged in aqueous solution and its contribution to the conductivity is negligible Therefore a direct determination of the dissociation rate with the conductometric detector was not possible

Therefore an indirect method was applied based on a competition reaction using sodium-dodecylsulfate (SDS) which forms an inclusion complex as well SDS as a salt is dissociated in aqueous solution and contributes sufficiently to conductivity When the SD anion binds to β-Cyclodextrin, the inclusion complex formed will be less mobile as the free SD ion in water and the electrical conductivity of the solution will decrease

The difference in conductivity of the free DS^- anion and the complexed anion was used to detect the release kinetic of ethinyl estradiol from the clathrate complex with a stopped flow kinetic apparatus with conductivity detector

As complexation of SDS with β-Cyclodextrin is very rapid the dissociation of the EE-β-CD complex becomes rate determining and can be measured by stopped flow experiments

At higher β-Cyclodextrin concentrations higher ordered Ethinyl estradiol-β-Cyclodextrin complexes are formed Therefore the dissociation rate of the 1 2 complex could not be determined

Summary of Results

The dissociation rate constant of the Ethinyl estradiol-β-Cyclodextrin 1 1 complex was determined through stopped-flow conductometric studies of the competition reaction between sodiumdodecylsulfate and Ethinyl estradiol to form inclusion complexes with β-Cyclodextrin to be

$$K_d = 4\ 45\ \ 10^{-3}\ s^{-1}$$

Under first order conditions the half live of dissociation of the Ethinyl estradiol-β-Cyclodextrin 1 1 complex was calculated to be

$$t_{1/2} = 155\ 8\ s\ (2\ 6\ min)$$

Example 7

Determination of the Equilibrium Stability Constant (Formation Constant) of the EE-β-CD complex in aqueous solution.

Background

The drug substance ethinyl estradiol-β-cyclodextrin inclusion complex is a clathrate complex containing one molecule Ethinyl estradiol and two molecules of β-cyclodextrin The formation of the ethinyl estradiol-β-cyclodextrin clathrate in aqueous solution from its components ethinyl estradiol (S) and the ligand β-cyclodextrin (L) are defined by the following equations according to the law of mass action

1 $S + L = SL$ $K_{11} = \frac{c_{SL}}{c_S \; c_L}$

2 $SL + L = SL_2$ $K_{12} = \frac{c_{SL_2}}{c_{SL} \; c_L}$

The equilibrium stability constant (formation constants) K_{11} was determined with a phase solubility technique For K_{12} only a rough estimation was obtained

Summary of Results

The following data were obtained with the phase solubility diagram technique (PSD) in aqueous solutions at 20 °C

Stability constant of the 1 1 complex	$K_{11} = 9\,5 \;\; 10^{4}\ M^{-1}$
Solubility of Ethinyl estradiol	$S_{EE} = 2\,17 \;\; 10^{-6}$ mol/l (6 43 10^{-3} g/l)
Solubility of the 1 1 complex	$S_{11} = 1\,82 \;\; 10^{-3}$ mol/l (2 75 g/l)
Solubility of the 1 2 complex	$S_{12} = 1\,44 \;\; 10^{-3}$ mol/l (3 7 g/l)

Example 8

Determination of the Equilibrium Stability Constant (Formation Constant) of the EE-β-CD complex in 0.1 M HCl

Background

The drug substance ethinyl estradiol-β-cyclodextrin complex is an inclusion complex complex containing one molecule of ethinyl estradiol and two molecules of β-cyclodextrin.

The formation of the ethinyl estradiol-β-cyclodextrin inclusion complex in aqueous solution from its components ethinyl estradiol (EE) and the ligand β-cyclodextrin (βCD) are defined by the following equations according to the law of mass action

1 $EE + \beta CD = EE\beta CD \qquad K_{11} = \frac{c_{EE\beta CD}}{c_{\beta CD}\ c_{EE}}$

2 $EE\beta CD + \beta CD = EE\beta CD_2 \qquad K_{12} = \frac{c_{EE\beta CD_2}}{c_{EE\beta CD}\ c_{\beta CD}}$

c_i = equilibrium concentrations of the respective entities (mol/l)

Summary of Results

The following data were obtained with the phase solubility diagram technique (PSD) in 0 1 M HCl at 20 °C

Stability constant of the 1 1 complex	K_{11} = 1 56 10^4 M^{-1}
Overall stability constant of the 1 2 complex (= K_{11} K_{12})	K'_{12} = approx 1 6 10^4 M^{-1}
Solubility of ethinyl estradiol	S_{EE} = 1 68 10^{-4} mol/l (0 05 g/l)
Solubility of the 1 1 complex	S_{11} = 2 10^{-3} mol/l (2 9 g/l)
Solubility of the 1 2 complex	S_{12} = 5 10^{-4} mol/l (1 3 g/l)

Example 9

Determination of the Acid Dissociation Constant of the EE-β-CD complex in aqueous media

Background

The drug substance ethinyl estradiol-β-cyclodextrin inclusion complex is a clathrate complex containing one molecule of ethinyl estradiol and two molecules of β-cyclodextrin

In aqueous solution the ethinyl estradiol-β-cyclodextrin inclusion complex dissociates into its components according to the law of mass action To restrain the dissociation of the ethinyl estradiol-β-cyclodextrin inclusion complex an aqueous solution containing an approx 300 fold (0 0114 molar) excess of β-cyclodextrin over ethinyl estradiol was used in the measurements.

The pKa was measured by a photometric titration method following the guidance given in the Environmental Assessment Technical Handbook.

Summary of Results

The acid dissociation constant of the ethinyl estradiol-β-cyclodextrin inclusion complex was determined at 20 C in aqueous solutions containing mixtures of ethinyl estradiol with an approx. 300 fold excess of β-cyclodextrin with a photometric titration method as.

$$pK_a = 10.51 \pm 0.03$$

For comparison the pKa of ethinyl estradiol in the absence of ß-cyclodextrin is

$$pK_a = 10.25 \pm 0.04$$

Example 10

Determination of the n-octanol/water partition coefficient

Background

The drug substance ethinyl estradiol-β-cyclodextrin inclusion complex is a complex containing one molecule of ethinyl estradiol and two of molecules β-cyclodextrin

If the ethinyl estradiol-β-cyclodextrin inclusion complex is equilibrated in the two-phase system, n-octanol/water, a number of simultaneously occuring equilibria are involved partitioning of the complex and the free components between the aqueous phase and n-octanol and dissociation of the inclusion complex The dissociation equilibria will be shifted after phase separation for analysis of both phases Therefore only the total amount of ethinyl estradiol in the aqueous and the octanolic phase can be determined The result is the apparent n-octanol/water partition coefficient of ethinyl estradiol

For determination of the pH dependence of the apparent n-octanol/water partition coefficient of ethinyl estradiol measurements were performed at pH 5 7 and 9 with the flask-shaking method according to OECD guideline 107[1)]

Summary of Results

The flask-shaking method was used to determine the apparent partition coefficient of ethinyl estradiol after partitioning the ethinyl estradiol-ß-cyclodextrin inclusion complex

between aqueous buffer solutions and n-octanol Measurements were performed with aqueous solutions buffered to pH 5 7 and 9 The ethinyl estradiol concentration in each phase after equilibration at 25 °C was determined by HPLC

Table 1 The pH dependence of the apparent partition coefficient of ethinyl estradiol

pH	mean app P_{ow} with standard deviations	app log P_{ow}	95 % confidence intervals for app log P_{ow}
5	2395 ± 623	3 38	3 28 - 3 48
7	3424 ± 1298	3 53	3 35 - 3 67
9	1579 ± 505	3 20	3 08 - 3 29

Example 11

Determination of whether the compound consisting of the ethinyl estradiol-β-cyclodextrin inclusion complex can exist in multiple solid state forms and to provide test methods which can detect and distinguish between such forms

Background

In order to establish whether the compound consisting of the ethinyl estradiol-β-cyclodextrin inclusion complex exists in different solid state forms a variety of crystallization products obtained under different crystallization, drying and storage conditions are investigated with respect to their solid state form A selection of the following analytical methods is applied in order to identify and characterise solid state forms as deemed appropriate and possible

X-ray powder diffraction (XRPD)

differential thermal analysis (DTA) in combination with thermogravimetry (TG)

differential scanning calorimetry (DSC) in combination with thermogravimetry (TG)

Summary of Results

Evidences of complex formation is obtained by investigation of pure ethinyl estradiol and beta-cyclodextrin mechanical mixtures of both substances as well as samples of the ethinyl estradiol-beta-cyclodextrin complex with X-ray powder diffraction and thermal analysis According to these investigations at least about 90 % of the ethinyl estradiol should be bonded in the complex.

The prevalent form of the ethinyl estradiol-beta-cyclodextrin inclusion complex is that of a hydrate containing varying amounts of water The variability of the water content is a consequence of an inherent property of free cyclodextrin as well as of its inclusion compounds (inclusion complexes or clathrates), the equilibration of at least part of the hydrate water with the ambient atmosphere On storage, an equilibrium water content is established which depends on temperature pressure and relative humidity The hydrate water can be readily lost from the crystal lattice Under more servere drying conditions all crystal water can be removed however the resulting material is extremely hygroscopic and therefore not of relevance for the drug substance The same applies to a fully water-saturated hydrate which is stable only in the presence of mother liquid or under relative humidity of more than 97 % Thus, any discussion on the solid state forms of the ethinyl estradiol-β-cyclodextrin complex has to concentrate on the characterisation of a range of hydrates having intermediate water contents with an upper limit at water saturation

The hydrate water is a part of the crystal lattice and therefore alterations of the water content are connected with changes in the crystal lattice This is manifested by differences in the X-ray powder pattern of batches of clathrate with varying water content. According to these patterns four different types can be distinguished Batches of type I contain less than 1 % water In batches of types II and III between 4 % and 10 % water, and 8 % and 15 % water respectively are found Type IV is characterised by a water content of more than 15 % However there's no clear dividing line between two neighbouring types The position of the diffraction peaks is changed gradual due to swelling and shrinking of the crystal lattice during water sorption or desorption Investigations of the four types by differential thermal analysis in combination with thermogravimetry have shown that the dehydration takes place between 25°C and 170°C The different forms are readily and reversibly interchanged by adjustment of the ambient humidity conditions This behaviour indicates considerable rigidity of the structural framework which does not allow profound alteration of the basic arrangement of the beta-cyclodextrin/ethinyl estradiol building blocks of the solid during hydration and dehydration

Example 12

Preparation of the ethinyl estradiol-beta-cyclodextrin complex

The ethinyl estradiol-beta-cyclodextrin complex is obtained by co-precipitation as follows

Process 1 (P1) Ethinyl estradiol is dissolved in ethanol β-cyclodextrin is dissolved at 45 °C in water The ethinyl estradiol solution is added to the β-cyclodextrin solution The obtained suspension is stirred for some hours at 20 to 25°C and afterwards at 2 °C The crystallization product is isolated and dried by methods described *infra*.

Process 2 (P2) Ethinyl estradiol is dissolved in acetone β-cyclodextrin is dissolved at 45 C in water The ethinyl estradiol solution is added to the beta-cyclodextrin solution The obtained suspension is stirred for some hours at temperatures below 25 °C Afterwards the crystallization product is isolated and dried by methods described *infra*

The mechanical mixtures of β-cyclodextrin and ethinyl estradiol are prepared by weighing and afterwards homogenization by grinding in an agate mortar

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Table 12 1a Crystallization products of the complex

batch	solvent / treatment conditions	content of EE [%]	water content [%]
Im2180	P 1 dried in a vacuum drying cabinet	10 9	5 57
Im2181	P 1 dried in a vacuum drying cabinet	11 2	5 26
Im2182/1	P 1 dried 1 h at r t. over P_2O_5 in a vacuum desiccator	n.d	6 5
Im2182/2	P 1, dried 2 h at r t. over P_2O_5 in a vacuum desiccator	n d.	6 5
Im2182/3	P 1 dried 4 h at r t. over P_2O_5 in a vacuum desiccator	n d	6 4
Im2182/4	P 1, dried 4 h at r t. over P_2O_5 in a vacuum desiccator	n d	7 7
Im2182/5	P 1 dried 43 5 h at r t. over P_2O_5 in a vacuum desiccator	10 8	4.47
Im2182/6 Act.	P 1 washed with acetone dried 3 h at 2°C over P_2O_5 in a vacuum desiccator	10.9	4.85
Im2182/7	P 1 washed with acetone and water dried 3 h at 2°C over P_2O_5 in a vacuum desiccator	10 6	4 47
Im2183/V	P 1, dried some hours at r t. over P_2O_5 in a vacuum desiccator	11 4	4 21
Im2183/VT	P 1 dried in a vacuum drying cabinet	10 7	5 59
Im2183/L	P 1 stored at air	11 4	10 2
Im2183/VT+L	P 1 dried in a vacuum drying cabinet and than storage at air	10 6	8 75
Im2184	P 1 dried in a vacuum drying cabinet	10 9	5.60
Im2188	P 1 20 h at r t.	10 8	11 85
Im2190f	P 1 dried in a vacuum drying cabinet - 1d	n d	-
Im2191f	P 1 dried in a vacuum drying cabinet - 1d	n.d	-
Im2190	P 1 dried in a vacuum drying cabinet - 5d	10 6	7 5
Im2191	P 1 dried in a vacuum drying cabinet - 5d	10.8	7 7
28052691	batch Im2190 micronized	10 7	8.23
Im2220	P 2 dried in a vacuum drying cabinet	10.7	5 61
Im2221	P 1 dried in a vacuum drying cabinet	10 2	5 78
Im2222	P 1 dried in a vacuum drying cabinet	10 4	5 57
Im2223	P 1, dried in a vacuum drying cabinet	10 1	6 64
Im2224	P 2, dried in a vacuum drying cabinet	10.4	5.75

Table 12 1b Crystallization products of the complex

batch	solvent / treatment conditions	content of EE [%]	water content [%]
Im2225/1	P 1 washed 2 x water dried in a vacuum drying cabinet	11 2	3.34
Im2225/2	P 1 washed 2 x water 1 x acetone dried in a vacuum drying cabinet	10 5	3 31
Im2225/3	P 1 washed 2 x water 1 x acetone 1 x water dried in a vacuum drying cabinet	10.9	3 8
Im2230	P 1 washed 1 x water 1 x acetone,1 x water dried in a vacuum drying cabinet	10 8	4 35
Im2231	P 1 washed 1 x water 1 x acetone 1 x water dried in a vacuum drying cabinet	11	2 63
Im2240	P 1, washed 1 x water 1 x acetone 1 x water dried in a vacuum drying cabinet	10 5	6 71
28052591 DVS1 0%RH	batch 28052591 after one sorption/desorption cycle stored at 0 % RH	n d	< 1%[a]
Im2180 DVS1 0% RH	batch Im2180 after sorption/desorption cycle stored at 0 % RH	n d	< 1%[a]
Im2180 DVS1 45% RH	batch Im2180 stored at 45 % RH	n d	6 5[a]
Im2180 DVS1 70% RH	batch Im2180 stored at 70 % RH	n d	9 6[a]
Im2180 DVS1 75% RH	batch Im2180 stored at 75 % RH	n d	9 5[a]
Im2180 DVS1 93% RH	batch Im2180 stored at 93 % RH	n.d	~15[a]
Im2180 3d $Mg(ClO_4)_2$	batch Im2180 stored 3 d over $Mg(ClO_4)_2$	n d	n d
Im2190 5d 97% RH	batch Im2190 stored 5 d at 97 % RH	n d	~16 7[a]
Im2190 7d 97% RH	batch Im2190 stored 7 d at 97 % RH	n d	~16 5[a]
28052591,7d $Mg(ClO_4)_2$	batch 28052591 stored 7 d over $Mg(ClO_4)_2$	n d	< 0 1[a]
28052591,7d 97% RH	batch 28052591 stored 7 d at 97 % RH	n d	16 9[a]
28052591 wet	batch 28052591 suspended in water no drying	-	-
28052591,7d 75% RH	batch 28052591 stores 7 d at 75 % RH	n d	10 5[a]

[a] calculated from the water content of the starting material and the observed mass change

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CLAIMS

1 A pharmaceutical composition comprising an inclusion complex between a cyclodextrin or derivative thereof, and an estrogen,
wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5 4, or 3% w/w, based on the total content of said estrogen
together with one or more pharmaceutically acceptable carriers or excipients

2 A composition comprising an inclusion complex between a cyclodextrin or derivatives thereof, and estrogen
wherein the composition is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w such as at the most 10 9 8 7, or 6% w/w, based on the total content of said estrogen,
together with one or more pharmaceutically acceptable carriers or excipients.

3 A pharmaceutical composition comprising an inclusion complex between a cyclodextrin or derivative thereof and an estrogen
suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen
together with one or more pharmaceutically acceptable carriers or excipients.

4 A composition according to any of claims 1 to 3 wherein the estrogen is selected from the group consisting of ethinyl estradiol (EE) estradiol, estradiol sulfamates, estradiol valerate estradiol benzoate estrone and estrone sulfate or mixtures thereof preferably ethinyl estradiol (EE), estradiol estradiol valerate, estradiol benzoate and estradiol sulfamates, most preferably ethinyl estradiol (EE)

5 A composition according to claim 3, wherein the estrogen is ethinyl estradiol

6 A composition comprising an inclusion complex between a cyclodextrin or derivative thereof and ethinyl estradiol
wherein the composition is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol 6-keto- ethinyl estradiol and Δ9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8%, such as at the most 0 7% and 0 6%, based on the total content of estrogen,
together with one or more pharmaceutically acceptable carriers or excipients

7 A composition comprising an inclusion complex between a cyclodextrin, or derivative thereof and ethinyl estradiol,
wherein the composition is such that said ethinyl estradiol has a 12-month stability at 40°C and 75% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol Δ6 7-ethinyl estradiol and Δ-9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 3%, such as at the most 2% based on the total content of estrogen,
together with one or more pharmaceutically acceptable carriers or excipients

8 A pharmaceutical composition comprising an inclusion complex between a cyclodextrin, or derivative thereof and an estrogen
suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol 6-β-hydroxy-ethinyl estradiol 6-keto-ethinyl estradiol, Δ6,7-ethinyl estradiol and Δ-9 11-ethinyl estradiol of said ethinyl estradiol totals at the most 3% such as at the most 2% based on the total content of estrogen
together with one or more pharmaceutically acceptable carriers or excipients

9 A composition according to any of claims 1 to 8 wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin and derivatives thereof

10 A composition according to claim 9 wherein the cyclodextrin is β-cyclodextrin or derivatives thereof

11 A composition according to claim 10 wherein the cyclodextrin is β-cyclodextrin

12 A composition according to any the preceding claims, further comprising one or more therapeutically active compounds

13 A composition comprising according to claim 12 wherein at least one of the therapeutically active compounds is a gestagen

14 A composition according to claim 13, wherein the gestagen is selected from the group consisting of drospirenone levonorgestrel norgestrel gestadene dienogest, cyproterone acetate norethisterone norethisterone acetate desorgestrel 3-keto-desorgestrel

15 A composition according to claim 14, wherein the gestagen is drospirenone

16 A composition according to claim 15 wherein the drospirenone is micronised

17 A composition according to any of claims 15 or 16 wherein all or substantially all the drospirenone is present as an inclusion complex with cyclodextrin

18 A composition according to claim 12, wherein the estrogen is ethinyl estradiol and a therapeutically active compound is drospirenone

19 A composition according to any of claims 5, 6 7 or 18, wherein the ethinyl estradiol is micronised

20 A composition according to any of the preceding claims, wherein the dose of the estrogen corresponds to a daily release of ethinyl estradiol between 0 002 and 1 mg

21 A composition according to any of claims 14 to 18, wherein the dose of drospirenone corresponds to a daily release of said gestagen of from 0 1 to 10 mg preferably from 0 25 to 6 mg, such as from 1 5 to 4 mg

22 A composition according to any of the preceding claims wherein the estrogen is ethinyl estradiol and the dose of ethinyl estradiol corresponds to a daily release of said estrogen of from 0 002 to 1 mg such as from 0 005 to 0 5 mg, such as from 0 01 to 0 25

mg preferably from 0 01 to 0 1 mg such as from 0 01 to 0 05 mg from 0 01 to 0 03 mg such as 0 02 mg

23 A composition according to claim 22 further comprising drospirenone, wherein the dose of drospirenone corresponds to a daily release of said gestagen between 1 and 5 mg, such as 3 mg

24 A composition according to any of the preceding claims adapted to be formulated by conventional granulation pelletation dry powder blend fluid bed granulation encapsulation or compactation

25 The use of a composition according to any of claims 1 to 24 for the preparation of a pharmaceutical for female contraception for hormone replacement therapy for the treatment of menopausal, pre-menopausal, and/or post-menopausal symptoms, for the treatment of acne or for the treatment of PMDD

26 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin or derivative thereof, wherein the total amount of oxidant in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5 4 or 3% w/w based on the total content of said estrogen

27 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin or derivative thereof wherein the total amount of oxidant in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10 9 8 7 or 6% w/w based on the total content of said estrogen

28 A pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin or derivative thereof, wherein the total amount of oxidant in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl

estradiol 6-keto- ethinyl estradiol and Δ9 11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8% such as at the most 0 7% and 0 6% based on the total content of estrogen

29 A formulation according to claim 28 wherein the total amount of oxidant in said formulation is such that the decrease in total estrogen content as measured at the 12-month mark at 40°C and 75% relative humidity (RH), is at least 0 1% less than such as at least 0 2 0 3 0 4 or 0 5% less than the decrease in estrogen content in pharmaceutical formulations of compositions not comprising an inclusion complex between a cyclodextrin or derivative thereof and an estrogen, as measured at the same time mark under the same conditions

30 A formulation according to claim 27 wherein the total amount of oxidant in said formulation is such that the decrease in total estrogen content, as measured at 3-month mark at 60°C and 75% relative humidity (RH) is at least 0 1% less than, such as at least 0 2 0 3 0 4 or 0 5% less than the decrease in estrogen content in pharmaceutical formulations of compositions not comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen as measured at the same time mark under the same conditions

31 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof wherein the amount of polyvinylpyrrolidone in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w such as at the most 5 4, or 3% w/w based on the total content of said estrogen

32 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin or derivative thereof wherein the amount of polyvinylpyrrolidone in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10 9, 8 7, or 6% w/w, based on the total content of said estrogen

33. A pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin or derivative thereof, wherein the amount of polyvinylpyrrolidone in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol 6-keto- ethinyl estradiol and Δ9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8%, such as at the most 0 7% and 0 6%, based on the total content of estrogen

34 A formulation according to any of claims 26 to 33 characterised in that it is a polyvinylpyrrolidone-free formulation

35 A formulation according to any of claims 26 to 34 further comprising an anti-oxidant

36 A formulation according to any of claims 26 to 35, comprising (wt/wt)

i) 0 002-1% ethinyl estradiol (micronised)
ii) 10-99% such as 45-60% lactose monohydrate
iii) 1-80%, such as 1-35% corn starch,
iv) 0-80% such as 0-35% cellulose (microcrystalline)
v) 0 05-5% magnesium stearate and
vi) 0-5% colloidal silicon dioxide

37 A formulation according to any of claims 26 to 35 comprising (wt/wt)

i) 0 1-15% drospirenone (micronised)
ii) 0 002-1% ethinyl estradiol (micronised)
iii) 10-99% such as 45-60% lactose monohydrate
iv) 1-80%, such as 1-35% corn starch
v) 0-80%, such as 0-35% cellulose (microcrystalline)
vi) 0 05-5% magnesium stearate and
vii) 0-5% colloidal silicon dioxide

38 A formulation according to any of claims 26 to 37 prepared by a method involving conventional granulation pelletation, dry powder blend, fluid bed granulation encapsulation or compactation

39 A formulation according to any of claims 26 to 38 in unit dosage form

40 A formulation according to any of claims 26 to 39 adapted for the preparation of solid dosage forms or dispersion forms.

41 A formulation according to any of claims 26 to 39 adapted to the preparation of tablets, capsules or sachets

42 A composition according to any of claims 1 to 24 adapted to be administered by oral parenteral mucosal, nasal, vaginal or topical administration.

43 A method for improving the stability of ethinyl estradiol in a pharmaceutical composition comprising the step of forming an inclusion complex between said ethinyl estradiol and cyclodextrin

44 A method of improving the stability of ethinyl estradiol in a pharmaceutical formulation comprising the step of a) complexing said ethinyl estradiol with cyclodextrin, and optionally of b) limiting the polyvinylpyrrolidone content to less than 5% such as less than 4% such as less than 3% such as less than 2%, such as less than 1% such as providing a substantially polyvinylpyrrolidone-free formulation

45 A process for the preparation of a formulation according to any of claims 26 to 41

REIVINDICACIONES

1 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno,
siendo la composición tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 10% peso/peso, por ejemplo de máximo 5, 4 o 3% peso/peso, respecto al contenido total de dicho estrógeno,
junto con uno o varios vehículos o excipientes farmacéuticamente aceptables

2 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o derivados de ella y estrógeno, siendo la composición tal que dicho estrógeno tiene una estabilidad de 3 meses a 60°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 15% peso/peso, por ejemplo de máximo 10, 9, 8, 7 o 6% peso/peso, respecto al contenido total de dicho estrógeno,
junto con uno o varios vehículos o excipientes farmacéuticamente aceptables

3 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno,
formulada apropiadamente de tal manera que la cantidad total de oxidante es tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 10% peso/peso, por ejemplo de máximo 5, 4 o 3% peso/peso, respecto al contenido total de dicho estrógeno,
junto con uno o varios vehículos o excipientes farmacéuticamente aceptables

4 Una composición de acuerdo con cualquiera de las reivindicaciones 1 a 3, en la cual el estrógeno seleccionado entre el grupo consituido por etinilo estradiol (EE), estradiol, sulfamatos de estradiol, valerato de estradiol, benzoato de estradiol, estrona y sulfato de estrona o mezclas de ellos, preferiblemente etinilo estradiol (EE), estradiol, valerato de estradiol, benzoato de estradiol y sulfamatos de estradiol, más preferiblemente etinilo estradiol (EE)

5 Una composición de acuerdo con la reivindicación 3, en la cual el estrógeno es etinilo estradiol

6 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un etinilo estradiol,
siendo la composición tal que dicho etinilo estradiol tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 0,8%, por ejemplo máximo 0,7% y 0,6%, respecto al contenido total de estrógeno,
junto con uno o varios vehículos o excipientes farmacéuticamente aceptables

7 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un etinilo estradiol,
siendo la composición tal que dicho etinilo estradiol tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol, Δ6,7-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 3%, por ejemplo máximo 2%, respecto al contenido total de estrógeno,
junto con uno o varios vehículos o excipientes farmacéuticamente aceptables

8 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno, apropiadamente formulada de tal manera que la cantidad total de oxidante es tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol, Δ6,7-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 3%, por ejemplo máximo 2%, respecto al contenido total de estrógeno,
junto con uno o varios vehículos o excipientes farmacéuticamente aceptables

9 Una composición de acuerdo con cualquiera de las reivindicaciones 1 a 8, en la cual la ciclodextrina se selecciona entre el grupo constituido por α-ciclodextrina, ß-ciclodextrina, γ-ciclodextrina y derivados de éstas

10 Una composición de acuerdo con la reivindicación 9, en la cual la ciclodextrina es ß-ciclodextrina o derivados de ella

11 Una composición de acuerdo con la reivindicación 10, en la cual la ciclodextrina es ß-ciclodextrina

12 Una composición de acuerdo con cualquiera de las anteriores reivindicaciones, la cual comprende además uno o varios compuestos activos terapéuticamente

13 Una composición de acuerdo con la reivindicación 12, en la cual al menos uno de los compuestos activos terapéuticamente es un gestágeno

14 Una composición de acuerdo con la reivindicación 13, en la cual el gestágeno se selecciona entre el grupo constituido por drospirenona, levonorgestrel, norgestrel, gestádeno, dienogest, acetato de ciproterona, norethisterona, acetato de norethisterona, desorgestrel, 3-ceto-desorgestrel

15 Una composición de acuerdo con la reivindicación 14, en la cual el gestágeno es drospirenona

16 Una composición de acuerdo con la reivindicación 15, en el cual la drospirenona es micronizada

17 Una composición de acuerdo con cualquiera de las reivindicaciones 15 o 16, en la cual toda la drospirenona o substancialmente toda la drospirenona está presente como un complejo de inclusión con ciclodextrina

18 Una composición de acuerdo con la reivindicación 12, en la cual el estrógeno es etinilo estradiol y un compuesto activo terapéuticamente es drospirenona

19 Una composición de acuerdo con cualquiera de las reivindicaciones 5, 6, 7 o 18, en la cual el etinilo estradiol es micronizado

20 Una composición de acuerdo con cualquiera de las anteriores reivindicaciones, en la cual la dosis de estrógeno corresponde a un aliberación diaria de etinilo estradiol entre 0,002 y 1 mg

21 Una composición de acuerdo con cualquiera de las reivindicaciones 14 a 18, en la cual la dosis de drospirenona corresponde a una liberación diaria de dicho gestágeno de 0,1 a 10 mg, preferiblemente de 0,25 a 6 mg, por ejemplo de 1,5 a 4 mg

22 Una composición de acuerdo con cualquiera de las anteriores reivindicaciones, en la cual el estrógeno es etinilo estradiol y la dosis de etinilo estradiol corresponde a una liberación diaria de dicho estrógeno de 0,002 a 1 mg, tal como de 0,005 a 0,5 mg, por ejemplo de 0,01 a 0,25 mg, preferiblemente de 0,01 a 0,1 mg, tal como de 0,01 mg a 0,05 mg o de 0,01 a 0,03 mg, por ejemplo 0,02 mg

23 Una composición de acuerdo con la reivindicación 22, la cual comprende además drispirenona, correspondiendo la dosis de drospirenona a una liberación diaria de dicho gestágeno entre 1 y 5 mg, por ejemplo 3 mg

24 Una composición de acuerdo con cualquiera de las anteriores reivindicaciones, adaptada para ser formulada mediante granulación, empastillado, mezcla de polvo seco, granulación de lecho fluidizado, encapsulación o compactación convencionales

25 El uso de una composición de acuerdo con cualquiera de las reivindicaciones 1 a 24 para la preparación de un producto farmacéutico para la anticoncepción femenina, para la terapia de reemplazo hormonal, para el tratamiento de los síntomas de menopausia, premenopausia y/o pos-menopausia, para el tratamiento del acné o para el tratamiento de PMDD

26 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad total de oxidante en dicha formulación tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 10% peso/peso, por ejemplo de máximo 5, 4 o 3%, respecto al contenido total de dicho estrógeno

27 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad total de oxidante en dicha formulación tal que dicho estrógeno tiene una estabilidad de 3 meses a 60°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 15% peso/peso, por ejemplo de máximo 10, 9, 8 7 o 6%, respecto al contenido total de dicho estrógeno

28 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad total de oxidante en dicha formulación tal que dicho etinilo estradiol tiene una estabilidad de 12 meses a 25°C y 60% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 0,8%, por ejemplo máximo 0,7% y 0,6%, respecto al contenido total de estrógeno

29 Una formulación de acuerdo con la reivindicación 26, siendo la cantidad total de oxidante en dicha formulación tal que la disminución en el contenido total de estrógeno, medido en la marca de los 12 meses a 40°C y 75% de humedad relativa, es al menos 0,1%, por ejemplo al menos 0,2, 0,3, 0,4 o 0,5%, que la disminución en el contenido de estrógeno en formulaciones farmacéuticas de composiciones que no comprenden un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno, siendo medido este contenido en la misma marca de tiempo bajo las mismas condiciones

30 Una formulación de acuerdo con la reivindicación 27, siendo la cantidad total de oxidante en dicha formulación tal que la disminución en el contenido total de estrógeno, medido en la marca de los 3 meses a 60°C y 75% de humedad relativa, es al menos 0,1% menos, por ejemplo al menos 0,2, 0,3, 0,4 o 0,5%, que la disminución en el contenido de estrógeno en formulaciones farmacéuticas de composiciones que no comprenden un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno, siendo medido este contenido en la misma marca de tiempo bajo las mismas condiciones

31 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una

ciclodextrina o un derivado de ella, siendo la cantidad de polivinilpirrolidona en dicha formulación tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 10% peso/peso, por ejemplo de máximo 5, 4 o 3% peso/peso, respecto al contenido total de dicho estrógeno

32 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad de polivinilpirrolidona en dicha formulación tal que dicho estrógeno tiene una estabilidad de 3 meses a 60°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 15% peso/peso, por ejemplo de máximo 10, 9, 8, 7 o 6% peso/peso, respecto al contenido total de dicho estrógeno

33 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad de polivinilpirrolidona en dicha formulación tal que dicho etinilo estradiol tiene una estabilidad de 12 meses a 25°C y 60% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 0,8%, por ejemplo máximo 0,7% y 0,6%, respecto al contenido total de estrógeno

34 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 33, caracterizada porque es una formulación que no contiene polivinilpirrolidona

35 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 34, la cual comprende además un anti-oxidante

36 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 35, la cual comprende (peso/peso)

i) 0,002-1% de etinilo estradiol (micronizado),
ii) 10-99%, por ejemplo 45-60%, de monohidrato de lactosa,
iii) 1-80%, por ejemplo 1-35%, de almidón de maiz,
iv) 0-90%, por ejemplo 0-35%, de celulosa (microcristalizada),
v) 0,05-5% de estearato de magnesio, y
vi) 0-5% de dióxido de silicona coloide

37 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 35, la cual comprende (peso/peso)

i) 0,1-15% de drospirenona (micronizada)

ii) 0,002-1% de etinilo estradiol (micronizado),

iii) 10-99%, por ejemplo 45-60%, de monohidrato de lactosa,

iv) 1-80%, por ejemplo 1-35%, de almidón de maíz,

v) 0-90%, por ejemplo 0-35%, de celulosa (microcristalizada),

vi) 0,05-5% de estearato de magnesio, y

vii) 0-5% de dióxido de silicona coloide

38 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 37, preparada mediante un método que involucra granulación, empastillado, mezcla de polvo seco, granulación de lecho fluidizado, encapsulación o compactación convencionales

39 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 38 en forma de dosis unitaria

40 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 39 adaptada para la preparación de formas de dosis sólidas o formas de dispersión

41 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 39 adaptada para la preparación de tabletas, cápsulas o bolsitas

42 Una composición de acuerdo con cualquiera de las reivindicaciones 1 a 24, adaptada para ser administrada mediante administración oral, parenteral, mucosal, nasal, vaginal o tópica

43 Un método para mejorar la estabilidad del etinilo estradiol en una composición farmacéutica, el cual comprende el paso de formar un complejo de inclusión entre dicho etinilo estradiol y ciclodextrina

44 Un método para mejorar la estabilidad del etinilo estradiol en una composición farmacéutica, el cual comprende el paso de a) complejizar dicho etinilo estradiol con ciclodextrina, y opcionalmente b) limitar el contenido de polivinilpirrolidona a menos de 5%, por ejemplo a menos de 4%, por ejemplo a menos de 3%, por ejemplo a menos de 2%, por ejemplo a menos de 1%, por ejemplo proporcionando una formulación que substancialmente no contiene polivinilpirrolidona

45 Un procedimiento para la preparación de una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 41

#F 210

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Bescheinigung	Certificate	Attestation
Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein	The attached documents are exact copies of the European patent application described on the following page, as originally filed	Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante

Patentanmeldung Nr	Patent application No	Demande de brevet n°

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Der Präsident des Europäischen Patentamts
im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

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THE HAGUE, 24/07/03
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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention
(Falls die Bezeichnung der Erfindung nicht angegeben ist siehe Beschreibung
If no title is shown please refer to the description
Si aucun titre n'est indiqué se referer à la description)

Compositions of estrogen-cyclodextrin complexes

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COMPOSITIONS OF ESTROGEN-CYCLODEXTRIN C MPLEXES

FIELD OF INVENTION

The present invention relates to pharmaceutical composition comprising a cyclodextrin-estrogen inclusion complex that confers very high chemical stability to the estrogen The composition according to the present invention allows for an increased stability of ethinyl estradiol upon storage

BACKGROUND OF THE INVENTION

Degradation of estrogens, such as ethinyl estradiol, in conventional formulations is one of the most critical issues with regard to product shelf life The stabilisation of the estrogen may be achieved by either product packaging in hermetic containers or, more effectively, as in the present invention, by actual stabilisation of the formulation

Formulations comprising naturally or synthetically derived sex hormones often consist of low dosages of these active ingredients Given the small amounts of active ingredient required per single dosage, often ranging between 0 1 μg and 500 μg, content uniformity of the preparation is a significant contributor to fluctuations in actual doses of these active ingredients

Similarly, the oxidative degradation of these small amounts of active ingredient is a further contributor to the strong fluctuations of the active ingredient in low dosage formulations In low dosage formulations, these fluctuations are critical to quality assurance

In general, these low dose formulations are problematic in terms of their preparation, storage and use

US 4,596,795 discloses a complex between α-, β- and γ-cyclodextrins and derivatives thereof with testosterone, progesterone, and estradiol and the solubility of said complexes

US 4,727,064 discloses a method of producing a stabilizing amorphous complex of a drug and a mixture of cyclodextrin derivatives

US 4,383,992 discloses a water soluble inclusion compound formed by complexing beta-cyclodextrin with a steroid compound, such an estogen

US 5,798,338 discloses a composition of a clathrate between β-cyclodextrin and 17-α-ethinyl estradiol for reducing the oxidative degradation of 17-α-ethinyl estradiol

SUMMARY OF THE INVENTION

An object of the present invention is to provide a pharmaceutical composition comprising an estrogen wherein the stability of said estrogen is significantly improved over that of conventional formulations without complexed estrogens Degradation of estrogens, such as ethinyl estradiol, in conventional formulations is one of the most critical issue with regard to product shelf life The stabilisation of the estrogen may be achieved by either product packaging in hermetic containers (e g pouch) or, more effectively, by actual stabilisation of the formulation

It has surprisingly been found that a complex of cyclodextrin and estrogen significantly improves the stability of the estrogen and consequently the shelf-life of an estrogen-containing composition Accordingly, the present invention relates to a pharmaceutical composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and an estrogen, wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, 3, or 2% w/w, based on the total content of said estrogen, together with one or more pharmaceutically acceptable carriers or excipients

Moreover, an alternative embodiment of the present invention relates to a pharmaceutical composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and an estrogen, wherein the composition is such that said estrogen has a 12-month stability at 25°C and 60% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w such as at the most 5, 4, 3 or 2% w/w,

based on the total content of said estrogen, together with one or more pharmaceutically acceptable carriers or excipients

The present invention further relates to a pharmaceutical composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and estrogen wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10%, such as at the most 5, 4, 3 or 2% based on the total content of estrogen, and a therapeutically active compound, such as a gestagen, such as drospirenone, together with one or more pharmaceutically acceptable carriers or excipients

Furthermore, the invention relates to a pharmaceutical composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen, suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5 4, or 3% w/w, based on the total content of said estrogen, together with one or more pharmaceutically acceptable carriers or excipients

Compositions of the present invention may be used as medicaments Accordingly, the use of a composition described infra for the preparation of a pharmaceutical for female contraception, for hormone replacement therapy, for the treatment of menopausal, pre-menopausal, and/or post-menopausal symptoms, for the treatment of acne or for the treatment of PMDD is a further aspect of the present invetion

As the formulation of the complex is another important aspect to achieve the improved effects, the present invention further relates to a pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the total amount of oxidant in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen

Alternatively measured the present invention provides a pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between

a cyclodextrin, or derivative thereof, wherein the total amount of oxidant in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10, 9, 8, 7, or 6% w/w, based on the total content of said estrogen

Still further, the present invention relates to pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the total amount of oxidant in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto- ethinyl estradiol and Δ9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8%, such as at the most 0 7% and 0 6%, based on the total content of estrogen

In a broad sense, the present invention relates a method of improving the stability of ethinyl estradiol in a pharmaceutical formulation comprising the step of a) complexing said ethinyl estradiol with cyclodextrin, and optionally of b) limiting the polyvinylpyrrolidone content to less than 5%, such as less than 4%, such as less than 3%, such as less than 2%, such as less than 1%, such as providing a substantially polyvinylpyrrolidone-free formulation

Generally, an object of the present invention is to provide a pharmaceutical composition comprising an estrogen wherein the stability of said estrogen is significantly improved over that of conventional formulations

DETAILED DESCIPTION OF THE INVENTION

The term "complex" is intended to mean an inclusion complex between estrogen and cyclodextrin, wherein a molecule of said estrogen is at least partially inserted into the cavity of one or more cyclodextrin molecules, wherein for example two moieties of a single estrogen molecule are each inserted into one cyclodextrin molecule to give 2 1 ratio between cyclodextrin and estrogen Similarly, the complex may comprise of more than one molecule of estrogen at least partially inserted into one or more cyclodextrin

molecules, wherein for example 2 estrogen molecules are at least partially inserted into a single cyclodextrin molecule, to give a 1 2 ratio between cyclodextrin and estrogen Complexes wherein one estrogen molecule is complexed with one or more cyclodextrin molecules are certainly anticipated such as 1 estrogen molecule complexed with 2 cyclodextrin molecules or 3 cyclodextrin molecules Typically, the ethinyl estradiol-β-cyclodextrin inclusion complex as prepared by the present invention is preferably a complex between one molecule of ethinyl estradiol and two molecules of β-Cyclodextrin

The term "ethinyl estradiol-β-Cyclodextrin inclusion complex" or "EE-β-CD" is intended to mean a complex, of any ratio, between ethinyl estradiol and β-cyclodextrin

The term "oxidant-free" relates to formulations substantially devoid of all agents having substantial oxidizing capacity whereas the term "oxidant-restricted" relates to formulations substantially devoid of at least one agent having substantial oxidizing capacity For example, a polyvinylpyrrolidone-free formulation is an oxidant-restricted formulation

The present investigators have developed formulations wherein a remarkable improvement of the stability of the estrogen ethinyl estradiol (EE) has been achieved by individual or combined means One such means is the protection of EE by forming a β-cyclodextrin complex Another such means is by the judicious selection of additives and excipients to the formulation such that oxidants are minimised or excluded from the formulation Individually, or acting in concert, these means have resulted in formulations wherein said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of between 3 and 10 % w/w, compared to conventional formulations wherein estrogen degrades by up to 25% under identical conditions (see Table 1 3, Example 1) Thus, a preferred embodiment of the invention is that of a pharmaceutical composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and an estrogen, wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen, together with one or more pharmaceutically acceptable carriers or excipients

It is evident that the stability test may be performed under alternative conditions such as higher temperatures Thus an alternative embodiment wherein the composition is such

that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10, 9, 8, 7, 6, or 5% w/w, based on the total content of said estrogen

As stated, the formulation of the estrogen-cyclodextrin complex is critical to achieve the desired effect of improved stability of a composition comprising said complex The present inventors have developed a pharmaceutical composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen, suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen, together with one or more pharmaceutically acceptable carriers or excipients

An embodiment of an oxidant-restricted formulation (see Table 1 3, Example 1) comprising EE complexed with βCD compares surprisingly well with known formulations in 3-month stability studies at 60°C and 75% relative humidity (RH), wherein a less than 4% decrease in EE content was observed in said embodiment compared to an almost 30% decrease was observed in known formulations or free-estrogen formulations

As the person skilled in the art will appreciate, the estrogen may be selected from the group consisting of ethinyl estradiol (EE), estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, estriol, estriol succinate and conjugated estrogens, including conjugated equine estrogens such as estrone sulfate, 17β-estradiol sulfate, 17α-estradiol sulfate, equilin sulfate, 17β-dihydroequilin sulfate, 17α-dihydroequilin sulfate, equilenin sulfate, 17β-dihydroequilenin sulfate and17α-dihydroequilenin sulfate or mixtures thereof Particularly interesting estrogens are selected from the group consisting of ethinyl estradiol (EE), estradiol estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof, notably ethinyl estradiol (EE), estradiol, estradiol valerate, estradiol benzoate and estradiol sulfamates Most preferred is ethinyl estradiol (EE)

In the preferred embodiment wherein the estrogen is ethinyl estradiol (EE), some of the degradation products are well known Thus it is possible to express the stability of the formulation in terms of the amount of these degradation products Accordingly, the

composition according to one embodiment of the present invention comprises an inclusion complex between cyclodextrin, or derivative thereof, and ethinyl estradiol, wherein the composition is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol, Δ9,11-ethinyl estradiol and Δ6,7-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8%, such as at the most 0 7% and 0 6%, based on the total content of estrogen, together with one or more pharmaceutically acceptable carriers or excipients

A pharmaceutical composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, and ethinyl estradiol, suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol, Δ6,7-ethinyl estradiol and Δ-9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 3%, such as at the most 2% based on the total content of estrogen, together with one or more pharmaceutically acceptable carriers or excipients

When exposed to an alternative stability test, the composition comprises an inclusion complex between cyclodextrin, or derivative thereof, and ethinyl estradiol, wherein the composition is such that said ethinyl estradiol has a 12-month stability at 40°C and 75% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol 6-keto- ethinyl estradiol and Δ-9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 3%, such as at the most 2 % based on the total content of estrogen together with one or more pharmaceutically acceptable carriers or excipients

The cyclodextrin may be selected from α- cyclodextrin, β- cyclodextrin, γ- cyclodextrin and derivatives thereof The cyclodextrin may be modified such that some or all of the primary or secondary hydroxyls of the macrocycle, or both, may be alkylated or acylated Methods of modifying these alcohols are well known to the person skilled in the art and many are commercially available Thus, some or all of the hydroxyls of cyclodextrin may modified cyclodextrins have be substituted with an O-R group or an O-C(O)-R, wherein R is an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally

substituted C_{2-6} alkynyl, an optionally substituted aryl or heteroaryl group Thus, R may be methyl, ethyl, propyl, butyl, pentyl, or hexyl group Consequently, O-C(O)-R may be an acetate Furthermore, with the commonly employed 2-hydroxyethyl group, or 2-hydroxypropyl group R may be used to derivatize cyclodextrin Moreover, the cyclodextrin alcohols may be per-benzylated, per-benzoylated, or benzylated or benzoylated on just one face of the macrocycle, or wherein only 1, 2, 3, 4, 5, or 6 hydroxyls are benzylated or benzoylated Naturally, the cyclodextrin alcohols may be per-alkylated or per-acylated such as per-methylated or per-acetylated, or alkylated or acylated, such as methylated or acetylated, on just one face of the macrocycle, or wherein only 1, 2, 3, 4, 5, or 6 hydroxyls are alkylated or acylated, such as methylated or acetylated
Preferably, the complex comprises of β-cyclodextrin or a derivative thereof, most preferably β-cyclodextrin

Thus, in a particularly preferred embodiment which is a combination of preferred embodiments, the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin

The estrogen-cyclodextrin complex may be obtained by methods known to the person skilled in the art (e g US 5,798,338)

The ethinyl estradiol-β-cyclodextrin complex may also be obtained by co-precipitation as follows Ethinyl estradiol is dissolved in ethanol, β-cyclodextrin is dissolved at 45°C in water; the ethinyl estradiol solution is added to the beta-cyclodextrin solution, the obtained suspension is stirred for some hours at 20 to 25°C and afterwards at 2°C, the crystallisation product is isolated and dried

Alternatively, the ethinyl estradiol-β-cyclodextrin complex may be obtained as follows Ethinyl estradiol is dissolved in acetone, β-cyclodextrin is dissolved at 45°C in water, the ethinyl estradiol solution is added to the β-cyclodextrin solution, the obtained suspension is stirred for some hours at temperatures below 25°C, afterwards, the crystallisation product is isolated and dried

In an alternative embodiment of the invention, the composition further comprises a therapeutically active compound Thus, in this embodiment, the composition comprises an inclusion complex between cyclodextrin, or derivative thereof, and estrogen

wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10%, such as at the most 5, 4, 3 or 2% based on the total content of estrogen, and a therapeutically active compound, such as a gestagen, preferably drospirenone together with one or more pharmaceutically acceptable carriers or excipients

In the preferred embodiment wherein the therapeutically active substance is drospirenone, said drospirenone is preferably micronised Micronization of drospirenone provides for improved dissolution in aqueous media, potentially improving bioavailability of the gestagen

In the preferred embodiment where the therapeutically active substance is drospirenone, all or substantially all of said drospirenone may be present as an inclusion complex with cyclodextrin As the person skilled in the art will appreciate, the dissociation constant of the drospirenone cyclodextrin complex may result in a mixture of cyclodextrin-complexed drospirenone and uncomplexed (free) drospirenone As was the case for uncomplexed drospirenone, the complexed drospirenone may also be micronized

The complex of EE and cyclodextrin also has a more rapid dissolution in water than EE itself, putatively improving bioavailability of the estrogen

An object of the invention is to provide a stable composition wherein said composition comprises an inclusion complex between cyclodextrin, preferably β-cyclodextrin, and ethinyl estradiol wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10%, such as at the most 5, 4, 3 or 2% based on the total content of estrogen, and a therapeutically active compound, such as a gestagen, preferably drospirenone together with one or more pharmaceutically acceptable carriers or excipients

It can be easily appreciated that in embodiments where the estrogen is ethinyl estradiol, said ethinyl estradiol may be micronized Similarly, complexes between ethinyl estradiol and cyclodextrins may be micornized

In embodiments wherein the composition comprises the estrogen ethinyl estradiol, the dose of the ethinyl estradiol may correspond to a daily release of the said estrogen of from 0 002 to 1 mg, such as from 0 005 to 0 5 mg, such as from 0 01 to 0 25 mg, preferably from 0 01 to 0 1 mg, such as from 0 01 to 0 05 mg, from 0 01 to 0 03 mg, such as 0 02 mg

Thus, one embodiment of the invention is a composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and ethinyl estradiol having a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said ethinyl estradiol of at the most 10%, such as at the most 5, 4, 3 or 2%, based on the total content of ethinyl estradiol, wherein the dose of ethinyl estradiol corresponds to a daily release of estrogen of from 0 002 to 1 mg, such as from 0 005 to 0 5 mg, such as from 0 01 to 0 25 mg, preferably from 0 01 to 0 1 mg, such as from 0 01 to 0 05 mg, from 0 01 to 0 03 mg, such as 0 02 mg, together with one or more pharmaceutically acceptable carriers or excipients

In embodiments wherein the composition further comprises a therapeutically active compound and that said compound is drospirenone, the dose of drospirenone may correspond to a daily release of said gestagen of from 0 1 to 10 mg, preferably from 0 2 to 8 mg, such as from 0 25 to 6 mg, preferably from 0 5 to 5 mg, such as from 1 5 to 4 mg, such as 1, 2, 3, 4 mg

One embodiment of the invention relates to composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and ethinyl estradiol having a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said ethinyl estradiol of at the most 10%, such as at the most 5, 4, 3 or 2%, based on the total content of ethinyl estradiol, and drospirenone wherein the dose of drospirenone corresponds to a daily release of said gestagen between 1 and 5 mg, such as 3 mg, together with one or more pharmaceutically acceptable carriers or excipients

A particularly preferred embodiment comprises of a composition comprising an inclusion complex between cyclodextrin, or derivative thereof, and ethinyl estradiol having a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said ethinyl estradiol of at the most 10%, such as at the most 5, 4, 3, or 2%, based on the total content of ethinyl estradiol, wherein the dose of ethinyl estradiol

corresponds to a daily release of estrogen of from 0 002 to 1 mg, such as from 0 005 to 0 5 mg, such as from 0 01 to 0 25 mg, preferably from 0 01 to 0 1 mg, such as from 0 01 to 0 05 mg, from 0 01 to 0 03 mg, such as 0 02 mg, and drospirenone and wherein the dose of drospirenone corresponds to a daily release of said gestagen between 1 and 5 mg, such as 3 mg, together with one or more pharmaceutically acceptable carriers or excipients

As stated, an object of the present invention is to provide a pharmaceutical composition comprising an estrogen wherein the stability of said estrogen is significantly improved over that of conventional formulations Degradation of estrogens, such as ethinyl estradiol, in conventional formulations is the most critical issue with regard to product shelf life One means of increasing the stability of an estrogen such as ethinyl estradiol (EE) in a composition is by the judicious selection of additives and excipients to the formulation such that oxidants are minimised or excluded from the formulation

Thus, the formulation of the compositions of the present invention is also critical The gain stability of the estrogen by means of complexation with cyclodextrin must be maintained in the formulation A vigilant control of the amount of oxidant used in formulation is critical to maintaining the stability of the estrogen Consequently, the present invention relates to a pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the total amount of oxidant in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen

Again, alternatively measured, the present invention relates to a pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the total amount of oxidant in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10, 9, 8, 7, or 6% w/w, based on the total content of said estrogen

Furthermore, the present invention relates to a pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the total amount of oxidant in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto- ethinyl estradiol and Δ9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8%, such as at the most 0 7% and 0 6%, based on the total content of estrogen

Consequently, in one embodiment of the invention, the amount of oxidants is such that the decrease in estrogen content is a further 0 1% less, such as at least 0 2, 0 3, 0 4 or 0 5% less than the decrease in estrogen content in pharmaceutical formulations of compositions not comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen, as measured at the same time mark under the same conditions

The EE-cyclodextrin complex has been found by the present investigators to be sensitive to polyvinylpyrrolidone, which is typically used as a binder for fluid bed granulations Polyvinylpyrrolidone has a deleterious effect on the stability of estrogen, whether complexed or uncomplexed, and hence on the formulations comprising estrogens

Thus, another aspect of the invention relates to a pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof wherein the amount of polyvinylpyrrolidone in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4 or 3% w/w, based on the total content of said estrogen

Again alternatively measured the invention relates to a pharmaceutical particulate formulation of a composition said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof,
wherein the amount of polyvinylpyrrolidone in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10, 9, 8, 7, or 6% w/w, based on the total content of said estrogen

The invention further provides a pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the amount of polyvinylpyrrolidone in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto- ethinyl estradiol and Δ9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8%, such as at the most 0 7% and 0 6%, based on the total content of estrogen

Most preferably, a formulation of the present invention may be characterised in that it is a polyvinylpyrrolidone-free formulation

The investigators have prepared formulations possessing remarkable stability of the estrogen ethinyl estradiol wherein the amount of polyvinylpyrrolidone has been strictly restricted Thus, a preferred formulation is one wherein the amount of polyvinylpyrrolidone is such that the said decrease in estrogen content is at least 0 1% less, such as at least 0 2, 0 3, 0 4 or 0 5% less than the decrease in estrogen content in pharmaceutical formulations of compositions not comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen, as measured at the same time mark under the same conditions

As can be seen from the Example 1 3, the stability of EE in formulations wherein EE is present as an inclusion complex with cyclodextrin is greater than wherein EE is present as a free steroid The present invention thus relates to the compositions comprising EE as an inclusion complex with cyclodextrin Furthermore, the Examples illustrates that formulations of the inclusion complex not comprising polyvinylpyrrolidone have increased stability of EE Thus, the present invention further relates to the formulations comprising EE as an inclusion complex with cyclodextrin, preferably formulated to be polyvinylpyrrolidone-free Example 2 demonstrates that the total amount of degradation products in formulations according to the present invention is dramatically reduced in comparison to conventional formulations

The Examples teach that oxidation of EE by oxidants is significant in reducing the stability of EE Consequently, it is anticipated that a formulation according to the present invention may further comprise an anti-oxidant.

A further object of the invention is to provide a composition as described *infra* adapted to be formulated for conventional granulation, pelletation, dry powder blend, fluid bed granulation, encapsulation, or compactation

A preferred embodiment of the invention provides a particulate formulation comprising a composition as described *infra* The particulate formulation may be prepared by a method involving a fluid bed granulation procedure, or conventional granulation, pelletation, dry powder blend, encapsulation, or compactation

The formulations comprising a composition as described *infra* may be in unit dosage form and may be adapted for the preparation of solid dosage forms or dispersion forms, as well as adapted to the preparation of tablets, capsules or sachets

A further aspect of the invention is to provide a composition as described *infra* adapted to be administered by oral, parenteral, mucosal, nasal, vaginal or topical administration

Formulations comprising either EE or EE-cyclodextrin complex, either with or without polyvinylpyrrolidone, and either with or without drospirenone, and with varying common excipients were prepared to establish features or combination of features which improve the stability of EE

A typical formulation may comprise (wt/wt)

i) 0 002-1% ethinyl estradiol (micronised)
ii) 10-99%, such as 45-80% lactose monohydrate
iii) 1-80%, such as 1-35% corn starch
iv) 0-90%, such as 0-35% cellulose (microcrystallised)
v) 0 05-5% magnesium stearate
vi) 0-5% colloidal silicon dioxide

In the embodiment wherein the composition further comprises a therapeutically active compound, such as a gestagen, preferably drospirenone, a typical formulation may comprise (wt/wt)

i) 0 1-15% drospirenone (micronised)
ii) 0 002-1% ethinyl estradiol (micronised)
iii) 10-99% such as 45-60% lactose monohydrate
iv) 1-80%, such as 1-35% corn starch
v) 0-90%, such as 0-35% cellulose (microcrystallised)
vi) 0 05-5% magnesium stearate
vii) 0-5% colloidal silicon dioxide

A preferred formulation of a tablet core consists of 1 5 to 4 mg, most preferably 3 mg of drospirenone, 0 01 to 0 03 mg, most preferably 0 02 mg of EE as an EE-βCD complex, lactose monohydrate, corn starch, magnesium stearate

A further object of the invention is to provide a process for preparing a formulation as described *infra* the process comprising suspending maize starch in purified water, adding lactose monohydrate, ethinyl estradiol-cyclodextrin complex, optionally adding drospirenone, granulating and drying in a fluid bed granulator

Formulations and compositions described *infra* and in the Examples are anticipated for use in the preparation of a pharmaceutical for female contraception, for hormone replacement therapy, for the treatment of menopausal, pre-menopausal, and/or post-menopausal symptoms, for the treatment of acne or for the treatment of PMDD

A still further object of the invention is to provide a method of improving the stability of ethinyl estradiol in a pharmaceutical composition comprising the step of complexing said ethinyl estradiol with cyclodextrin Moreover, an object of the present invention is to provide a method of improving the stability of ethinyl estradiol in a pharmaceutical formulation comprising the step of a) complexing said ethinyl estradiol with cyclodextrin, and optionally of b) limiting the polyvinylpyrrolidone content to less than 5% such as less than 4%, such as less than 3%, such as less than 2%, such as less than 1%, such as providing a substantially polyvinylpyrrolidone-free formulation

The present invention is further defined by the Examples herein which are not intended to be limiting in any way

BRIEF DESCRIPTION OF THE EXAMPLES

Example 1 discloses a composition and a formulation according to some embodiments of the present invention The content of formulations known to the person skilled in the art are outlined in comparison with the contents of embodiments of the present invention and in comparison to a formulation which is oxidant-restricted, i e free of povidone Table 1 3 illustrates the performance in terms of stability in comparison to known formulations after a fixed period of time under controlled environmental conditions Direct compression of the powder blend resulted in a dramatic improvement in the stability of EE in comparison to blends which comprise the free steroid The Formulation E was prepared to be povidone-free This also results in increased stability of the active ingredient By comparison, the fluid-bed formulation, which is also povidone-free, does not perform as well as those formulations wherein EE is complexed with cyclodextrin Complexation of EE with cyclodextrin improves the stability of EE

Example 2 illustrates the stability of EE in Formulations D and E in comparison to other formulations in terms of the breakdown products isolated from samples upon storage after a fixed period of time under controlled environmental conditions

Example 3 discloses the contents of one embodiment of the present invention, wherein the composition further comprises drospirenone

Example 4 describes the morphology or some physical characteristics of a typical dosage form of a formulation according to the present invention

Example 5 discloses a typical process for the preparation of a tablet.

Example 6 describes the method in which certain physical properties, namely the rate constant of the dissociation constant of the inclusion complex between EE and CD, was studied The half-life of the 1 1 complex was determined to be 155 8 s and the dissociation constant was determined to be 4 45 x 10^{-3} s^{-1}

Example 7 describes the method in which the equilibrium stability constant (formation constant) of the inclusion complex between EE and CD was studied The stability constant of the 1 1 complex was found to be 9 5 x 10^{-4} M^{-1} The solubility of complexed ethinyl estradiol was found to improve in comparison to the free steroid

Example 8 describes the method in which the equilibrium stability constant (formation constant) of the inclusion complex between EE and CD in acidic medium was studied The stability constant of the 1 1 and 1 2 complex in acidic medium is disclosed The solubility of complexed ethinyl estradiol was found to improve in comparison to the free steroid in acidic medium

Example 9 discloses the method in which the acid dissociation constant (pK_a) of the EE-CD complex in aqueous media was determined to be approx 10 51 in comparison to the pK_a of approx 10 25 of the free-steroid

Example 10 describes the method in which the n-octanol/water partition coefficient of the EE-CD inclusion complex was determined and its dependence on pH Its log P value ranges from 3 20 to 3 53

Example 11 discussed whether the ethinyl estradiol-β-cyclodextrin inclusion complex can exist in multiple solid state forms and to provide test methods which can detect and distinguish between such forms

Example 12 describes typical preparations of an EE-CD complex

EXAMPLES

Example 1

Comparative of EE Content After Storage of Test Formulations

1 Summary of Contents of Film-Coated Tablets

a) **Formulation A**

EE-β-CD complex, fluid bed granulation, with polyvinylpyrrolidone (povidone)

b) **Formulation B (a standard formulation)**

EE as free steroid, fluid bed granulation with polyvinylpyrrolidone

c) **Formulation C**

EE as free steroid, fluid bed granulation without polyvinylpyrrolidone

d) **Formulation D**

EE-β-CD complex, direct compression of powder blend (without povidone)

e) **Formulation E**

EE-β-CD complex, fluid bed granulation, without polyvinylpyrrolidone

2 Composition of Test Formulations

Table 1 2

formulation	Formulation A	Formulation B	Formulation C	Formulation D	Formulation E
EE	-	✓	✓	-	-
EE-β-CD	✓	-	-	✓	✓
DRSP	-	✓	✓	✓	✓
lactose	✓	✓	✓	✓	✓
maize starch	✓	✓	✓	✓	✓
micro cellulose	-	-	-	✓	-
starch 1500	✓	✓	-	-	-
povidone 25 000	✓	✓	-	-	-
Mg Stearate	✓	✓	✓	✓	✓

3 EE-Content After Storage

Table 1 3

formulation	start	3 months		12 months	
		40°C 75% RH	60°C 75% RH	25°C 60% RH	40°C 75% RH
Formulation A	93 1	86 3	77 8	93 8	75 9
Formulation B	98 9	94 9	70 7	95 6	85 7
Formulation C	100 1 99 1	95 8 96 2	86 1 86 1	100 1 99 1	92 1 92 1
Formulation D	101 5 102 7	98 8 100 7	96 4 98 6	101 4 101 8	99 9 100 0
Formulation E	103 2 103 3	101 3 102 0	96.4 96 6	100 5 101 8	98 9 99 3

5 **Example 2**

Comparative of Known Degradation Products After Storage

Table 2 1, *After 12 months, 25°C, 60% RH*

formulation	6-α-OH-EE	6-β-OH-EE	6-Keto-EE	Δ9,11-EE	total known
EE	0 004	0 005	n d	0 38	0 389
EE-β-CD	0 002	0 003	n d	0 38	0 385
Formulation B	0 04	0 07	0 32	0 74	1 20
Formulation C	0 05 0 04	0 09 0 07	0 11 0 08	0 73 0 70	1 00 0 91
Formulation D	0 01 0 01	0 02 0 01	n d n d	0 49 0 45	0 52 0 47
Formulation E	0 03 0 02	0 01 0 01	n d n d	0 46 0 40	0 50 0.43
specification	≤ 0 5	≤ 0 5	≤ 2 0	≤ 1 0	-

n d = not detectable, 6-α-OH-EE = 6-α-hydroxy-ethinyl estradiol, 6-β-OH-EE = 6-β-hydroxy-ethinyl estradiol, 6-Keto-EE = 6-keto- ethinyl estradiol, Δ9,11-EE = Δ9,11-ethinyl estradiol

Table 2 2, *After 12 months, 40°C, 75% RH*

formulation	6-α-OH-EE	6-β-OH-EE	6-Keto-EE	Δ9,11-EE	total known
EE	0 004	0 005	n d	0 38	0 389
EE-β-CD	0 002	0 003	n d	0 38	0 385
Formulation B	0 16	0 25	1 92	3 14	5.47
Formulation C	0 33 0 28	0 61 0 54	1 03 0 87	1 86 1 59	3 83 3 28
Formulation D	0 03 0 03	0 09 0 10	0 10 0 09	0 79 0 79	1 01 0 98
Formulation E	0 08 0 08	0 19 0 19	0 30 0.41	0 93 0 89	1 50 1 58
specification	≤ 0 5	≤ 0 5	≤ 2 0	≤ 1 0	-

n d = not detectable, 6-α-OH-EE = 6-α-hydroxy-ethinyl estradiol 6-β-OH-EE = 6-β-hydroxy-ethinyl estradiol, 6-Keto-EE = 6-keto- ethinyl estradiol, Δ9,11-EE = Δ9,11-ethinyl estradiol

5

Example 3

Typical composition

The drug product consists of the components listed below The batch size is determined by 200,000 - 550,000 tablets (development site) and 2 5 Mio tablets (production site), respectively Water is used as a processing aid for the manufacture of the tablet mass (fluid bed granulation) and film-coating

Component	mg per tablet	kg per batch (pilot site), batch size = 550,000 tablets	kg per batch (production site), batch size = 2 5 mio tablets
drospirenone, micro 15	3 0	1 650	7 500
ethinyl estradiol-ß-cyclodextrine complex, micro	0 020 *	0 011 *	0 050 *
lactose monohydrate	48 18	26 499	120 450
maize starch	28 0	15 400	70 000
magnesium stearate	0 8 **	0 440 **	2 000 **
tablet mass weight	**80 0 mg**	**44 000 kg**	**200 000 kg**
hydroxypropylmethyl cellulose	1 5168	0 83424	3 792
talc	0 3036	0 16698	0 759
titanium dioxide	1 1748	0 64614	2 937
ferric oxide pigment, red	0 0048	0 00264	0 012
weight of film-coat	**3.0 mg**	**1 650 kg**	**7 500 kg**
total weight	**83 0 mg**	**45.650 kg**	**207 500 kg**

* quantities given state the amount of ethinyl estradiol

Example 4

Description of the dosage form

Core	Shape	round, biconvex
	Diameter	6 mm
	Curvature radius	6 mm
	Height	2 95 mm
	Weight	80 0 mg
	Hardness	40 N
	Friability (Ph Eur / USP)	≤ 0 5 %
	Disintegration time	≤ 10 min
Coated tablet	Color	light pink
	Weight	83 0 mg

Example 5

Description of manufacturing process

- Weigh all ingredients
- Prepare the granulation liquid

  -Suspend maize starch in purified water and add this suspension to purified water while stirring

- Prepare the tablet mass

  -Introduce lactose, drospirenone micro 15, ethinyl estradiol-ß-cyclodextrine complex micro and maize starch (portion) into the fluid bed granulator Activate a continuous fluid bed Dry Check relative humidity of the tablet mass Dry the tablet mass if necessary until the desired range of relative humidity is reached

- Check yield
- Compress the tablet mass

  -Perform on a rotary tableting machine to tablet cores Pass the cores through a tablet deduster

- Prepare the film-coating suspension

  -Suspend talc, ferric oxide pigment red and titanium dioxide in purified water and homogenise the suspension Dissolve hydroxypropylmethyl cellulose in purified water while stirring Combine and homogenise the mixture and check yield

- Film-coating

  -Introduce the tablet cores into a suitable coater and warm them up

  -Spray the appropriate amount of film-coating suspension continuously on the rotating cores while drying with warm air Polish and check weight uniformity, disintegration time and yield

  -Equilibrate the film-coated tablets

  Check the disintegration time of at least 6 tablets

Example 6

Determination of Rate Constant of the Dissociation Constant of EE-β-CD complex in aqueous solution

Background

The ethinyl estradiol-β-Cyclodextrin inclusion complex as prepared by the present invention is preferably a clathrate complex containing one molecule ethinyl estradiol and two molecules of β-Cyclodextrin

When dissolved in water, the ethinyl estradiol-β-Cyclodextrin inclusion complex dissociates into its components ethinyl estradiol (EE) and the ligand β-Cyclodextrin (CD) following law of mass action equilibria

1 $EE + CD \Leftrightarrow EE\,CD \qquad K_{11} = \frac{c_{EECD}}{c_{EE}\ c_{CD}}$

2 $EE\,CD + CD \Leftrightarrow EE\text{-}CD_2 \qquad K_{12} = \frac{c_{EECD_2}}{c_{EECD}\ c_{CD}}$

In this study the dissociation rate of the 1 1 complex was determined using a stopped flow relaxation method with conductometric detection

Ethinyl estradiol is practically undissociated at pH = 7 (pKa = 10 25) For this reason it remains uncharged in aqueous solution and its contribution to the conductivity is negligible Therefore a direct determination of the dissociation rate with the conductometric detector was not possible

Therefore an indirect method was applied based on a competition reaction using sodium-dodecylsulfate (SDS) which forms an inclusion complex as well SDS as a salt is dissociated in aqueous solution and contributes sufficiently to conductivity When the SD^- anion binds to β-Cyclodextrin, the inclusion complex formed will be less mobile as the free SD^- ion in water and the electrical conductivity of the solution will decrease

The difference in conductivity of the free DS^- anion and the complexed anion was used to detect the release kinetic of ethinyl estradiol from the clathrate complex with a stopped flow kinetic apparatus with conductivity detector

As complexation of SDS with β-Cyclodextrin is very rapid, the dissociation of the EE-ß-CD complex becomes rate determining and can be measured by stopped flow experiments

At higher ß-Cyclodextrin concentrations higher ordered Ethinyl estradiol-β-Cyclodextrin complexes are formed Therefore the dissociation rate of the 1 2 complex could not be determined

Summary of Results

The dissociation rate constant of the Ethinyl estradiol-β-Cyclodextrin 1 1 complex was determined through stopped-flow conductometric studies of the competition reaction between sodiumdodecylsulfate and Ethinyl estradiol to form inclusion complexes with β-Cyclodextrin to be

$$K_d = 4\,45 \quad 10^{-3}\ s^{-1}$$

Under first order conditions the half live of dissociation of the Ethinyl estradiol-ß-Cyclodextrin 1 1 complex was calculated to be

$$t_{1/2} = 155\ 8\ s\ (2\ 6\ min)$$

Example 7

Determination of the Equilibrium Stability Constant (Formation Constant) of the EE-β-CD complex in aqueous solution

Background

The drug substance ethinyl estradiol-ß-cyclodextrin inclusion complex is a clathrate complex containing one molecule Ethinyl estradiol and two molecules of β-cyclodextrin The formation of the ethinyl estradiol-β-cyclodextrin clathrate in aqueous solution from its components ethinyl estradiol (S) and the ligand β-cyclodextrin (L) are defined by the following equations according to the law of mass action

1 $S + L = SL$ $K_{11} = \frac{c_{SL}}{c_S \; c_L}$

2 $SL + L = SL_2$ $K_{12} = \frac{c_{SL_2}}{c_{SL} \; c_L}$

The equilibrium stability constant (formation constants) K_{11} was determined with a phase solubility technique For K_{12} only a rough estimation was obtained

Summary of Results

The following data were obtained with the phase solubility diagram technique (PSD) in aqueous solutions at 20 °C

Stability constant of the 1 1 complex	$K_{11} = 9\,5 \;\; 10^4 \; M^{-1}$
Solubility of Ethinyl estradiol	$S_{EE} = 2\,17 \;\; 10^{-5}$ mol/l (6 43 10^{-3} g/l)
Solubility of the 1 1 complex	$S_{11} = 1\,92 \;\; 10^{-3}$ mol/l (2 75 g/l)
Solubility of the 1 2 complex	$S_{12} = 1\,44 \;\; 10^{-3}$ mol/l (3 7 g/l)

Example 8

Determination of the Equilibrium Stability Constant (Formation Constant) of the EE-β-CD complex in 0 1 M HCl

Background

The drug substance ethinyl estradiol-β-cyclodextrin complex is an inclusion complex complex containing one molecule of ethinyl estradiol and two molecules of β-cyclodextrin

The formation of the ethinyl estradiol-ß-cyclodextrin inclusion complex in aqueous solution from its components ethinyl estradiol (EE) and the ligand β-cyclodextrin (βCD) are defined by the following equations according to the law of mass action

1 $EE + \beta CD = EE\beta CD \qquad K_{11} = \frac{c_{EE\beta CD}}{c_{\beta CD}\ c_{EE}}$

2 $EE\beta CD + \beta CD = EE\beta CD_2 \qquad K_{12} = \frac{c_{EE\beta CD_2}}{c_{EE\beta CD}\ c_{\beta CD}}$

c_i = equilibrium concentrations of the respective entities (mol/l)

Summary of Results

The following data were obtained with the phase solubility diagram technique (PSD) in 0 1 M HCl at 20 °C

Stability constant of the 1 1 complex	K_{11} = 1 56 10^4 M^{-1}
Overall stability constant of the 1 2 complex (= K_{11} K_{12})	K_{12} = approx 1 6 10^4 M^{-1}
Solubility of ethinyl estradiol	S_{EE} = 1 68 10^{-4} mol/l (0 05 g/l)
Solubility of the 1 1 complex	S_{11} = 2 10^{-3} mol/l (2 9 g/l)
Solubility of the 1 2 complex	S_{12} = 5 10^{-4} mol/l (1 3 g/l)

Example 9

Determination of the Acid Dissociation Constant of the EE-β-CD complex in aqueous media

Background

The drug substance ethinyl estradiol-β-cyclodextrin inclusion complex is a clathrate complex containing one molecule of ethinyl estradiol and two molecules of β-cyclodextrin

In aqueous solution, the ethinyl estradiol-β-cyclodextrin inclusion complex dissociates into its components according to the law of mass action To restrain the dissociation of the ethinyl estradiol-β-cyclodextrin inclusion complex an aqueous solution containing an approx 300 fold (0 0114 molar) excess of β-cyclodextrin over ethinyl estradiol was used in the measurements

The pKa was measured by a photometric titration method following the guidance given in the Environmental Assessment Technical Handbook.

Summary of Results

The acid dissociation constant of the ethinyl estradiol-β-cyclodextrin inclusion complex was determined at 20 C in aqueous solutions containing mixtures of ethinyl estradiol with an approx 300 fold excess of β-cyclodextrin with a photometric titration method as

$$pK_a = 10\,51 \pm 0\,03$$

For comparison the pKa of ethinyl estradiol in the absence of ß-cyclodextrin is

$$pK_a = 10\,25 \pm 0\,04$$

Example 10

Determination of the n-octanol/water partition coefficient

Background

The drug substance ethinyl estradiol-β-cyclodextrin inclusion complex is a complex containing one molecule of ethinyl estradiol and two of molecules β-cyclodextrin

If the ethinyl estradiol-β-cyclodextrin inclusion complex is equilibrated in the two-phase system n-octanol/water a number of simultaneously occuring equilibria are involved partitioning of the complex and the free components between the aqueous phase and n-octanol and dissociation of the inclusion complex The dissociation equilibria will be shifted after phase separation for analysis of both phases Therefore only the total amount of ethinyl estradiol in the aqueous and the octanolic phase can be determined The result is the apparent n-octanol/water partition coefficient of ethinyl estradiol

For determination of the pH dependence of the apparent n-octanol/water partition coefficient of ethinyl estradiol measurements were performed at pH 5, 7 and 9 with the flask-shaking method according to OECD guideline 107[1)]

Summary of Results

The flask-shaking method was used to determine the apparent partition coefficient of ethinyl estradiol after partitioning the ethinyl estradiol-ß-cyclodextrin inclusion complex

between aqueous buffer solutions and n-octanol Measurements were performed with aqueous solutions buffered to pH 5, 7 and 9 The ethinyl estradiol concentration in each phase after equilibration at 25 °C was determined by HPLC

Table 1 The pH dependence of the apparent partition coefficient of ethinyl estradiol

pH	mean app P_{ow} with standard deviations	app log P_{ow}	95 % confidence intervals for app log P_{ow}
5	2395 ± 623	3 38	3 28 - 3 46
7	3424 ± 1298	3 53	3 35 - 3 67
9	1579 ± 505	3 20	3 08 - 3 29

Example 11

Determination of whether the compound consisting of the ethinyl estradiol-β-cyclodextrin inclusion complex can exist in multiple solid state forms and to provide test methods which can detect and distinguish between such forms

Background

In order to establish whether the compound consisting of the ethinyl estradiol-β-cyclodextrin inclusion complex exists in different solid state forms a variety of crystallization products obtained under different crystallization, drying and storage conditions are investigated with respect to their solid state form A selection of the following analytical methods is applied in order to identify and characterise solid state forms as deemed appropriate and possible

X-ray powder diffraction (XRPD)

differential thermal analysis (DTA) in combination with thermogravimetry (TG)

differential scanning calorimetry (DSC) in combination with thermogravimetry (TG)

Summary of Results

Evidences of complex formation is obtained by investigation of pure ethinyl estradiol and beta-cyclodextrin, mechanical mixtures of both substances as well as samples of the ethinyl estradiol-beta-cyclodextrin complex with X-ray powder diffraction and thermal analysis According to these investigations at least about 90 % of the ethinyl estradiol should be bonded in the complex

The prevalent form of the ethinyl estradiol-beta-cyclodextrin inclusion complex is that of a hydrate containing varying amounts of water The variability of the water content is a consequence of an inherent property of free cyclodextrin as well as of its inclusion compounds (inclusion complexes or clathrates), the equilibration of at least part of the hydrate water with the ambient atmosphere On storage, an equilibrium water content is established which depends on temperature, pressure and relative humidity The hydrate water can be readily lost from the crystal lattice Under more servere drying conditions all crystal water can be removed, however the resulting material is extremely hygroscopic and therefore not of relevance for the drug substance The same applies to a fully water-saturated hydrate which is stable only in the presence of mother liquid or under relative humidity of more than 97 % Thus, any discussion on the solid state forms of the ethinyl estradiol-β-cyclodextrin complex has to concentrate on the characterisation of a range of hydrates having intermediate water contents with an upper limit at water saturation

The hydrate water is a part of the crystal lattice and therefore alterations of the water content are connected with changes in the crystal lattice This is manifested by differences in the X-ray powder pattern of batches of clathrate with varying water content. According to these patterns four different types can be distinguished Batches of type I contain less than 1 % water In batches of types II and III between 4 % and 10 % water, and 8 % and 15 % water, respectively, are found Type IV is characterised by a water content of more than 15 % However, there's no clear dividing line between two neighbouring types The position of the diffraction peaks is changed gradual due to swelling and shrinking of the crystal lattice during water sorption or desorption Investigations of the four types by differential thermal analysis in combination with thermogravimetry have shown that the dehydration takes place between 25°C and 170°C The different forms are readily and reversibly interchanged by adjustment of the ambient humidity conditions This behaviour indicates considerable rigidity of the structural framework which does not allow profound alteration of the basic arrangement of the beta-cyclodextrin/ethinyl estradiol building blocks of the solid during hydration and dehydration

Example 12

Preparation of the ethinyl estradiol-beta-cyclodextrin complex

The ethinyl estradiol-beta-cyclodextrin complex is obtained by co-precipitation as follows

Process 1 (P1) Ethinyl estradiol is dissolved in ethanol β-cyclodextrin is dissolved at 45 °C in water The ethinyl estradiol solution is added to the β-cyclodextrin solution The obtained suspension is stirred for some hours at 20 to 25°C and afterwards at 2 °C The crystallization product is isolated and dried by methods described *infra*

Process 2 (P2) Ethinyl estradiol is dissolved in acetone β-cyclodextrin is dissolved at 45 C in water The ethinyl estradiol solution is added to the beta-cyclodextrin solution The obtained suspension is stirred for some hours at temperatures below 25 °C Afterwards, the crystallization product is isolated and dried by methods described *infra*

The mechanical mixtures of β-cyclodextrin and ethinyl estradiol are prepared by weighing and afterwards homogenization by grinding in an agate mortar

Table 12 1a Crystallization products of the complex

batch	solvent / treatment conditions	content of EE [%]	water content [%]
Im2180	P 1, dried in a vacuum drying cabinet	10 9	5 57
Im2181	P 1, dried in a vacuum drying cabinet	11 2	5 26
Im2182/1	P 1, dried 1 h at r t. over P_2O_5 in a vacuum desiccator	n d	6 5
Im2182/2	P 1, dried 2 h at r t. over P_2O_5 in a vacuum desiccator	n d	6 5
Im2182/3	P 1, dried 4 h at r t. over P_2O_5 in a vacuum desiccator	n d	6 4
Im2182/4	P 1 dried 4 h at r t. over P_2O_5 in a vacuum desiccator	n d	7 7
Im2182/5	P 1, dried 43 5 h at r t. over P_2O_5 in a vacuum desiccator	10 8	4 47
Im2182/6 Act.	P 1, washed with acetone, dried 3 h at 2°C over P_2O_5 in a vacuum desiccator	10 9	4 65
Im2182/7	P 1, washed with acetone, and water, dried 3 h at 2°C over P_2O_5 in a vacuum desiccator	10 8	4 47
Im2183/V	P 1, dried some hours at r t. over P_2O_5 in a vacuum desiccator	11 4	4 21
Im2183/VT	P 1, dried in a vacuum drying cabinet	10 7	5 59
Im2183/L	P 1 stored at air	11 4	10 2
Im2183/VT+L	P 1, dried in a vacuum drying cabinet and than storage at air	10 6	8 75
Im2184	P 1 dried in a vacuum drying cabinet	10 9	5 60
Im2188	P 1 20 h at r t.	10 8	11 85
Im2190f	P 1 dried in a vacuum drying cabinet - 1d	n d	-
Im2191f	P 1, dried in a vacuum drying cabinet - 1d	n d	-
Im2190	P 1, dried in a vacuum drying cabinet - 5d	10 6	7 5
Im2191	P 1, dried in a vacuum drying cabinet - 5d	10 6	7 7
28052591	batch Im2190 micronized	10 7	8 23
Im2220	P 2, dried in a vacuum drying cabinet	10 7	5 61
Im2221	P 1, dried in a vacuum drying cabinet	10 2	5 78
Im2222	P 1 dried in a vacuum drying cabinet	10 4	5 57
Im2223	P 1, dried in a vacuum drying cabinet	10 1	5 64
Im2224	P 2 dried in a vacuum drying cabinet	10 4	5 75

Table 12 1b: Crystallization products of the complex

batch	solvent / treatment conditions	content of EE [%]	water content [%]
Im2225/1	P 1, washed 2 x water, dried in a vacuum drying cabinet	11 2	3 34
Im2225/2	P 1 washed 2 x water, 1 x acetone, dried in a vacuum drying cabinet	10 5	3 31
Im2225/3	P 1, washed 2 x water, 1 x acetone,1 x water dried in a vacuum drying cabinet	10 9	3 8
Im2230	P 1, washed 1 x water, 1 x acetone,1 x water dried in a vacuum drying cabinet	10 8	4 35
Im2231	P 1 washed 1 x water 1 x acetone,1 x water; dried in a vacuum drying cabinet	11	2 63
Im2240	P 1, washed 1 x water 1 x acetone,1 x water dried in a vacuum drying cabinet	10 5	6 71
28052591,DVS1 0%RH	batch 28052591 after one sorption/desorption cycle, stored at 0 % RH	n d	< 1%[5]
Im2180,DVS1 0% RH	batch Im2180 after sorption/desorption cycle stored at 0 % RH	n d	< 1%[5]
Im2180,DVS1 45% RH	batch Im2180 stored at 45 % RH	n d	6 5[5]
Im2180 DVS1 70% RH	batch Im2180 stored at 70 % RH	n d	9 5[5]
Im2180,DVS1 75% RH	batch Im2180 stored at 75 % RH	n d	9 5[5]
Im2180 DVS1 93% RH	batch Im2180 stored at 93 % RH	n d	~15[5]
Im2180 3d $Mg(ClO_4)_2$	batch Im2180 stored 3 d over $Mg(ClO_4)_2$	n d	n d
Im2190,5d 97% RH	batch Im2190 stored 5 d at 97 % RH	n d	~16 7[5]
Im2190 7d 97% RH	batch Im2190 stored 7 d at 97 % RH	n d	~16 5[5]
28052591,7d $Mg(ClO_4)_2$	batch 28052591 stored 7 d over $Mg(ClO_4)_2$	n d	< 0 1[5]
28052591,7d 97% RH	batch 28052591 stored 7 d at 97 % RH	n d	16 9[5]
28052591 wet	batch 28052591 suspended in water no drying	-	-
28052591,7d 75% RH	batch 28052591 stores 7 d at 75 % RH	n d	10 5[5]

[5] calculated from the water content of the starting material and the observed mass change

CLAIMS

1 A pharmaceutical composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen
wherein the composition is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5 4, or 3% w/w, based on the total content of said estrogen,
together with one or more pharmaceutically acceptable carriers or excipients

2 A composition comprising an inclusion complex between a cyclodextrin, or derivatives thereof, and estrogen
wherein the composition is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10, 9, 8, 7, or 6% w/w, based on the total content of said estrogen,
together with one or more pharmaceutically acceptable carriers or excipients

3 A pharmaceutical composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen
suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen,
together with one or more pharmaceutically acceptable carriers or excipients

4 A composition according to any of claims 1 to 3, wherein the estrogen is selected from the group consisting of ethinyl estradiol (EE), estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof, preferably ethinyl estradiol (EE), estradiol, estradiol valerate, estradiol benzoate and estradiol sulfamates, most preferably ethinyl estradiol (EE)

5 A composition according to claim 3, wherein the estrogen is ethinyl estradiol

6 A composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, and ethinyl estradiol,
wherein the composition is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol 6-β-hydroxy-ethinyl estradiol, 6-keto- ethinyl estradiol and Δ9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8%, such as at the most 0 7% and 0 6%, based on the total content of estrogen,
together with one or more pharmaceutically acceptable carriers or excipients

7 A composition comprising an inclusion complex between a cyclodextrin or derivative thereof, and ethinyl estradiol,
wherein the composition is such that said ethinyl estradiol has a 12-month stability at 40°C and 75% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol, Δ6,7-ethinyl estradiol and Δ-9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 3%, such as at the most 2% based on the total content of estrogen,
together with one or more pharmaceutically acceptable carriers or excipients

8 A pharmaceutical composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen,
suitably formulated such that the total amount of oxidant is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol, Δ6,7-ethinyl estradiol and Δ-9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 3%, such as at the most 2% based on the total content of estrogen,
together with one or more pharmaceutically acceptable carriers or excipients

9 A composition according to any of claims 1 to 8, wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin and derivatives thereof

10 A composition according to claim 9, wherein the cyclodextrin is β-cyclodextrin or derivatives thereof

11 A composition according to claim 10, wherein the cyclodextrin is β-cyclodextrin

12 A composition according to any the preceding claims, further comprising one or more therapeutically active compounds

13 A composition comprising according to claim 12, wherein at least one of the therapeutically active compounds is a gestagen

14 A composition according to claim 13, wherein the gestagen is selected from the group consisting of drospirenone, levonorgestrel, norgestrel, gestadene, dienogest, cyproterone acetate, norethisterone, norethisterone acetate, desorgestrel, 3-keto-desorgestrel

15 A composition according to claim 14, wherein the gestagen is drospirenone

16 A composition according to claim 15, wherein the drospirenone is micronised

17 A composition according to any of claims 15 or 16, wherein all or substantially all the drospirenone is present as an inclusion complex with cyclodextrin

18 A composition according to claim 12, wherein the estrogen is ethinyl estradiol and a therapeutically active compound is drospirenone

19 A composition according to any of claims 5, 6, 7 or 18, wherein the ethinyl estradiol is micronised

20 A composition according to any of the preceding claims wherein the dose of the estrogen corresponds to a daily release of ethinyl estradiol between 0 002 and 1 mg

21 A composition according to any of claims 14 to 18, wherein the dose of drospirenone corresponds to a daily release of said gestagen of from 0 1 to 10 mg, preferably from 0 25 to 6 mg, such as from 1 5 to 4 mg

22 A composition according to any of the preceding claims, wherein the estrogen is ethinyl estradiol and the dose of ethinyl estradiol corresponds to a daily release of said estrogen of from 0 002 to 1 mg, such as from 0 005 to 0 5 mg, such as from 0 01 to 0 25

mg, preferably from 0 01 to 0 1 mg, such as from 0 01 to 0 05 mg, from 0 01 to 0 03 mg, such as 0 02 mg

23 A composition according to claim 22, further comprising drospirenone, wherein the dose of drospirenone corresponds to a daily release of said gestagen between 1 and 5 mg, such as 3 mg

24 A composition according to any of the preceding claims, adapted to be formulated by conventional granulation, pelletation, dry powder blend, fluid bed granulation, encapsulation, or compactation

25 The use of a composition according to any of claims 1 to 24 for the preparation of a pharmaceutical for female contraception, for hormone replacement therapy, for the treatment of menopausal, pre-menopausal, and/or post-menopausal symptoms, for the treatment of acne or for the treatment of PMDD

26 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the total amount of oxidant in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen

27 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof wherein the total amount of oxidant in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10, 9, 8, 7, or 6% w/w, based on the total content of said estrogen

28 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the total amount of oxidant in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl

estradiol, 6-keto- ethinyl estradiol and Δ9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8%, such as at the most 0 7% and 0 6%, based on the total content of estrogen

29 A formulation according to claim 28, wherein the total amount of oxidant in said formulation is such that the decrease in total estrogen content, as measured at the 12-month mark at 40°C and 75% relative humidity (RH), is at least 0 1% less than, such as at least 0 2, 0 3, 0 4 or 0 5% less than the decrease in estrogen content in pharmaceutical formulations of compositions not comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen, as measured at the same time mark under the same conditions

30 A formulation according to claim 27, wherein the total amount of oxidant in said formulation is such that the decrease in total estrogen content, as measured at 3-month mark at 60°C and 75% relative humidity (RH) is at least 0 1% less than, such as at least 0 2, 0 3, 0 4 or 0 5% less than the decrease in estrogen content in pharmaceutical formulations of compositions not comprising an inclusion complex between a cyclodextrin, or derivative thereof, and an estrogen as measured at the same time mark under the same conditions

31 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the amount of polyvinylpyrrolidone in said formulation is such that said estrogen has a 12-month stability at 40°C and 75% relative humidity (RH) corresponding to a decrease in the content of said estrogen of at the most 10% w/w, such as at the most 5, 4, or 3% w/w, based on the total content of said estrogen

32 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof wherein the amount of polyvinylpyrrolidone in said formulation is such that said estrogen has a 3-month stability at 60°C and 75% relative humidity (RH) corresponding to a decrease in content of said estrogen of at the most 15% w/w, such as at the most 10, 9, 8, 7, or 6% w/w, based on the total content of said estrogen

33 A pharmaceutical particulate formulation of a composition, said composition comprising an inclusion complex between a cyclodextrin, or derivative thereof, wherein the amount of polyvinylpyrrolidone in said formulation is such that said ethinyl estradiol has a 12-month stability at 25°C and 60% relative humidity (RH) such that the sum product of the degradation products 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto- ethinyl estradiol and Δ9,11-ethinyl estradiol of said ethinyl estradiol totals at the most 0 8%, such as at the most 0 7% and 0 6%, based on the total content of estrogen

34 A formulation according to any of claims 26 to 33 characterised in that it is a polyvinylpyrrolidone-free formulation

35 A formulation according to any of claims 26 to 34, further comprising an anti-oxidant.

36 A formulation according to any of claims 26 to 35, comprising (wt/wt)

i) 0 002-1% ethinyl estradiol (micronised),
ii) 10-99%, such as 45-60% lactose monohydrate,
iii) 1-80%, such as 1-35% corn starch,
iv) 0-90%, such as 0-35% cellulose (microcrystallised),
v) 0 05-5% magnesium stearate and
vi) 0-5% colloidal silicon dioxide

37 A formulation according to any of claims 26 to 35 comprising (wt/wt)

i) 0 1-15% drospirenone (micronised),
ii) 0 002-1% ethinyl estradiol (micronised),
iii) 10-99% such as 45-60% lactose monohydrate,
iv) 1-80%, such as 1-35% corn starch
v) 0-90%, such as 0-35% cellulose (microcrystallised),
vi) 0 05-5% magnesium stearate and
vii) 0-5% colloidal silicon dioxide

38 A formulation according to any of claims 26 to 37 prepared by a method involving conventional granulation, pelletation, dry powder blend, fluid bed granulation, encapsulation, or compactation

39 A formulation according to any of claims 26 to 38 in unit dosage form

40 A formulation according to any of claims 26 to 39 adapted for the preparation of solid dosage forms or dispersion forms

41 A formulation according to any of claims 26 to 39 adapted to the preparation of tablets, capsules or sachets

42 A composition according to any of claims 1 to 24 adapted to be administered by oral, parenteral, mucosal, nasal, vaginal or topical administration

43 A method for improving the stability of ethinyl estradiol in a pharmaceutical composition comprising the step of forming an inclusion complex between said ethinyl estradiol and cyclodextrin

44 A method of improving the stability of ethinyl estradiol in a pharmaceutical formulation comprising the step of a) complexing said ethinyl estradiol with cyclodextrin, and optionally of b) limiting the polyvinylpyrrolidone content to less than 5%, such as less than 4%, such as less than 3%, such as less than 2%, such as less than 1%, such as providing a substantially polyvinylpyrrolidone-free formulation

45 A process for the preparation of a formulation according to any of claims 26 to 41

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Los documentos adjuntos son copia fiel y exacta de la versión originalmente presentada de la solicitud de patente que se especifica en la siguiente página

Solicitud de Patente No

00610135 6

El Presidente de la Oficina Europea de Patentes

Por encargo R C van Dijk

(Firma y Sello Oficial)

LA HAYA, 24/07/03

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Página 2 del Certificado

Solicitud No 00610135 6

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Solicitante
Schering Aktiengesellschaft
13353 Berlín
ALEMANIA

Título de la invención
Composiciones de complejos de estrógeno-ciclodextrina

Prioridades reivindicadas
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Países contratantes designados en la fecha de la solicitud
AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR

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REIVINDICACIONES

1 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno,
siendo la composición tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 10% peso/peso, por ejemplo de máximo 5, 4 o 3% peso/peso, respecto al contenido total de dicho estrógeno,
junto con uno o varios vehículos o excipientes farmacéuticamente aceptables

2 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o derivados de ella y estrógeno, siendo la composición tal que dicho estrógeno tiene una estabilidad de 3 meses a 60°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 15% peso/peso, por ejemplo de máximo 10, 9, 8, 7 o 6% peso/peso, respecto al contenido total de dicho estrógeno,
junto con uno o varios vehículos o excipientes farmacéuticamente aceptables

3 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno,
formulada apropiadamente de tal manera que la cantidad total de oxidante es tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 10% peso/peso, por ejemplo de máximo 5, 4 o 3% peso/peso, respecto al contenido total de dicho estrógeno,
junto con uno o varios vehículos o excipientes farmacéuticamente aceptables

4 Una composición de acuerdo con cualquiera de las reivindicaciones 1 a 3, en la cual el estrógeno seleccionado entre el grupo consituido por etinilo estradiol (EE), estradiol, sulfamatos de estradiol, valerato de estradiol, benzoato de estradiol, estrona y sulfato de estrona o mezclas de ellos, preferiblemente etinilo estradiol (EE), estradiol, valerato de estradiol, benzoato de estradiol y sulfamatos de estradiol, más preferiblemente etinilo estradiol (EE)

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5 Una composición de acuerdo con la reivindicación 3, en la cual el estrógeno es etinilo estradiol

6 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un etinilo estradiol,
siendo la composición tal que dicho etinilo estradiol tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 0,8%, por ejemplo máximo 0,7% y 0,6%, respecto al contenido total de estrógeno,
junto con uno o varios vehiculos o excipientes farmacéuticamente aceptables

7 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un etinilo estradiol,
siendo la composición tal que dicho etinilo estradiol tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol, Δ6,7-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 3%, por ejemplo máximo 2%, respecto al contenido total de estrógeno,
junto con uno o varios vehiculos o excipientes farmacéuticamente aceptables

8 Una composición farmacéutica que comprende un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno, apropiadamente formulada de tal manera que la cantidad total de oxidante es tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol, Δ6,7-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 3%, por ejemplo máximo 2%, respecto al contenido total de estrógeno,
junto con uno o varios vehiculos o excipientes farmacéuticamente aceptables

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9 Una composición de acuerdo con cualquiera de las reivindicaciones 1 a 8, en la cual la ciclodextrina se selecciona entre el grupo constituido por α-ciclodextrina, ß-ciclodextrina, γ-ciclodextrina y derivados de éstas

10 Una composición de acuerdo con la reivindicación 9, en la cual la ciclodextrina es ß-ciclodextrina o derivados de ella

11 Una composición de acuerdo con la reivindicación 10, en la cual la ciclodextrina es ß-ciclodextrina

12 Una composición de acuerdo con cualquiera de las anteriores reivindicaciones, la cual comprende además uno o varios compuestos activos terapéuticamente

13 Una composición de acuerdo con la reivindicación 12, en la cual al menos uno de los compuestos activos terapéuticamente es un gestágeno

14 Una composición de acuerdo con la reivindicación 13, en la cual el gestágeno se selecciona entre el grupo constu¿ituido por drospirenona, levonorgestrel, norgestrel, gestádeno, dienogest, acetato de ciproterona, norethisterona, acetato de norethisterona, desorgestrel, 3-ceto-desorgestrel

15 Una composición de acuerdo con la reivindicación 14, en la cual el gestágeno es drospirenona

16 Una composición de acuerdo con la reivindicación 15, en el cual la drospirenona es micronizada

17 Una composición de acuerdo con cualquiera de las reivindicaciones 15 o 16, en la cual toda la drospirenona o substancialmente toda la drospirenona está presente como un complejo de inclusión con ciclodextrina

18 Una composición de acuerdo con la reivindicación 12, en la cual el estrógeno es etinilo estradiol y un compuesto activo terapéuticamente es drospirenona

19 Una composición de acuerdo con cualquiera de las reivindicaciones 5, 6, 7 o 18, en la cual el etinilo estradiol es micronizado

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20 Una composición de acuerdo con cualquiera de las anteriores reivindicaciones, en la cual la dosis de estrógeno corresponde a un aliberación diaria de etinilo estradiol entre 0,002 y 1 mg

21 Una composición de acuerdo con cualquiera de las reivindicaciones 14 a 18, en la cual la dosis de drospirenona corresponde a una liberación diaria de dicho gestágeno de 0,1 a 10 mg, preferiblemente de 0,25 a 6 mg, por ejemplo de 1,5 a 4 mg

22 Una composición de acuerdo con cualquiera de las anteriores reivindicaciones, en la cual el estrógeno es etinilo estradiol y la dosis de etinilo estradiol corresponde a una liberación diaria de dicho estrógeno de 0,002 a 1 mg, tal como de 0,005 a 0,5 mg, por ejemplo de 0,01 a 0,25 mg, preferiblemente de 0,01 a 0,1 mg, tal como de 0,01 mg a 0,05 mg o de 0,01 a 0,03 mg, por ejemplo 0,02 mg

23 Una composición de acuerdo con la reivindicación 22, la cual comprende además drispirenona, correspondiendo la dosis de drospirenona a una liberación diaria de dicho gestágeno entre 1 y 5 mg, por ejemplo 3 mg

24 Una composición de acuerdo con cualquiera de las anteriores reivindicaciones, adaptada para ser formulada mediante granulación, empastillado, mezcla de polvo seco, granulación de lecho fluidizado, encapsulación o compactación convencionales

25 El uso de una composición de acuerdo con cualquiera de las reivindicaciones 1 a 24 para la preparación de un producto farmacéutico para la anticoncepción femenina, para la terapia de reemplazo hormonal, para el tratamiento de los síntomas de menopausia, premenopausia y/o pos-menopausia, para el tratamiento del acné o para el tratamiento de PMDD

26 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad total de oxidante en dicha formulación tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 10% peso/peso, por ejemplo de máximo 5, 4 o 3%, respecto al contenido total de dicho estrógeno

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27 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad total de oxidante en dicha formulación tal que dicho estrógeno tiene una estabilidad de 3 meses a 60°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 15% peso/peso, por ejemplo de máximo 10, 9, 8 7 o 6%, respecto al contenido total de dicho estrógeno

28 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad total de oxidante en dicha formulación tal que dicho etinilo estradiol tiene una estabilidad de 12 meses a 25°C y 60% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 0,8%, por ejemplo máximo 0,7% y 0,6%, respecto al contenido total de estrógeno

29 Una formulación de acuerdo con la reivindicación 26, siendo la cantidad total de oxidante en dicha formulación tal que la disminución en el contenido total de estrógeno, medido en la marca de los 12 meses a 40°C y 75% de humedad relativa, es al menos 0,1%, por ejemplo al menos 0,2, 0,3, 0,4 o 0,5%, que la disminución en el contenido de estrógeno en formulaciones farmacéuticas de composiciones que no comprenden un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno, siendo medido este contenido en la misma marca de tiempo bajo las mismas condiciones

30 Una formulación de acuerdo con la reivindicación 27, siendo la cantidad total de oxidante en dicha formulación tal que la disminución en el contenido total de estrógeno, medido en la marca de los 3 meses a 60°C y 75% de humedad relativa, es al menos 0,1% menos, por ejemplo al menos 0,2, 0,3, 0,4 o 0,5%, que la disminución en el contenido de estrógeno en formulaciones farmacéuticas de composiciones que no comprenden un complejo de inclusión entre una ciclodextrina o un derivado de ella y un estrógeno, siendo medido este contenido en la misma marca de tiempo bajo las mismas condiciones

31 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una

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ciclodextrina o un derivado de ella, siendo la cantidad de polivinilpirrolidona en dicha formulación tal que dicho estrógeno tiene una estabilidad de 12 meses a 40°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 10% peso/peso, por ejemplo de máximo 5, 4 o 3% peso/peso, respecto al contenido total de dicho estrógeno

32 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad de polivinilpirrolidona en dicha formulación tal que dicho estrógeno tiene una estabilidad de 3 meses a 60°C y 75% de humedad relativa correspondiente a una disminución en el contenido de dicho estrógeno de máximo 15% peso/peso, por ejemplo de máximo 10, 9, 8, 7 o 6% peso/peso, respecto al contenido total de dicho estrógeno

33 Una formulación particulada farmacéutica de una composición, comprendiendo dicha composición un complejo de inclusión entre una ciclodextrina o un derivado de ella, siendo la cantidad de polivinilpirrolidona en dicha formulación tal que dicho etinilo estradiol tiene una estabilidad de 12 meses a 25°C y 60% de humedad relativa, de tal manera que el producto suma de los productos de degradación 6-α-hidroxi-etinilo estradiol, 6-ß-hidroxi-etinilo estradiol, 6-ceto-etinilo estradiol y Δ9,11-etinilo estradiol del mencionado etinilo estradiol es en total máximo 0,8%, por ejemplo máximo 0,7% y 0,6%, respecto al contenido total de estrógeno

34 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 33, caracterizada porque es una formulación que no contiene polivinilpirrolidona

35 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 34, la cual comprende además un anti-oxidante

36 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 35, la cual comprende (peso/peso)

i) 0,002-1% de etinilo estradiol (micronizado),
ii) 10-99%, por ejemplo 45-60%, de monohidrato de lactosa,
iii) 1-80%, por ejemplo 1-35%, de almidón de maiz,
iv) 0-90%, por ejemplo 0-35%, de celulosa (microcristalizada),
v) 0,05-5% de estearato de magnesio, y
vi) 0-5% de dióxido de silicona coloide

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37 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 35, la cual comprende (peso/peso)

i) 0,1-15% de drospirenona (micronizada)

ii) 0,002-1% de etinilo estradiol (micronizado),

iii) 10-99%, por ejemplo 45-60%, de monohidrato de lactosa,

iv) 1-80%, por ejemplo 1-35%, de almidón de maíz,

v) 0-90%, por ejemplo 0-35%, de celulosa (microcristalizada),

vi) 0,05-5% de estearato de magnesio, y

vii) 0-5% de dióxido de silicona coloide

38 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 37, preparada mediante un método que involucra granulación, empastillado, mezcla de polvo seco, granulación de lecho fluidizado, encapsulación o compactación convencionales

39 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 38 en forma de dosis unitaria

40 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 39 adaptada para la preparación de formas de dosis sólidas o formas de dispersión

41 Una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 39 adaptada para la preparación de tabletas, cápsulas o bolsitas

42 Una composición de acuerdo con cualquiera de las reivindicaciones 1 a 24, adaptada para ser administrada mediante administración oral, parenteral, mucosal, nasal, vaginal o tópica

43 Un método para mejorar la estabilidad del etinilo estradiol en una composición farmacéutica, el cual comprende el paso de formar un complejo de inclusión entre dicho etinilo estradiol y ciclodextrina

44 Un método para mejorar la estabilidad del etinilo estradiol en una composición farmacéutica, el cual comprende el paso de a) complejizar dicho etinilo estradiol con ciclodextrina, y opcionalmente b) limitar el contenido de polivinilpirrolidona a menos de 5%, por ejemplo a menos de 4%, por ejemplo a menos de 3%, por ejemplo a menos de 2%, por ejemplo a menos de 1%, por ejemplo proporcionando una formulación que substancialmente no contiene polivinilpirrolidona

45 Un procedimiento para la preparación de una formulación de acuerdo con cualquiera de las reivindicaciones 26 a 41

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Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D C ,

Doctor
GUSTAVO HOLLMANN RESTREPO
Apoderado
SCHERING AKTIENGESELLSCHAFT

Oficio N°
10121

ASUNTO

Radicación N°	03-059764
Solicitud internacional	PCT/IB01/02605
Fecha inicio fase nacional	20/07/2003
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisón 486 de la Comisón de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Unica de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante (Art. 26-k) Decisón 486)

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

21 DIC 2003

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

202054