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OLARTE RAISBECK MOURE & CASTRO LTDA.

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Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S.

Ref: Expediente No. 03-059.764
Solicitud de patente de invención titulada: "COMPOSICIONES DE COMPLEJOS DE ESTRÓGENO-CICLODEXTRINA"
Solicitante: BAYER SCHERING AKTIENGESELLSCHAFT.
N. REF: P2003/00176

RESPUESTA AL OFICIO No. 6793 NOTIFICADO POR FIJACIÓN EN LISTA No. 176, DE FECHA 12 DE JUNIO DE 2009
(EXAMEN DE FONDO)

J. IAN RAISBECK, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad Solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal de prórroga previsto en el artículo 45 de la Decisión 486, en los siguientes términos:

1. En primer lugar, y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado al momento de radicar esta solicitud.

La Reivindicación 1 ha sido limitada para definir más específicamente una composición que está libre de PVP.
Se eliminan las Reivindicaciones 17 y 28-31.
Se eliminan las Reivindicaciones 32-38.

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Creemos que todas las demás enmiendas se hacen evidentes de las modificaciones introducidas en el actual pliego de reivindicaciones

Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

2. a- El Examinador señala que la Reivindicación 17 no es clara puesto que reclama una composición ya reivindicada, indicando además que la humedad relativa es un resultado a alcanzar. Igualmente, el Examinador objeta la Reivindicación 28, por estar caracterizada por su método de obtención. Además el Examinador rechaza las Reivindicaciones 29 por tener el mismo alcance que la Reivindicación 22, y las Reivindicaciones 29 y 30 por presentar falsas dependencias.

b- Las Reivindicaciones 17 y 28-31 han sido canceladas, por lo tanto, las objeciones elevadas por el Examinador con respecto a estas reivindicaciones han sido superadas.

3. a- El Examinador argumenta que la Reivindicación 23 no es clara por cuanto reclama un proceso para fabricar una composición sin aportar ninguna característica técnica y anota que la humedad relativa de la preparación es un resultado o fin a alcanzar.

b- Respecto de la Reivindicación original 23 (nuevas Reivindicaciones 20-22), deseo señalar lo siguiente:

El Examinador ha observado la frase "la humedad relativa de los gránulos". Sin embargo, parece que el Examinador ha atribuido un significado erróneo al término "humedad relativa" en este contexto, ya que al parecer interpreta este término como sinónimo de la expresión "contenido de agua" o " contenido de humedad". Esto, por supuesto, no es correcto ya que los gránulos con un contenido de "agua" de un 60% serían claramente un lodo.

Sin embargo, es bien conocido por el experto que el contenido de humedad de una preparación de polvos o granulados está directamente relacionado con la humedad del aire circundante. Por lo tanto, una estrategia común, rápida y fácil - y perfectamente adecuada- para el control de proceso de describir el contenido de humedad de una preparación de polvos o granulados es medir la humedad relativa, es decir, la cantidad relativa de humedad en el aire que rodea a la preparación de polvos o granulados, a una temperatura dada. En consecuencia, el término "humedad relativa"

describe las características de un proceso (paso operativo) perfectamente adecuado para ser incorporada en una reivindicación de proceso.

Así, el experto en la materia no otorgará ningún otro significado a la expresión: "gránulos con una humedad relativa no superior al 60%, determinada a una temperatura entre 20°C y 40°C", mas que "gránulos con un contenido de humedad que corresponde a una humedad relativa del aire circundante de un máximo del 60%, determinado a una temperatura entre 20 ° C y 40 ° C".

Por consiguiente, la frase en cuestión seria calificada como claramente definida por una persona medianamente versada en la materia y por lo tanto admisible.

3. a- El Examinador argumenta que las Reivindicaciones 32-38 no son patentables por referirse a usos y métodos de tratamiento.

b- Considero superada la anterior objeción en tanto que las reivindicaciones en mención han sido eliminadas del Capitulo Reivindicatorio Modificado.

4. a- El Examinador establece que la patente US5798338 (D1) afecta el nivel inventivo de la presente invención.

b- Tal como lo señala el Examinador en su informe, la presente invención se refiere a una preparación de gránulos (**gránulos**). Estos gránulos son útiles ya que pueden ser procesados en tabletas o pueden ser utilizados "tal como están" para llenado de cápsulas de gelatina.

Como también se ha señalado acertadamente por el Examinador, varios de los citados documentos de la técnica ni siquiera se refieren a preparaciones de gránulos, aunque si se refieren a comprimidos preparados por compresión directa.

La Solicitante está de acuerdo con el Examinador en que la patente US 5.798.338 (D1) constituye el arte previo más cercano, puesto que dicha patente se refiere a la preparación de composiciones estables que contienen estrógeno.

Por otra parte, D1 también revela composiciones que contienen gránulos de complejos de inclusión entre una ciclodextrina y un estrógeno.

En D1 se explica que los complejos de inclusión pueden ser procesados en tabletas, polvos o gránulos, (ver. la columna 2, línea 46).

Por otra parte, D1 enseña que los comprimidos pueden ser preparados ya sea mediante la preparación de gránulos (que posteriormente se comprimen en tabletas, ver Ejemplo 3) o por la compresión directa, ver el Ejemplo 4. Los Ejemplos 3 y 4 de D1 no proporcionan datos de estabilidad para el estrógeno.

Como se mencionó anteriormente, la presente invención está dirigida a gránulos, es decir, el objeto de la presente invención no es mejorar todos los aspectos de las enseñanzas reveladas en la patente D1 (tal como mejorar la estabilidad de comprimidos preparados por compresión directa), sino proporcionar una mejora en la estabilidad de los gránulos. En consecuencia, el punto de partida para el análisis de la actividad inventiva de la presente invención es el Ejemplo 3 de D1.

El Ejemplo 3 revela la fabricación de gránulos que contienen un complejo de inclusión entre etinilestradiol y beta-ciclodextrina. Los gránulos de Ejemplo 3 contienen, además, alrededor del 5% en peso w / w polivinil pirrolidona (PVP), comúnmente utilizado como aglutinante.

Ciertamente, el Ejemplo 4 de D1 enseña la fabricación de un comprimido libre de PVP preparado por compresión directa (es decir, no son gránulos). Sin embargo, la presente invención está dirigida a gránulos, por lo tanto el experto en la materia no tomaría en consideración la composición de polvo del ejemplo 4. Evidentemente, el experto se vería motivado a seguir las enseñanzas del ejemplo 3, a fin de obtener información sobre los excipientes a utilizar en el proceso de granulación, etc.

En consecuencia, a partir del Ejemplo 3 de D1, el problema objetivo a resolver debe ser considerado como una modificación de los gránulos del Ejemplo 3 de D1 para obtener gránulos aún más estables.

Este problema fue resuelto mediante la preparación de gránulos libres de PVP.

Como puede deducirse del Ejemplo 1 de la presente solicitud, los gránulos (posteriormente comprimido en pastillas), que incluye un complejo entre etinilestradiol y beta-ciclodextrina fabricadas de acuerdo con el Ejemplo 3 de D1, tienen una estabilidad pobre.. Sólo el 77,8% del

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contenido inicial de etinilestradiol está presente después de almacenamiento a 60 ° C durante 3 meses (ver datos para la formulación A en el cuadro 1.3).

Así, los gránulos que comprende un complejo entre un estrógeno y una ciclodextrina poseen una pobre estabilidad para el estrógeno, cuando se incluye PVP en la formulación de los gránulos en una concentración de alrededor del 5% en peso. También se demuestra que los gránulos que contienen etinilestradiol libre (es decir etinilestradiol que no está acomplejado con ciclodextrina) muestran una estabilidad pobre cuando contienen alrededor del 5% peso de PVP.

En este caso sólo el 70,7% del contenido inicial de etinilestradiol está presente después de almacenamiento a 60 ° C durante 3 meses (ver datos para la formulación B en el cuadro 1.3).

Los presentes inventores han establecido sorprendentemente que cuando la PVP no está incluida en los gránulos, se observa una mejora significativa en la estabilidad del estrógeno.

Por ejemplo, la Formulación C de la Tabla 1.3, que comprende gránulos libres de PVP muestran una mayor estabilidad en comparación con las Formulaciones A y B que comprenden gránulos que contienen PVP -aunque el etinilestradiol que contienen los gránulos de la Formulación C ni siquiera es un complejo con ciclodextrina!.

Los gránulos más estables (y esto es el objeto de la presente solicitud) son los que corresponden a la Formulación de E.

Como puede verse en los datos de la tabla 1.3, el 96,5% del contenido inicial de etinilestradiol está presente después de un almacenamiento a 60 ° C durante 3 meses.

Así, los gránulos que comprenden un complejo entre un estrógeno y ciclodextrina exhiben una estabilidad mejorada del estrógeno cuando la PVP ha sido eliminada de los gránulos.

Volviendo a la cuestión del nivel inventivo, el punto decisivo para evaluar la actividad inventiva es si la persona medianamente versada en la materia, basándose en el estado de la técnica citado por el Examinador, hubiese tenido la motivación necesaria para eliminar la PVP de los gránulos divulgados en el Ejemplo 3 de D1 con la expectativa de obtener una mayor estabilidad de los estrógenos.

El Examinador declara que el experto en la materia podría fácilmente haber eliminado la PVP de los gránulos.

Mientras que la Solicitante está de acuerdo con el Examinador en que el experto podría haber eliminado la PVP de las formulaciones para gránulos, aún es necesario aportar evidencias que demuestren que el experto hubiese hecho esto. Dicho de otra manera, el estado de la técnica tiene que proporcionar la motivación necesaria para que la persona calificada en la materia avance en la dirección de la invención reivindicada.

En la opinión de la Solicitante no existen en el estado de la técnica ninguna enseñanza que podría conducir a la persona experta en la materia en esta dirección.

En primer lugar, la patente D1 tiene como objeto mejorar la estabilidad del componente de estrógeno. Así, desde el primer momento el experto con conocimientos medios en la materia asume que los gránulos divulgado en la patente D1 serían estables. El problema de la estabilidad, no fue reconocido por la patente D1, o en cualquier otro documento de la técnica en el expediente.

En segundo lugar, es importante señalar que la PVP es considerado el "aglutinante de primera elección" en relación con la técnica de granulación húmeda, ver la copia adjunta del Manual de excipientes farmacéuticos. De esta manera, cuando el experto en la materia considera la posibilidad de aplicar la técnica de granulación a un complejo entre un estrógeno, como el etinilestradiol, y una ciclodextrina, se verá realmente motivado a utilizar PVP como aglutinante. Además, un complejo entre un estrógeno, como el etinilestradiol, y una ciclodextrina es muy sensible al agua resultando en la separación de estrógeno libre del complejo de ciclodextrina frente a la exposición al agua (véase Ejemplo 6 de la presente solicitud). Sin embargo, al seleccionar PVP como aglutinante en un proceso de granulación, el experto esperaría que la sensibilidad al agua sea menos afectada, ya que la PVP es la que posee menores propiedades higroscópicas que otros aglutinantes tales como el almidón. Por lo tanto, la Solicitante respetuosamente, está en desacuerdo con los argumentos del Examinador acerca de que el experto en la materia consideraría el Ejemplo 4 de la patente US5.798.338 (comprimido preparado por compresión directa, libre de PVP) y luego "con poco esfuerzo" ajustaría los gránulos del Ejemplo 3, eliminando el uso de PVP.

El Examinador falla en su apreciación al no aportar una explicación razonable de por qué el experto prestaría atención a un proceso de elaboración de comprimidos por compresión directamente cuando el objetivo es preparar gránulos estables.

Contrariamente a las expectativas de la persona calificada en el arte, los presentes inventores dan a conocer que el empleo de PVP ocasiona problemas de estabilidad en el estrógeno contenido en gránulos - un problema que no habían sido reconocido hasta el momento de la presente invención-. Los inventores han resuelto este problema de estabilidad mediante la selección adecuada de las condiciones de granulación, tales como la selección de la humedad relativa adecuada durante el proceso de granulación, y mediante la exclusión de la PVP como aglomerante.

Si bien la solución al problema antes mencionado puede parecer simple y directa, considerado en retrospectiva, cabe recordar que antes de las enseñanzas de la presente solicitud, el experto no tenía conocimiento de los problemas de estabilidad conferidos por la PVP que es considerado de lejos, con el aglutinante más frecuentemente utilizado.

Por lo tanto la presente invención ha dado a conocer que para preparar gránulos estables que contienen un complejo de estrógeno-ciclodextrina, es un requisito previo que la PVP, que suele ser empleada como aglutinante en los procesos de granulación húmeda, no forme parte de estos gránulos.

Por último, la Solicitante desea llamar la atención del Examinador sobre el hecho de que las composiciones granuladas, en comparación con las obtenidas por compresión directa, son más utilizadas en la industria farmacéutica, ya que ofrecen varias ventajas en comparación con la técnica de compresión directa. Esto se explica en la copia adjunta del libro de texto escrito por Aulton.

Un problema particular que se asocia a menudo con la compresión directa es la falta de uniformidad de contenido de principio activo. Esto se discute en la página 617 del libro de texto de Aulton. Más concretamente, se afirma que: "Muchos polvos, debido a su pequeño tamaño o características de la superficie, son cohesivos y no fluye bien. El flujo pobre de estos polvos a menudo se traduce en una amplia variación del peso en el producto final debido a un llenado variable de los moldes de comprimidos, etc. Los granulados producidos a partir de este sistema cohesivo serán mayores y más isodiamétricos, factores que contribuyen a las propiedades de flujo mejoradas".

Esto demuestra que para el experto medio en la fabricación de preparados con muy baja dosis de hormonas, la uniformidad del contenido de hormona es de extrema importancia, por lo tanto siempre considerará la técnica de granulación y no la técnica de compresión directa, ya que es el método de fabricación por elección.

En opinión de la Solicitante, esto sólo refuerza la idea de que el experto sólo podría considerar la preparación granulada que se describe en el Ejemplo 3 de la patente US 5.798.338 como punto de partida, y no tomaría en consideración el ejemplo 4 del mismo documento.

5. Por último, deseamos señalar que la presente invención ha dado origen a numerosas patentes en diferentes jurisdicciones entre las cuales podemos señalar las patentes EP 1 353 700 B1, US 6.958.326 y US 7.163.931 así como PE 3698.

6. Por todo lo anterior, considero que las objeciones presentadas por el Examinador en su examen de fondo No. 1553 han sido resueltas y por consiguiente solicito respetuosamente se tengan por cumplidos los requisitos de patentabilidad, en tanto no se logró desvirtuar ninguno de ellos por parte del Despacho, y se proceda con la concesión de la patente. En el evento que ese Despacho considere que persisten objeciones sobre cualquier reivindicación, solicito se emita un nuevo auto de fondo para poder atenderlas

Atentamente,

J. IAN RAISBECK
C.C. 79.376.996 de Bogotá
T.P. 135.799

Anexos:

- Capítulo Reivindicatorio Modificado;
- copia de la patente US 7163931;
- copia de la patente US 6958326;
- copia de la patente PE 3698;
- copia del Handbook de excipientes;
- copia de la publicación AULTON

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CAPITULO REIVINDICATORIO MODIFICADO

1. Una composición que comprende:

i) un preparado granulado que comprende un complejo entre un estrógeno y una ciclodextrina; y opcionalmente

ii) uno o más excipientes,

donde la composición que tiene una estabilidad tal que dicho estrógeno se encuentra en una cantidad de al menos 85% p/p con relación al contenido inicial de dicho estrógeno después de un almacenamiento por 12 meses a 40°C y 75% de humedad relativa (RH).

2. La composición de acuerdo con la reivindicación 1, donde el estrógeno se selecciona del grupo que consiste en etinilestradiol (EE), estradiol, sulfamatos de estradiol, valerato de estradiol, benzoato de estradiol, estrona y sulfato de estrona, o mezcla de los mismos.

3. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, donde el estrógeno es etinil estradiol.

4. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, donde la ciclodextrina se selecciona del grupo que consiste en α-ciclodextrina, β-ciclodextrina, γ-ciclodextrina y derivados de las mismas.

5. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, donde la ciclodextrina es β-ciclodextrina o derivados de la misma.

6. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, donde el estrógeno se encuentra en una cantidad que corresponde a una cantidad equivalente desde el punto de vista terapéutico de etinilestradiol de entre 0,002% p/p y 2% p/p.

7. La composición de acuerdo con una de las reivindicaciones 1 a 5, donde el estrógeno está en una cantidad de entre 0,002% p/p y 2% p/p,.

8. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, donde el estrógeno es etinilestradiol y la ciclodextrina es β-ciclodextrina, el etinilestradiol está en una cantidad respecto del complejo de etinil-estradiol-β-ciclodextrina de entre 5% p/p y 20% p/p.

9. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, donde el estrógeno se encuentra en una cantidad respecto de la ciclodextrina tal que la relación molar entre el estrógeno y la ciclodextrina es de entre 2:1 y 1:10.

10. La composición de acuerdo con cualquiera de las reivindicaciones precedentes que, además, comprende uno o más agentes activos desde el punto de vista terapéutico.

11. La composición de acuerdo con la reivindicación 10, donde el o los agentes activos desde el punto de vista terapéutico son progestágenos.

12. La composición de acuerdo con la reivindicación 11, donde el progestágeno se selecciona del grupo que consiste en drospirenona, levonorgestrel, norgestrel, gestodene, dienogest, acetato de ciproterona, noretisterona, acetato de noretisterona, desorgestrel, 3-ceto-desorgestrel.

13. La composición de acuerdo con la reivindicación 12, donde el progestágeno es la drospirenona.

14. La composición de acuerdo con la reivindicación 13, donde la drospirenona está micronizada.

15. La composición de acuerdo con la reivindicación 13 ó 14, donde la drospirenona se encuentra en una cantidad de entre aproximadamente 0,4% y 20% p/p.

16. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, donde el o los excipientes se eligen del grupo formado por el almidón, la celulosa, la hidroxipropilcelulosa, la hidroxipropilmetilcelulosa y la maltodextrina.

17. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, donde el complejo está micronizado.

18. La composición de acuerdo con cualquiera de las reivindicaciones precedentes, que comprende, además, un antioxidante.

19. Un proceso para fabricar una composición de acuerdo con la reivindicación 1, que comprende los pasos de:

i) obtener un complejo entre un estrógeno y una ciclodextrina;

ii) cargar el complejo y uno o más excipientes en un granulador;

iii) aplicar un líquido en el complejo cargado y uno o más excipientes bajo condiciones de granulación, de modo de obtener gránulos que tienen una humedad relativa que no excede el 60%, determinada a una temperatura de entre 20°C y 40°C.

20. El proceso de acuerdo con la reivindicación 19, donde la humedad relativa de la preparación granulada no excede el 55% determinada a una temperatura de entre 20°C y 40°C.

21. El proceso de acuerdo con la reivindicación 20, donde la humedad relativa de la preparación granulada no excede el 45% determinada a una temperatura de entre 20°C y 40°C.

22. El proceso de acuerdo con la reivindicación 21, donde la humedad relativa de la preparación granulada no excede el 40% determinada a una temperatura de entre 20°C y 40°C.

23. El proceso de acuerdo con cualquiera de las reivindicaciones 19 a 22, donde el estrógeno se selecciona del grupo que consiste en etinilestradiol (EE), estradiol, sulfamatos de estradiol, valerato de estradiol, benzoato de

estradiol, estrona y sulfato de estrona, o mezcla de los mismos.

24. El proceso de acuerdo con cualquiera de la reivindicación 23, donde el estrógeno es etinil estradiol.

25. El proceso de acuerdo con cualquiera de las reivindicaciones 19 a 24, donde el o los excipientes se eligen del grupo formado por el almidón, la celulosa, la hidroxipropilcelulosa, la hidroxipropilmetilcelulosa y la maltodextrina.

Anexo 1

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(12) **United States Patent**
Backensfeld et al.

(10) **Patent No.: US 7,163,931 B2**
(45) **Date of Patent: Jan. 16, 2007**

(54) **COMPOSITIONS OF ESTROGEN-CYCLODEXTRIN COMPLEXES**

(75) Inventors: **Thomas Backensfeld**, Berlin (DE); **Wolfgang Heil**, Berlin (DE); **Ralph Lipp**, Berlin (DE)

(73) Assignee: **Schering Aktiengesellchaft**, Berlin (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 73 days.

(21) Appl. No.: **11/102,681**

(22) Filed: **Apr. 11, 2005**

(65) **Prior Publication Data**

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Related U.S. Application Data

(62) Division of application No. 10/022,845, filed on Dec. 20, 2001, now Pat. No. 6,958,326.

(60) Provisional application No. 60/256,484, filed on Dec. 20, 2000.

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
A01N 43/04 (2006.01)
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C08B 37/16 (2006.01)

(52) **U.S. Cl.** **514/58**; 514/23; 514/25; 514/54; 514/60; 536/103; 536/123.1; 536/124

(58) **Field of Classification Search** 514/23, 514/25, 54, 58, 60; 536/103, 124, 123.1
See application file for complete search history.

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Primary Examiner—Patrick Lewis

(57) **ABSTRACT**

Pharmaceutical compositions comprising low doses of sensitive complexes between an estrogen and a cyclodextrin are provided with improved stability. In specific embodiments the composition comprises a complex between ethinyl estradiol and β-cyclodextrin in a granulate preparation and in yet another embodiment the composition comprises a limited amount of polyvinylpyrrolidone since this excipient was found to degrade ethinyl estradiol. Furthermore, a method for improving the stability of an estrogen in a composition and for manufacturing such a stable composition is provided. Essentially, the granulate preparation are manufactured under careful control of the relative humidity.

52 Claims, No Drawings

COMPOSITIONS OF ESTROGEN-CYCLODEXTRIN COMPLEXES

This application is a divisional of U.S. Ser. No. 10/022,845, filed Dec. 20, 2001 now U.S. Pat. No. 6,958,326.

This application claims priority to U.S. Provisional Application No. 60/256,484, filed Dec. 20, 2000.

FIELD OF INVENTION

The present invention relates to pharmaceutical compositions and formulations comprising a cyclodextrin-estrogen complex that confers very high chemical stability to the estrogen. The invention allows for an improved physical stability of cyclodextrin-estrogen complexes and of the chemical stability of estrogens such ethinyl estradiol upon storage.

BACKGROUND OF THE INVENTION

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

Pharmaceutical products 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, it is problematic to manufacture unit dosage formulations with reliably consistent amounts of active agent which do not fluctuate within one batch or between batches. Thus, the requirements of content uniformity as set forth by health authorities may not be met.

Moreover, degradation of these small amounts of active ingredient is a further contributor to the fluctuations of the active ingredient in low dosage formulations.

In general, these low dose formulations comprising unstable active agents are problematic in terms of their preparation, storage and use, and there is a need for providing means for stabilization of such formulations.

Complexation of estrogens with cyclodextrins is widely used for improving stability, solubility or bioavailability. For example, EP 0 349 091 discloses compositions containing complexes between 17-β-estradiol and dimethyl-β-cyclodextrin for improving nasal administration, Fridriksdottir et al (*Die Pharmazie*, vol. 51, 1996, pages 39–42) describes complexes between cyclodextrin and 17-β-estradiol for improving the solubility in aqueous solution so as to improve sublinqual application. Improved solubility is also the focus of U.S. Pat. No. 4,596,795, which relates to a complex between α-, β- and γ-cyclodextrins and derivatives thereof with testosterone, progesterone, and estradiol. U.S. Pat. No. 4,383,992 discloses a water soluble inclusion compound formed by complexing a steroid compound, such as an estrogen with beta-cyclodextrin.

Moreover, U.S. Pat. No. 5,798,338 discloses that the oxidative degradation of 17-α-ethinyl estradiol is reduced upon forming clathrates (complexes) between β-cyclodextrin and 17-α-ethinyl estradiol.

However, although complexation of estrogens with cyclodextrins may solve critical issues with regards to solubility, bioavailability and stability, there are still further problems to solve before complexes between active agents, such as estrogens, and cyclodextrins are suitable for use in pharmaceutical products. Namely, the complexes are prone to dissociation into the free estrogen and the cyclodextrin, particularly upon contact with water. The lack of physical stability of cyclodextrin-estrogen complexes results in significant amounts of free estrogen present in compositions due to, for instance, exposure to aqueous media during the manufacturing process, particularly during granulation. As a consequence, the lifetime of the composition may be decreased due to degradation of free estrogen.

Moreover, the intended improved bioavailability sought by complexing estrogen with cyclodextrin is not achieved due to the lack of physical stability of the cyclodextrin-estrogen complex and the chemical instability of the free estrogen.

Various attempts have been made in order to stabilize compositions comprising complexes between a cyclodextrin and an estrogen. For example, the composition may be stabilized by stabilizing the complex itself. Thus, U.S. Pat. No. 4,727,064 attempts the stabilization of complexes upon using amorphous forms of the complex. Alternatively, complexes may be stabilized and their solubility increased upon adding polymers to the reaction medium upon complexation , as disclosed by Loftsson et al. (*Int. J. Pharmaceutics*, Vol. 110, 1994, pp 169–177). EP 0579435 also discloses complexes between estradiol and cyclodextrins wherein the addition of polymers to the reaction medium increases the stability constant of the complex.

The compositions may also be stabilized upon avoiding a granulation step in the manufacturing process of the composition, as disclosed in WO 00/21570.

There is a need in the art for processes for preparing physically stable complexes of cyclodextrin and estrogen and for compositions, which improve the stability of both the complex and the free estrogen. There is furthermore a need in the art for granulate formulations which allow for physically stable cyclodextrin-estrogen complexes.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a stable and homogenous pharmaceutical product comprising an estrogen, wherein the stability of the estrogen is significantly improved over that of conventional products, which have complexed estrogens or sensitive complexes between a cyclodextrin and an estrogen. Degradation of estrogens, such as ethinyl estradiol, in conventional products, is one of the most critical issues with regard to product shelf life.

It has surprisingly been found that products with improved stability of the estrogen are achieved by means of complexing estrogen with cyclodextrins, the judicious selection of excipients and/or proper adaptation of the manufacturing process. Consequently, the shelf-life of an estrogen-containing product is improved.

Thus, an important aspect of the invention relates to formulations and compositions comprising complexes between an estrogen and a cyclodextrin that are stable in spite of being manufactured by granulation. That is to say that the invention relates in a first aspect to a formulation comprising a complex between an estrogen and a cyclodextrin, wherein the formulation is a granulate preparation, said granulation preparation having a relative humidity of at most 60%, as determined at a temperature between 20° C. and 40° C.

In a further aspect, the invention relates to compositions comprising i) a complex between an estrogen and a cyclodextrin; and ii) one or more excipient(s), the composition having a stability such that said estrogen is in amount of at

least 85% w/w in relation to the initial content of the estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH). In a suitable embodiment thereof, the composition comprises a granulate preparation comprising said complex. In a further suitable embodiment, the composition is compressed directly into a tablet or equivalent unit dosage forms. Upon further study of the specification and appended claims, further aspects and advantages of this invention will become apparent to those skilled in the art.

Thus, contrarily to previous findings, it is possible to obtain stable compositions comprising an estrogen-cyclodextrin-complex in a granulate preparation.

Compositions of the present invention may be used as medicaments. Accordingly, the use of a composition described infra for the preparation of a medicament for female contraception, for hormone replacement therapy, or for treating acne or PMDD (pre-menstrual dysfunction disorders), is a further aspect of the present invention.

In a broad sense, the present invention relates to a method of improving the stability of an estrogen in a pharmaceutical composition that comprises an estrogen-cyclodextrin complex and one or more excipients in a granulate preparation, the method comprises the steps of:

i) forming a complex between said estrogen and a cyclodextrin; and

ii) mixing under granulation conditions the said complex with the one or more excipients such that the relative humidity of the final granulate does not exceed 60%, as determined at a temperature between 20° C. and 40° C.

Finally, the invention relates to a process for manufacturing a composition comprising a granulate preparation of a complex between an estrogen and a cyclodextrin, wherein the processing of the granulate preparation comprises the steps of

i) loading the complex, one or more excipients and optionally one or more therapeutically active agent(s) into a granulator;

ii) applying a liquid onto the loaded complex and the one or more excipients under granulation conditions so as to obtain granules having a relative humidity not exceeding 60%, as determined at a temperature between 20° C. and 40° C.

DETAILED DESCRIPTION OF THE INVENTION

The term "complex" is intended to mean a complex between an estrogen and a cyclodextrin, wherein a molecule of said estrogen is at least partially inserted into the cavity of one cyclodextrin molecule. Furthermore, the molecule of an estrogen may at least partially be inserted into the cavity of more cyclodextrin molecules, and two moieties of a single estrogen molecule may each be inserted into one cyclodextrin molecule to give 2:1 ratio between cyclodextrin and estrogen. Thus, the complex may be termed as an inclusion complex (clathrate) between an estrogen and a cyclodextrin. Similarly, the complex may comprise 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 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 complex" or "EE-β-CD" is intended to mean a complex, of any ratio, between ethinyl estradiol and β-cyclodextrin.

The term "granulate preparation" relates to a preparation of a powder, wherein the particle size of the powder is either increased upon processing with a liquid or by compression. The liquid may be of any kind of aqueous or organic solvents, or mixtures thereof, optionally further comprising a binder such as a starch. Thus, a "granulate preparation" relates in a broad sense to granules, pellets and compressed powder or any particle formed by granulation, pelletation or compression of powder such that a mean particle size of at least about 100 μm are formed.

The term "cyclodextrin" is intended to mean a cyclodextrin or a derivative thereof as well as mixtures of various cyclodextrins, mixtures of various derivatives of cyclodextrins and mixtures of various cyclodextrins and their derivatives. The cyclodextrin is further defined according to the invention.

The present inventors have developed products, wherein a remarkable improvement of the stability of an estrogen has been achieved by combined means. One such means is by the protection of the estrogen by forming a cyclodextrin complex. Another such means is by the judicious adaptation of the granulation process such that e.g. the dissociation of the complex into free estrogen and cyclodextrin is restricted during the manufacturing of the granulate preparation. The present inventors have provided data indicating that a complex between ethinyl estradiol and β-cyclodextrin is poorly stable when exposed to water. Actually, in the event where the complex is dissolved in water, about 50% of the complex are dissociated into free ethinyl estradiol and cyclodextrin within 3 minutes (see Example 6 herein). Thus, without being limited to a particular theory, the stability of the products is, at least in part, improved by limiting the dissociation of the complex into free estrogen during the manufacturing process, thereby limiting the content of free estrogen in the final product.

Therefore, in a first aspect the invention relates to a formulation comprising a complex between an estrogen and a cyclodextrin, wherein the formulation is a granulate preparation, said granulation preparation having a relative humidity of at most 60%, as determined at a temperature between 20° C. and 40° C. Preferably, the relative humidity is at most 55%, preferably of at most 45%, most preferably of at most 40%, as determined at a temperature between 20° C. and 40° C.

As stated, the present invention has lead to stable products comprising sensitive complexes between an estrogen and a cyclodextrin. Thus, in a second aspect, the invention relates to a composition comprising:

i) a complex between an estrogen and a cyclodextrin; and

ii) one or more excipient(s), the composition having a stability such that said estrogen is in an amount of at least 85% w/w in relation to the initial content of the estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH). The initial content of estrogen should be understood as the weighed quantity of estrogen included in the composition upon manufacturing the final formulation.

In one embodiment hereof, the composition is in a form of a tablet manufactured by direct compression of the

composition. Preferably the composition comprises a restricted amount of polyvinylpyrrolidone as disclosed further herein.

In yet another embodiment, the complex between an estrogen and a cyclodextrin is formulated into the granulate preparation as defined herein.

In preferred embodiments, the composition has a stability such that said estrogen is in an amount of at least 90% w/w, more preferably of at least 95% w/w, most preferably of at least 97% w/w such as of at least 98% in relation to the initial content of the estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH).

One further means for improving the stability of an estrogen in such formulations and compositions comprises the judicious selection of excipients such that the content of excipients capable of inducing degradation of ethinyl estradiol are minimised or excluded from the formulations. One such critical excipient is polyvinylpyrrolidone, which is typically used as a binding agent for fluid bed granulation. As disclosed herein, the ethinyl estradiol is sensitive to polyvinylpyrrolidone and significant quantities of ethinyl estradiol is degraded in formulations and compositions, nonetheless the ethinyl estradiol is protected in the form of a clathrate. For example, compositions comprising polyvinylpyrrolidone and prepared as disclosed in Example 3 of U.S. Pat. No. 5,798,338, by fluid bed granulation have a poor stability with respect to ethinyl estradiol. The present inventors has found that in such a composition the content of ethinyl estradiol is decreased by 25% in relation to the initial content of the ethinyl estradiol after storage for 12 months at 40° C. and 75% relative humidity (See table 1.4, Example 1, Table A). Therefore, one aspect of the invention relates to compositions/formulations low in the content of compounds with relatively high oxidising potential such as an oxidising potential greater than or similar to polyvinylpyrrolidone. For example, the compositions/formulations of the present invention preferably have less polyvinylpyrrolidone than the compositions of Example 3 of U.S. Pat. No. 5,798,338. More preferably, suitable embodiments of the invention relate to compositions/formulations comprising at most 2% w/w of polyvinylpyrrolidone, preferably at most 1% w/w, more preferably at most 0.5% w/w, most preferably at most 0.2% w/w of polyvinylpyrrolidone. Moreover, particular interesting embodiments relate to compositions/formulations essentially free of polyvinylpyrrolidone.

Individually, or acting in concert, the above mentioned means have resulted in compositions, wherein the estrogen is more stable than in conventional compositions comprising polyvinylpyrrolidone that are manufactured by direct compression or by an improper fluid bed granulation process. The thus provided stable compositions is characterised by having a content of said estrogen of at least 90% w/w in relation to the initial content of said estrogen after storage for 3 months at 40° C. and 75% relative humidity (RH). Preferably, the content of said estrogen is least 92% w/w, more preferably at least 94% w/w, even more preferably at least 96% w/w and most preferably at least 98% w/w in relation to the initial content of estrogen after storage for 3 months at 40° C. and 75% relative humidity (RH).

Likewise, the compositions are also stable at higher temperatures, e.g. at 60° C. and 75% relative humidity, wherein the stability is such that a content of estrogen, as determined after 3 months storage at 60° C. and 75% relative humidity (RH), is 85% w/w in relation to the initial content of said estrogen, preferably at least 90% w/w, more preferably at least 92% w/w, even more preferably at least 94% w/w, most preferably at least 96% w/w in relation to the initial content of said estrogen.

Importantly, the compositions according to the invention are more stable at ambient conditions in comparison to conventional compositions. Thus, the compositions as disclosed herein have improved stability upon storage for 12 months at 25° C. and 60% relative humidity (RH), such that said estrogen is in an amount of at least 95% w/w in relation to the initial content of said estrogen. Preferably, the content of estrogen is at least 96% w/w, more preferably at least 97% w/w, most preferably at least 98% w/w in relation to the initial content of estrogen after storage for 12 months at 25° C. and 60% relative humidity (RH).

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 and 17α-dihydroequilenin sulfate or mixtures thereof. Particular interesting estrogens are selected from the group consisting of ethinyl estradiol (EE), estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof, notably ethinyl estradiol (EE), 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, unstable compositions, e.g. those comprising a sensitive complex between an ethinyl estradiol and a cyclodextrin that are manufactured by said conventional granulation methods, comprises degradation products of ethinyl estradiol, in particular following storage for a period of time. Moreover, since more ethinyl estradiol is degraded in said conventional compositions than in those developed by the present inventors (see Example 2, table 1.3), the conventional compositions may comprise higher quantities of these degradation products.

Accordingly, the stability according to one embodiment of the present invention is such that a molar sum product of known degradation products of ethinyl estradiol is at most 0.8% in relation to the initial content of ethinyl estradiol. Thus, wherein the estrogen is ethinyl estradiol, the molar sum product of 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol, Δ6,7-ethinyl estradiol and Δ-9,11-ethinyl estradiol totals at the most 0.8% in relation to the initial molar content of ethinyl estradiol as determined after storage for 12 months at 25° C. and 60% relative humidity (RH). Preferably, the molar sum product totals at the most 0.7% and more preferably at the most 0.6% at these storage conditions.

Furthermore, the stability is such that a molar sum product 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol, Δ6,7-ethinyl estradiol and Δ-9,11-ethinyl estradiol, totals at the most 3% in relation to the initial molar content of ethinyl estradiol as determined after storage for 12 months at 40° C. and 75% relative humidity (RH). Preferably, the molar sum product totals at most 2% and more preferably at the most 0.6% at those storage conditions.

As stated, an object of the present invention is to provide a pharmaceutical composition/pharmaceutical formulation comprising a complex between an estrogen and cyclodextrin, wherein the stability of said estrogen is significantly

improved over that of conventional compositions/formulations. Thus, for further improving the stability or ensuring the stability of embodiments according to the invention, the composition/formulations further comprises an antioxidant. The antioxidant may either be included in the granulate preparation or added to the composition as a further excipient.

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.

The estrogen-cyclodextrin complex may be obtained by methods known to the person skilled in the art (e.g. U.S. Pat. No. 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.

Preferably, the complex between a cyclodextrin and an estrogen may have a given lipophilicity (hydrophobicity). Thus, suitable embodiments according to the invention relates to those, wherein the complex has a n-octanol/water partition coefficient of the complex at pH 7 ranging from about 2 to 5, preferably from about 3 to 4. Further interesting embodiments comprises the complex in crystalline form. Thus, in a limited aspect, the invention relates to crystalline complexes between an estrogen and a cyclodextrin. The term "crystalline" relates to various modifications of the physical structure of a compound, wherein a part of the compound can be in amorphous form. Crystalline compounds may be characterised by being hydrated and containment of crystal water. Finally, the complexes may be defined by the examples provided herein such as those hydrated complexes disclosed in Example 12. Moreover, the crystalline complex may contain parts of free ethinyl estradiol and free cyclodextrin.

Preferably, the complex comprises of β-cyclodextrin or a derivative thereof, most preferably β-cyclodextrin. Thus, in a particularly preferred embodiment of the invention, which is a combination of preferred embodiments, the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin.

In an alternative embodiment of the invention, the composition further comprises one or more therapeutically active agent. Thus, in this embodiment, the composition further comprises a progestogen. The progestogen may be selected from the group consisting of drospirenone, levonorgestrel, norgestrel, gestodene, dienogest, cyproterone acetate, norethisterone, norethisterone acetate, desorgestrel, 3-keto-desorgestrel. However, the preferred progestogen is drospirenone.

In the preferred embodiment wherein the therapeutically active substance is drospirenone, said drospirenone may optionally be micronized. In the preferred embodiment where the therapeutically active substance is drospirenone, all or substantially all of said drospirenone may be present as a complex with cyclodextrin. As the person skilled in the art will appreciate, the dissociation 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.

Thus, a preferred embodiment of the invention relates to a composition/formulation wherein the estrogen is ethinyl estradiol and the one or more therapeutically active agent(s) is drospirenone. A further interesting embodiment in connection hereto is where both the estrogen-cyclodextrin complex and the drospirenone are micronized.

As stated, the compositions and formulations comprises low doses of active agent, such that typical embodiments according to the invention comprises estrogen in an amount corresponding to a therapeutically equivalent amount of ethinyl estradiol of from about 0.002% w/w to 2% w/w.

In yet other typical embodiments, the composition/formulations comprises the estrogen, ethinyl estradiol, in an amount from about 0.002% w/w to 2% w/w. Preferably, the amount is from about 0.004% w/w to 0.2% w/w, more preferably from about 0.008% w/w to 0.1% w/w, most preferably from about 0.02% w/w to 0.05% w/w.

When taking the amount of the cyclodextrin into account such as in preferred embodiments wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 5% w/w to 20% w/w, preferably from about 8% w/w to 15% w/w, most preferably from about 9% w/w to 13% w/w.

Furthermore, according to the invention, the ratio between the estrogen and the cyclodextrin may be adjusted. Therefore, in suitable embodiments, the estrogen is in an amount relative to the cyclodextrin such that a molar ratio between the estrogen and the cyclodextrin is from about 2:1 to 1:10, preferably from about 1:1 to 1:5, most preferably from about 1:1 to 1:3, such as 1:1 and 1:2.

In embodiments wherein the composition further comprises a therapeutically active compound and that said compound is drospirenone, the drospirenone is in an amount from about 0.4% to 20% w/w, preferably from about 0.8% w/w to 10% w/w, more preferably from about 1.5% w/w to 5% w/w.

A further object of the invention is to provide a composition Or a formulation as described herein further formulated as a unit dosage form, preferably such as a tablet, capsule or sachets.

A typical embodiment of the invention relates to a composition or a formulation in form of granules, pellets or dry compressed blends that may be filled into hard gelatine capsules or sachets, or compressed into tablet cores. In that event, the composition or formulation comprises (% wt/wt):

i) Active agent: complex between ethinyl estradiol arid β-cyclodextrins;
ii) 0–95% w/w of filling agents such as lactose, starch, cellulose and/or others;
iii) 0–15% w/w of binding agents such as starch, cellulose, hydroxypropylcellulose hydroxypropylmethylcellulose, maltodextrine and/or others;
iv) 0–5% w/w of glidants such as colloidal silicon dioxide and/or others;
v) 0–15% w/w of disintegrating agents such as starch, carmellose-calcium, crosscarmellose-sodium, carboxymethylstarch sodium and/or others;
vi) 0–5% w/w of stabilizers/antioxidants such as tocopherole acetate, propyl gallate, ascorbic acid, ascorbic palmitate and/or others; and
vii) 0–5% w/w of lubricants such as magnesium stearate and/or others.

In the embodiment wherein the composition/formulation further comprises a therapeutically active compound, such as a progestogen, preferably drospirenone, a typical formulation may further comprise 0.1–15% w/w of drospirenone.

A particular interesting embodiment relates to a unit dosage form comprising:

Drospirenone (micronized)	3.00 mg
Ethinyl estradiol as β-cyclodextrin clathrate (micronized)	0.02 mg*
Lactose	48.18 mg**
Corn starch	28.00 mg
Magnesium stearate	0.8 mg
Water	(processing aid)

*0.02 is the concentration of ethinyl estradiol (not taken β-cyclodextrin into consideration). The amount of ethinyl estradiol in the β-cyclodextrin clathrate is 9.5 to 12.5%.
**the amount of lactose is to be adjusted to the amount of β-cyclodextrin.

A further aspect of the invention relates to a method for improving the stability of an estrogen in a pharmaceutical composition that comprises an estrogen and one or more excipients in a granulate preparation, the method comprises the steps of:

i) forming an complex between said estrogen and a cyclodextrin; and
ii) mixing under granulation conditions the said complex with the one or more excipients such that the relative humidity of the final granulate does not exceed 60%, as determined at a temperature between 20° C. and 40° C.

As described herein, this method of stabilizing results in compositions that are more stable than reported for conventional compositions. The important features leading to the improved stability relates, at least in part, to the granulation process and to the proper choice of excipients. Thus, the method of improving the stability relates to the proper adjusting of the relative humidity of the granulate preparation. Most importantly, the relative humidity may not exceed 60% relative humidity, as determined at a temperature between 20° C. and 40° C. Preferably, the relative humidity does not exceed 55%, more preferably does not exceed 45%, most preferably does not exceed 40%, as determined at a temperature between 20° C. and 40° C.

In a further related aspect hereof, the invention relates to a method for improving the stability of an estrogen in a pharmaceutical composition that comprises an estrogen and one or more excipients, the method comprises the steps of:

i) forming an complex between said estrogen and a cyclodextrin; and
ii) adding excipients in an amount so as to minimise the overall amount of excipients which have an oxidising potential greater than or similar to polyvinylpyrrolidone.

The aim is to restrict or minimise the amount of excipients, which have oxidising potentials greater than or similar to polyvinylpyrrolidone.

Thus, the method of stabilizing also relates to limiting the content of excipients with an oxidising potential greater than or similar to polyvinylpyrrolidone, including limiting the content of polyvinylpyrrolidone in the compositions/formulations. Thus, interesting embodiments of the invention relate to those wherein the one or more excipient(s) comprises polyvinylpyrrolidone in an amount of at most 2% w/w. Preferably, the amount is at most 1% w/w, more preferably at most 0.5% w/w, most preferably at most 0.2% w/w. In a very preferred embodiment, the method of improving stability relates to excluding polyvinylpyrrolidone from the pharmaceutical composition. Thus, a method of stabilizing an estrogen in a pharmaceutical composition relates to a composition/formulation essentially free of polyvinylpyrrolidone.

A still further object of the invention is to provide a process for preparing compositions and formulations that are stable and homogenous and as described supra. Suitable process conditions comprise the steps of preparing a granulation liquid, individually loading the active agents and the one or more excipient(s) into equipment suitable for granulation, granulating and drying. In a preferred embodiment hereof, the thus obtained granules have a relative humidity of at most 60%.

Thus, the invention relates to a process for manufacturing a granulate preparation comprising a complex between an estrogen and a cyclodextrin, wherein the processing of the granulate preparation comprises the steps of:

i) loading the complex and one or more excipients into a granulator;
ii) applying a liquid onto the loaded complex and the one or more excipients under granulation conditions so as to obtain granules having a relative humidity not exceeding 60%, as determined at a temperature between 20° C. and 40° C.

The process has lead to novel compositions comprising less degraded estrogen and less degradation products in comparison to those compositions manufactured by conventional processes such as those granulation techniques using polyvinylpyrrolidone and/or techniques wherein the relative humidity are not properly adjusted.

Thus, in preferred embodiments according to the invention, the granulation conditions are even more restricted such as the relative humidity of the granulate preparation does not exceed 55%, preferably does not exceed 45%, most preferably does not exceed 40%, as determined at a temperature between 20° C. and 40° C. Furthermore, the amount of polyvinylpyrrolidone is restricted.

As stated, the formulation comprises low doses of the active agents, in particularly of the ethinyl-estradiol-cyclodextrin complex. Consequently, it is critical to achieve homogenous formulations and to meet the requirements of content uniformity. Thus, an important issue to consider,

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when manufacturing compositions/formulations containing low doses of the active ingredient, is the homogeneity of the granulate preparation. Common practice applies to the use of pre-mixes of the active ingredient with an excipient, e.g. lactose when manufacturing low-dosages formulations. The pre-mix is normally made in a separate blending step. However, the present inventors have developed a process for manufacturing low-dosage formulations without using a step of pre-mixing the active agent with a suitable excipient.

Thus, an interesting embodiment of the invention relates to a method as described supra wherein the complex and the optionally further one or more therapeutically active agent (s) are provided as individual agent(s) without being pre-mixed with excipients. In a further embodiment related hereto, one or more therapeutically active agent(s), such as drospirenone, is further added to the granulator.

As stated, the properly adapted process of the invention has lead to the manufacturing of homogenous batches of the granulate preparation. In the event where the process further lead to unit dosage forms, such as a tablet, content uniformity is achieved. Thus, in very suitable embodiments of the invention, batches of final granulate and/or final unit dosage forms comply with the content uniformity so as to be within the range of 85% and 115%, preferably within the range of 90% and 110%, more preferably within 95% and 115%. The content uniformity is determined by taking 10 random samples of the granulate preparation or by randomly taken 10 tablets from a batch of tablets, determining the quantitative content of estrogen in each sample or tablet, and finally calculating the coefficient of variation based on the individual quantities of estrogen.

The low doses referred to in this context relate to compositions/formulations comprising the complex in an amount of from about 0.005% w/w to 20% w/w, preferably from about 0.01% w/w to 2% w/w, more preferably from about 0.05% w/w to 1% w/w, even more preferably from about 0.1% w/w to 0.7% w/w, most preferably from about 0.15% w/w to 0.5% w/w.

The granulation may be provided by any equipment that will provide a stable and homogenous granulate according to the invention. That is to say any equipment suitable for obtaining granules having a relative humidity of at most 60% at temperatures from 20° C. to 40° C. However, in a preferred embodiment, the granulation conditions are provided by fluidised bed granulation.

A further object of the invention is related to the use of compositions described herein and in the Examples in the preparation of a medicament for female contraception, for hormone replacement therapy, or for treating acne or PMDD (pre-menstrual dysfunction disorder).

The use of a compound of the present invention for hormone replacement therapy relates to treating menopausal, pre-menopausal, and/or post-menopausal symptoms in a female. The medicament is suitably formulated according to general knowledge for a person skilled in the pharmaceutical art typically for oral administration.

In a preferred embodiment, the medicament is suitable for inhibiting ovulation in a female. Apart from its ability to inhibit ovulation, the composition of the invention has been found to possess pronounced anti-androgenic properties and may therefore be used in the prevention or treatment of androgen-induced disorders, in particular acne. Such use may be independent from or concomitant with the use as a contraceptive disclosed above. Furthermore, since drospirenone is an aldosterone antagonist, it has diuretic properties and is therefore suitable for counteracting the water-retentive properties of ethinyl estradiol.

As stated, the use of compositions for the preparation of a medicament for oral administration, preferably comprises the use of compositions comprising a complex between ethinyl estradiol and β-cyclodextrin and further comprising a therapeutically active agent. Most preferably, the agent is drospirenone. In a combination of preferred embodiments, the dose of ethinyl estradiol is from 0.015 mg to 0.04 mg, in particular from about 0.015 mg to 0.03 mg, and the dose of drospirenone is from about 2.5 mg to 3.5 mg, in particular about 3 mg for a daily dosage unit. More particularly, the compositions of the invention comprise an amount of drospirenone corresponding to a daily dosage of from about 3.0 to 3.5 mg and ethinyl estradiol in an amount corresponding to from about 0.015 to 0.03 mg.

The medicament for use in inhibiting ovulation may be an one-phase composition, i.e. a preparation wherein the amounts of either active agent remains constant for the entire at least 21-day period, or the amounts of either or both active agents may be varied over the at least 21-day period to generate a multiple-phase preparation, e.g. a two- or three-phase preparation, substantially as disclosed in, e.g., EP 148 724.

In an interesting embodiment of the present invention relating to the use of a medicament for inhibiting ovulation, the medicament is administered on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinyl estradiol in an amount from about 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit containing no active agent, or alternatively, administering no dosage units for 7 days or less.

In a further suitable embodiment, each of the daily dosage units comprising a combination of drospirenone and ethinyl estradiol are to be administered for 21, 22, 23 or 24 consecutive days, and each of the daily dosage units containing no active agent may be administered for 7, 6, 5 or 4 consecutive days, as appropriate. Furthermore, the daily dosage units comprising the combination of drospirenone and ethinyl estradiol may be administered for 28 consecutive days or 30 or 31 consecutive days. Suitably, the use of said medicament comprises administering, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinyl estradiol in an amount from about 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit containing ethinyl estradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

In this alternative method, the daily dosage units comprising the combination of drospirenone and ethinyl estradiol may suitably be administered for 21, 22, 23 or 24 consecutive days, and wherein the daily dosage units comprising ethinyl estradiol alone may then be administered for 7, 6, 5 or 4 consecutive days, as appropriate. In a further embodiment of the method, the daily dosage units comprising the combination of drospirenone and ethinyl estradiol are administered for 2–4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinyl estradiol for 21 consecutive days and subsequently administration of the daily dosage units comprising ethinyl estradiol alone for 7 consecutive days.

The entire disclosures of all applications, patents and publications, cited herein, and of U.S. Provisional Applica-

tion Ser. No. 60/256,484, filed Dec. 20, 2000, and of EP Application No. 00610135.6, filed Dec. 20, 2000, are hereby incorporated by reference.

The present invention is further defined by the Examples.

BRIEF DESCRIPTION OF THE EXAMPLES

Example 1 discloses a pharmaceutical product according to some embodiments of the present invention along with pharmaceutical products known to the person skilled in the art. 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. The data shows that direct compression of the powder blend results in good stability of ethinyl estradiol when provided in the form of a cyclodextrin complex (Product D). The product E was prepared to be polyvinylpyrrolidone-free according to the present invention. This product also shows good stability of the ethinyl estradiol in spite of being manufactured by granulation. However, in the case where the product includes polyvinylpyrrolidone and is manufactured according to Example 3 in U.S. Pat. No. 5,798,338 (Tablet A), the product is poorly stable.

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 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 4.45×10^{-3} s^{-1}.

Example 7 describes the method in which the equilibrium stability constant (formation constant) of the complex between EE and CD was studied. The stability constant of the 1:1 complex was found to be 9.5×10^{-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 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 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 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

The following examples are not a limitation on the invention. All temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

Example 1

Degradation of Ethinyl Estradiol in Various Formulations

Comparative stability data of five tablet formulations comprising ethinyl estradiol has been investigated. The various formulations differ from each other with respect to the manufacturing process, use of ethinyl estradiol in the form of a cyclodextrin complex and use of polyvinylpyrrolidone 25.000 (PVP). Tablet A was prepared as disclosed in U.S. Pat. No. 5,798,338, Example 3, such as by fluid bed granulation based on pre-mixing of active ingredient with lactose and no adjusting of the relative humidity of the granules. Tablets, B, C and E were prepared according to the manufacturing process disclosed herein.

TABLE 1.1

Summary of Parameters of Film-Coated Tablets

Tablet	Manufacturing Process	Active agent	Excipient
A	fluid bed granulation*	EE-β-CD complex	+PVP
B	fluid bed granulation**	EE	+PVP
C	fluid bed granulation**	EE	
D	Direct compression	EE-β-CD complex	
E	fluid bed granulation**	EE-β-CD complex	

*Fluid bed granulation as disclosed in Example 3 of U.S. Pat. No. 5,798,338,

**fluid bed granulation as disclosed in example 5 herein,

PVP = polyvinylpyrrolidone.

TABLE 1.2

Composition of Test Formulations

	Tablets				
Composition:	A	B	C	D	E
EE	—	✓	✓	—	—
EE-β-CD	✓	—	—	✓	✓
DRSP	—	✓	✓	✓	✓
Lactose	✓	✓	✓	✓	✓
maize starch	✓	✓	✓	✓	✓
micro cellulose	—	—	—	✓	—
starch 1500	✓	✓	—	—	—
PVP 25.000	✓	✓	—	—	—
Mg Stearate	✓	✓	✓	✓	✓

Results

The content of ethinyl estradiol was determined by HPLC just after manufacturing (start) and following storage at various conditions for 3 and 12 months. The content of ethinyl estradiol is expressed relatively to the initial content of ethinyl estradiol that was added to each formulation.

TABLE 1.3

Content of ethinyl estradiol (% recovered)

Formulation	start	3 months 40° C., 75% RH	3 months 60° C., 75% RH	12 months 25° C., 60% RH	12 months 40° C., 75% RH
A	93.1	86.3	77.8	93.8	75.9
B	98.9	94.9	70.7	95.6	85.7
C	100.1	95.8	86.1	100.1	92.1
	99.1	96.2	86.1	99.1	92.1
D	101.5	98.8	96.4	101.4	99.9
	102.7	100.7	98.6	101.8	100.0
E	103.2	101.3	96.4	100.5	98.9
	103.3	102.0	96.6	101.8	99.3

Example 2

Formation of Oxidative Degradation Products of Ethinyl Estradiol

The content of known oxidative degradation products of ethinyl estradiol was determined by HPLC following storage for 12 months at 25° C. and 60% relative humidity (RH) for 12 months. The molar content of each degradation products is expressed relatively to the initial molar content of ethinyl estradiol that was added to each formulation. Four formulations as well as the pure ethinyl estradiol and the ethinyl estradiol β-cyclodextrin complex were investigated.

TABLE 2.1

Stability results after 12 months, 25° C., 60% RH
Formation of degradation products (% of initial content of EE)

Formulations	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
B	0.04	0.07	0.32	0.74	1.20
C	0.05	0.09	0.11	0.73	1.00
	0.04	0.07	0.08	0.70	0.91
D	0.01	0.02	n.d	0.49	0.52
	0.01	0.01	n.d	0.45	0.47
E	0.03	0.01	n.d	0.46	0.50
	0.02	0.01	n.d	0.40	0.43

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

Stability results after 12 months, 40° C., 75% RH
Formation of degradation products (% of initial content of EE)

Formulations	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
B	0.16	0.25	1.92	3.14	5.47
C	0.33	0.61	1.03	1.86	3.83
	0.28	0.54	0.87	1.59	3.28
D	0.03	0.09	0.10	0.79	1.01
	0.03	0.10	0.09	0.79	0.98

TABLE 2.2-continued

Stability results after 12 months, 40° C., 75% RH
Formation of degradation products (% of initial content of EE)

Formulations	6-α-OH-EE	6-β-OH-EE	6-Keto-EE	Δ9,11-EE	total known
E	0.08	0.19	0.30	0.93	1.50
	0.08	0.19	0.41	0.89	1.58

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.

Example 3

Typical compositions consisting of a tablet core is described. The tablet core may optionally be film-coated or sugar coated using the described ingredients. The specific ingredients are typical suitable ingredients according to the invention, but are not limited to those.

TABLE 3

Ingredient	Specific ingredients	Amount % w/w
Tablet core:		
Active agent I	estrogens in the form of an complex with a cyclodextrin	
Active agent II	a progestogen	
Filler	lactose, starch, cellulose	0–95%
Binder	starch, cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, maltodextrine	0–15%
Glidant	colloidal silicon dioxide	0–5%
Disintegrant	starch, carmellose-calcium, crosscarmellosesodium, carboxymethylstarch sodium	0–15%
Stabilizer/ antioxidant	tocopherole acetate, Propyl gallate, ascorbic acid, ascorbic palmitate	0–5%
Lubricant	magnesium stearate	0–5%
Film coating:		
Film-binding agent	hydroxypropylmethylcellulose, polyacrylic acid derivatives, Eudragit	20–100%
Plasticizer	polyethylene glycole	0–20%
Filler	talc, titanium dioxide, calcium carbonate	0–20%
Pigment	titanium dioxide, calcium carbonate	0–20%
Colorant	ferric oxide pigments	0–10%
Sugar coating		
Coating agent	sucrose	30–90%
Plasticizer	povidone 700000, polyethylene-glycol 6000	0–10%
Filler/coating agent:	talc, titanium dioxide, calcium carbonate	10–50%
Humidifier	glycerol	0–5%
Pigment	titanium dioxide, calcium carbonate	0–10%
Colorant	ferric oxide pigments	0–10%
Polishing agent	wax	0–0.5%

Example 4

Preferred Compositions

A preferred composition consists of the components listed below. The batch size is 200,000–550,000 tablets (develop-

ment site) and 2.5 Mio tablets up to 5 Mio tablets (production site), respectively. Water is used as a processing aid for the manufacture of the tablet mass (fluid bed granulation) and the film-coating.

Ingredient	One tablet (mg)	Development (kg)	Production (kg)
Drospirenone, micro 15	3.0	1.650	7.500
Ethinyl estradiol-β-cyclodextrine complex, micro	0.020 *	0.011 *	0.050 *
Lactose monohydrate	48.18	26.499	120.450
Corn 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 5

Manufacturing Process

The manufacturing process comprises the following steps:

- Prepare the granulation liquid: Suspend maize starch in purified water and add this suspension to purified water while stirring.
- Prepare the granules: Introduce lactose, drospirenone micro 15, ethinyl estradiol-β-cyclodextrine complex micro and maize starch (portion) into the fluid bed granulator. Activate a continuous fluid bed and apply granulation liquid. Dry. Check relative humidity of the granulate mass. Dry the granulate mass if necessary until the desired range of relative humidity is reached (30%–45%).
- Prepare the tablet mass: Introduce maize starch (portion) and magnesium stearate into the fluid bed granulator. Mix.
- Compress the tablet mass Perform on a rotary tableting machine to tablet cores
- 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.

Example 6

Dissociation of the EE-β-CD Complex

The rate constant of the dissociation constant of EE-β-CD complex in aqueous solution has been determined.

Test method

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

1. $EE + CD \Leftrightarrow EE \cdot CD \qquad K_{11} = \frac{C_{EECD}}{C_{EE} \cdot C_{CD}}$

2. $EE \cdot CD + CD \Leftrightarrow EE \cdot CD_2 \qquad K_{12} = \frac{C_{EECD_2}}{C_{EECD} \cdot C_{CD}}$

In this study, the dissociation rate of the 1:1 complex was determined using a stopped flow relaxation method with conductometric detection. An indirect method was applied based on a competition reaction using sodium-dodecylsulfate (SDS) which forms a 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 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.

Summary of Results

The dissociation rate constant of the Ethinyl estradiol-β-Cyclodextrin 1:1 complex was determined to be: $K^d=4.45 \cdot 10^{-3}\ s^{-1}$

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

Stability Constant of the EE-β-CD Complex in Aqueous Solution

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

Background

The drug substance ethinyl estradiol-β-cyclodextrin 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. $S + L = SL \qquad K_{11} = \frac{C_{SL}}{C_S \cdot C_L}$

2. $SL + L = SL_2 \qquad K_{12} = \frac{C_{SL_2}}{C_{SL} \cdot C_L}$

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:	$K_{11} = 9.5 \cdot 10^4\ M^{-1}$
Solubility of Ethinyl estradiol:	$S_{EE} = 2.17 \cdot 10^{-5}$ mol/l ($6.43 \cdot 10^{-3}$ g/l)
Solubility of the 1:1 complex:	$S_{11} = 1.92 \cdot 10^{-3}$ mol/l (2.75 g/l)
Solubility of the 1:2 complex:	$S_{12} = 1.44 \cdot 10^{-3}$ mol/l (3.7 g/l)

Example 8

Stability Constant of the EE-β-CD Complex in 0.1 M HCl

The Equilibrium Stability Constant (Formation Constant) of the EE-β-CD complex in 0.1 M HCl was Determined as Described in Example 7.

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:	$K_{11} = 1.56 \cdot 10^4\ M^{-1}$
Overall stability constant of the 1:2 complex ($= K_{11} \cdot K_{12}$):	K^*_{12} = approx. $1.6 \cdot 10^4\ M^{-1}$
Solubility of ethinyl estradiol:	$S_{EE} = 1.68 \cdot 10^{-4}$ mol/l (0.05 g/l)
Solubility of the 1:1 complex:	$S_{11} = 2 \cdot 10^{-3}$ mol/l (2.9 g/l)
Solubility of the 1:2 complex:	$S_{12} = 5 \cdot 10^{-4}$ mol/l (1.3 g/l)

Example 9

Dissociation Constant of the EE-β-CD Complex in Aqueous Solution

The Acid Dissociation Constant of the EE-β-CD complex in aqueous media was determined.

Background

The drug substance ethinyl estradiol-β-cyclodextrin 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 complex dissociates into its components according to the law of mass action. To restrain the dissociation of the ethinyl estradiol-β-cyclodextrin 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 complex was determined at 20° C. to be:

$pK_a = 10.51 \pm 0.03$

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

$pK_a = 10.25 \pm 0.04$

Example 10

Log P Value of the EE-β-CD Complex

Background

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

The partition of the ethinyl estradiol-β-cyclodextrin complex is determined upon equilibration in a two-phase system, n-octanol/water. 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]). 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.

Summary of Results

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

Solid State Forms of the Ethinyl Estradiol-β-cyclodextrin Complex

Multiple solid state forms of the ethinyl estradiol-β-cyclodextrin were determined, and test methods that can detect and distinguish between such forms were provided.

Background

A variety of crystallisation products obtained under different crystallisation, 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 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 (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 severe 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 fully water-saturated hydrates, 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	10.6	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 - 1 d	n.d.	—
Im2191f.	P 1, dried in a vacuum drying cabinet - 1 d	n.d.	—
Im2190	P 1, dried in a vacuum drying cabinet - 5 d	10.6	7.5
Im2191	P 1, dried in a vacuum drying cabinet - 5 d	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 × water; dried in a vacuum drying cabinet	11.2	3.34
Im2225/2	P 1; washed 2 × water, 1 × acetone; dried in a vacuum drying cabinet	10.5	3.31

TABLE 12.1b-continued

Batch	solvent/treatment conditions	content of EE [%]	water content [%]
	Crystallization products of the complex		
Im2225/3	P 1; washed 2 × water, 1 × acetone, 1 × water; dried in a vacuum drying cabinet	10.9	3.8
Im2230	P 1; washed 1 × water, 1 × acetone, 1 × water; dried in a vacuum drying cabinet	10.8	4.35
Im2231	P 1; washed 1 × water, 1 × acetone, 1 × water; dried in a vacuum drying cabinet	11	2.63
Im2240	P 1; washed 1 × water, 1 × acetone, 1 × 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, 3 d $Mg(ClO_4)_2$	batch Im2180 stored 3 d over $Mg(ClO_4)_2$	n.d.	n.d.
Im2190, 5 d 97% RH	batch Im2190 stored 5 d at 97% RH	n.d.	~16.7[5]
Im2190, 7 d 97% RH	batch Im2190 stored 7 d at 97% RH	n.d.	~16.5[5]
28052591, 7 d $Mg(ClO_4)_2$	batch 28052591 stored 7 d over $Mg(ClO_4)_2$	n.d.	<0.1[5]
28052591, 7 d 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, 7 d 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

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

The invention claimed is:

1. A method for inhibiting ovulation in a female comprising administering to the female a composition comprising:

i) a complex between an estrogen and a cyclodextrin;

ii) drospirenone; and

iii) one or more excipients,

the composition having a stability such that said estrogen is in amount of at least 85% w/w in relation to the initial content of said estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH).

2. The method of claim **1**, wherein the complex between an estrogen and a cyclodextrin is a granulate preparation having a relative humidity of at most 60%, as determined at a temperature between 20° C. and 40° C.

3. The method of claim **1**, wherein the estrogen is in an amount corresponding to a therapeutically equivalent amount of ethinyl estradiol of from about 0.002% w/w to 2% w/w, based on the total composition.

4. The method of claim **1**, wherein the estrogen is in an amount from about 0.002% w/w to 2% w/w, based on the total composition.

5. The method of claim **1**, wherein the estrogen is in an amount from about 0.004% w/w to 0.2% w/w, based on the total composition.

6. The method of claim **1**, wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, and the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 5% w/w to 20% w/w.

7. The method of claim **1**, wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, and the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 8% w/w to 15% w/w.

8. The method of claim **1**, wherein the amount of drospirenone is from about 0.4% to 20% w/w.

9. The method of claim **1**, wherein the amount of drospirenone is from about 0.8% w/w to 10% w/w, based on the total composition.

10. The method of claim **1**, wherein the amount of drospirenone is from about 1.5% w/w to 5% w/w, based on the total composition.

11. The method of claim **1**, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 2% w/w.

12. The method according to claim **1**, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 1% w/w.

13. The method according to claim **1**, wherein the one or more excipients comprises polyvinylpyrrolidone in ah amount of at most 0.5% w/w.

14. The method according to claim **1**, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 0.2% w/w.

15. The method according to claim **1**, wherein the composition is essentially free of polyvinylpyrrolidone.

16. The method according to claim **1**, wherein the composition comprises one or more excipient(s) which is/are selected from the group consisting of starch, cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and maltodextrin.

17. The method according to claim **1**, wherein the estrogen in the composition is selected from the group consisting of ethinyl estradiol, estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, estrone sulfate and mixtures thereof.

18. The method according to claim **1**, wherein the estrogen is ethinyl estradiol.

19. The method according to claim **1**, wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin and alkylated or acylated derivatives thereof.

20. The method according to claim **1**, wherein the cyclodextrin is β-cyclodextrin or an alkylated or acylated derivative thereof.

21. The method according to claim **1**, wherein the estrogen is in an amount relative to the cyclodextrin such that a molar ratio between the estrogen and the cyclodextrin is from about 2:1 to 1:10.

22. The method according to claim 1, wherein the drospirenone is in micronized form.

23. The method according to claim 1, wherein the complex between an estrogen and a cyclodextrin is micronized.

24. The method according to claim 1, wherein the composition further comprises an antioxidant.

25. The method according to claim 1, wherein the granulated preparation has a mean particle size of at least about 100 μm.

26. The method of claim 1, wherein the composition has a stability such that said estrogen is in an amount of at least 90% w/w in relation to the initial content of said estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH).

27. A method for hormone replacement therapy in a female comprising administering to the female a composition comprising:

i) a complex between an estrogen and a cyclodextrin;

ii) drospirenone; and

iii) one or more excipients,

the composition having a stability such that said estrogen is in amount of at least 85% w/w in relation to the initial content of said estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH).

28. The method of claim 27, wherein the complex between an estrogen and a cyclodextrin is a granulate preparation having a relative humidity of at most 60%, as determined at a temperature between 20° C. and 40° C.

29. The method of claim 27, wherein the estrogen is in an amount corresponding to a therapeutically equivalent amount of ethinyl estradiol of from about 0.002% w/w to 2% w/w, based on the total composition.

30. The method of claim 27, wherein the estrogen is in an amount from about 0.002% w/w to 2% w/w, based on the total composition.

31. The method of claim 27, wherein the estrogen is in an amount from about 0.004% w/w to 0.2% w/w, based on the total composition.

32. The method of claim 27, wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, and the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 5% w/w to 20% w/w.

33. The method of claim 27, wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, and the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 8% w/w to 15% w/w.

34. The method of claim 27, wherein the amount of drospirenone is from about 0.4% to 20% w/w.

35. The method of claim 27, wherein the amount of drospirenone is from about 0.8% w/w to 10% w/w, based on the total composition.

36. The method of claim 27, wherein the amount of drospirenone is from about 1.5% w/w to 5% w/w, based on the total composition.

37. The method of claim 27, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 2% w/w.

38. The method according to claim 27, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 1% w/w.

39. The method according to claim 27, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 0.5% w/w.

40. The method according to claim 27, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 0.2% w/w.

41. The method according to claim 27, wherein the composition is essentially free of polyvinylpyrrolidone.

42. The method according to claim 27, wherein the composition comprises one or more excipient(s) which is/are selected from the group consisting of starch, cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and maltodextrin.

43. The method according to claim 27, wherein the estrogen in the composition is selected from the group consisting of ethinyl estradiol, estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, estrone sulfate and mixtures thereof.

44. The method according to claim 27, wherein the estrogen is ethinyl estradiol.

45. The method according to claim 27, wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin and alkylated or acylated derivatives thereof.

46. The method according to claim 27, wherein the cyclodextrin is β-cyclodextrin or an alkylated or acylated derivative thereof.

47. The method according to claim 27, wherein the estrogen is in an amount relative to the cyclodextrin such that a molar ratio between the estrogen and the cyclodextrin is from about 2:1 to 1:10.

48. The method according to claim 27, wherein the drospirenone is in micronized form.

49. The method according to claim 27, wherein the complex between an estrogen and a cyclodextrin is micronized.

50. The method according to claim 27, wherein the composition further comprises an antioxidant.

51. The method according to claim 27, wherein the granulated preparation has a mean particle size of at least about 100 μm.

52. The method of claim 27, wherein the composition has a stability such that said estrogen is in an amount of at least 90% w/w in relation to the initial content of said estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH).

* * * * *

Anexo No 2

US006958326B2

(12) **United States Patent**
Backensfeld et al.

(10) **Patent No.: US 6,958,326 B2**
(45) **Date of Patent: Oct. 25, 2005**

(54) **CYCLODEXTRIN-DROSPIRENONE INCLUSION COMPLEXES**

(75) Inventors: **Thomas Backensfeld**, Berlin (DE); **Wolfgang Heil**, Berlin (DE); **Ralph Lipp**, Berlin (DE)

(73) Assignee: **Schering AG**, Berlin (DE)

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(58) **Field of Search** 514/23, 25, 54, 514/58, 60; 536/103, 124, 123.1

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Primary Examiner—James O. Wilson
Assistant Examiner—Patrick T. Lewis
(74) *Attorney, Agent, or Firm*—Millen, White, Zelano, Branigan, P.C.

(57) **ABSTRACT**

Pharmaceutical compositions comprising low doses of sensitive complexes between an estrogen and a cyclodextrin are provided with improved stability. In specific embodiments the composition comprises a complex between ethinyl estradiol and β-cyclodextrin in a granulate preparation and in yet another embodiment the composition comprises a limited amount of polyvinylpyrrolidone since this excipient was found to degrade ethinyl estradiol. Furthermore, a method for improving the stability of an estrogen in a composition and for manufacturing such a stable composition is provided. Essentially, the granulate preparation are manufactured under careful control of the relative humidity.

32 Claims, No Drawings

CYCLODEXTRIN-DROSPIRENONE INCLUSION COMPLEXES

This application claims priority to U.S. Provisional Application No. 60/256,484, filed Dec. 20, 2000.

FIELD OF INVENTION

The present invention relates to pharmaceutical compositions and formulations comprising a cyclodextrin-estrogen complex that confers very high chemical stability to the estrogen. The invention allows for an improved physical stability of cyclodextrin-estrogen complexes and of the chemical stability of estrogens such ethinyl estradiol upon storage.

BACKGROUND OF THE INVENTION

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

Pharmaceutical products 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, it is problematic to manufacture unit dosage formulations with reliably consistent amounts of active agent which do not fluctuate within one batch or between batches. Thus, the requirements of content uniformity as set forth by health authorities may not be met.

Moreover, degradation of these small amounts of active ingredient is a further contributor to the fluctuations of the active ingredient in low dosage formulations.

In general, these low dose formulations comprising unstable active agents are problematic in terms of their preparation, storage and use, and there is a need for providing means for stabilization of such formulations.

Complexation of estrogens with cyclodextrins is widely used for improving stability, solubility or bioavailability. For example, EP 0 349 091 discloses compositions containing complexes between 17-β-estradiol and dimethyl-β-cyclodextrin for improving nasal administration, Fridriksdottir et al (*Die Pharmazie*, vol. 51, 1996, pages 39–42) describes complexes between cyclodextrin and 17-β-estradiol for improving the solubility in aqueous solution so as to improve sublinqual application. Improved solubility is also the focus of U.S. Pat. No. 4,596,795, which relates to a complex between α-, β- and γ-cyclodextrins and derivatives thereof with testosterone, progesterone, and estradiol. U.S. Pat. No. 4,383,992 discloses a water soluble inclusion compound formed by complexing a steroid compound, such as an estrogen with beta-cyclodextrin.

Moreover, U.S. Pat. No. 5,798,338 discloses that the oxidative degradation of 17-α-ethinyl estradiol is reduced upon forming clathrates (complexes) between β-cyclodextrin and 17-α-ethinyl estradiol.

However, although complexation of estrogens with cyclodextrins may solve critical issues with regards to solubility, bioavailability and stability, there are still further problems to solve before complexes between active agents, such as estrogens, and cyclodextrins are suitable for use in pharmaceutical products. Namely, the complexes are prone to dissociation into the free estrogen and the cyclodextrin, particularly upon contact with water. The lack of physical stability of cyclodextrin-estrogen complexes results in significant amounts of free estrogen present in compositions due to, for instance, exposure to aqueous media during the manufacturing process, particularly during granulation. As a consequence, the lifetime of the composition may be decreased due to degradation of free estrogen.

Moreover, the intended improved bioavailability sought by complexing estrogen with cyclodextrin is not achieved due to the lack of physical stability of the cyclodextrin-estrogen complex and the chemical instability of the free estrogen.

Various attempts have been made in order to stabilize compositions comprising complexes between a cyclodextrin and an estrogen. For example, the composition may be stabilized by stabilizing the complex itself. Thus, U.S. Pat. No. 4,727,064 attempts the stabilization of complexes upon using amorphous forms of the complex. Alternatively, complexes may be stabilized and their solubility increased upon adding polymers to the reaction medium upon complexation, as disclosed by Loftsson et al. (*Int. J. Pharmaceutics*, Vol. 110, 1994, pp169–177). EP 0579435 also discloses complexes between estradiol and cyclodextrins wherein the addition of polymers to the reaction medium increases the stability constant of the complex.

The compositions may also be stabilized upon avoiding a granulation step in the manufacturing process of the composition, as disclosed in WO 00/21570.

There is a need in the art for processes for preparing physically stable complexes of cyclodextrin and estrogen and for compositions, which improve the stability of both the complex and the free estrogen. There is furthermore a need in the art for granulate formulations which allow for physically stable cyclodextrin-estrogen complexes.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a stable and homogenous pharmaceutical product comprising an estrogen, wherein the stability of the estrogen is significantly improved over that of conventional products, which have complexed estrogens or sensitive complexes between a cyclodextrin and an estrogen. Degradation of estrogens, such as ethinyl estradiol, in conventional products, is one of the most critical issues with regard to product shelf life.

It has surprisingly been found that products with improved stability of the estrogen are achieved by means of complexing estrogen with cyclodextrins, the judicious selection of excipients and/or proper adaptation of the manufacturing process. Consequently, the shelf-life of an estrogen-containing product is improved.

Thus, an important aspect of the invention relates to formulations and compositions comprising complexes between an estrogen and a cyclodextrin that are stable in spite of being manufactured by granulation. That is to say that the invention relates in a first aspect to a formulation comprising a complex between an estrogen and a cyclodextrin, wherein the formulation is a granulate preparation, said granulation preparation having a relative humidity of at most 60%, as determined at a temperature between 20° C. and 40° C.

In a further aspect, the invention relates to compositions comprising i) a complex between an estrogen and a cyclodextrin; and ii) one or more excipient(s), the composition having a stability such that said estrogen is in amount of at least 85% w/w in relation to the initial content of the estrogen after storage for 12 months at 40° C. and 75%

relative humidity (RH). In a suitable embodiment thereof, the composition comprises a granulate preparation comprising said complex. In a further suitable embodiment, the composition is compressed directly into a tablet or equivalent unit dosage forms. Upon further study of the specification and appended claims, further aspects and advantages of this invention will become apparent to those skilled in the art.

Thus, contrarily to previous findings, it is possible to obtain stable compositions comprising an estrogen-cyclodextrin-complex in a granulate preparation.

Compositions of the present invention may be used as medicaments. Accordingly, the use of a composition described infra for the preparation of a medicament for female contraception, for hormone replacement therapy, or for treating acne or PMDD (pre-menstrual dysfunction disorders), is a further aspect of the present invention.

In a broad sense, the present invention relates to a method of improving the stability of an estrogen in a pharmaceutical composition that comprises an estrogen-cyclodextrin complex and one or more excipients in a granulate preparation, the method comprises the steps of:

i) forming a complex between said estrogen and a cyclodextrin; and

ii) mixing under granulation conditions the said complex with the one or more excipients such that the relative humidity of the final granulate does not exceed 60%, as determined at a temperature between 20° C. and 40° C.

Finally, the invention relates to a process for manufacturing a composition comprising a granulate preparation of a complex between an estrogen and a cyclodextrin, wherein the processing of the granulate preparation comprises the steps of

i) loading the complex, one or more excipients and optionally one or more therapeutically active agent(s) into a granulator;

ii) applying a liquid onto the loaded complex and the one or more excipients under granulation conditions so as to obtain granules having a relative humidity not exceeding 60%, as determined at a temperature between 20° C. and 40° C.

DETAILED DESCRIPTION OF THE INVENTION

The term "complex" is intended to mean a complex between an estrogen and a cyclodextrin, wherein a molecule of said estrogen is at least partially inserted into the cavity of one cyclodextrin molecule. Furthermore, the molecule of an estrogen may at least partially be inserted into the cavity of more cyclodextrin molecules, and two moieties of a single estrogen molecule may each be inserted into one cyclodextrin molecule to give 2:1 ratio between cyclodextrin and estrogen. Thus, the complex may be termed as an inclusion complex (clathrate) between an estrogen and a cyclodextrin. Similarly, the complex may comprise 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 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 complex" or "EE-β-CD" is intended to mean a complex, of any ratio, between ethinyl estradiol and β-cyclodextrin.

The term "granulate preparation" relates to a preparation of a powder, wherein the particle size of the powder is either increased upon processing with a liquid or by compression. The liquid may be of any kind of aqueous or organic solvents, or mixtures thereof, optionally further comprising a binder such as a starch. Thus, a "granulate preparation" relates in a broad sense to granules, pellets and compressed powder or any particle formed by granulation, pelletation or compression of powder such that a mean particle size of at least about 100 μm are formed.

The term "cyclodextrin" is intended to mean a cyclodextrin or a derivative thereof as well as mixtures of various cyclodextrins, mixtures of various derivatives of cyclodextrins and mixtures of various cyclodextrins and their derivatives. The cyclodextrin is further defined according to the invention.

The present inventors have developed products, wherein a remarkable improvement of the stability of an estrogen has been achieved by combined means. One such means is by the protection of the estrogen by forming a cyclodextrin complex. Another such means is by the judicious adaptation of the granulation process such that e.g. the dissociation of the complex into free estrogen and cyclodextrin is restricted during the manufacturing of the granulate preparation. The present inventors have provided data indicating that a complex between ethinyl estradiol and β-cyclodextrin is poorly stable when exposed to water. Actually, in the event where the complex is dissolved in water, about 50% of the complex are dissociated into free ethinyl estradiol and cyclodextrin within 3 minutes (see Example 6 herein). Thus, without being limited to a particular theory, the stability of the products is, at least in part, improved by limiting the dissociation of the complex into free estrogen during the manufacturing process, thereby limiting the content of free estrogen in the final product.

Therefore, in a first aspect the invention relates to a formulation comprising a complex between an estrogen and a cyclodextrin, wherein the formulation is a granulate preparation, said granulation preparation having a relative humidity of at most 60%, as determined at a temperature between 20° C. and 40° C. Preferably, the relative humidity is at most 55%, preferably of at most 45%, most preferably of at most 40%, as determined at a temperature between 20° C. and 40° C.

As stated, the present invention has lead to stable products comprising sensitive complexes between an estrogen and a cyclodextrin. Thus, in a second aspect, the invention relates to a composition comprising:

i) a complex between an estrogen and a cyclodextrin; and

ii) one or more excipient(s), the composition having a stability such that said estrogen is in an amount of at least 85% w/w in relation to the initial content of the estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH). The initial content of estrogen should be understood as the weighed quantity of estrogen included in the composition upon manufacturing the final formulation.

In one embodiment hereof, the composition is in a form of a tablet manufactured by direct compression of the composition. Preferably the composition comprises a restricted amount of polyvinylpyrrolidone as disclosed further herein.

In yet another embodiment, the complex between an estrogen and a cyclodextrin is formulated into the granulate preparation as defined herein.

In preferred embodiments, the composition has a stability such that said estrogen is in an amount of at least 90% w/w, more preferably of at least 95% w/w, most preferably of at least 97% w/w such as of at least 98% in relation to the initial content of the estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH).

One further means for improving the stability of an estrogen in such formulations and compositions comprises the judicious selection of excipients such that the content of excipients capable of inducing degradation of ethinyl estradiol are minimised or excluded from the formulations. One such critical excipient is polyvinylpyrrolidone, which is typically used as a binding agent for fluid bed granulation. As disclosed herein, the ethinyl estradiol is sensitive to polyvinylpyrrolidone and significant quantities of ethinyl estradiol is degraded in formulations and compositions, nonetheless the ethinyl estradiol is protected in the form of a clathrate. For example, compositions comprising polyvinylpyrrolidone and prepared as disclosed in Example 3 of U.S. Pat. No. 5,798,338, by fluid bed granulation have a poor stability with respect to ethinyl estradiol. The present inventors has found that in such a composition the content of ethinyl estradiol is decreased by 25% in relation to the initial content of the ethinyl estradiol after storage for 12 months at 40° C. and 75% relative humidity (See table 1.4, Example 1, Table A). Therefore, one aspect of the invention relates to compositions/formulations low in the content of compounds with relatively high oxidising potential such as an oxidising potential greater than or similar to polyvinylpyrrolidone. For example, the compositions/formulations of the present invention preferably have less polyvinylpyrrolidone than the compositions of Example 3 of U.S. Pat. No. 5,798,338. More preferably, suitable embodiments of the invention relate to compositions/formulations comprising at most 2% w/w of polyvinylpyrrolidone, preferably at most 1% w/w, more preferably at most 0.5% w/w, most preferably at most 0.2% w/w of polyvinylpyrrolidone. Moreover, particular interesting embodiments relate to compositions/formulations essentially free of polyvinylpyrrolidone.

Individually, or acting in concert, the above mentioned means have resulted in compositions, wherein the estrogen is more stable than in conventional compositions comprising polyvinylpyrrolidone that are manufactured by direct compression or by an improper fluid bed granulation process. The thus provided stable compositions is characterised by having a content of said estrogen of at least 90% w/w in relation to the initial content of said estrogen after storage for 3 months at 40° C. and 75% relative humidity (RH). Preferably, the content of said estrogen is least 92% w/w, more preferably at least 94% w/w, even more preferably at least 96% w/w and most preferably at least 98% w/w in relation to the initial content of estrogen after storage for 3 months at 40° C. and 75% relative humidity (RH).

Likewise, the compositions are also stable at higher temperatures, e.g. at 60° C. and 75% relative humidity, wherein the stability is such that a content of estrogen, as determined after 3 months storage at 60° C. and 75% relative humidity (RH), is 85% w/w in relation to the initial content of said estrogen, preferably at least 90% w/w, more preferably at least 92% w/w, even more preferably at least 94% w/w, most preferably at least 96% w/w in relation to the initial content of said estrogen.

Importantly, the compositions according to the invention are more stable at ambient conditions in comparison to conventional compositions. Thus, the compositions as disclosed herein have improved stability upon storage for 12 months at 25° C. and 60% relative humidity (RH), such that said estrogen is in an amount of at least 95% w/w in relation to the initial content of said estrogen. Preferably, the content of estrogen is at least 96% w/w, more preferably at least 97% w/w, most preferably at least 98% w/w in relation to the initial content of estrogen after storage for 12 months at 25° C. and 60% relative humidity (RH).

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 and 17β-dihydroequilenin sulfate or mixtures thereof. Particular interesting estrogens are selected from the group consisting of ethinyl estradiol (EE), estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof, notably ethinyl estradiol (EE), 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, unstable compositions, e.g. those comprising a sensitive complex between an ethinyl estradiol and a cyclodextrin that are manufactured by said conventional granulation methods, comprises degradation products of ethinyl estradiol, in particular following storage for a period of time. Moreover, since more ethinyl estradiol is degraded in said conventional compositions than in those developed by the present inventors (see Example 2, table 1.3), the conventional compositions may comprise higher quantities of these degradation products.

Accordingly, the stability according to one embodiment of the present invention is such that a molar sum product of known degradation products of ethinyl estradiol is at most 0.8% in relation to the initial content of ethinyl estradiol. Thus, wherein the estrogen is ethinyl estradiol, the molar sum product of 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol, Δ6,7-ethinyl estradiol and Δ-9,11-ethinyl estradiol totals at the most 0.8% in relation to the initial molar content of ethinyl estradiol as determined after storage for 12 months at 25° C. and 60% relative humidity (RH). Preferably, the molar sum product totals at the most 0.7% and more preferably at the most 0.6% at these storage conditions.

Furthermore, the stability is such that a molar sum product 6-α-hydroxy-ethinyl estradiol, 6-β-hydroxy-ethinyl estradiol, 6-keto-ethinyl estradiol, Δ6,7-ethinyl estradiol and Δ-9,11-ethinyl estradiol, totals at the most 3% in relation to the initial molar content of ethinyl estradiol as determined after storage for 12 months at 40° C. and 75% relative humidity (RH). Preferably, the molar sum product totals at most 2% and more preferably at the most 0.6% at those storage conditions.

As stated, an object of the present invention is to provide a pharmaceutical composition/pharmaceutical formulation comprising a complex between an estrogen and cyclodextrin, wherein the stability of said estrogen is significantly improved over that of conventional compositions/formulations. Thus, for further improving the stability or ensuring the stability of embodiments according to the invention, the composition/formulations further comprises an antioxidant. The antioxidant may either be included in the granulate preparation or added to the composition as a further excipient.

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.

The estrogen-cyclodextrin complex may be obtained by methods known to the person skilled in the art (e.g. U.S. Pat. No. 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.

Preferably, the complex between a cyclodextrin and an estrogen may have a given lipophilicity (hydrophobicity). Thus, suitable embodiments according to the invention relates to those, wherein the complex has a n-octanol/water partition coefficient of the complex at pH 7 ranging from about 2 to 5, preferably from about 3 to 4. Further interesting embodiments comprises the complex in crystalline form. Thus, in a limited aspect, the invention relates to crystalline complexes between an estrogen and a cyclodextrin. The term "crystalline" relates to various modifications of the physical structure of a compound, wherein a part of the compound can be in amorphous form. Crystalline compounds may be characterised by being hydrated and containment of crystal water. Finally, the complexes may be defined by the examples provided herein such as those hydrated complexes disclosed in Example 12. Moreover, the crystalline complex may contain parts of free ethinyl estradiol and free cyclodextrin.

Preferably, the complex comprises of β-cyclodextrin or a derivative thereof, most preferably β-cyclodextrin. Thus, in a particularly preferred embodiment of the invention, which is a combination of preferred embodiments, the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin.

In an alternative embodiment of the invention, the composition further comprises one or more therapeutically active agent. Thus, in this embodiment, the composition further comprises a progestogen. The progestogen may be selected from the group consisting of drospirenone, levonorgestrel, norgestrel, gestodene, dienogest, cyproterone acetate, norethisterone, norethisterone acetate, desorgestrel, 3-keto-desorgestrel. However, the preferred progestogen is drospirenone.

In the preferred embodiment wherein the therapeutically active substance is drospirenone, said drospirenone may optionally be micronized. In the preferred embodiment where the therapeutically active substance is drospirenone, all or substantially all of said drospirenone may be present as a complex with cyclodextrin. As the person skilled in the art will appreciate, the dissociation 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.

Thus, a preferred embodiment of the invention relates to a composition/formulation wherein the estrogen is ethinyl estradiol and the one or more therapeutically active agent(s) is drospirenone. A further interesting embodiment in connection hereto is where both the estrogen-cyclodextrin complex and the drospirenone are micronized.

As stated, the compositions and formulations comprises low doses of active agent, such that typical embodiments according to the invention comprises estrogen in an amount corresponding to a therapeutically equivalent amount of ethinyl estradiol of from about 0.002% w/w to 2% w/w.

In yet other typical embodiments, the composition/formulations comprises the estrogen, ethinyl estradiol, in an amount from about 0.002% w/w to 2% w/w. Preferably, the amount is from about 0.004% w/w to 0.2% w/w, more preferably from about 0.008% w/w to 0.1% w/w, most preferably from about 0.02% w/w to 0.05% w/w.

When taking the amount of the cyclodextrin into account such as in preferred embodiments wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 5% w/w to 20% w/w, preferably from about 8% w/w to 15% w/w, most preferably from about 9% w/w to 13% w/w.

Furthermore, according to the invention, the ratio between the estrogen and the cyclodextrin may be adjusted. Therefore, in suitable embodiments, the estrogen is in an amount relative to the cyclodextrin such that a molar ratio between the estrogen and the cyclodextrin is from about 2:1 to 1:10, preferably from about 1:1 to 1:5, most preferably from about 1:1 to 1:3, such as 1:1 and 1:2.

In embodiments wherein the composition further comprises a therapeutically active compound and that said compound is drospirenone, the drospirenone is in an amount from about 0.4% to 20% w/w, preferably from about 0.8% w/w to 10% w/w, more preferably from about 1.5% w/w to 5% w/w.

A further object of the invention is to provide a composition or a formulation as described herein further formulated as a unit dosage form, preferably such as a tablet, capsule or sachets.

A typical embodiment of the invention relates to a composition or a formulation in form of granules, pellets or dry compressed blends that may be filled into hard gelatine capsules or sachets, or compressed into tablet cores. In that event, the composition or formulation comprises (% wt/wt):

i) Active agent: complex between ethinyl estradiol and β-cyclodextrins;

ii) 0–95% w/w of filling agents such as lactose, starch, cellulose and/or others;

iii) 0–15% w/w of binding agents such as starch, cellulose, hydroxypropylcellulose hydroxypropylmethylcellulose, maltodextrine and/or others;

iv) 0–5% w/w of glidants such as colloidal silicon dioxide and/or others;

v) 0–15% w/w of disintegrating agents such as starch, carmellose-calcium, crosscarmellose-sodium, carboxymethylstarch sodium and/or others;

vi) 0–5% w/w of stabilizers/antioxidants such as tocopherole acetate, propyl gallate, ascorbic acid, ascorbic palmitate and/or others; and

vii) 0–5% w/w of lubricants such as magnesium stearate and/or others.

In the embodiment wherein the composition/formulation further comprises a therapeutically active compound, such as a progestogen, preferably drospirenone, a typical formulation may further comprise 0.1–15% w/w of drospirenone.

A particular interesting embodiment relates to a unit dosage form comprising:

Drospirenone (micronized)	3.00 mg
Ethinyl estradiol as β-cyclodextrin clathrate (micronized)	0.02 mg*
Lactose	48.18 mg**
Corn starch	28.00 mg
Magnesium stearate	0.8 mg
Water	(processing aid)

*0.02 is the concentration of ethinyl estradiol (not taken β-cyclodextrin into consideration). The amount of ethinyl estradiol in the β-cyclodextrin clathrate is 9.5 to 12.5%.

**the amount of lactose is to be adjusted to the amount of β-cyclodextrin.

A further aspect of the invention relates to a method for improving the stability of an estrogen in a pharmaceutical composition that comprises an estrogen and one or more excipients in a granulate preparation, the method comprises the steps of:

i) forming an complex between said estrogen and a cyclodextrin; and

ii) mixing under granulation conditions the said complex with the one or more excipients such that the relative humidity of the final granulate does not exceed 60%, as determined at a temperature between 20° C. and 40° C.

As described herein, this method of stabilizing results in compositions that are more stable than reported for conventional compositions. The important features leading to the improved stability relates, at least in part, to the granulation process and to the proper choice of excipients. Thus, the method of improving the stability relates to the proper adjusting of the relative humidity of the granulate preparation. Most importantly, the relative humidity may not exceed 60% relative humidity, as determined at a temperature between 20° C. and 40° C. Preferably, the relative humidity does not exceed 55%, more preferably does not exceed 45%, most preferably does not exceed 40%, as determined at a temperature between 20° C. and 40° C.

In a further related aspect hereof, the invention relates to a method for improving the stability of an estrogen in a pharmaceutical composition that comprises an estrogen and one or more excipients, the method comprises the steps of:

i) forming an complex between said estrogen and a cyclodextrin; and

ii) adding excipients in an amount so as to minimise the overall amount of excipients which have an oxidising potential greater than or similar to polyvinylpyrrolidone. The aim is to restrict or minimise the amount of excipients, which have oxidising potentials greater than or similar to polyvinylpyrrolidone.

Thus, the method of stabilizing also relates to limiting the content of excipients with an oxidising potential greater than or similar to polyvinylpyrrolidone, including limiting the content of polyvinylpyrrolidone in the compositions/formulations. Thus, interesting embodiments of the invention relate to those wherein the one or more excipient(s) comprises polyvinylpyrrolidone in an amount of at most 2% w/w. Preferably, the amount is at most 1% w/w, more preferably at most 0.5% w/w, most preferably at most 0.2% w/w. In a very preferred embodiment, the method of improving stability relates to excluding polyvinylpyrrolidone from the pharmaceutical composition. Thus, a method of stabilizing an estrogen in a pharmaceutical composition relates to a composition/formulation essentially free of polyvinylpyrrolidone.

A still further object of the invention is to provide a process for preparing compositions and formulations that are stable and homogenous and as described supra. Suitable process conditions comprise the steps of preparing a granulation liquid, individually loading the active agents and the one or more excipient(s) into equipment suitable for granulation, granulating and drying. In a preferred embodiment hereof, the thus obtained granules have a relative humidity of at most 60%.

Thus, the invention relates to a process for manufacturing a granulate preparation comprising a complex between an estrogen and a cyclodextrin, wherein the processing of the granulate preparation comprises the steps of:

i) loading the complex and one or more excipients into a granulator;

ii) applying a liquid onto the loaded complex and the one or more excipients under granulation conditions so as to obtain granules having a relative humidity not exceeding 60%, as determined at a temperature between 20° C. and 40° C.

The process has lead to novel compositions comprising less degraded estrogen and less degradation products in comparison to those compositions manufactured by conventional processes such as those granulation techniques using polyvinylpyrrolidone and/or techniques wherein the relative humidity are not properly adjusted.

Thus, in preferred embodiments according to the invention, the granulation conditions are even more restricted such as the relative humidity of the granulate preparation does not exceed 55%, preferably does not exceed 45%, most preferably does not exceed 40%, as determined at a temperature between 20° C. and 40° C. Furthermore, the amount of polyvinylpyrrolidone is restricted.

As stated, the formulation comprises low doses of the active agents, in particularly of the ethinyl-estradiol-cyclodextrin complex. Consequently, it is critical to achieve homogenous formulations and to meet the requirements of content uniformity. Thus, an important issue to consider, when manufacturing compositions/formulations containing low doses of the active ingredient, is the homogeneity of the granulate preparation. Common practice applies to the use of pre-mixes of the active ingredient with an excipient, e.g. lactose when manufacturing low-dosages formulations. The pre-mix is normally made in a separate blending step. However, the present inventors have developed a process for manufacturing low-dosage formulations without using a step of pre-mixing the active agent with a suitable excipient.

Thus, an interesting embodiment of the invention relates to a method as described supra wherein the complex and the optionally further one or more therapeutically active agent (s) are provided as individual agent(s) without being premixed with excipients. In a further embodiment related hereto, one or more therapeutically active agent(s), such as drospirenone, is further added to the granulator.

As stated, the properly adapted process of the invention has lead to the manufacturing of homogenous batches of the granulate preparation. In the event where the process further lead to unit dosage forms, such as a tablet, content uniformity is achieved. Thus, in very suitable embodiments of the invention, batches of final granulate and/or final unit dosage forms comply with the content uniformity so as to be within the range of 85% and 115%, preferably within the range of 90% and 110%, more preferably within 95% and 105%. The content uniformity is determined by taking 10 random samples of the granulate preparation or by randomly taken 10 tablets from a batch of tablets, determining the quantitative content of estrogen in each sample or tablet, and finally calculating the coefficient of variation based on the individual quantities of estrogen.

The low doses referred to in this context relate to compositions/formulations comprising the complex in an amount of from about 0.005% w/w to 20% w/w, preferably from about 0.01% w/w to 2% w/w, more preferably from about 0.05% w/w to 1% w/w, even more preferably from about 0.1% w/w to 0.7% w/w, most preferably from about 0.15% w/w to 0.5% w/w.

The granulation may be provided by any equipment that will provide a stable and homogenous granulate according to the invention. That is to say any equipment suitable for obtaining granules having a relative humidity of at most 60% at temperatures from 20° C. to 40° C. However, in a preferred embodiment, the granulation conditions are provided by fluidised bed granulation.

A further object of the invention is related to the use of compositions described herein and in the Examples in the preparation of a medicament for female contraception, for hormone replacement therapy, or for treating acne or PMDD (pre-menstrual dysfunction disorder).

The use of a compound of the present invention for hormone replacement therapy relates to treating menopausal, pre-menopausal, and/or post-menopausal symptoms in a female. The medicament is suitably formulated according to general knowledge for a person skilled in the pharmaceutical art typically for oral administration.

In a preferred embodiment, the medicament is suitable for inhibiting ovulation in a female. Apart from its ability to inhibit ovulation, the composition of the invention has been found to possess pronounced anti-androgenic properties and may therefore be used in the prevention or treatment of androgen-induced disorders, in particular acne. Such use may be independent from or concomitant with the use as a contraceptive disclosed above. Furthermore, since drospirenone is an aldosterone antagonist, it has diuretic properties and is therefore suitable for counteracting the water-retentive properties of ethinyl estradiol.

As stated, the use of compositions for the preparation of a medicament for oral administration, preferably comprises the use of compositions comprising a complex between ethinyl estradiol and β-cyclodextrin and further comprising a therapeutically active agent. Most preferably, the agent is drospirenone. In a combination of preferred embodiments, the dose of ethinyl estradiol is from 0.015 mg to 0.04 mg, in particular from about 0.015 mg to 0.03 mg, and the dose of drospirenone is from about 2.5 mg to 3.5 mg, in particular about 3 mg for a daily dosage unit. More particularly, the compositions of the invention comprise an amount of drospirenone corresponding to a daily dosage of from about 3.0 to 3.5 mg and ethinyl estradiol in an amount corresponding to from about 0.015 to 0.03 mg.

The medicament for use in inhibiting ovulation may be an one-phase composition, i.e. a preparation wherein the amounts of either active agent remains constant for the entire at least 21-day period, or the amounts of either or both active agents may be varied over the at least 21-day period to generate a multiple-phase preparation, e.g. a two- or three-phase preparation, substantially as disclosed in, e.g., EP 148 724.

In an interesting embodiment of the present invention relating to the use of a medicament for inhibiting ovulation, the medicament is administered on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinyl estradiol in an amount from about 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit containing no active agent, or alternatively, administering no dosage units for 7 days or less.

In a further suitable embodiment, each of the daily dosage units comprising a combination of drospirenone and ethinyl estradiol are to be administered for 21, 22, 23 or 24 consecutive days, and each of the daily dosage units containing no active agent may be administered for 7, 6, 5 or 4 consecutive days, as appropriate. Furthermore, the daily dosage units comprising the combination of drospirenone and ethinyl estradiol may be administered for 28 consecutive days or 30 or 31 consecutive days. Suitably, the use of said medicament comprises administering, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinyl estradiol in an amount from about 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit containing ethinyl estradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

In this alternative method, the daily dosage units comprising the combination of drospirenone and ethinyl estradiol may suitably be administered for 21, 22, 23 or 24 consecutive days, and wherein the daily dosage units comprising ethinyl estradiol alone may then be administered for 7, 6, 5 or 4 consecutive days, as appropriate. In a further embodiment of the method, the daily dosage units comprising the combination of drospirenone and ethinyl estradiol are administered for 2–4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinyl estradiol for 21 consecutive days and subsequently administration of the daily dosage units comprising ethinyl estradiol alone for 7 consecutive days.

The entire disclosures of all applications, patents and publications, cited herein, and of U.S. Provisional Application Ser. No. 60/256,484, filed Dec. 20, 2000, and of EP Application No. 00610135.6, filed Dec. 20, 2000, are hereby incorporated by reference.

The present invention is further defined by the Examples.

BRIEF DESCRIPTION OF THE EXAMPLES

Example 1 discloses a pharmaceutical product according to some embodiments of the present invention along with pharmaceutical products known to the person skilled in the art. 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. The data shows that direct compression of the powder blend results in good stability of ethinyl estradiol when provided in the form of a cyclodextrin complex (Product D). The product E was prepared to be polyvinylpyrrolidone-free according to the present invention. This product also shows good stability of the ethinyl estradiol in spite of being manufactured by granulation. However, in the case where the product includes polyvinylpyrrolidone and is manufactured according to Example 3 in U.S. Pat. No. 5,798,338 (Tablet A), the product is poorly stable.

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 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 4.45×10^{-3} s^{-1}.

Example 7 describes the method in which the equilibrium stability constant (formation constant) of the complex between EE and CD was studied. The stability constant of the 1:1 complex was found to be 9.5×10^{-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 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 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 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

The following examples are not a limitation on the invention. All temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

Example 1

Degradation of Ethinyl Estradiol in Various Formulations.

Comparative stability data of five tablet formulations comprising ethinyl estradiol has been investigated. The various formulations differ from each other with respect to the manufacturing process, use of ethinyl estradiol in the form of a cyclodextrin complex and use of polyvinylpyrrolidone 25.000 (PVP). Tablet A was prepared as disclosed in U.S. Pat. No. 5,798,338, Example 3, such as by fluid bed granulation based on pre-mixing of active ingredient with lactose and no adjusting of the relative humidity of the granules. Tablets, B, C and E were prepared according to the manufacturing process disclosed herein.

TABLE 1.1

Summary of Parameters of Film-Coated Tablets

Tablet	Manufacturing Process	Active agent	Excipient
A	fluid bed granulation*	EE-β-CD complex	+ PVP
B	fluid bed granulation**	EE	+ PVP
C	fluid bed granulation**	EE	
D	Direct compression	EE-β-CD complex	
E	fluid bed granulation**	EE-β-CD complex	

*Fluid bed granulation as disclosed in Example 3 of U.S. Pat. No. 5,798,338,
**fluid bed granulation as disclosed in example 5 herein, PVP = polyvinylpyrrolidone.

TABLE 1.2

Composition of Test Formulations

	Tablets				
Composition:	A	B	C	D	E
EE	–	✓	✓	–	–
EE-β-CD	✓	–	–	✓	✓
DRSP	–	✓	✓	✓	✓
Lactose	✓	✓	✓	✓	✓
maize starch	✓	✓	✓	✓	✓
micro cellulose	–	–	–	✓	–
starch 1500	✓	✓	–	–	–
PVP 25.000	✓	✓	–	–	–
Mg Stearate	✓	✓	✓	✓	✓

Results

The content of ethinyl estradiol was determined by HPLC just after manufacturing (start) and following storage at various conditions for 3 and 12 months. The content of ethinyl estradiol is expressed relatively to the initial content of ethinyl estradiol that was added to each formulation.

TABLE 1.3

Content of ethinyl estradiol (% recovered)

		3 months		12 months	
Formulation	start	40° C., 75% RH	60° C., 75% RH	25° C., 60% RH	40° C., 75% RH
A	93.1	86.3	77.8	93.8	75.9
B	98.9	94.9	70.7	95.6	85.7
C	100.1	95.8	86.1	100.1	92.1
	99.1	96.2	86.1	99.1	92.1
D	101.5	98.8	96.4	101.4	99.9
	102.7	100.7	98.6	101.8	100.0
E	103.2	101.3	96.4	100.5	98.9
	103.3	102.0	96.6	101.8	99.3

Example 2

Formation of Oxidative Degradation Products of Ethinyl Estradiol

The content of known oxidative degradation products of ethinyl estradiol was determined by HPLC following storage for 12 months at 25° C. and 60% relative humidity (RH) for 12 months. The molar content of each degradation products is expressed relatively to the initial molar content of ethinyl estradiol that was added to each formulation. Four formulations as well as the pure ethinyl estradiol and the ethinyl estradiol β-cyclodextrin complex were investigated.

TABLE 2.1

Stability results after 12 months, 25° C., 60% RH
Formation of degradation products (% of initial content of EE)

Formulations	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
B	0.04	0.07	0.32	0.74	1.20
C	0.05	0.09	0.11	0.73	1.00
	0.04	0.07	0.08	0.70	0.91
D	0.01	0.02	n.d	0.49	0.52
	0.01	0.01	n.d	0.45	0.47
E	0.03	0.01	n.d	0.46	0.50
	0.02	0.01	n.d	0.40	0.43

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

Stability results after 12 months, 40° C., 75% RH
Formation of degradation products (% of initial content of EE)

Formulations	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
B	0.16	0.25	1.92	3.14	5.47
C	0.33	0.61	1.03	1.86	3.83
	0.28	0.54	0.87	1.59	3.28
D	0.03	0.09	0.10	0.79	1.01
	0.03	0.10	0.09	0.79	0.98
E	0.08	0.19	0.30	0.93	1.50
	0.08	0.19	0.41	0.89	1.58

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.

Example 3

Typical compositions consisting of a tablet core is described. The tablet core may optionally be film-coated or sugar coated using the described ingredients. The specific ingredients are typical suitable ingredients according to the invention, but are not limited to those.

TABLE 3

Ingredient	Specific ingredients	Amount % w/w
Tablet core:		
Active agent I	estrogens in the form of an complex with a cyclodextrin	
Active agent II	a progestogen	
Filler	lactose, starch, cellulose	0–95%
Binder	starch, cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, maltodextrine	0–15%
Glidant	colloidal silicon dioxide	0–5%
Disintegrant	starch, carmellose-calcium, crosscarmellose-sodium, carboxymethylstarch sodium	0–15%
Stabilizer/antioxidant	tocopherole acetate, Propyl gallate, ascorbic acid, ascorbic palmitate	0–5%
Lubricant	magnesium stearate	0–5%
Film coating:		
Film-binding agent	hydroxypropylmethylcellulose, polyacrylic acid derivatives, Eudragit	20–100%
Plasticizer	polyethylene glycole	0–20%
Filler	talc, titanium dioxide, calcium carbonate	0–20%
Pigment	titanium dioxide, calcium carbonate	0–20%
Colorant	ferric oxide pigments	0–10%
Sugar coating		
Coating agent	sucrose	30–90%
Plasticizer	povidone 700000, polyethyleneglycol 6000	0–10%
Filler/coating agent:	talc, titanium dioxide, calcium carbonate	10–50%
Humidifier	glycerol	0–5%
Pigment	titanium dioxide, calcium carbonate	0–10%
Colorant	ferric oxide pigments	0–10%
Polishing agent	wax	0–0.5%

Example 4

Preferred Compositions

A preferred composition consists of the components listed below. The batch size is 200,000–550,000 tablets (development site) and 2.5 Mio tablets up to 5 Mio tablets (production site), respectively. Water is used as a processing aid for the manufacture of the tablet mass (fluid bed granulation) and the film-coating.

Ingredient	One tablet (mg)	Development (kg)	Production (kg)
Drospirenone, micro 15	3.0	1.650	7.500
Ethinyl estradiol-β-cyclodextrine complex, micro	0.020 *	0.011 *	0.050 *
Lactose monohydrate	48.18	26.499	120.450
Corn 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 5

Manufacturing Process

The manufacturing process comprises the following steps:

Prepare the granulation liquid:	Suspend maize starch in purified water and add this suspension to purified water while stirring.
Prepare the granules:	Introduce lactose, drospirenone micro 15, ethinyl estradiol-β-cyclodextrine complex micro and maize starch (portion) into the fluid bed granulator. Activate a continuous fluid bed and apply granulation liquid. Dry. Check relative humidity of the granulate mass. Dry the granulate mass if necessary until the desired range of relative humidity is reached (30%-45%).
Prepare the tablet mass:	Introduce maize starch (portion) and magnesium stearate into the fluid bed granulator. Mix.
Compress the tablet mass	Perform on a rotary tableting machine to tablet cores

-continued

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.

Example 6

Dissociation of the EE-β-CD Complex

The rate constant of the dissociation constant of EE-β-CD complex in aqueous solution has been determined.

Test Method

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

$$EE+CD \Leftrightarrow EE\cdot CD \quad 1.$$

$$EE\cdot CD+CD \Leftrightarrow EE\cdot CD_2 \quad 2.$$

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

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

In this study, the dissociation rate of the 1:1 complex was determined using a stopped flow relaxation method with conductometric detection. An indirect method was applied based on a competition reaction using sodium-dodecylsulfate (SDS) which forms a 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 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.

Summary of Results

The dissociation rate constant of the Ethinyl estradiol-β-Cyclodextrin 1:1 complex was determined to be: $K_d=4.45\cdot10^{-3}s^{-1}$

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

Stability Constant of the EE-β-CD Complex in Aqueous Solution.

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

Background

The drug substance ethinyl estradiol-β-cyclodextrin 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.

$$S+L=SL \quad 1.$$

$$SL+L=SL_2 \quad 2.$$

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

$$2.\ SL+L=SL_2 \qquad K_{12}=\frac{c_{SL_2}}{c_{SL}\cdot c_L}$$

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:	$K_{11}=9.5\cdot10^4\ M^{-1}$
Solubility of Ethinyl estradiol:	$S_{EE}=2.17\cdot10^{-5}$ mol/l ($6.43\cdot10^{-3}$ g/l)
Solubility of the 1:1 complex:	$S_{11}=1.92\cdot10^{-3}$ mol/l (2.75 g/l)
Solubility of the 1:2 complex:	$S_{12}=1.44\cdot10^{-3}$ mol/l (3.7 g/l)

Example 8

Stability Constant of the EE-β-CD Complex in 0.1 M HCl

The Equilibrium Stability Constant (Formation Constant) of the EE-β-CD complex in 0.1 M HCl was determined as described in example 7.

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:	$K_{11}=1.56\cdot10^4\ M^{-1}$
Overall stability constant of the 1:2 complex ($=K_{11}\cdot K_{12}$):	$K^*_{12}=$ approx. $1.6\cdot10^4\ M^{-1}$
Solubility of ethinyl estradiol:	$S_{EE}=1.68\cdot10^{-4}$ mol/l (0.05 g/l)
Solubility of the 1:1 complex:	$S_{11}=2\cdot10^{-3}$ mol/l (2.9 g/l)
Solubility of the 1:2 complex:	$S_{12}=5\cdot10^{-4}$ mol/l (1.3 g/l)

Example 9

Dissociation Constant of the EE-β-CD Complex in Aqueous Solution

The Acid Dissociation Constant of the EE-β-CD complex in aqueous media was determined.

Background

The drug substance ethinyl estradiol-β-cyclodextrin 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 complex dissociates into its components according to the law of

mass action. To restrain the dissociation of the ethinyl estradiol-β-cyclodextrin 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 complex was determined at 20° C. to be: pK_a=10.51±0.03 For comparison the pKa of ethinyl estradiol in the absence of β-cyclodextrin is: pK_a=10.25±0.04

Example 10

Log P Value of the EE-β-CD Complex

Background

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

The partition of the ethinyl estradiol-β-cyclodextrin complex is determined upon equilibration in a two-phase system, n-octanol/water. 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]). 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.

Summary of Results

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

Solid State Forms of the Ethinyl Estradiol-β-cyclodextrin Complex.

Multiple solid state forms of the ethinyl estradiol-β-cyclodextrin were determined, and test methods that can detect and distinguish between such forms were provided.

Background

A variety of crystallisation products obtained under different crystallisation, 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 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 (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 severe 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 fully water-saturated hydrates, 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	10.6	4.47
Im2183/V	P1, 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	P1, 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 × water; dried in a vacuum drying cabinet	11.2	3.34
Im2225/2	P 1; washed 2 × water, 1 × acetone; dried in a vacuum drying cabinet	10.5	3.31
Im2225/3	P 1; washed 2 × water, 1 × acetone, 1 × water; dried in a vacuum drying cabinet	10.9	3.8
Im2230	P 1; washed 1 × water, 1 × acetone, 1 × water; dried in a vacuum drying cabinet	10.8	4.35
Im2231	P 1; washed i × water, 1 × acetone, 1 × water; dried in a vacuum drying cabinet	11	2.63
Im2240	P 1; washed 1 × water, 1 × acetone, 1 × 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]

TABLE 12.1b-continued

Batch	solvent / treatment conditions	content of EE [%]	water content [%]
	Crystallization products of the complex		
Im2180, 3d $Mg(ClO_4O)_2$	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.	~16.7[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

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

We claim:

1. A composition comprising:

i) a granulated preparation comprising a complex between an estrogen and a cyclodextrin; and

ii) optionally, one or more excipients,

the composition having a stability such that said estrogen is in an amount of at least 90% w/w in relation to the initial content of said estrogen after storage for 12 months at 40° C. and 75% relative humidity (RH); and

the composition being essentially free of polyvinylpyrrolidone.

2. The composition according to claim 1, wherein the estrogen is in an amount from about 0.002% w/w to 2% w/w.

3. The composition according to claim 1, wherein the estrogen is in an amount from about 0.004% w/w to 0.2% w/w.

4. The composition according to claim 1, wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 5% w/w to 20% w/w.

5. The composition according to claim 1, wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 8% w/w to 15% w/w.

6. A method for improving the stability of an estrogen in a pharmaceutical composition that comprises an estrogen and one or more excipients in a granulate preparation, which method comprises:

i) forming a complex between said estrogen and a cyclodextrin; and

ii) granulating the complex to provide the granulate preparation;

provided that, the composition is prepared so that it is essentially free of polyvinylpyrrolidone.

7. A process for manufacturing a granulate preparation comprising a complex between an estrogen and a cyclodextrin, which comprises:

i) loading the complex, optionally one or more other therapeutically active agent(s), and one or more excipients into a granulator;

ii) applying a liquid onto the loaded complex and the one or more excipients, and

granulating and drying, so as to obtain granules having a relative humidity not exceeding 60%, as determined at a temperature between 20° C. and 40° C.

8. The process according to claim 7, wherein the complex and the optionally further one or more therapeutically active agent(s) are provided as individual agent(s) without being pre-mixed with excipients.

9. The process according to claim 7, wherein the relative humidity of the granulate preparation does not exceed 55%, as determined at a temperature between 20° C. and 40° C.

10. The process according to claim 7, wherein the relative humidity of the granulate preparation does not exceed 45%, as determined at a temperature between 20° C. and 40° C.

11. The process according to claim 7, wherein the relative humidity of the granulate preparation does not exceed 40%, as determined at a temperature between 20° C. and 40° C.

12. The composition according to claim 1, wherein the composition comprises one or more excipient(s) which is/are selected from the group consisting of starch, cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and maltodextrin.

13. The composition according to claim 1, wherein the estrogen is selected from the group consisting of ethinyl estradiol, estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, estrone sulfate and mixtures thereof.

14. The composition according to claim 13, wherein the estrogen is ethinyl estradiol.

15. The composition according to claim 1, wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin and alkylated or acylated derivatives thereof.

16. The composition according to claim 1, wherein the cyclodextrin is β-cyclodextrin or an alkylated or acylated derivative thereof.

17. The composition according to claim 1, wherein the estrogen is in an amount relative to the cyclodextrin such that a molar ratio between the estrogen and the cyclodextrin is from about 2:1 to 1:10.

18. The composition according to claim 1, further comprising one or more other therapeutically active agent(s).

19. The composition according to claim 18, wherein the one or more other therapeutically active agent(s) is a progestogen.

20. The composition according to claim 19, wherein the progestogen is selected from the group consisting of drospirenone, levonorgestrel, norgestrel, gestodene, dienogest, cyproterone acetate, norethisterone, norethisterone acetate, desorgestrel, and 3-keto-desorgestrel.

21. The composition according to claim 20, wherein the progestogen is drospirenone.

22. The composition according to claim 21, wherein drospirenone is in micronized form.

23. The composition according to claim 22, wherein drospirenone is in an amount from about 0.4% to 20% w/w.

24. The composition according to claim 1, wherein the complex is micronized.

25. The composition according to claim 1, further comprising an antioxidant.

26. The composition of claim 1, wherein the granulated preparation has a mean particle size of at least about 100 μm.

27. The method according to claim 6, provided that the one or more excipient(s) is/are selected from the group consisting of starch, cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and maltodextrin.

28. The process according to claim 7, provided that, when the granulated preparation comprises polyvinylpyrrolidone, it is present in an amount of at most 2% w/w.

29. The method according to claim 7, provided that the one or more excipient(s) is/are selected from the group consisting of starch, cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and maltodextrin.

30. The process according to claim 7, wherein the estrogen is selected from the group consisting of ethinyl estradiol (EE), estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, estrone sulfate and mixtures thereof.

31. The process according to claim 30, wherein the estrogen is ethinyl estradiol.

32. The process of claim 7, wherein the granulating is by fluidized bed granulation.

* * * * *

Anexo 3

República del Perú

Registro de la Propiedad Industrial
Oficina de Invenciones y Nuevas Tecnologías

554

TITULO N° 3698

La Oficina de Invenciones y Nuevas Tecnologías del Indecopi certifica que por mandato de la Resolución N° 001135-2004/OIN-INDECOPI de fecha 29 de septiembre de 2004, ha quedado inscrita en el Registro de Patentes de Invención, la siguiente invención:

Denominación	:	COMPOSICIONES DE COMPLEJOS DE ESTROGENO-CICLODEXTRINA
Clasificación	:	A61K 47/48; A61K 31/565
Solicitud	:	001280-2001
Fecha de Presentación	:	20 de diciembre de 2001
Fecha de Prioridad	:	20 de diciembre de 2000
Titular	:	SCHERING AKTIENGESELLSCHAFT
País	:	Alemania
Inventores	:	THOMAS BACKENSFELD; WOLFGANL HEIL; RALPH LIPP
Vigencia	:	20 de diciembre de 2021

NÉSTOR ESCOBEDO FERRADAS
Jefe de la Oficina de Invenciones
y Nuevas Tecnologías
INDECOPI

REPUBLICA DEL PERU

11 OCT. 2004
ESTUDIO
FRANCISCO ESPINOSA BELLIDO
ABOGADOS S.C.R.L.

EXPEDIENTE Nº 001280-2001/OIN

RESOLUCION Nº 001135-2004/OIN-INDECOPI

Lima, 29 de setiembre de 2004

Mediante expediente Nº 001280-2001/OIN, iniciado el 20 de diciembre de 2001, con prioridad de fecha 20 de diciembre de 2000, SCHERING AKTIENGESELLSCHAFT de Alemania, solicita patente de invención para "COMPOSICIONES DE COMPLEJOS DE ESTROGENO-CICLODEXTRINA", C.I.P.7 A61K 47/48; A61K 31/565, cuyos inventores son THOMAS BACKENSFELD; WOLFGANL HEIL y RALPH LIPP.

1. EXAMEN DE PATENTABILIDAD

La invención solicitada reúne los requisitos establecidos en la Decisión 486 de la Comisión de la Comunidad Andina que aprueba el Régimen Común sobre Propiedad Industrial, conforme aparece del informe que corre de fojas 215 a 217 del expediente.

La presente resolución se emite en aplicación de la norma legal antes mencionada y en uso de las facultades conferidas por los artículos 31 y 34 de la Ley de Organización y Funciones del Instituto Nacional de Defensa de la Competencia y de la Protección de la Propiedad Intelectual (INDECOPI) sancionada por Decreto Ley Nº 25868.

2. RESOLUCION DE LA OFICINA DE INVENCIONES Y NUEVAS TECNOLOGIAS

OTORGAR, patente de invención para "COMPOSICIONES DE COMPLEJOS DE ESTROGENO-CICLODEXTRINA", C.I.P.7 A61K 47/48; A61K 31/565, a favor de SCHERING AKTIENGESELLSCHAFT de Alemania, por un plazo de veinte (20) años, contados desde el 20 de diciembre de 2001, fecha de presentación de la solicitud, aprobándose las 25 reivindicaciones que corren de fojas 192 a 196 del expediente.

Regístrese y Comuníquese

NÉSTOR ESCOBEDO FERRADAS
Jefe de la Oficina de Invenciones
y Nuevas Tecnologías
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E-mail: postmaster@indecopi.gob.pe | Web: www.indecopi.gob.pe

Informe Técnico GM 48-2003 / b

A: Néstor Escobedo Ferradas
Jefe de la Oficina de Invenciones y Nuevas Tecnologías

De: Q.F. Gianinna del Carmen Márquez Mendoza – Examinador Interno

Asunto: Examen adicional de la solicitud de patente de invención titulada:
"COMPOSICIONES DE COMPLEJOS DE ESTROGENO-CICLODEXTRINA"
Expediente 001280-2001/OIN de fecha 20.12.2001.
Prioridad EP 00610135.6 de fecha 20.12.2000.

1. ANTECEDENTES

- Informe técnico GM 48-2003, donde se concluye que:
- Las reivindicaciones 1 a 24 y 27 a 31 NO CUMPLEN con el requisito de claridad del Art. 30 de la Decisión 486.

- Las reivindicaciones 25 a 26 referidas al uso, no son patentables en concordancia con la interpretación del artículo 14 de la Decisión 486 por el Tribunal de Justicia de la Comunidad Andina en el Proceso 89-AI-2000 publicado en la Gaceta Oficial N. 722 del 12 de octubre de 2001.

- Escrito de fecha 27.11.2003, donde el solicitante presenta un pliego de 25 reivindicaciones, en el cual indica que se ha respetado la sugerencia de la examinadora de incorporar a las reivindicaciones independientes la referencia a la cantidad limitante de polivinilpirrolidona.

- Informe técnico GM 48-2003/A, donde se concluye que:
  Las reivindicaciones 1 a 25 CUMPLEN con el requisito de Novedad (Art. 16), pero NO CUMPLEN con el requisito de Nivel Inventivo (Art. 18),definidos en la Decisión 486 de la Comisión de la Comunidad Andina.

- Escrito de fecha 17.09.2004, donde el solicitante respecto al nivel inventivo indica que la formulación granulada (E) tiene la ventaja frente a la formulación por compresión directa (D) en que permite la obtención de una composición homogénea aún con dosis bajas de los ingredientes activos. Esto no se puede esperar de una formulación manufacturada por compresión directa.

2. TEXTOS A ANALIZAR

(x) Memoria Descriptiva y 31 reivindicaciones originalmente presentadas.
(x) Pliego de 25 Reivindicaciones presentadas con el escrito de fecha 27.11.2003.
(x) Escrito de fecha 17.09.2004 donde el solicitante presenta argumentos respecto al nivel inventivo.

MODIFICACIÓN DE LA SOLICITUD

Las reivindicaciones 1 a 25 del pliego de fecha 27.11.2003 no implican una ampliación de la invención originalmente presentada según el artículo 34 de la Decisión 486, tal como se indicó en el informe técnico GM 48-2003/A.

3. SUFICIENCIA Y CLARIDAD

Las reivindicaciones 1 a 25 del pliego de fecha 27.11.2003 CUMPLEN con el requisito de claridad del Artículo 30 de la Decisión 486 tal como se indicó en el informe técnico GM 48-2003/A.

4. NO INVENCIONES Y EXCLUSIONES A LA PATENTABILIDAD

Las reivindicaciones 1 a 18 al definir un producto y las reivindicaciones 19 a 25 al definir un procedimiento, serían patentables de acuerdo al artículo 14 de la Decisión 486, más aún al no estar afectadas por los artículos 15 y 20 de la Decisión 486, se consideran susceptibles de patentarse.

5. UNIDAD DE INVENCIÓN

Del análisis efectuado a las reivindicaciones se ha observado que el elemento a patentar común a las reivindicaciones 1 a 25 son las composiciones que comprenden una formulación granulada de estrogeno y una ciclodextrina, y su proceso de producción; por lo tanto, se establece que las reivindicaciones guardan unidad de invención y CUMPLEN lo establecido en el Artículo 25 de la Decisión 486.

6. NOVEDAD

Tal como se indicó en el informe técnico GM 48-2003/A las reivindicaciones 1 a 25 del pliego de fecha 27.11.2003 CUMPLEN con el requisito de novedad del artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina.

7. NIVEL INVENTIVO

El problema que se pretende resolver es la necesidad de creación de composiciones que contengan etinil estradiol, que **no presenten problemas en el almacenamiento del producto y que tengan uniformidad en contenido aún en dosis bajas**.

La solución propuesta por la presente solicitud es crear composiciones que contengan una formulación **granulada** con estabilidad mejorada del estrogeno, mediante la formación de un complejo entre el estrógeno y ciclodextrina, el cual puede contener **un máximo de 2% p/p de polivinilpirrolidona.**

La solución no resulta obvia respecto al documento D7 (antecedente más cercano) ya que D7 describe una tableta que contiene etinil estradiol/beta ciclo dextrina y polivinilpirrolidona pero no limita la cantidad del mencionado excipiente (PVP), el que era responsable del elevado potencial de oxidación; por lo que la restricción de polivinilpirrolidona, no estaba sugerida en el arte previo.

El solicitante presenta una serie de tablas respecto a las composiciones de la invención en las páginas 32 y 34 de la memoria descriptiva:

Tabla 1.1

Tableta	Proceso de fabricación	Agente activo	Excipiente
A (descrita en el documento D7)	Granulación de lecho fluido	Complejo EE-β-CD	+ PVP
B (composición de la presente solicitud)	**Granulación de lecho fluido**	**EE**	**+PVP**
C (composición de la presente solicitud)	**Granulación de lecho fluido**	**EE**	
D	Compresión directa	Complejo EE-β-CD	
E (composición de la presente solicitud)	**Granulación de lecho fluido**	**Complejo EE-β-CD**	

La tableta A se preparó como se describe en el documento **D7** (ejemplo 3), por granulación de lecho fluido, sobre la base de la mezcla previa del ingrediente activo con lactosa y sin ajustar la humedad relativa de los gránulos.

Las tabletas B, C y E se prepararon de acuerdo con el proceso de fabricación de la presente solicitud de patente.
La tableta D es estradiol cuando se lo provee en la forma de ciclodextrina (indicado en la página 30 de la memoria descriptiva).

Tabla 1.3

Contenido de etinil estradiol (% recuperado)					
Formulación	Inicio	3 meses		12 meses	
		40°C 75% RH	60°C 75%RH	25°C 60% RH	40°C 75%RH
A (descrita en el documento D7)	93.1	86.3	77.8	93.8	75.9
B (composición de la presente solicitud)	98.9	94.9	70.7	**95.6**	**85.7**
C (composición de la presente solicitud)	100.1 99.1	95.8 96.2	86.1 86.1	**100.1** **99.1**	**92.1** **92.1**
D	100.5 102.7	98.8 100.7	96.4 98.6	101.4 101.8	99.9 100.0
E (composición de la presente solicitud)	103.2 103.3	101.3 102.0	96.4 96.6	**100.5** **101.8**	**98.9** **99.3**

En la página 29 el solicitante indica que en la tabla 1.3 se ilustra la estabilidad de las composiciones de la invención en comparación con formulaciones conocidas después de un periodo de tiempo bajo condiciones ambientales controladas, además señalan que los datos muestran que la compresión directa de la mezcla en polvo resulta en una buena estabilidad del etinil estradiol cuando se lo provee en la forma de ciclodextrina (producto D); y que el producto E se preparó de modo que estuviera libre de povidona de acuerdo con la presente invención; indican que este producto mostró también una buena estabilidad del etinil estradiol a pesar de estar fabricado por granulación; sin embargo, en el caso en el que el producto incluía polivinilpirrolidona y estaba fabricado de acuerdo con el ejemplo 3 de D7 (tableta A), el producto fue pobremente estable.

La ventaja de la composición de la invención respecto a la composición D (estradiol cuando se lo provee en la forma de ciclodextrina por **compresión directa**) es que no solo no presenten problemas en el almacenamiento del producto sino que tienen uniformidad en contenido aún en dosis bajas, es así como cuando las formulaciones son preparadas por medios de técnicas de granulación, la variación de la dosificación entre lotes y dentro de los lotes es baja, por consiguiente, el requisito de uniformidad de contenido que exigen diversas farmacopeas puede ser alcanzado con la formulación E pero no con la D, tal como es mencionado por el solicitante en su escrito de fecha 17.09.2004.

Por lo tanto, las reivindicaciones 1 a 25 del pliego de fecha 27.11.2003 CUMPLEN con el requisito de Nivel Inventivo (Art. 18) de la Decisión 486 de la Comisión de la Comunidad Andina

8. APLICACIÓN INDUSTRIAL

El objeto de la presente invención puede ser utilizado en la industria farmacéutica; por lo tanto las reivindicaciones 1 a 25 del pliego de fecha 27.11.2003 cumplen con el Artículo 19 de la Decisión 486.

9. CONCLUSIONES

Las reivindicaciones 1 a 25 del pliego de fecha 27.11.2003 CUMPLEN con los requisitos de Novedad (Art. 16), Nivel Inventivo (Art. 18) y Aplicación industrial (Art. 19) definidos en la Decisión 486 de la Comisión de la Comunidad Andina.

Realizado por

.....

Gianinna Márquez Mendoza
C.Q.F. 6519-Examinador Interno

Anexo 4

Handbook of Pharmaceutical Excipients

FOURTH EDITION

Edited by

Raymond C Rowe

BPharm, PhD, DSc, FRPharmS, CChem, FRSC, CPhys, MInstP

Senior Principal Scientist

AstraZeneca

Macclesfield, UK

Paul J Sheskey

BSc, RPh

Technical Service Leader

Water Soluble Polymers R&D

The Dow Chemical Company

Midland

MI, USA

Paul J Weller

BSc, MSc, CChem, MRSC

Publisher – Science and Practice

Royal Pharmaceutical Society of Great Britain

London, UK

London • Chicago Pharmaceutical Press

APhA American Pharmaceutical Association

Povidone

1 Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Povidonum
USP: Povidone

2 Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2- pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula Molecular Weight

$(C_6H_9NO)_n$ 2500–3 000 000

The USP 25 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, ranging from 10 to 120. The *K*-value is calculated using Fikentscher's equation:[1]

$$\log z = c\left(\frac{75k^2}{1+1.5kc}\right)+k$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value $\times 10^{-3}$, and c is the concentration in % w/v.

Alternatively, the *K*-value may be determined from the following equation:

$$K\text{-value} \sqrt{\frac{300c\log z(c+1.5c\log z)^2+1.5}{0.15c+0.003c^2}}$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value $\times 10^{-3}$, and c is the concentration in % w/v.

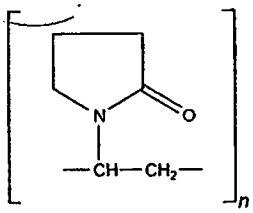
Approximate molecular weights for different povidone grades are shown in Table I.

Table I: Approximate molecular weights for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5 Structural Formula



6 Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.[2,3] Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.[4–6] Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. *See* Table II.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations; *see* Section 14.

Table II: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8 Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

9 Pharmacopeial Specifications

See Table III.

Anexos

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Pharmaceutics: The Science of Dosage Form Design

EDITED BY

Michael E. Aulton BPharm PhD MPS
Reader in Pharmacy, Leicester Polytechnic, Leicester, UK

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37

M P Summers

Granulation

INTRODUCTION TO GRANULATION

Granulation is the process in which powder particles are made to adhere to form larger particles called granules. In the majority of cases this will be undertaken in the production of tablets or capsules, when granules will be made as an intermediate product, but granules may also be used as a dosage form (see Chapter 17). Granulation will commence after mixing the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. After granulation, the granules will be packed when used as a dosage form or they may be mixed with other excipients prior to tablet compression or capsule filling.

Reasons for granulation

The reasons why granulation is often necessary are as follows.

To prevent segregation of the constituents in the powder mix

Segregation is primarily due to differences in the size or density of the components, the smaller particles concentrating at the base of a container with the large particles above them. An ideal granulation will contain all the constituents of the mix

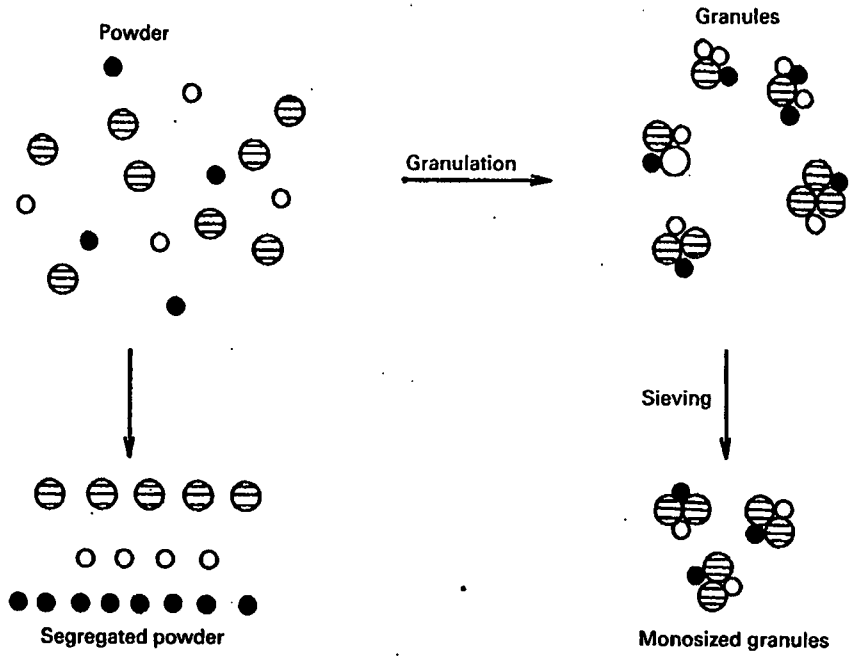

Fig. 37.1 Granulation to prevent powder segregation

in each granule and segregation of the ingredients will not occur (Fig. 37.1).

It is also important to control the particle size distribution of the granules because, although the individual components may not segregate, if there is a wide size distribution, the granules themselves may segregate. If this occurs in the hoppers of sachet filling machines, capsule filling machines or tablet machines, products having large weight variations will result. This is because these machines fill by volume rather than weight and if different regions in the hopper contain granules of different sizes (and hence bulk density), a given volume in each region will contain a different weight of granules. This will lead to an unacceptable distribution of the drug content within the batch of finished product even though the drug is evenly distributed weight per weight, through the granules.

To improve the flow properties of the mix

Many powders, because of their small size or surface characteristics, are cohesive and do not flow well. Poor flow will often result in a wide weight variation within the final product due to variable fill of tablet dies, etc. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.

To improve the compression characteristics of the mix

Some powders are difficult to compress even if a readily compressed adhesive is included in the mix but granules of the same formulation are often more easily compressed and produce stronger tablets. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule (Seager *et al.*, 1979).

Other reasons

These are the primary reasons for the granulation of pharmaceutical products but there are other reasons which may necessitate the granulation of powdered material:

1 The granulation of toxic materials will reduce

the hazard of the generation of toxic dust which may arise when handling powders. Suitable precautions must be taken to ensure that such dust is not a hazard during the granulation process.

2 Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard as the granules will be able to absorb some moisture and yet retain their flowability because of their size.

3 Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

Methods of granulation

Granulation methods can be divided into two types: wet methods which utilize a liquid in the process and dry methods in which no liquid is used.

In a suitable formulation a number of different excipients will be needed in addition to the drug. The common types used are diluents, to produce a unit dose weight of suitable size and disintegrating agents which are added to disintegrate the granule in a liquid medium, e.g. on ingestion by the patient. Adhesives in the form of a dry powder may also be added, particularly if dry granulation is employed. These ingredients will be mixed before granulation.

Dry granulation

In the dry methods of granulation the powder particles are aggregated using high pressure. There are two main processes. Either a large tablet (known as a 'slug') is produced in a heavy duty tableting press (a process known as 'slugging') or squeezed between two rollers to produce a sheet of material ('roller compaction'). In both cases these are broken using a suitable milling technique to produce granular material which is usually sieved to separate the desired size fraction. The unused fine material may be recycled to avoid waste. This dry method may be used for drugs which do not compress well after wet granulation or those which are sensitive to moisture.

Wet granulation (or wet massing)

Wet granulation involves the massing of the powder mix using a solvent. The solvents used must be volatile, so that they can be removed by drying, and non-toxic. Typical solvents include water, ethanol and isopropanol either alone or in combination. The solvent may be used alone or it may contain a dissolved adhesive (also referred to as binder or binding agent) which is used to cause particle adhesion. The disadvantages of water as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products and it needs a longer drying time than organic solvents. This long drying time increases the length of the process and again may affect stability because of the extended exposure to heat. The primary advantage of water is that it is non-flammable which means that expensive safety precautions such as the use of flame-proof equipment need not be taken. Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required.

In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent sieving stage breaks agglomerates of granules and removes the fine material which can be recycled. Variations of this traditional method are dependent upon the equipment used but the general principle of initial particle adhesion using a liquid remains in all of the processes.

Effect of granulation method on granule structure

The type and capacity of granulating mixers significantly influences the work input and time necessary to produce a cohesive mass, adequate liquid distribution and intragranular porosity of the granular mass. The method and conditions of granulation affect intergranular and intragranular pore structure by changing the degree of packing within the granules. Seager *et al.* (1979) investigated the structure of granules prepared by various granulation methods. They showed that precompressed granules, consisting of compressed drug and binder particles, were held together by simple bonding during compaction. Granules

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James C. Boylan

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Wet Granulation

Introduction

Wet granulation is the most extensively used method of granulation in the pharmaceutical industry. In general, granulation is defined as a process which causes the powdered particles to adhere permanently to each other to form large particles called granules. (See also the article "Granulation" by H. G. Kristensen and T. Schaefer, Vol. 7, pp. 121–160, of this encyclopedia.) In the wet granulation method, in contrast to dry granulation, the aggregation of particles is obtained by using a liquid phase.

Normally, this liquid phase is a solution, suspension, or slurry of a binding agent. This binder solution is added to a homogeneous powdered mixture containing the active ingredient. The binder solution is homogeneously distributed in the powdered mixture by kneading the lumps of the liquid–solid mixture. The solvent evaporates during a drying step.

Products obtained by wet granulation are spherical-like, cylindrical-shaped, free-flowing multiparticular systems with a previously defined particle size (ranging from 0.1 to 2 mm) with constant composition. These products can be used as such as a dosage form or as intermediates in the production of tablets and capsules.

Pharmaceutical granules, made up of small irregular and cylindrical particles, have been used since the 19th century. One of the early references is credited to a professor from Algiers, Dr. Dordant, who proposed the form of granules for administering large amounts of medicinal powders. These granules were obtained by "forming a homogeneous paste of medicinal powder with water containing gum in the 1:20 proportion of powder. The bulk mass was placed over a screen and pressed down with a wooden roller which forced the wet mass to pass through the holes. The granules were then dried in an oven. . . ." [1]. In this reference the profile of different stages of traditional wet granulation is observed. Pharmaceutical granulations attained their highest usage in the first half of the 20th century; thereafter their use started to decline. Nowadays, single-dose specialties with the vermicular-shaped classical granules are used in the pharmaceutical market. Recently, however, suppliers of raw materials have found a new application for wet granulation in the production of granular excipients for direct compression.

The wet granulation method has been used for the longest time in the industrial production of tablets. The two important material properties required to form a compact and reproducible tablet are compressibility and fluidity; both can be obtained by means of granulation. In dry granulation and direct compression methods, compressibility depends on the inherent deformation and cohesive properties of the active substance and diluents. In wet granulation, distribution of binders over the surface of the granules creates an adhesive property in the materials that makes up for the lack of cohesiveness in the drugs and the diluents.

In the pharmaceutical industry, the advantages obtained by using wet granulation procedures in the development of pharmaceutical granules, tablet, and capsule formulations must remain during large-scale production. To assure biopharmaceutical qual-

ity, pharmaceutical industries must develop products and machinery resulting in reproducible, controllable quality. Wet granulation has the disadvantage of complexity because it requires several stages. For this reason, recent research has been devoted to the design of equipment that allows to carry out several stages in the same unit and to develop control systems that guarantee the characteristics of product from batch to batch. Attempts have also been made to improve the wet granulation process by utilizing fluidized-bed and spray-drying techniques. In practice, by using these techniques the difference between wet granulation and microencapsulation is only based on the particle size of the resultant product. Finally, spherical granules ("pellets") with a narrow particle size distribution can be obtained by means of pelletization techniques, mainly by the use of extruders, as a special method of wet granulation.

Raw Materials

Besides active substances, production of granulations involves different types of excipients. Each is selected according to the nature of the active ingredient, the processing requirements, and the use of the end product [2–5].

Raw materials required for wet granulation can be divided in two categories:

- Dry Powder Constituents. These are the powders which will be granulated. In addition to the active substance, this mixture normally contains diluents and disintegrating agents. These excipients are necessary from the biopharmaceutical or technological view point. Other types like flavors can be added to improve patients' acceptability, and antioxidants or preservatives for maintaining product quality.
- Liquid Constituents. The liquid phase contains binders and solvents which confer adhesion to the dry powder particles; coloring agents are frequently incorporated into this phase.

This classification is general and not rigid. For example, there are formulations in which binders are part of the dry powdery mixture and the granulating liquid contains only solvent. In other formulations, the active substance is dissolved in the granulating liquid and the solution is added to the excipients mixture [2,6]. The formulation shown in Table 1 corresponds to a standard granulation.

TABLE 1 Inert Granulation Prepared by the Wet Granulation Process[a]

Ingredient	Quantity (% w/w)
Lactose (fine powder)	75
Corn starch	25
Gelatin (5% solution)	q.s.

[a]Mix lactose and starch and moisten with the gelatin solution to proper wetness. Granulate by passing the wet mass through a 14 mesh (1.12 mm) screen and dry at 60°C. Pass the dry granulation through a 16 mesh (1 mm) screen.

Disintegrants

Disintegrants facilitate the breakup of granules and tablets into fine particles in the gastrointestinal tract. Their function is to counteract the action of binders and physical forces of compression necessary to form tablets.

The three principal mechanisms of disintegrants are swelling, wicking, and breaking. Some disintegrants like clay and veegum act through swelling and lose their properties if previously in contact with aqueous media; for this reason they cannot be used as internal additives in wet granulation [2]. Frequently used disintegrants are listed in Table 7.

Corn starch is the most widely used disintegrant. In wet granulation, it may also be used as diluent or binder (Tables 1 and 4). In association with Avicel it forms an excellent combination of disintegrants. Acid-base systems are used in the manufacture of effervescents tablets (Table 7) [12].

Materials like low-substituted carboxymethyl starches, cross-linked carboxymethyl cellulose, and cross-linked polyvinylpyrrolidone (PVP) represent a new generation of disintegrants which substantially decreased disintegration time. This property is particularly useful in the formulation of tablets containing water-insoluble drugs. These substances are used in lower concentration than traditional starch (2–3% for cross-linked cellulose and crospovidone, and 4–6% for cross-linked starch in wet granulation formulations) [2,13].

Color, Flavor, and Flavor Modifiers

Colors used in granulations designed for oral drug administration are limited to those certified by the FDA as food, drug, and cosmetic colors (FD&C) and drug and cosmetic colors (D&C). These colors are dyes, their lakes, and certain natural and derived colorants. Normally they are added to the formulation in a maximum concentration of 0.05%. Since they are used in very low concentrations, certified dyes are often treated

TABLE 7 Disintegrating Agents

Disintegrant	Concentration in Granulation (% w/w)
Traditional	
Starch (corn, potato)	5–20
Microcrystalline cellulose	5–20
Alginic acid	5–10
Sodium alginate	2–5
Clays (Veegum)	5–15
Cellulose floc	5–15
Ion exchange resins	0.5–5
Effervescent acid-base systems	3–20
Recent	
Modified starch (sodium starch glycolate NF)	1–8
Modified carboxymethylcellulose (Croscarmelose NF)	5–10
Cross-linked polyvinylpyrrolidone (Crospovidone NF)	0.5–5

as inert materials. However, dyes can react with various pharmaceutical excipients. For example, sugars like lactose, sucrose, and dextrose increase the fading rate of FD&C Blue No. 2, but this does not occur with mannitol and sorbitol [2].

Colors are incorporated into the granulation by dissolution (in case of soluble dyes) or dispersion (in case of lakes) in the granulating solvent. To avoid the migration problems of soluble dyes during drying they should be first adsorbed on calcium sulfate, tricalcium phosphate, starch, or some other major granulation ingredient.

An improvement in the palatability of granulations can be attained by means of the proper selection of fillers; sugars, for example, impart sweetness. Flavors are mixed with dry powder constituents or, more frequently, distributed in a fine spray over the dried granulation after dissolving in an alcoholic solution. Microencapsulated flavors are one of the most recent forms of incorporating flavors in dried granules just before compression (14).

Granulating Solvents

Solvents used in wet granulation should be nontoxic and volatile, so that they can be removed from the granulation during drying. Water is the most frequently used granulating fluid. Under some circumstances, organic solvents, mainly ethanol and isopropanol, are used neat or in aqueous mixtures [15,16].

Water

Water has the advantage of being nonflammable, and expensive safety precautions, like flameproof equipment, are not needed. Its use may be disadvantageous in some cases, where it may adversely affect the stability of the drug by causing hydrolysis of a water-sensitive product. Furthermore, it may need longer drying times than organic solvents. This may affect the stability of the active ingredients due to prolonged exposure to heat [11].

Organic Solvents

Organic solvents are used for water-sensitive drugs as an alternative to dry granulation. They are also used when fast drying is necessary and in the production of effervescent granulations [12,15]. Ethanol is mostly utilized. It may be used alone or mixed with water in different proportions. Isopropyl alcohol and methylene chloride are alternative solvents. The last trace of the solvent should be carefully eliminated to avoid an odor of alcohol. Another very important disadvantage of the use of organic solvents is the generation of toxic vapors which can affect the workers or cause explosions.

Binders

Binders are substances with cohesive and adhesive properties capable of agglomerating dry powdered particles to form granules after drying. Binders can be added to the dry powder by dissolving in the granulation solvent, or in dry form, as other constituent of dry mixtures, and after moistening with water, alcohol, or water-alcohol mixture to form a binder solution. (See also the article "Binders" by H. G. Kristensen, Vol. 1, pp. 461–464, of this encyclopedia).

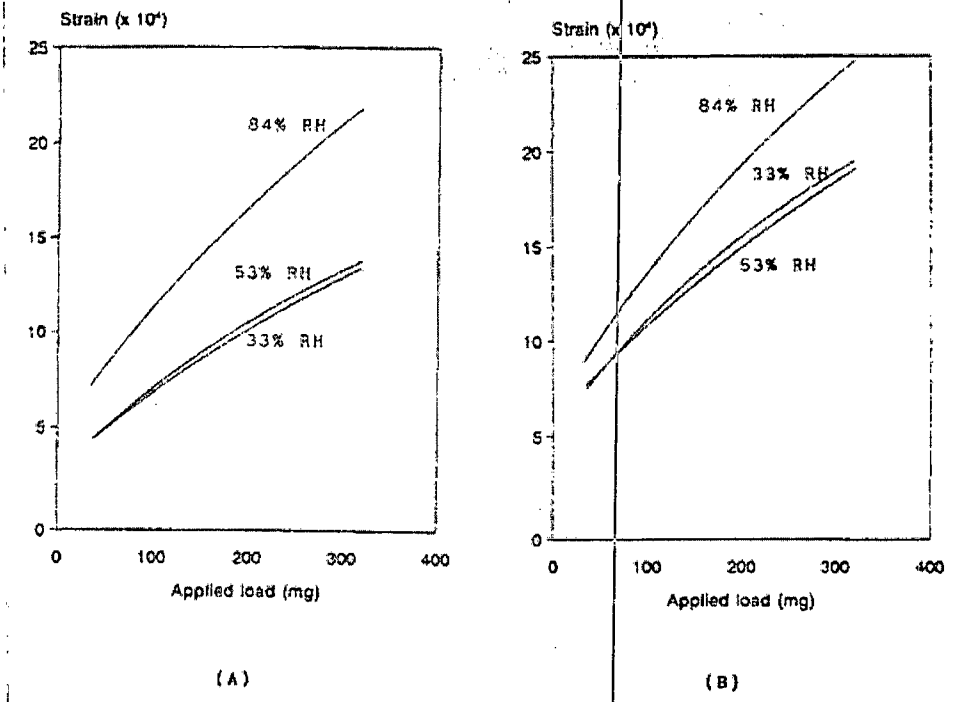

FIG. 1. Effect of relative humidity (RH) of granule storage on the relationship between strain and applied load for granules containing (A) starch and (B) PVP as binding agents. (From Ref. 20.)

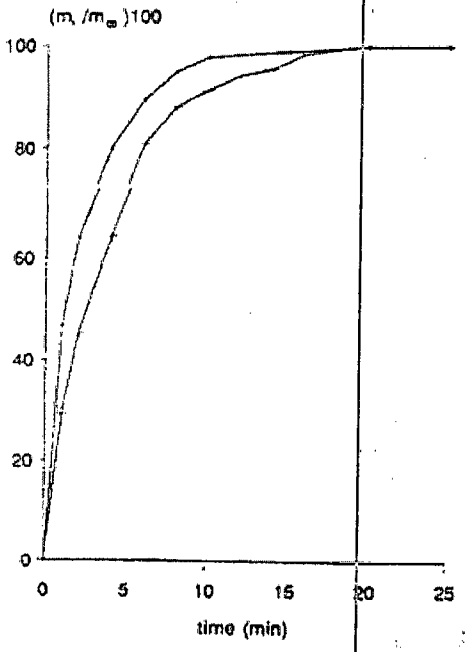

FIG. 2. Increase of dissolution rate of a hydrophobic drug (Mitonafide) during wet granulation; —·— Granulation —+— Drug substance. (Data from the authors.)

TABLE 9 Evaluation of Binder Properties

Indirect Methods	Dry Granulation	Direct Methods
Binder	Size distribution	Torque
Breaking force of binder films	Bulk volume	Conductivity
Reological behavior	Hardness and friability	Power consumption
Surface tension force and contact angle	Porosity	Extruder test
	Compressibility	
	Drug release	

[a]Adapted from Ref. 22.

The binders most widely used in wet granulation are shown in Table 10. Binders can be divided into sugars and polymeric materials. The latter group can be divided into natural polymers such as starch and gums (acacia and tragacanth) and synthetic polymers such as PVP and methylcellulose [2,23].

Natural binders in wet granulation are associated with two difficulties. On the one hand, batch-to-batch variations in the product characteristics make it difficult to standardize the process. On the other hand, binding solutions should be freshly prepared or should contain some preservative. Before using these solutions, straining or centrifugation may also be necessary to eliminate debris.

Starch, in the form of paste, has probably been the most commonly used binder in the past. It gives rise to granulations that disintegrate quickly (Table 4). Its high viscosity is its main disadvantage which makes handling and mixing difficult. To avoid this problem, starch may be added in dry pregelatinized form to the powder mix and

TABLE 10 Binders Commonly Used in the Wet Granulation Process

Binder	Concentration in Granulating Liquid (% w/v)	Granulating Solvent
Starch	5–10	Water
Pregelatinized starch	2–10	Water
Gelatin	2–10	Water
Acacia, tragacanth	5–20	Water
Sugars (glucose, sucrose)	up to 50	Water
Polyvinylpyrrolidone	2–20	Water or alcohol
Methylcellulose (various viscosity grades)	2–10	Water
Sodium carboxymethylcellulose (low-viscosity grade)	2–10	Water
Ethylcellulose (various	5–10	Alcohol or water-
Ethylcellulose (various viscosity grades)	5–10	Alcohol or water-alcohol mixtures
Polyacrylamides	2–8	Water
Polyvinyloxazolidones	5–10	Water or water-alcohol mixtures
Polyvinyl alcohols	5–20	Water

later moistened with water. This process needs two to four times more starch to obtain granulations of the same hardness. Pregelatinized starch may also be used in the form of paste. Its binding properties are slightly better and it offers the advantage of being soluble in warm water without boiling [2].

When a stronger binder is needed, gelatin may be a good choice. Gelatin solutions should be used at elevated temperature to avoid gellification. Gelatin produces hard granulations that tend to harden even more with age.

Acacia and tragacanth solutions have been used as binder agents in the past. However, due to bacterial contamination problems, they have been replaced by the recently developed synthetic polymers.

The most widely used binder is probably PVP. It is inert and has the advantage of being soluble in both water and alcohol. It is used in aqueous and dilute alcoholic solutions to granulate insoluble powders and in alcoholic solutions for soluble powders. It may also be added in dry form. It is widely used in anhydrous alcoholic solutions in the manufacture of effervescent tablets. PVP is also an excellent binder for chewable tablets. Although it is a hydroscopic, tablets harden only slightly with age. To avoid hardening, 2–3% of glycerin may be included in the formulation.

Methylcellulose is used as 1–5% aqueous solution, depending on the viscosity grade [3]. Low viscosity grades (10–50 cP) allow higher concentrations than high viscosity grades (1000–10000 cP). With both soluble and insoluble powders, methylcellulose gives granulations that compress easily and produces tablets which do not harden with age. Sodium carboxymethylcellulose (CMC) can also be used to granulate both soluble and insoluble powders. It produces granulations softer than those with PVP, but the tablets have relatively long disintegration times and greater tendency to harden. Ethylcellulose is insoluble in water and is only used in alcoholic solution. Low viscosity grades are used in concentrations of 2 to 10% in ethanol and less frequently in methylene chloride. Tablets prepared with ethylcellulose have relatively short disintegration times without hardening tendency, but dissolution may be delayed due to low solubility of ethylcellulose in water. Hydroxypropyl methylcellulose (HPMC) is soluble in water, aqueous alcohol solutions, and methylene chloride; it is available in various viscosity grades. It competes with methylcellulose and PVP with regard to versatility and inertness.

Polyacrylamides are water-soluble polymers available in various viscosity grades. In a 2–5% solution they produce granulations similar to those produced with starch paste. The tablets are somewhat softer with the disadvantage of having longer disintegration and dissolution times. Polyvinyloxazolidones resemble PVP in practice but with the advantage of nonhygroscopicity. Since some are water soluble and some are soluble in alcohol or in aqueous alcoholic mixtures, they offer a wide range of applicability and utility.

Theory of Granule Formation

Theories explaining the formation of granules can be divided in two groups:

- Theories about the mechanism of bonding among fundamental particles
- Theories about the enlargement mechanism of agglomerates

- *Layering*. When a second batch of powder mixture is added to the granule bed, it adheres to the already formed granules increasing their size. This mechanism is only important in pelletization for the production of layered granules using spheronization equipment.

Steps in the Traditional Wet Granulation Process

The different steps of traditional wet granulation process are shown in Fig. 7. The process parameters that must be under control during each step depend on the raw material characteristics or the objectives of the granulation process.

Milling and Mixing of Dry Powder Constituents

The dry powder constituents to be granulated should be well mixed to ensure a good distribution of the active ingredient. It is a solid-solid mixing operation [36] which is usually preceeded by a pulverization step to guarantee mix uniformity. An inadequate mixer could give rise to lack of a nonuniform drug content in the end product. These considerations are of special importance for intermediate products in small capsule and tablet manufacturing and when the drug concentration in the mix is relatively low [30,37,38].

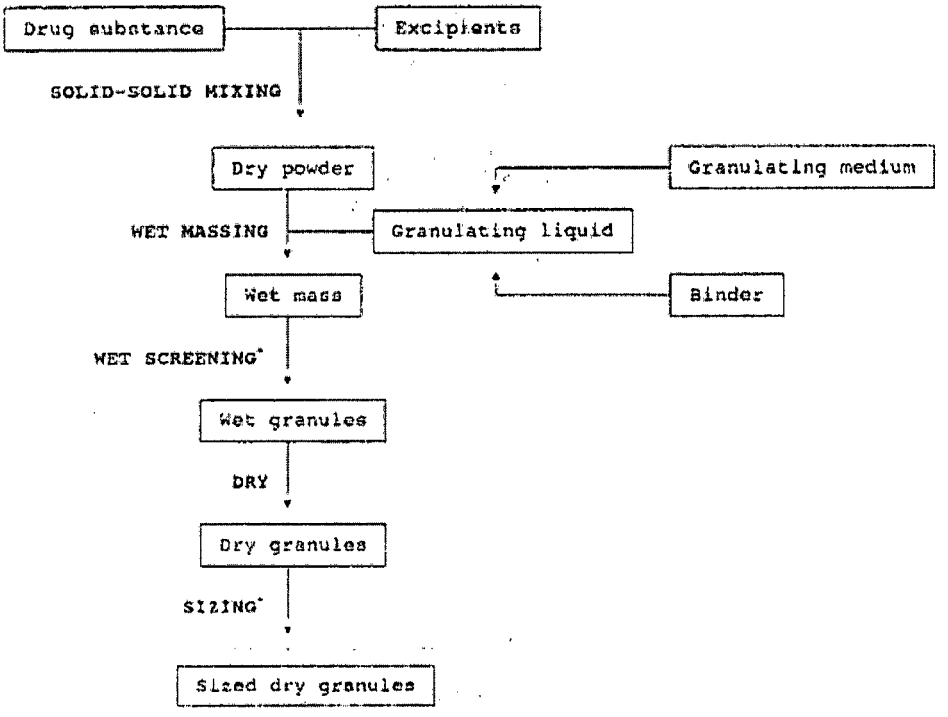

FIG. 7. Steps in the traditional wet granulation process. (*These steps may be omited.)

Advantages and Limitations of Wet Granulation

Wet granulation is a size-enlargement procedure of a powder particle, involving improvements in the powder characteristics. It is, however, not free of problems. The most important ones are related to heat- and moisture-sensitive drugs and soluble substances. In spite of these limitations, wet granulation is extensively used in the industrial manufacturing of tablets and pharmaceutical granules. This is partly due to the improvements in the traditional wet granulation method.

Advantages

Granulation increases the particle size and material sphericity. Moreover, the granules are discrete and rigid structures with a very slight tendency to be compacted by vibration or gravity and with a very low cohesive capacity among themselves. The use of a liquid medium can also change the surface free energy of the material. All these properties determine the high flowability of the granulations.

This improvement in the flowability of a granulated material is especially important in the tablet or capsule manufacture of high-dosage drugs which have a poor flow. Wet granulation gives a free-flowing product and guarantees uniform die filling in the tablet machine and of the capsules [2,17,21,54,55].

In spite of the fact that the granulation reduces cohesivity, the capacity of the granule to form a compact mass under pressure, that is, the compressibility, increases substantially. This increase is due to two fundamental facts. First, the granulation reduces the amount of retained air among the particles and thus reduces the possibility of elastic effects of this trapped air during the compression. Second, the binder films distributed inside and around of the granules are plastically deformed during the compression and join to other binder surfaces by hydrogen bonding [54–58]. As shown in Fig. 13, sulfadiazine forms weak tablets when used alone and capping is produced at high compression pressures, whereas with PVP stronger tablets are obtained without capping [20]. The granules with PVP are deformed plastically with the greatest ease and, with the same applied pressure, give rise to the greatest pressures in the die wall of the tablet machine which results in a harder tablet.

The application of lower pressures in the tablet machine to obtain tablets with the same hardness increases tooling life and machine wear.

Wet granulation improves the content-uniformity of low-dosage drugs. It adds a liquid phase to the solid constituent mixture in which low-dosage drugs and color additives can be dissolved, giving a more homogeneous distribution. This represents a distinct advantage over direct compression, where content uniformity of drugs and uniform color dispersion can be a problem [2].

Wet granulation prevents segregation of components of a homogenous powder mix during processing, transfer, and handling. The powder mix is constituted normally by particles of different density, size, and shape. All the granules, although of different size, present the same composition, which is the same as, or very nearly, that of the powder mixture at the time of the liquid and binder addition. Segregation has a very small effect on the chemical composition variation of the final pharmaceutical form. The dissolution rate of hydrophobic drugs may be improved by wet granulation employing hydrophilic binders.