



Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente No. 09-000.752

Solicitud de patente de invención titulada: "COMPOSICIÓN FARMACÉUTICA
QUE CONTIENE UN ÁCIDO TETRAHIDROFÓLICO"

Solicitante: BAYER SCHERING PHARMA AKTIENGESELLSCHAFT

Nuestra Ref.: P2008/000245

RESPUESTA A LA OPOSICIÓN NOTIFICADA MEDIANTE OFICIO No. 11434
POR FIJACIÓN EN LISTA No. 276 DE FECHA 22 DE JULIO DE 2011

Yo, CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, reasumiendo el poder a mi conferido por la sociedad Bayer Schering Pharma Aktiengesellschaft, me permito manifestar lo siguiente, dentro del plazo legal de prórroga previsto en el artículo 43 de la Decisión 486, ante la oposición interpuesta por el Doctor Tito Noc Parra, actuando como apoderado de la sociedad LAFRANCOL S.A.:

1. En primer lugar, me permito resaltar que, como parte de la respuesta a la Oposición interpuesta por TECNOQUÍMICAS S.A. (notificada mediante el Oficio No. 11436), en este mismo expediente, presenté un **Capítulo Reivindicatorio Modificado** que reemplaza en su totalidad al Capítulo Reivindicatorio Modificado de fecha 20 de septiembre de 2010, en el que se limitó la Reivindicación 1 a una composición que contiene i) una sal farmacéuticamente aceptable del ácido 5-metil-(6S)-tetrahidrofólico, y ii) gránulos que comprenden un progestágeno, un estrógeno y celulosa microcristalina.

Adicionalmente, se eliminaron las antiguas Reivindicaciones 7, 10 a 13, 18 y 19, las antiguas Reivindicaciones 8, 9, 14 a 16 y 20 se reenumeraron en las nuevas Reivindicaciones 7 a 11 y 13, respectivamente, y se introdujo la nueva Reivindicación 12, en la que se combina la materia de las antiguas Reivindicaciones 17 y 19, de acuerdo con las limitaciones de la nueva Reivindicación 1.

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, por el contrario, éstas corresponden a una franca limitación de la materia reivindicada.

2. a- El Opositor argumenta que la presente invención carece de novedad y nivel inventivo, puesto que las composiciones y combinaciones que comprenden un progestágenos, estrógenos y un ácido tetrahidrofólico, ya eran conocidas en el estado del arte. El Opositor anota que el norgestrel, dienogest, ciproterona, estradiol y drospirenona son moléculas conocidas y reveladas por ejemplo en el Index Merck y diferentes patentes (BE623844 y US3959322 para el norgestrel; DE2718872 y US4167517 para dienogest; DE118991 y US3234093 para ciproterona; US2096744 para estradiol, y DE2652761y US4129564 para la drospirenona). El Opositor concluye que no es posible conceder el beneficio de patente a formulaciones que contienen moléculas conocidas en el arte previo.

Adicionalmente, el Opositor señala que se pretende reivindicar materia no patentable, específicamente métodos de tratamiento.

b- i) Con el fin de dar mayor claridad a la materia reivindicada, me permito a continuación explicar los desafíos que debieron enfrentar los presentes inventores que estaban a cargo de la tarea de desarrollar una forma de dosificación que contenga una sal del ácido 5-metil-(6S)-tetrahidrofólico, sensible a la humedad, así como explicar la esencia del invento y los antecedentes que deben ser tenidos en cuenta a la hora de evaluar la actividad inventiva del objeto reivindicado en la presente solicitud de patente.

El formulador que pretende formular una nueva forma de dosificación oral y sólida debe tener en cuenta ciertas consideraciones. Por ejemplo, el formulador deberá concentrar su atención en desarrollar una forma de dosificación que i) proporcione una dosis exacta, efectiva y segura

del/los principio/s activo/s, y ii) mantenga la estabilidad del/los principio/s activo/s durante la manufacturación, el almacenamiento y la administración (es decir, hasta que el principio activo alcance el sitio de absorción en el intestino delgado). En el presente caso, el formulador debió tener en cuenta diversos aspectos:

A) En primer lugar, la sal del ácido 5-metil-(6S)-tetrahidrofólico es sensible a la humedad, al aire y a la tensión mecánica. Por tal motivo, la sal del ácido 5-metil-(6S)-tetrahidrofólico suele ser considerada demasiado sensible como para soportar las condiciones usualmente empleadas, por ejemplo, en un proceso de granulación húmeda.

B) En segundo lugar, sabiendo que un anticonceptivo oral contiene hormonas sexuales poco solubles, tales como el etinilestradiol y la drospirenona, es esencial que la forma de dosificación permita una liberación suficientemente rápida de estas hormonas a fin de asegurar una biodisponibilidad suficientemente alta (y, por ende, una seguridad anticonceptiva alta). En la patente EP1214076 (ver Anexo 1) se demostró la importancia de proporcionar la drospirenona en una forma de liberación inmediata, a pesar de que dicho fármaco tiende a isomerizarse en medio ácido.

En vista de lo anterior, la primera opción del formulador sería preparar la forma de dosificación oral y sólida por compresión directa.

Al seleccionar la compresión directa en lugar de la granulación seguida de la compresión, se evitarían los problemas de inestabilidad de la sal del ácido 5-metil-(6S)-tetrahidrofólico que el formulador supone que ocurrirían si dicho compuesto fuera sometido a un proceso de granulación. Además, el proceso de compresión directa contempla menos pasos o etapas y es más económico que el proceso de granulación seguido de la compresión.

Asimismo, es sabido que, en líneas generales, una sustancia activa se libera más rápidamente y más fácilmente a partir de una forma de dosificación oral y sólida, tal como un comprimido, que ha sido preparada por compresión directa que a partir de un comprimido preparado por granulación y luego por compresión. Esto se demuestra, por ejemplo, en la figura 31-9, página 594, del libro "Remington's Pharmaceutical Sciences" (ver Anexo 2 donde se encuentra copia de la página 594).

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Además, el técnico en la materia elegiría la celulosa microcristalina como excipiente principal para la preparación de una forma de dosificación oral y sólida por compresión directa.

En la publicación de Suzuki et al. (se adjunta copia de dicho documento como Anexo 3) se explica que la celulosa microcristalina se usa ampliamente como excipiente en los procesos de compresión directa (sin embargo, dicha publicación no enseña nada respecto del empleo de la celulosa microcristalina en relación con la granulación) debido a sus buenas propiedades mecánicas (fluidez y compactabilidad).

En la publicación de Suzuki et al. se investiga el efecto de la cristalinidad de la celulosa microcristalina sobre, entre otras cosas, la disolución. De esta publicación se desprende -como era de esperarse- que la compresión directa de tabletas que contienen Avicel®PH101 sin tratar produce una liberación rápida del fármaco activo (véase la Figura 5, página 229, del artículo de Suzuki et al.).

Una enseñanza similar se desprende a partir de la página 1635 del libro “Remington’s Pharmaceutical Science” (ver Anexo 2), en donde se explica que la “celulosa microcristalina (Avicel) se emplea generalmente como excipiente en las fórmulas de compresión directa”.

En resumen, el técnico en la materia que pretende formular una forma de dosificación oral y sólida que contiene un fármaco inestable, tal como una sal del ácido 5-metil-(6S)-tetrahidrofólico, y hormonas sexuales poco solubles que deben ser liberadas inmediatamente a partir de la forma de dosificación, habría contemplado, como primera opción, la preparación por compresión directa de una tableta que contiene celulosa microcristalina, tal como Avicel® PH 101, como excipiente principal. Esto mismo hicieron los inventores de la invención aquí reivindicada.

Tal como se puede apreciar en el Ejemplo 1 de la presente solicitud de patente, se preparó una tableta que contenía celulosa microcristalina (Avicel® PH 101) por compresión directa. Tal como se indica en el mismo ejemplo, esta tableta exhibió una estabilidad satisfactoria respecto del ácido 5-metil-(6S)-tetrahidrofólico durante el ensayo en condiciones aceleradas de almacenamiento.

Sin embargo, los inventores descubrieron con sorpresa que la disolución de la drospirenona a partir de tales tabletas era lenta e insatisfactoria. Lo anterior se demuestra en la Figura 1 de la presente solicitud de patente, en donde se observa que la liberación del etinilestradiol y la sal del ácido 5-metil-(6S)-tetrahidrofólico fue inmediata, mientras que la disolución de la drospirenona fue sorprendentemente lenta.

A fin de resolver el problema de la disolución lenta de la drospirenona los inventores de la presente invención optaron por variar el tipo y la cantidad de excipiente. Sin embargo, y tal como se demuestra en los Ejemplos 2 a 4 de la presente solicitud de patente, los inventores no lograron obtener una liberación rápida y satisfactoria de la drospirenona a pesar de su intento de incluir un cierto número de excipientes adicionales tales como lactosa monohidrato, polvo de celulosa, y una combinación de celulosa microcristalina y lactosa monohidrato.

Finalmente, los inventores de la presente solicitud de patente tomaron la decisión sorprendente de intentar de resolver el problema a través de la preparación de gránulos que contenían celulosa microcristalina.

Esta decisión no era para nada convencional pues, además de emplear un proceso de manufacturación más complicado y más costoso donde la sal del ácido 5-metil-(6S)-tetrahidrofólico era agregada al final del proceso de granulación, contradecía las enseñanzas del arte previo.

Tal como se discutió más arriba, y tal como se desprende de las enseñanzas de Remington, las tabletas (o comprimidos) preparadas a partir de gránulos suelen liberar el principio activo en forma más lenta que las tabletas preparadas por compresión directa (véase la página 594 del libro de Remington, la cual se adjunta al presente escrito)

Asimismo, la celulosa microcristalina es uno de los materiales de relleno (o diluyente) más elegidos para el proceso de compresión directa. Sin embargo, ningún documento del arte previo, incluyendo el artículo de Suzuki et al., se refiere a la celulosa microcristalina como “relleno de elección” en relación con la granulación. De hecho, el único comentario al respecto se encuentra en Remington (página 1635), en donde se enseña que pequeñas cantidades de celulosa microcristalina (5-15%) pueden ser ventajosas en relación con la granulación húmeda a fin de reducir la cementación (case-hardening) y el moteado de tabletas. Sin embargo, Remington no

hace referencia alguna respecto de la capacidad de la celulosa microcristalina de proporcionar una liberación rápida y suficiente del fármaco activo.

Finalmente, Remington (página 1635) enseña que en relación con la granulación húmeda de fármacos poco solubles (tales como las hormonas sexuales) es conveniente emplear diluyentes solubles en agua a fin de evitar problemas de biodisponibilidad. Sin embargo, la celulosa microcristalina es insoluble en agua. Esto se desprende claramente a partir de la ficha técnica referente al Avicel® que se adjunta al presente escrito, en donde al final de la página 2 del Anexo 4, en donde se menciona “Solubilidad en agua (% en peso): insoluble”.

Por consiguiente, si la persona versada en la materia hubiera tenido la idea inusual de manufacturar la forma de dosificación oral y sólida por granulación, habría preferido seleccionar un relleno (o diluyente) soluble en agua, tal como la lactosa, la sacarosa o el manitol, y no un relleno insoluble en agua como la celulosa microcristalina.

Los presentes inventores desafiaron las enseñanzas del arte previo y no sólo decidieron manufacturar la forma de dosificación oral y sólida por granulación, sino que, además, decidieron emplear celulosa microcristalina como material de relleno.

Tal como se explica en los ejemplos 5 y 6 de la presente solicitud de patente, las tabletas preparadas a partir de gránulos que contienen celulosa microcristalina fueron estables en lo que respecta a la “vida de estante” (período de almacenamiento) de la sal del ácido 5-metil-(6S)-tetrahidrofólico y simultáneamente exhibieron una liberación suficientemente rápida de la drospirenona (véase la Figura 3 de la presente solicitud de patente). Este resultado sorprendente no podría haber sido previsto a partir de las enseñanzas del arte previo ni a partir de los experimentos que condujeron al presente invento.

ii) Habiendo explicado la invención aquí reivindicada, en primer lugar, me permito señalar que al parecer, el Opositor pasó por alto el Capítulo Reivindicatorio Modificado radicado el 16 de diciembre de 2009, en donde, dentro de otras limitaciones, se eliminaron las Reivindicaciones 36 a 39 y 48 a 53 dirigidas a usos y métodos de tratamiento, y las cuales tampoco se encuentran en el Capítulo Reivindicatorio Modificado adjunto.

Ahora bien, el Opositor se refiere a extractos de "The Merck Index" y considera que al menos uno de los componentes hormonales del presente invento no es novedoso (en forma aislada) frente a lo divulgado en estos extractos. En vista de la explicación del fundamento del invento proporcionada más arriba, me permito simplemente aclarar que la nueva Reivindicación 1 divulga una combinación novedosa de una sal de un ácido tetrahidrofólico específico y gránulos que comprenden un progestágeno, un estrógeno y celulosa microcristalina. En las páginas del "Merck Index" que presenta el oponente no se describe tal composición. Por consiguiente, el presente invento es claramente novedoso frente a la evidencia presentada por el oponente.

En vista de los argumentos presentados cabe concluir que las nuevas reivindicaciones que se acompañan junto con el presente escrito son novedosas e inventivas frente a las enseñanzas del arte previo citado por los oponentes.

3. Por todo lo anterior, considero que las observaciones presentadas por el Opositor han sido superadas y solicito respetuosamente se proceda con el examen de patentabilidad de la presente invención.

Atentamente,



CARLOS R. OLARTE

C.C. No. 79.782.747 de Bogotá

T.P. 74.295

Anexos:

- Anexo 1. Copia de EP1214076.
- Anexo 2. Copia de las páginas 594 y 1635 del libro "Remington's Pharmaceutical Sciences". Edición 18. 1990.
- Anexo 3. Copia del documento Suzuki T., Nakagami, H. "Effect of crystallinity of microcrystalline cellulose on the compactability and dissolution of tablets"

European Journal of Pharmaceutics and Biopharmaceutics. Vol. 47. Pages 225-230.
1999.

- Anexo 4. Copia de la ficha técnica referente al Avicel®.

(19)



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(54) PHARMACEUTICAL COMBINATION OF ETHINYLESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE

PHARMAZEUTISCHE KOMBINATION VON ETHINYLESTRADIOL UND DROSPIRENONE ALS EMPFÄNGNISVERHÜTENDES MITTEL

MELANGE PHARMACEUTIQUE D'ETHINYLESTRADIOL ET DE DROSPIRENONE UTILISE EN TANT QUE CONTRACEPTIF

(84) Designated Contracting States: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE Designated Extension States: LT LV RO SI (30) Priority: 31.08.1999 EP 99202826 31.08.1999 US 386274 (43) Date of publication of application: 19.06.2002 Bulletin 2002/25 (60) Divisional application: 03017743.0 (73) Proprietor: SCHERING AKTIENGESELLSCHAFT 13342 Berlin (DE) (72) Inventors: • HEIL, Wolfgang D-10825 Berlin (DE) • HILMAN, Jürgen D-13351 Berlin (DE) • LIPP, Ralph D-14169 Berlin (DE) • HEITHECKER, Renate D-14163 Berlin (DE) (74) Representative: Plougmann & Vingtoft A/S Sundkrogsgade 9 P.O. Box 831 2100 Copenhagen O (DK)	(56) References cited: WO-A-95/17194 WO-A-95/26730 WO-A-97/01342 WO-A-98/04267 WO-A-98/04269 • OELKERS W K H: "Effects of estrogens and progestogens on the renin-aldosterone system and blood pressure" STEROIDS: STRUCTURE, FUNCTION, AND REGULATION,US,ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, vol. 61, no. 4, 1 April 1996 (1996-04-01), pages 166-171, XP004026568 ISSN: 0039-128X • OELKERS W ET AL: "EFFECTS OF A NEW ORAL CONTRACEPTIVE CONTAINING AN ANTIMINERALOCORTICOID PROGESTOGEN, DROSPIRENONE, ON THE RENIN-ALDOSTERONE SYSTEM, BODY WEIGHT, BLOOD PRESSURE, GLUCOSE TOLERANCE, AND LIPID METABOLISM" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM,US,NEW YORK, NY, vol. 80, no. 6, 1 June 1995 (1995-06-01), pages 1816-1821, XP002046619 ISSN: 0021-972X • MUHN P ET AL: "Drospirenone: a novel progestogen with antimineralocorticoid and antiandrogenic activity. Pharmacological characterization in animal models." CONTRACEPTION, (1995 FEB) 51 (2) 99-110., XP000908817
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Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

- NUERNBERG E.: "[Manufacturing and properties of spray dried products]. HERSTELLUNG UND EIGENSCHAFTEN PHARMAZEUTISCHER SPRUHTROCKNUNGSPRODUKTE." ACTA PHARMACEUTICA HUNGARICA, (1978) 48/1 (19-35). CODEN: APHGAO, XP000908820

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

FIELD OF THE INVENTION

[0001] The present invention relates to a pharmaceutical composition comprising drospirenone and ethinylestradiol, a method of providing dissolution of drospirenone, methods of inhibiting ovulation by administration of drospirenone and the use of drospirenone and ethinylestradiol for inhibiting ovulation.

BACKGROUND OF THE INVENTION

[0002] Oral contraceptives containing a combination of a gestagen and an estrogen component have been used since the 1960's. The earliest contraceptive preparations consisted of 21 tablets containing the combination of active agents and 7 tablets containing no active agent, and the amount of each active agent was the same in each tablet (the so-called one-phase preparations). Subsequently, preparations were developed that consisted of tablets containing different amounts and ratios of the active agents over the cycle of administration (the so-called multiple-phase preparations).

[0003] Contraceptive reliability is mainly provided by the gestagen component. The daily dosage should be at least the minimum of what is needed for the gestagen in question to inhibit ovulation effectively. The estrogen component acts to increase the ovulation inhibitory effect of gestagen and to ensure cycle stability. Since the introduction of oral contraceptives, the daily dosage of gestagen has been reduced through the development of new and more efficient gestagens than were present in the earlier contraceptive preparations. It has also been possible to reduce the daily dosage of estrogen.

[0004] $6\beta,7\beta;15\beta,16\beta$ -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) is known from DE 26 52 761 in which its use as a diuretic compound is disclosed.

[0005] In DE 30 22 337, the gestagen-like activity of the compound and its consequent utility as a contraceptive agent is described at dosage levels of 0.5-50 mg of drospirenone per day. It is also noted that the mechanism of action of the compound is very similar to that of the natural corpus luteum hormone progesterone, and that it does not give rise to increased blood pressure for which reason it may be administered to women who have or are at risk of developing increased blood pressure. It is further described that drospirenone may be administered together with ethinylestradiol in an amount of 0.03-0.05 mg per day.

[0006] DE 30 51 166 discloses the use of the drospirenone for the treatment of gynaecological irregularities and for contraception at a dosage level of 0.5-50 mg per day.

[0007] EP 398 460 discloses the use of drospirenone for the treatment of androgen-induced disorders, aldosterone-induced disorders and hormonal irregularities as

well as for contraception at dosage levels of 0.5-50 mg, preferably 1-10 mg per day. Ethinylestradiol may be co-administered at a level of 0.02-0.04 mg per day.

[0008] US 5,756,490 discloses pharmaceutical combination preparations comprising 23 or 24 dosage units containing a combination of a gestagen and an estrogen and 4-10 dosage units containing estrogen alone. Drospirenone is mentioned as a possible, but not preferred, gestagenic compound and ethinylestradiol is mentioned as a possible, but not preferred, estrogenic compound.

[0009] Micronised particles are disclosed in Bauer KH, Frömming KH and Führer C (Pharmazeutische Technologie; 4. Aufl.; Thieme, Stuttgart/New York; 1993).

SUMMARY OF THE INVENTION

[0010] In the course of research leading to the present invention, it has surprisingly been found that a hitherto undisclosed minimum dosage level of drospirenone is required for reliable contraceptive activity. Similarly, a preferred maximum dosage has been identified at which unpleasant side effects, in particular excessive diuresis, may substantially be avoided.

[0011] Accordingly, in a first aspect, the present invention relates to a pharmaceutical composition comprising, as a first active agent, $6\beta,7\beta;15\beta,16\beta$ -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.

[0012] Apart from the active substances themselves, it is envisaged that an ester or prodrug of drospirenone may be employed in the present composition, e.g. an oxyiminopregnane carbolactone as disclosed in WO 98/24801. Likewise, it is envisaged that esters or ethers of ethinylestradiol may be included in the composition.

[0013] In a further aspect, the invention relates to a method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, drospirenone in an amount in the range of from about 2 mg to about 4 mg of per day, together with ethinylestradiol in an amount of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to inhibit ovulation in said mammal.

[0014] In a still further aspect, the invention relates to the use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the composition,

of from about 0.01 to about 0.05 mg.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The invention is further described with reference to the drawings in which

Fig. 1 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, V1-V7 being batches containing micronized drospirenone, and V8 being a batch containing macrocrystalline drospirenone;

Fig. 2 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, different lines representing different test batches;

Fig. 3 is a graph showing the in vitro dissolution rate of drospirenone from film-coated tablets, different lines representing different test batches;

Fig. 4 is a graph showing the in vitro dissolution rate of ethinylestradiol from tablet cores, different lines representing different test batches; and

Fig. 5 is a graph showing the in vitro dissolution rate of ethinylestradiol from film-coated tablets, different lines representing different test batches.

DETAILED DISCLOSURE OF THE INVENTION

[0016] Drospirenone, which may be prepared substantially as described in, e.g., US 4,129,564 or WO 98/06738, is a sparingly soluble substance in water and aqueous buffers at various pH values. Furthermore, drospirenone is rearranged to an inactive isomer under acid conditions and hydrolysed under alkaline conditions. To ensure good bioavailability of the compound, it is therefore advantageously provided in a form that promotes rapid dissolution thereof.

[0017] It has surprisingly been found that when drospirenone is provided in micronized form (so that particles of the active substance have a surface area of more than 10,000 cm²/g, and the following particle size distribution as determined under the microscope: not more than 2 particles in a given batch with a diameter of more than 30 µm, and preferably ≤ 20 particles with a diameter of ≥ 10 µm and ≤ 30 µm) in a pharmaceutical composition, rapid dissolution of the active compound from the composition occurs in vitro ("rapid dissolution" is defined as the dissolution of at least 70% over about 30 minutes, in particular at least 80% over about 20 minutes, of drospirenone from a tablet preparation containing 3 mg of drospirenone in 900 ml of water at 37°C determined by the USP XXIII Paddle Method using a USP dissolution test apparatus 2 at 50 rpm). Instead of providing the drospirenone in micronized form, it is possible to dissolve it in a suitable solvent, e.g. methanol or ethyl acetate,

and spray it onto the surface of inert carrier particles followed by incorporation of the particles containing drospirenone on their surface in the composition.

[0018] Without wishing to be limited to any particular theory, it appears that the in vitro dissolution rate of drospirenone is connected to the dissolution rate in vivo resulting in rapid absorption of drospirenone in vivo on oral administration of the compound. This is an advantage because isomerization of the compound in the gastric environment and/or hydrolysis in the intestine is substantially reduced, leading to a high bioavailability of the compound.

[0019] With respect to ethinylestradiol which is also a sparingly soluble substance, though less sensitive to degradation than drospirenone under conditions prevailing in the gastrointestinal tract, it is also an advantage to provide it in micronized form or sprayed from a solution, e.g. in ethanol, onto the surface of inert carrier particles. This has the added advantage of facilitating a more homogenous distribution of the ethinylestradiol throughout the composition which might otherwise be difficult to obtain because ethinylestradiol is incorporated in extremely small amounts. When ethinylestradiol is provided in micronized form, it preferably has the following particle size distribution as determined under the microscope: 100% of the particles have a diameter of ≤ 15.0 µm, 99% of the particles have a diameter of ≤ 12.5 µm, 95% of the particles have a diameter of ≤ 10.0 µm, and 50% of the particles have a diameter of ≤ 3.0 µm. Furthermore, no particle is larger than 20 µm, and ≤ 10 particles have a diameter of ≥ 15 µm and ≤ 20 µm.

[0020] To obtain a more rapid rate of dissolution, it is preferred to include carriers or excipients which act to promote dissolution of both active substances. Examples of such carriers and excipients include substances that are readily soluble in water such as cellulose derivatives, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, gelled starch, gelatin or polyvinylpyrrolidone. In particular, it appears as though polyvinylpyrrolidone might be particularly helpful to promote dissolution.

[0021] The composition of the invention preferably comprises drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about 3 mg. The amount of ethinylestradiol preferably corresponds to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.015 mg to about 0.03 mg. More particularly, the present composition comprises an amount of drospirenone corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

[0022] 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 con-

traceptive disclosed above. Furthermore, since drospirenone is an aldosterone antagonist, it has diuretic properties and is therefore suitable for counteracting the water-retentive properties of ethinylestradiol.

[0023] In a particular embodiment, the invention relates to a pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein each of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

[0024] In one embodiment, the preparation further comprises 7 or less said daily dosage units containing no active agent. Alternatively, it is possible to include, in the dosage regimen, a period of 7 days or less during which no dosage units are ingested. For compliance reasons, however, it may be preferred to include an appropriate number of blanks in the preparation, in which case the total number of daily dosage units in the preparation is at least 28. The inclusion of blanks, or the pill-free days, will then trigger withdrawal bleeding.

[0025] The preparation may be a 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 case of multiple-phase preparation, it may be possible to include a natural estrogen such as estradiol, e.g. in an amount of from about 0.5 mg to about 4 mg per day, instead of ethinylestradiol.

[0026] In suitable embodiments of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol may be 21, 22, 23 or 24, and the number of daily dosage units containing no active agent may then be 7, 6, 5 or 4, as the case may be. In a further embodiment of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.

[0027] In an alternative embodiment, the invention relates to a contraceptive preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, and wherein 7 or less of said daily dosage units contain ethinylestradiol alone in an amount from about 0.01 to about 0.05 mg.

[0028] By including an appropriate number of dosage

units comprising ethinylestradiol alone, high contraceptive reliability, low follicular development and satisfactory cycle control with little or no intermenstrual bleeding may be obtained.

[0029] In this case, too, the preparation may be one in which the amounts of either active agent remains constant for the entire at least 21-day period (i.e. a two-phase preparation), 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 three- or four-phase preparation, it substantially as disclosed in, e.g., EP 148 724. In case of multiple-phase preparation, it may be possible to include a natural estrogen such as estradiol, e.g. in an amount of from about 0.5 mg to about 4 mg per day, instead of ethinylestradiol.

[0030] In suitable embodiments of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol may be 21, 22, 23 or 24, and the number of daily dosage units containing ethinylestradiol alone may then be 7, 6, 5 or 4, as the case may be.

[0031] In one embodiment of the present method of inhibiting ovulation, the method comprises administering, to said mammal, 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 ethinylestradiol 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.

[0032] In suitable embodiments of this method, the daily dosage units comprising the combination of drospirenone and ethinylestradiol may be administered for 21, 22, 23 or 24 consecutive days, and the daily dosage units containing no active agent may then be administered for 7, 6, 5 or 4 consecutive days, as appropriate. Furthermore, the daily dosage units comprising the combination of drospirenone and ethinylestradiol may be administered for 28 consecutive days. In a variant of this embodiment, the daily dosage units comprising the combination of drospirenone and ethinylestradiol 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 ethinylestradiol for 21, 22, 23 or 24 consecutive days and subsequently administration of the daily dosage units containing no active agent, or administration of no daily dosage units, for 7, 6, 5 or 4 consecutive days.

[0033] Alternatively, the present method 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 ethinylestradiol 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 ethinylestradiol alone in an amount of from

about 0.01 mg to about 0.05 mg.

[0034] In this alternative method, the daily dosage units comprising the combination of drospirenone and ethinylestradiol may suitably be administered for 21, 22, 23 or 24 consecutive days, and wherein the daily dosage units comprising ethinylestradiol 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 ethinylestradiol 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 ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units comprising ethinylestradiol alone for 7 consecutive days.

[0035] For use according to the invention, the pharmaceutical preparation may suitably be in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein each of said daily dosage units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

[0036] As indicated above, the preparation may further comprise 7 or less daily dosage units containing no active agent (or may contain 7 or less empty "places", e.g. in the form of empty blisters in a blister pack, marking the days on which no daily dosage units are administered).

[0037] Alternatively, the pharmaceutical preparation may be in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount of from about 0.01 to about 0.05 mg, said packaging unit further comprising 7 or less daily dosage units comprising ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

[0038] The composition of the invention may be formulated in any manner known in the pharmaceutical art. In particular, as indicated above, the composition may be formulated by a method comprising providing drospirenone and, if desired, ethinylestradiol in micronized form in said unit dosage form, or sprayed from a solution onto particles of an inert carrier in admixture with one or more pharmaceutically acceptable excipients that promote dissolution of the drospirenone and ethinylestradiol so as to promote rapid dissolution of drospirenone and preferably ethinylestradiol on oral administration. Examples of suitable excipients include fillers, e.g. sugars such as lactose, glucose or sucrose, sugar alcohols such as mannitol, sorbitol or xylitol, starch such as

wheat, corn or potato starch, modified starch or sodium starch glycolate, lubricants such as talc, magnesium stearate, calcium stearate, colloidal silica or stearic acid, and binders such as polyvinylpyrrolidone, cellulose derivatives, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose or gelatin, for making oral dosage forms such as tablets, pills or capsules.

[0039] Tablets may conveniently be coated with a suitable film-forming agent, e.g. hydroxypropylmethyl cellulose, hydroxypropyl cellulose or ethyl cellulose, to which a suitable excipient may optionally be added, e.g. a softener such as glycerol, propylene glycol, diethylphthalate or glycerol triacetate, filler such as sucrose, sorbitol, xylitol, glucose or lactose, a colorant such as titanium hydroxide, etc.

[0040] The present composition may also be formulated in liquid form, e.g. as a solution, suspension or emulsion, together with conventional diluents or excipients in a manner known per se in the pharmaceutical art.

[0041] A packaging unit comprising the daily dosage units described above may be prepared in a manner analogous to that of making other oral contraceptives. This may for instance be a conventional blister pack or any other form known for this purpose, for instance a pack comprising the appropriate number of dosage units (in this case at least 21, or for particular applications, 28 or a multiple of 28) in a sealed blister pack with a cardboard, paperboard, foil or plastic backing and enclosed in a suitable cover. Each blister container may conveniently be numbered or otherwise marked, e.g. starting with the first of the at least 21 dosage units that contain the combination of drospirenone and ethinylestradiol, optionally followed by 7 or less empty blisters or by the 7 or less dosage units that contain no active agent or that only contain ethinylestradiol (although the numbering may also start with the first of the 7 or less dosage units that only contain ethinylestradiol).

[0042] It is also envisaged that the present composition may be in the form of a parenteral formulation such as a subcutaneous implant or transdermal formulation. For making implants, the active agents may suitably be formulated together with one or more polymers that are gradually eroded or degraded when in use, e.g. silicone polymers; ethylene vinylacetate, polyethylene or polypropylene.

[0043] Where transdermal formulations are concerned, they may be prepared in the form of matrices or membranes or as fluid or viscous formulations in oil or hydrogels. For transdermal patches, an adhesive which is compatible with the skin should be included, such as polyacrylate, a silicone adhesive or polyisobutylene, as well as a foil made of, e.g. polyethylene, polypropylene, ethylene vinylacetate, polyvinylchloride, polyvinylidene chloride or polyester, and a removable protective foil made from, e.g., polyester or paper coated with silicone or a fluoropolymer. For the preparation of transdermal solutions or gels, water or organic solvents or mixtures

thereof may be used. Transdermal gels may furthermore contain one or more suitable gelling agents or thickeners such as silicone, tragacanth, starch or starch derivatives, cellulose or cellulose derivatives or polyacrylic acids or derivatives thereof. Transdermal formulations may also suitably contain one or more substances that enhance absorption through the skin, such as bile salts or derivatives thereof and/or phospholipids. Suitable transdermal formulations may, for instance, be made in a manner analogous to that described in WO 94/04157 for 3-ketodesogestrel. Alternatively, transdermal formulations may be prepared according to a method disclosed in, e.g., BW Barry, "Dermatological Formulations, Percutaneous Absorption", Marcel Dekker Inc., New York - Basel, 1983, or YW Chien, "Transdermal Controlled Systemic Medications", Marcel Dekker Inc., New York - Basel, 1987.

[0044] The present invention is further described in the following examples.

EXPERIMENTAL

Example 1

Preparation of tablets containing drospirenone and ethinylestradiol

[0045] Tablet cores of the following composition

micronized drospirenone	3.00 mg
micronized ethinylestradiol	0.03 mg
lactose monohydrate	48.17 mg
corn starch	14.40 mg
modified starch	9.60 mg
polyvinylpyrrolidone 25,000	4.00 mg
magnesium stearate	0.80 mg

were prepared by charging a fluidized bed granulator with 31.68 kg corn starch, 21.12 kg modified starch, 6.60 kg micronized drospirenone, 0.066 kg micronized ethinylestradiol and 105.974 kg lactose monohydrate and activating the fluidized bed. An aqueous solution of 8.80 kg polyvinylpyrrolidone 25,000 in 46.20 kg purified water was sprayed continuously onto the fluidized bed while drying by heating the air stream of the fluidized bed. At the end of the process 1.76 kg magnesium stearate was sucked into the granulator and mixed with the granules by maintaining the fluidized bed. The resulting granulate was pressed into tablet cores by compression using a rotary tablet press.

[0046] 2.22464 kg of hydroxypropylmethylcellulose and 0.44528 kg macrogol 6000 were dissolved in 14.67 kg purified water. 0.44528 kg talc, 1.22430 kg titanium dioxide and 0.06050 kg ferric oxide pigment were suspended in 10.26 kg purified water with stirring and homogenized. The solution and suspension were combined and used to coat the tablet cores by continuous

application of the coating suspension in a coater.

Example 2

5 *Dissolution of drospirenone from tablets*

[0047] The rate of dissolution of drospirenone from the tablets prepared in Example 1 was determined by the USP XXIII Paddle Method using a USP Dissolution Test Apparatus 2 including 6 covered glass vessels and 6 paddles. Tablets were placed in 900 ml water at a temperature of 37°C ($\pm$ 0.5°C) and stirred at 50 rpm. The results appear from Figs. 1, 2 and 4. From Fig. 1, it appears that the batch numbered V8 containing macrocrystalline drospirenone (but otherwise identical to the tablets prepared in Example 1) exhibited an extremely slow dissolution rate of drospirenone, whereas all batches containing micronized drospirenone exhibited a dissolution rate of more than 70% within 30 minutes.

20 [0048] Fig. 2 and Fig. 4 shows the results of dissolution of drospirenone from tablet cores and film-coated tablets, respectively. In both cases more than 70% of the active agent is dissolved within 30 minutes. Thus, the film coating did not significantly influence the rate of dissolution.

Example 3

Dissolution rate of ethinylestradiol from tablets in vitro

30 [0049] The rate of dissolution of ethinylestradiol from tablets prepared as described in Example 1 was determined according to the USP Paddle Method as described in Example 2 for drospirenone. The results appear from Figs. 3 and 5 showing the dissolution rates from tablet cores and film-coated tablets, respectively. In both cases, more than 70% of the active agent was dissolved within 30 minutes. Thus, the film coating did not significantly influence the rate of dissolution.

Example 4

45 *Bioavailability of drospirenone and ethinylestradiol from tablets containing 3 mg of drospirenone and 0.03 mg ethinylestradiol*

[0050] 42 healthy women between 18 and 35 years of age were included in an open-label crossover study after their informed consent had been obtained. The aim of the study was to investigate the relative bioavailability of drospirenone and ethinylestradiol from a tablet formulation containing 3 mg drospirenone and 0.03 mg ethinylestradiol with reference to an oral suspension containing 6 mg of drospirenone and 0.06 mg ethinylestradiol per vial.

55 [0051] The bioavailability was determined using serum concentrations of each active agent as parameters. Compared to the oral suspension, the relative bioavail-

ability of drospirenone and ethinylestradiol from the tablets is 107% and 117%, respectively. It was therefore concluded that both drospirenone and ethinylestradiol are completely released from the tablets in vivo.

[0052] The absolute bioavailability of drospirenone was determined in two studies to be $76\% \pm 13\%$ after oral administration of 2 mg drospirenone to 8 young healthy women and $85\% \pm 24\%$ after oral administration of micronized drospirenone to 6 postmenopausal women.

[0053] The oral bioavailability of ethinylestradiol was determined in several studies, and mean values of from 36% to 59% were reported in the literature, indicating a first-pass effect.

Example 5

Contraceptive efficacy of formulations containing drospirenone and ethinylestradiol

[0054] An open-label, randomized trial with 52 female volunteers aged 20-35 years whose informed consent had been obtained included 1 pre-treatment cycle, 3 treatment cycles with two different tablets containing 2 mg and 3 mg drospirenone, respectively, but otherwise corresponding to the tablets prepared in Example 1, and a follow-up phase. A wash-out phase of 1 month preceded the treatment.

[0055] At defined time points, selected central and peripheral parameters were investigated: LH, FSH, 17β -estradiol, progesterone, cervical score, "spinnbarkeit", fern phenomenon. Ovarian function was checked by ultrasound. In addition, SHBG, CBG, prolactin, total testosterone, androstenedione, DHEA-S and selected metabolic parameters (serum glucose, triglycerides, cholesterol, HDL, LDL) were examined. Blood pressure, heart rate, body weight and cycle control were documented.

[0056] The results of the study showed that both LH and FSH were clearly suppressed with both trial preparations. Accordingly, the secretion of estradiol and progesterone were greatly reduced over all three treatment cycles with the exception of 3 volunteers receiving the 2 mg drospirenone preparation. This result was, in principle, confirmed by the accompanying ultrasound examinations. Follicular ripening occurred in several cases with both trial preparations. Although three ovulations were diagnosed with the preparation containing 2 mg drospirenone (one of which was described as "equivocal" and the other as a "tablet-taking error"), no differences were demonstrable statistically ($p > 0.05$) between the two trial preparations as regards the hormones LH, FSH, estradiol and progesterone, and the parameter "ovulation during the treatment cycles". In keeping with the hormones, cervical function was greatly limited and the "spinnbarkeit" and crystallisability of the cervical mucus was greatly reduced with both trial preparations. Prolactin increased minimally and SHBG

and CBG distinctly with both preparations. Triglycerides and HDL levels increased with both trial preparations, while LDL levels decreased. Total cholesterol was largely unchanged in both treatment groups. Oral glucose tolerance remained virtually unchanged or was slightly decreased. Testosterone, androstenedione and DHEA-S decreased minimally.

[0057] The subjective and objective tolerance was good with both treatments. This was also the case for cycle control with the exception of the first cycle with 2 mg drospirenone. Blood pressure, heart rate and body weight remained constant in the majority of cases or showed a slight tendency to decrease.

[0058] After three months' treatment, it was concluded:

[0059] The two trial preparations were equally good as regards the subjective and objective tolerance.

[0060] No negative metabolic effects were observed with either preparation. HDL was influenced positively in the sense of an increase.

The results confirmed the results of earlier studies that the 2 mg drospirenone preparation was in the threshold region of ovulation inhibition, whereas the 3 mg drospirenone preparation had a demonstrable ovulation-inhibiting effect in all cases examined.

Claims

1. A pharmaceutical composition comprising, as a first active agent drospirenone in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to 4 mg, and as a second active agent, ethinylestradiol in an amount corresponding to a daily dosage of from about 0.01 mg to 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients, wherein said drospirenone is in micronized form.
2. The composition according to claim 1, wherein the drospirenone has a surface area of more than 10 000 cm²/g.
3. The composition according to any one of claims 1 or 2, wherein at least 70% of said drospirenone is dissolved from said composition within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate.
4. The composition according to any one of claims 1 to 3, wherein drospirenone is sprayed from a solution of drospirenone onto particles of an inert carrier.
5. The composition according to any one of claims 1 to 4, wherein the in vitro dissolution of ethinylestradiol is such that at least 70% is dissolved within 30 minutes, as determined by USP XXIII Paddle Method II.

od II using water at 37°C as the dissolution media and 50 rpm as the stirring rate.

6. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to 4 mg and ethinylestradiol in an amount from about 0.01 to 0.05 mg, wherein said drospirenone is in micronized form.
7. The preparation according to claim 6, wherein the drospirenone has a surface area of more than 10 000 cm²/g.
8. The preparation according to any one of claims 6 or 7, wherein at least 70% of said drospirenone is dissolved from said dosage unit within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate.
9. The preparation according to any one of the claims 6 to 8, wherein said ethinylestradiol is in micronized form or sprayed from a solution onto particles of an inert carrier.
10. The preparation according to any one of claims 6 to 9, which additionally comprises 7 or less daily dosage units containing no active agent intended for oral administration subsequent to the period of at least 21 consecutive days, the total number of daily dosage units being at least 28.
11. The preparation according to any one of claims 6 to 9, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units containing no active agent is 7, 6, 5 or 4.
12. The preparation according to any one of claims 6 to 9 intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to 4 mg and ethinylestradiol in an amount from about 0.01 to 0.05 mg, and wherein 7 or less of said daily dosage units contain ethinylestradiol alone in an amount from about 0.01 to 0.05 mg.
13. The preparation according to any one of claims 6 to 9, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the

number of daily dosage units comprising ethinylestradiol alone is 7, 6, 5 or 4.

14. The preparation according to any one of claims 6 to 9, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.
15. The preparation according to claim 6, wherein the number of daily dosage units intended for oral administration is 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 ethinylestradiol for 21, 22, 23 or 24 consecutive days and subsequently administration of the daily dosage units containing no active agent, or administration of no daily dosage units, for 7, 6, 5 or 4 consecutive days.
16. Use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical composition for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the composition, of from about 0.01 to 0.05 mg, and wherein said drospirenone is in micronized form.
17. The use according to claim 16, wherein said drospirenone has a surface area of more than 10 000 cm²/g.
18. The use according to any one of claims 16 or 17, wherein at least 70% of said drospirenone is dissolved from said composition within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate.
19. The use according to any one of claims 16 to 18, wherein the dissolution of ethinylestradiol is such that at least 70% is dissolved within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate.

Patentansprüche

1. Pharmazeutische Zusammensetzung, die als ersten Wirkstoff Drospirenon in einer Menge enthält, die bei der Gabe der Zusammensetzung einer Tagesdosis von 2 mg bis 4 mg entspricht, und als zweiten Wirkstoff Ethinylestradiol in einer Menge,

- die einer Tagesdosis von etwa 0,01 mg bis 0,05 mg entspricht, gemeinsam mit einem oder mehreren pharmazeutisch annehmbaren Trägern oder Arzneimittelträgern, wobei das Drospirenon in mikronisierter Form vorliegt.
2. Zusammensetzung nach Anspruch 1, wobei das Drospirenon eine Oberfläche von mehr als 10 000 cm²/g hat.
 3. Zusammensetzung nach einem der Ansprüche 1 oder 2, wobei mindestens 70% des Drospirenons innerhalb von 30 Minuten aus der Zusammensetzung wie mit der USP XXIII Paddle-Methode II unter Verwendung von Wasser mit 37 °C als Lösefluid und 50 U/Min. als Rührgeschwindigkeit bestimmt herausgelöst werden.
 4. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei Drospirenon aus einer Drospirenonlösung auf Partikel eines inerten Trägers gesprüht wird.
 5. Zusammensetzung nach einem der Ansprüche 1 bis 4, wobei die in-vitro-Auflösung von Ethinylestradiol derart ist, dass mindestens 70% innerhalb von 30 Minuten wie mit der USP XXIII Paddle-Methode II unter Verwendung von Wasser mit 37 °C als Lösefluid und 50 U/Min. als Rührgeschwindigkeit bestimmt herausgelöst werden.
 6. Pharmazeutisches Präparat bestehend aus einer Anzahl getrennt verpackter und einzeln herausnehmbarer Tagesdosisseinheiten, in eine Verpackungseinheit platziert und für die orale Gabe für eine Dauer von mindestens 21 aufeinander folgenden Tagen bestimmt, wobei die Tagesdosisseinheiten eine Kombination aus Drospirenon in einer Menge von etwa 2 mg bis 4 mg und Ethinylestradiol in einer Menge von etwa 0,01 bis 0,05 mg enthalten, wobei das Drospirenon in mikronisierter Form vorliegt.
 7. Präparat nach Anspruch 6, wobei das Drospirenon eine Oberfläche von mehr als 10 000 cm²/g hat.
 8. Präparat nach einem der Ansprüche 6 oder 7, wobei mindestens 70% des Drospirenons aus der Tagesdosisseinheit innerhalb von 30 Minuten wie mit der USP XXIII Paddle-Methode II unter Verwendung von Wasser mit 37 °C als Lösefluid und 50 U/Min. als Rührgeschwindigkeit bestimmt herausgelöst werden.
 9. Präparat nach einem der Ansprüche 6 bis 8, wobei das Ethinylestradiol in mikronisierter Form oder aus einer Lösung auf Partikel eines inerten Trägers gesprüht vorliegt.
 10. Präparat nach einem der Ansprüche 6 bis 9, das zusätzlich 7 oder weniger Tagesdosisseinheiten enthält, die keinen Wirkstoff enthalten, die zur oralen Gabe im Anschluss an die Periode von mindestens 21 aufeinander folgenden Tagen bestimmt sind, wobei die Gesamtanzahl der Tagesdosisseinheiten mindestens 28 beträgt.
 11. Präparat nach einem der Ansprüche 6 bis 9, wobei die Anzahl der Tagesdosisseinheiten, die die Kombination aus Drospirenon und Ethinylestradiol enthalten, 21, 22, 23 oder 24 beträgt und wobei die Anzahl der Tagesdosisseinheiten, die keinen Wirkstoff enthalten, 7, 6, 5 oder 4 beträgt.
 12. Präparat nach einem der Ansprüche 6 bis 9, das zur oralen Gabe für eine Periode von mindestens 28 aufeinander folgenden Tagen bestimmt ist, wobei mindestens 21 der Tagesdosisseinheiten eine Kombination aus Drospirenon in einer Menge von etwa 2 mg bis 4 mg und Ethinylestradiol in einer Menge von etwa 0,01 bis 0,05 mg enthalten und wobei 7 oder weniger der Tagesdosisseinheiten nur Ethinylestradiol in einer Menge von etwa 0,01 bis 0,05 mg enthalten.
 13. Präparat nach einem der Ansprüche 6 bis 9, wobei die Anzahl der Tagesdosisseinheiten, die die Kombination aus Drospirenon und Ethinylestradiol enthalten, 21, 22, 23 oder 24 beträgt und wobei die Anzahl der Tagesdosisseinheiten, die nur Ethinylestradiol enthalten, 7, 6, 5 oder 4 beträgt.
 14. Präparat nach einem der Ansprüche 6 bis 9, wobei die Anzahl der Tagesdosisseinheiten, die die Kombination aus Drospirenon und Ethinylestradiol enthalten, 28 oder ein Vielfaches von 28 beträgt, wie zum Beispiel 2 bis 4 Mal, insbesondere 2 bis 3 Mal, 28.
 15. Präparat nach Anspruch 6, wobei die Anzahl der platzierten Tagesdosisseinheiten für die orale Gabe für 2 bis 4, vorzugsweise 2 oder 3, Mal 28 aufeinander folgende Tage bestimmt ist, gefolgt von der Gabe von Tagesdosisseinheiten, die die Kombination aus Drospirenon und Ethinylestradiol enthalten, während 21, 22, 23 oder 24 aufeinander folgenden Tagen und danach Gabe von Tagesdosisseinheiten, die keinen Wirkstoff enthalten, oder keine Gabe von Tagesdosisseinheiten während 7, 6, 5 oder 4 aufeinander folgenden Tagen.
 16. Verwendung von Drospirenon kombiniert mit Ethinylestradiol zur Zubereitung einer pharmazeutischen Zusammensetzung zur Inhibition des Eisprungs in einem Säugetier, insbesondere beim Menschen, wobei die Zusammensetzung eine Menge Drospirenon enthält, die bei der Gabe der

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- Zusammensetzung einer Tagesdosis von etwa 2 mg bis 4 mg entspricht, und die eine Menge Ethinylestradiol enthält, die bei der Gabe der Zusammensetzung einer Tagesdosis von etwa 0,01 bis 0,05 mg entspricht und wobei das Drospironon in mikronisierter Form vorliegt.
17. Verwendung nach Anspruch 16, wobei das Drospironon eine Oberfläche von mehr als 10 000 cm²/g hat.
18. Verwendung nach einem der Ansprüche 16 oder 17, wobei mindestens 70% des Drospironons aus der Zusammensetzung innerhalb von 30 Minuten wie mit der USP XXIII Paddle-Methode II unter Verwendung von Wasser mit 37 °C als Lösefluid und 50 U/Min. als Rührgeschwindigkeit bestimmt herausgelöst werden.
19. Verwendung nach einem der Ansprüche 16 bis 18, wobei die Auflösung von Ethinylestradiol derart ist, dass mindestens 70% innerhalb von 30 Minuten wie durch die USP XXIII Paddle-Methode II unter Verwendung von Wasser mit 37 °C als Lösefluid und 50 U/Min. als Rührgeschwindigkeit bestimmt herausgelöst werden.

Revendications

1. Composition pharmaceutique comprenant, comme premier agent actif, de la drospirénone, en quantité correspondant à une dose journalière, lors de l'administration de la composition, d'environ 2 mg à 4 mg et, comme second agent actif, de l'éthinylestradiol, en quantité correspondant à une dose journalière d'environ 0,01 mg à 0,05 mg, avec un ou plusieurs véhicules ou excipients pharmaceutiquement acceptables, dans laquelle ladite drospirénone est sous forme micronisée.
2. Composition selon la revendication 1, dans laquelle la drospirénone a une surface spécifique supérieure à 10 000 cm²/g.
3. Composition selon l'une quelconque des revendications 1 ou 2, dans laquelle au moins 70% de ladite drospirénone passent en solution depuis ladite composition en l'espace de 30 minutes, la détermination étant faite selon la Pharmacopée US XXIII par la méthode avec palettes II, en utilisant de l'eau à 37°C comme milieu de dissolution et une vitesse d'agitation de 50 tours/min.
4. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle la drospirénone est pulvérisée à partir d'une solution de drospirénone sur des particules d'un véhicule inerte.

5. Composition selon l'une quelconque des revendications 1 à 4, dans laquelle la dissolution in vitro de l'éthinylestradiol est telle qu'au moins 70% passent en solution en l'espace de 30 minutes, la détermination étant faite selon la Pharmacopée US XXIII par la méthode avec palettes II, en utilisant de l'eau à 37°C comme milieu de dissolution et une vitesse d'agitation de 50 tours/min.
6. Préparation pharmaceutique constituée d'un certain nombre de doses unitaires journalières conditionnées séparément et pouvant être retirées individuellement, placées dans un emballage unitaire et destinées à être administrées par voie orale pendant une durée d'au moins 21 jours consécutifs, dans laquelle lesdites doses unitaires journalières comprennent une association de drospirénone en quantité d'environ 2 mg à 4 mg et d'éthinylestradiol en quantité d'environ 0,01 à 0,05 mg, dans laquelle ladite drospirénone est sous forme micronisée.
7. Préparation selon la revendication 6, dans laquelle la drospirénone a une surface spécifique supérieure à 10 000 cm²/g.
8. Préparation selon l'une quelconque des revendications 6 ou 7, dans laquelle au moins 70% de ladite drospirénone passent en solution depuis ladite dose unitaire en l'espace de 30 minutes, la détermination étant faite selon la Pharmacopée US XXIII par la méthode avec palettes II, en utilisant de l'eau à 37°C comme milieu de dissolution et une vitesse d'agitation de 50 tours/min.
9. Préparation selon l'une quelconque des revendications 6 à 8, dans laquelle ledit éthinylestradiol est sous forme micronisée ou est pulvérisé à partir d'une solution sur des particules d'un véhicule inerte.
10. Préparation selon l'une quelconque des revendications 6 à 9, qui comprend en outre au plus 7 doses unitaires journalières ne contenant pas d'agent actif destinées à être administrées par voie orale à l'issue de la période d'au moins 21 jours consécutifs, le nombre total de doses unitaires journalières étant d'au moins 28.
11. Préparation selon l'une quelconque des revendications 6 à 9, dans laquelle le nombre de doses unitaires journalières comprenant l'association de drospirénone et d'éthinylestradiol est de 21, 22, 23 ou 24, et dans laquelle le nombre de doses unitaires journalières ne contenant pas d'agent actif est de 7, 6, 5 ou 4.
12. Préparation selon l'une quelconque des revendications 6 à 9 destinée à être administrée par voie orale

pendant une durée d'au moins 28 jours consécutifs, dans laquelle au moins 21 desdites doses unitaires journalières comprennent une association de drospirénone en quantité d'environ 2 mg à 4 mg et d'éthinylestradiol en quantité d'environ 0,01 à 0,05 mg, et dans laquelle au plus 7 desdites doses unitaires journalières contiennent de l'éthinylestradiol seul, en quantité d'environ 0,01 à 0,05 mg.

13. Préparation selon l'une quelconque des revendications 6 à 9, dans laquelle le nombre de doses unitaires journalières comprenant l'association de drospirénone et d'éthinylestradiol est de 21, 22, 23 ou 24, et dans laquelle le nombre de doses unitaires journalières comprenant de l'éthinylestradiol seul est de 7, 6, 5 ou 4.

14. Préparation selon l'une quelconque des revendications 6 à 9, dans laquelle le nombre de doses unitaires journalières comprenant l'association de drospirénone et d'éthinylestradiol est de 28, ou d'un multiple de 28 comme 2-4 fois 28, en particulier 2 ou 3 fois 28.

15. Préparation selon la revendication 6, dans laquelle le nombre de doses unitaires journalières destinées à l'administration orale est de 2-4 fois, de préférence 2 ou 3 fois, 28 jours consécutifs, suivie de l'administration des doses unitaires journalières comprenant l'association de drospirénone et d'éthinylestradiol pendant 21, 22, 23 ou 24 jours consécutifs, puis de l'administration des doses unitaires journalières ne contenant pas d'agent actif, ou de l'absence d'administration de doses unitaires journalières, pendant 7, 6, 5 ou 4 jours consécutifs.

16. Utilisation de drospirénone associée à de l'éthinylestradiol pour préparer une composition pharmaceutique destinée à inhiber l'ovulation chez un mammifère, en particulier un être humain, la composition comprenant une quantité de drospirénone correspondant à une dose journalière, lors de l'administration de la composition, d'environ 2 mg à 4 mg et comprenant une quantité d'éthinylestradiol correspondant à une dose journalière, lors de l'administration de la composition, d'environ 0,01 mg à 0,05 mg, et dans laquelle ladite drospirénone est sous forme micronisée.

17. Utilisation selon la revendication 16, dans laquelle ladite drospirénone possède une surface spécifique supérieure à 10 000 cm²/g.

18. Utilisation selon l'une quelconque des revendications 16 ou 17, dans laquelle au moins 70% de ladite drospirénone passent en solution depuis ladite composition en l'espace de 30 minutes, la détermination étant faite selon la Pharmacopée US XXIII

par la méthode avec palettes II, en utilisant de l'eau à 37°C comme milieu de dissolution et une vitesse d'agitation de 50 tours/min.

19. Utilisation selon l'une quelconque des revendications 16 à 18, dans laquelle la dissolution de l'éthinylestradiol est telle qu'au moins 70% passent en solution en l'espace de 30 minutes, la détermination étant faite selon la Pharmacopée US XXIII par la méthode avec palettes II, en utilisant de l'eau à 37°C comme milieu de dissolution et une vitesse d'agitation de 50 tours/min.

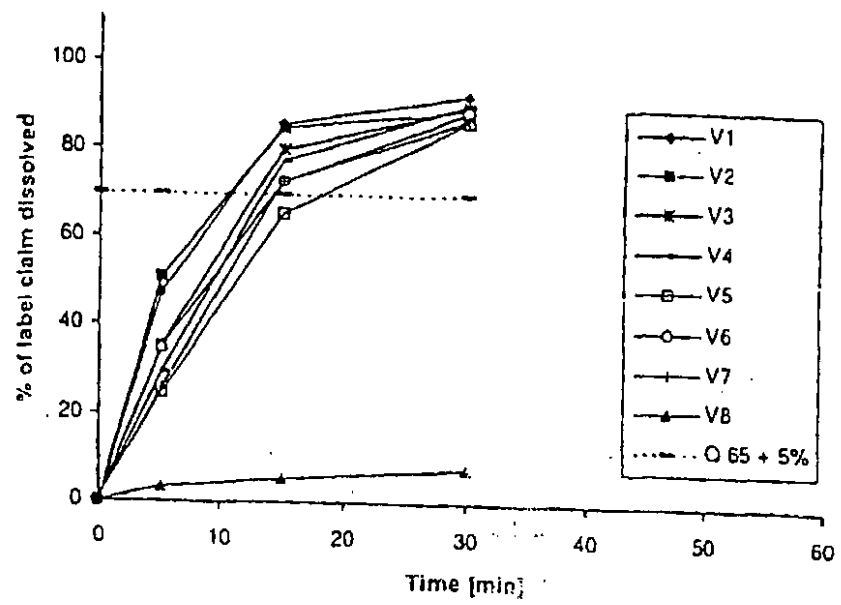


Fig. 1

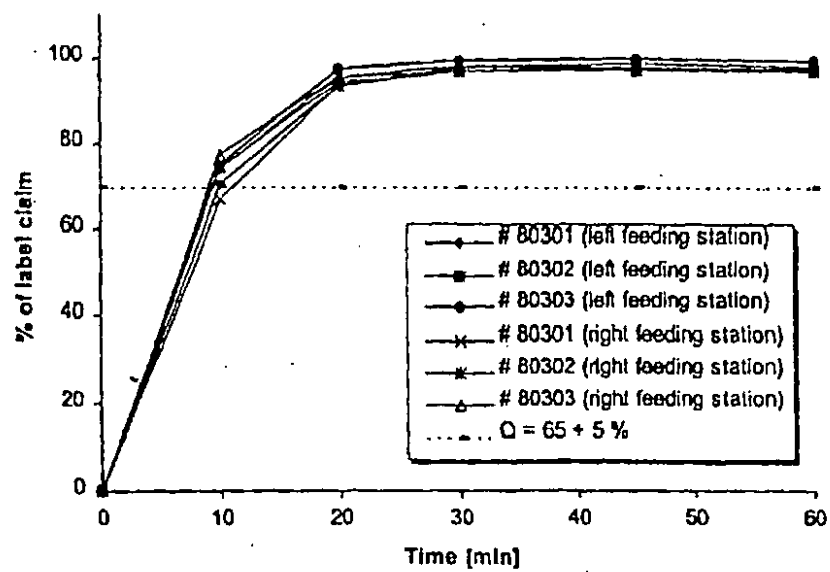


Fig. 2

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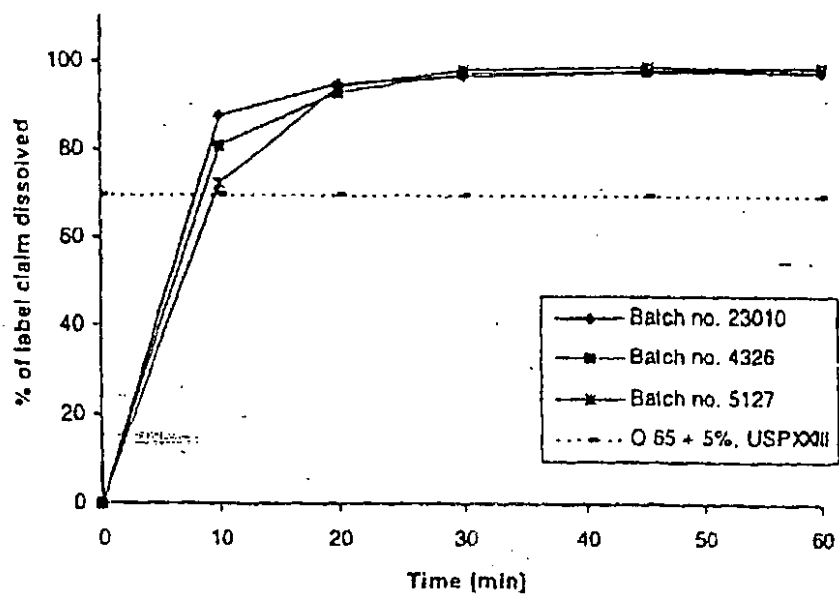


Fig. 3

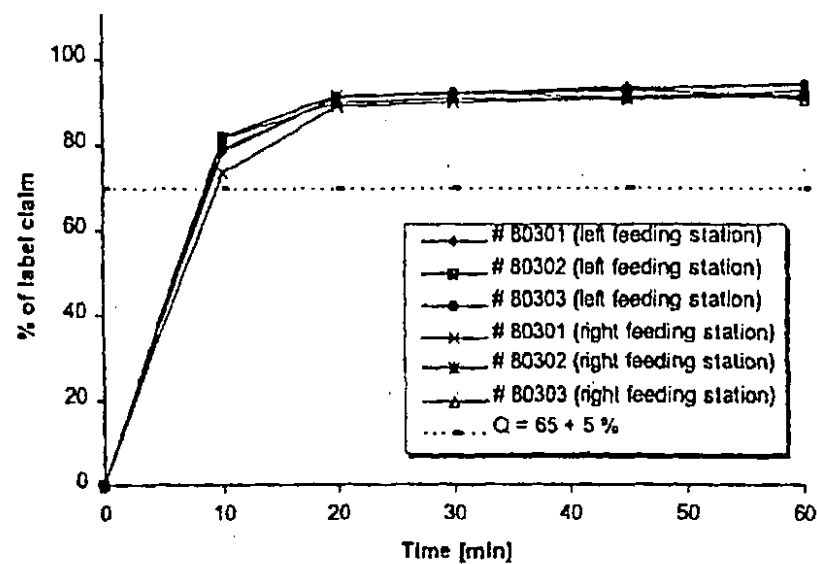


Fig. 4

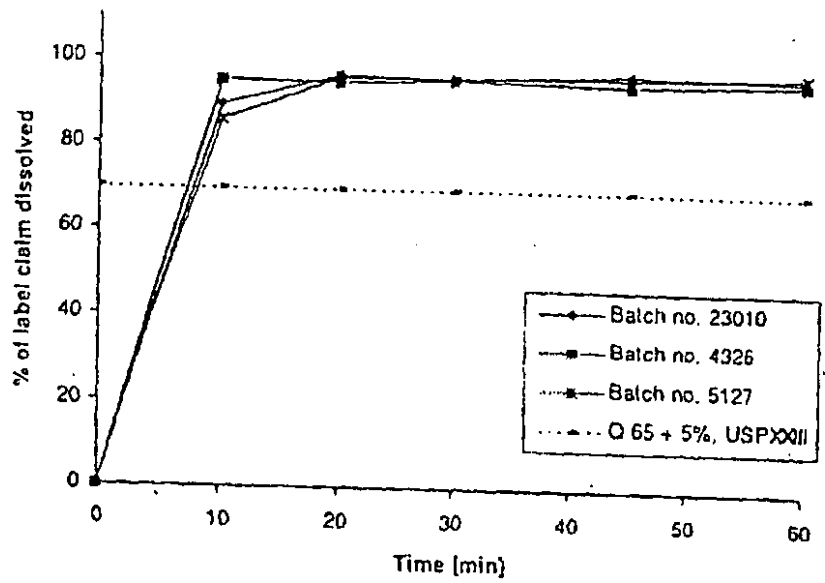


Fig. 5

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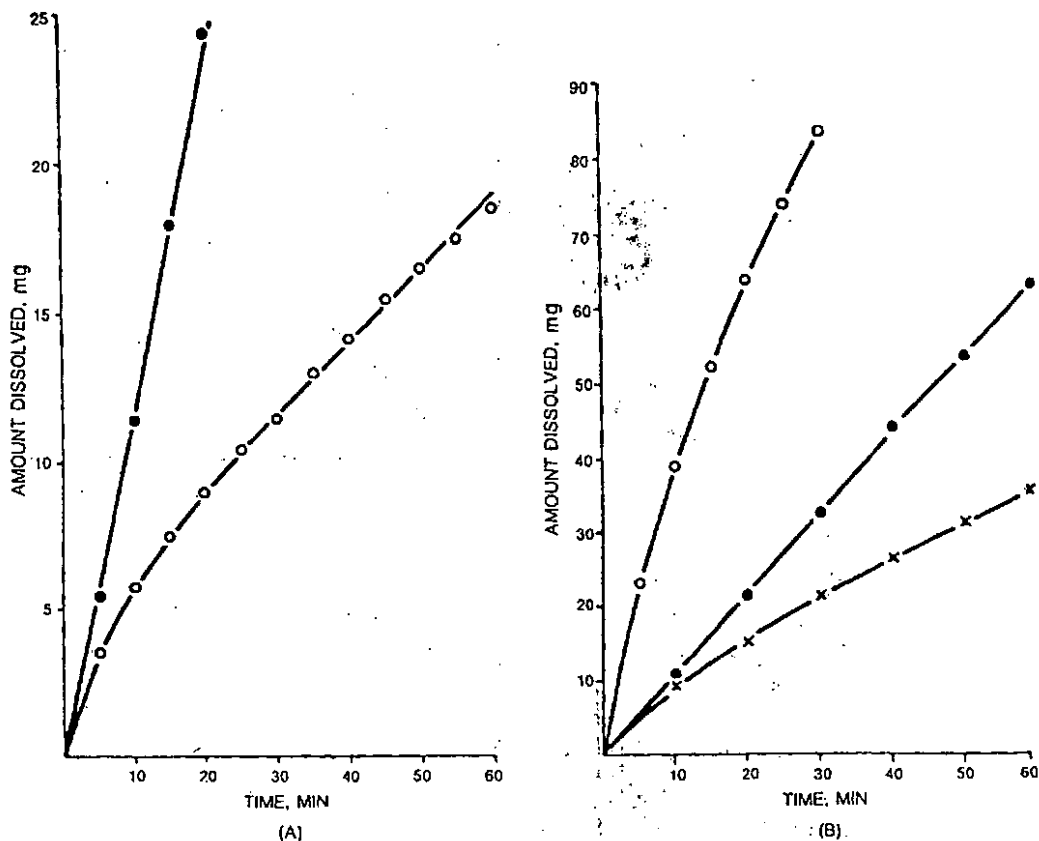


Fig 31-8. Effect of lubricant on the dissolution rate of tablets.⁶

(A) Effect of magnesium stearate on dissolution rate of salicylic acid from rotating disks made from fine salicylic acid powder. Key: O, 3% magnesium stearate; ●, no lubricant added. (B) Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets (formula A). Key: X, 3% magnesium stearate; ●, no lubricant; O, 3% sodium lauryl sulfate.

dissolution characteristics of the tablets and not the method of granulation per se. Figure 31-9 shows the effect of different granulation methods on the dissolution rate of tablets.

Effects of Compression Force on Dissolution Rate

In his early studies of the physics of tablet compression, T Higuchi (1953), pointed to the great influence of the com-

pressional force employed in the tableting process on the apparent density, porosity, hardness, disintegration time and average primary particle size of compressed tablets. There is always a competing relationship between the en-

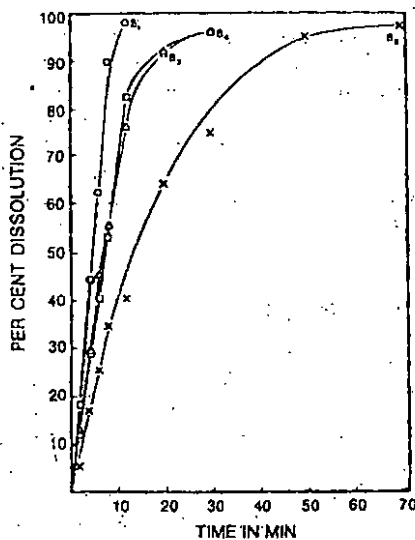


Fig 31-9. Effect of manufacturing process on the dissolution rate of tablets.⁷

Key: B₁ Direct compression with spray dried lactose, B₂ Wet granulation with ethylcellulose and lactose, B₃ Acacia muclage and lactose, B₄ Starch paste and lactose.

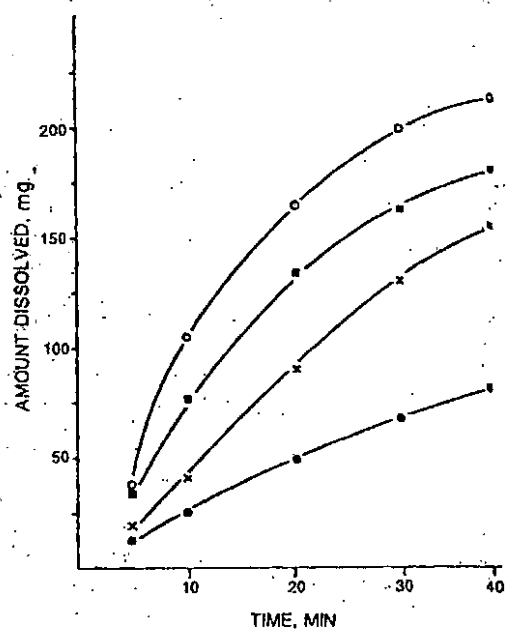


Fig 31-10. Effect of precompression pressure on the dissolution rate of tablets.⁴

Key: Effect of precompression pressure on dissolution rate of salicylic acid contained in compressed tablets. Key: ●, 715 Kg.; X, 1430 Kg.; ■, 2860 Kg.; O, 5730 Kg. pressure per cm.² (Average of five tablets each, formula D.)

the added ingredients are selected in order to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets. After compression the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics and uniformity which also are influenced both by the method of preparation and by the added materials present in the formulation. In the preparation of compressed tablets the formulator also must be cognizant of the effect which the ingredients and methods of preparation may have on the availability of the active ingredients and hence the therapeutic efficacy of the dosage form. In response to a request by physicians to change a dicumarol tablet in order that it might be broken more easily, a Canadian company reformulated to make a large tablet with a score. Subsequent use of the tablet containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response. On the other hand, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet, although containing the same quantity of drug substance, that gave the desired clinical response at half its original dose. Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed.^{2,14,15} See Chapters 36, 75 and 76.

Tablet Ingredients

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives or excipients. They may be classified according to the part they play in the finished tablet. The first group contains those which help to impart satisfactory processing and compression characteristics to the formulation. These include diluents, binders and glidants and lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, colors, and in the case of chewable tablets, flavors and sweetening agents, and in the case of controlled-release tablets, polymers or waxes or other solubility-retarding materials.

Although the term *inert* has been applied to these added materials, it is becoming increasingly apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them. Preformulation studies demonstrate their influence on stability, bioavailability and the processes by which the dosage forms are prepared. The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain. The result is called the *Handbook of Pharmaceutical Excipients*. This reference is now distributed widely throughout the world.¹⁶

Diluents

Frequently the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size for compression. Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible. Diluents used for this purpose include calcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing.

Such tablets commonly are called *chewable tablets*. Upon chewing, properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel and leave no unpleasant aftertaste in the mouth. Diluents used as excipients for direct compression formulas have been subjected to prior processing to give them flowability and compressibility. These are discussed under *Direct Compression*, page 1645.

Most formulators of immediate-release tablets tend to use consistently only one or two diluents selected from the above group in their tablet formulations. Usually, these have been selected on the basis of experience and cost factors. However, in the formulation of new therapeutic agents the compatibility of the diluent with the drug must be considered. For example, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the gastrointestinal tract. When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems. Highly adsorbent substances, eg, bentonite and kaolin, are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids and the synthetic estrogens. These drug substances may be adsorbed to the point where they are not completely available after administration. The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant, results in tablets which discolor on aging.

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct compression formulas. However, its presence in 5 to 15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling.

Many ingredients are used for several different purposes, even within the same formulation. For example, corn starch can be used in paste form as a binder. When added in drug or suspension form, it is a good disintegrant. Even though these two uses are to achieve opposite goals, some tablet formulas use corn starch in both ways. In some controlled-release formulas, the polymer hydroxypropylmethylcellulose (HPMC) is used both as an aid to prolong the release from the tablet, as well as a film-former in the tablet coating. Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary in order to use them rationally.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart a cohesiveness to the tablet formulation which insures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include starch, gelatin and sugars as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums which have been used include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum and larch arabogalactan. Other agents which may be considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water and alcohol.

The quantity of binder used has considerable influence on the characteristics of the compressed tablets. The use of too much binder or too strong a binder will make a hard tablet which will not disintegrate easily and which will cause excessive wear of punches and dies. Differences in binders used



Research paper

Effect of crystallinity of microcrystalline cellulose on the compactability and dissolution of tablets

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Abstract

Microcrystalline cellulose (MCC) was pulverized with a vibrational rod mill. The degree of crystallinity of MCC decreased from 65.5 to 12.1% with pulverization time due to mechanochemical effect. Pulverized MCCs were compressed at 155.6 MPa using a compression test apparatus, and the two parameters relating to compactability, the *B* value and yield pressure, were calculated using a Heckel plot. These values were lowered as the degree of crystallinity of MCC became smaller. These results suggest that the crystal region and the amorphous region in MCC particles may be mainly fractured and deformed plastically during compression, respectively. Then the dissolution test was performed for the acetaminophen-MCC (10:90) tablets. Dissolution profiles showed an interesting phenomenon, namely, the dissolution rate of acetaminophen from MCC tablet decreased when the degree of crystallinity of MCC was in the range from 65.5 to 37.6%, however, it increased markedly when the degree of crystallinity of MCC was in the range from 25.8 to 12.1%. The amount of water absorbed into tablets changed in accord with the dissolution rates of acetaminophen from tablets. The dissolution data indicate that drug release can be modified by changing the degree of crystallinity of MCC. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Microcrystalline cellulose; Crystallinity; Compactability; Heckel plot; Dissolution rate

1. Introduction

Microcrystalline cellulose (MCC) was commercialized as Avicel® by FMC corporation in 1962, and it was registered in the supplement to the National Formulary, twelfth edition, in 1966. Although Avicel was only the brand-name production of MCC until about 1980, since then, considerable numbers of MCC productions have been launched in various countries. MCC has been widely used as an additive for direct compression because of its good flowability and compactability.

MCC is manufactured by the following process: at first,

woodpulp made from needle-leaf trees or returnpulp made from cotton-seed fiber is hydrolyzed with mineral acid. The intermediates are then neutralized and washed after removing the amorphous region and impurities to purify the MCC [1]. Therefore, it has often been indicated that differences in the characteristics of MCC among manufacturers are due to the kinds of pulp used as raw materials and their manufacturing conditions, which affect the compactability [2,3]. Takamas et al. [4] reported that the Compactability Index differed among five brand-name MCCs. Rowe et al. [5] pointed out that the particle size of MCC affected tablet characteristics much more than the crystallinity of MCC because crystallinities among 11 brand-name MCCs measured by powder X-ray diffraction patterns and infra-red absorption spectra were almost the same, and their degree of crystallinity were in the range of 61.8–65.0% in powder XRD method, 57.7–69.4% in IR method. Pesonen et al. [6] reported that the compactability of Avicel and Emcocel® (Finnish Sugar) were almost equal as the results of evalua-

* Corresponding author. Pharmaceutical Formulation Research Laboratory, Daiichi Pharmaceutical, 16–13, Kita-kasai 1-chome Edogawa-ku, Tokyo 134, Japan. Tel.: +81-3-5658-1454; fax: +81-3-5696-8466.

tion using Kawakita's equation. They concluded that the most important materials property affecting the breaking strength of tablets was the specific surface area of the starting material, and no correlation between crystallinity, particle size or particle shape of starting material and the strength of tablets was observed. However, as the degree of crystallinity of MCC used in their study were almost the same, 63 and 68% for Avicel and Emcocel, respectively, the effect of crystallinity of MCC did not seem to be clear. Landin et al. reported that yield pressure, which is one of the parameters in a Heckel plot [7,8] related to the compactability of powder, exhibited no significant difference among four brand-name MCCs manufactured in Finland, India, Ireland and Japan, though their chemical composition, crystal structure and particle size were different [9]. Ikeda et al. evaluated the compactability of powder cellulose, which has a higher degree of polymerization than MCC, using Kawakita's equation and a Heckel plot [10]. Although some of these studies described the effect of the difference in crystallinity among various brand-named MCCs on the compactability, we could hardly find any articles examining the effect of change in crystallinity in the same brand-named MCC on the compactability and dissolution characteristics of tablets.

MCC as well as the other additives is often pulverized in pharmaceutical processes, therefore it is important for assurance of the quality of drug products to clarify the effect of changes in physicochemical properties of MCC caused by pulverization on physical characteristics, such as granulation and compression and chemical characteristics, such as content uniformity and dissolution.

We reported that the degree of crystallinity of MCC affects the characteristics of granules manufactured using a high-shear mixer in a previous paper [11]. In this study, we took notice of crystallinity in various physicochemical properties of MCC, and examined the effect of the degree of crystallinity of MCC on the compactability and dissolution characteristics of tablets.

2. Materials and methods

2.1. Materials

MCC (Avicel PH101, Asahi Chemical Industry) and acetaminophen (Yamamoto Chemical Industry), 75–150 μ m, were used. They were of JPXIII grade.

2.2. Pulverization of materials

Ten grams of MCC were pulverized using a vibrational rod mill (Sample Mill, Heiko, Japan) for 2–30 min and then passed through a 150 μ m sieve. In addition, MCC pulverized with a jet mill (PJM-NP, Nihon Pneumatic, Japan) under the following conditions was prepared in order to evaluate the effect of particle diameter on the dissolution rate: com-

pressed air consumption, 2.0 kg/nm³ per min; air pressure, 6.5 kg/cm²; sample feed, 0.5 kg/h, and then passed through a 150 μ m sieve.

2.3. Measurement

Powder X-ray diffraction patterns were measured using a Mac Science X-ray diffractometer with Ni-filtered Cu-K α radiation. Voltage 35 kV, current 20 mA, receiving slit 0.15 mm, scanning speed 2° per min. The crystallinity of each material was calculated by Harman's method.

The particle size of each material was measured in ethanol by a particle size analyzer using laser diffraction (Microtrac II, Leeds & Northrup, USA).

Electron micrographs were taken with a Hitachi S-2360 scanning electron microscope. The samples were coated with gold, using a direct current sputter technique.

The equilibrium moisture curves were measured with a Integrated Microbalance System MB 300G (VTI Corporation, USA).

Each material was compressed with a compression test apparatus (Autograph AG5000B, Shimadzu, Japan) using flat-face punches of 8 mm diameter ($n = 3$). The compression speed and the reverse speed of an upper punch was set at 10 mm/min and 100 mm/min, respectively. The compression force was removed at the time when the pressure of an upper punch reached at the set pressure. The time course was always identical in compression study. Tablet weight for each sample was 200 mg. No lubricant was used in this compression study. The stress transmission was calculated by dividing the lower punch pressure by the upper punch pressure at 155.6 MPa. The compression energy was calculated from a displacement-force curve for the upper punch.

Heckelplot analysis was applied to estimate how MCC deforms in the compression process. Heckel found that the reduction in voidage obeys a first-order kinetics type of reaction with applied pressure. Heckel's equation is as follows [12]:

$$\ln[1/(1 - \rho_r)] = KP_d + A$$

where ρ_r is the relative density of the compact, K and A are constants determined from the slope and intercept of the extrapolated linear region of the plot, respectively. K is expressed as the reciprocal of yield pressure (P_y) which reflects the plasticity of the sample. The difference between the relative density at the point where measurable force was applied, and the relative density calculated from the intercept of Heckel plot linear portion is expressed as the B value which reflects the extent of densification by movement and reorientation of the particles, and the magnitude of fracture of the sample particles.

Tablet hardness was measured with a tablet-hardness tester (Tablet Tester 6D, Schleuniger, $n = 3$), and the crushing strength, that is to say, tensile strength, was calculated.

Tablets containing 20 mg of acetaminophen and 180 mg of MCC with different degree of crystallinity were prepared

Table 1

Mean particle diameters of I-MCC and R-MCC

Pulverization time (min)	Degree of crystallinity (%)	Mean particle diameter (μm)
I-MCC		
0	65.5	44
R-MCC		
2	54.6	20
5	48.2	30
10	37.6	19
20	25.8	20
30	12.1	15
J-MCC	63.3	16

with the compression test apparatus described above. A dissolution tests for tablets were performed by the JPXIII paddle method at 50 rpm in 900 ml of water at 37 (n = 3). Acetaminophen was assayed spectrophotometrically (243 nm).

The amount of water absorbed into a tablet and the swelling ratio of the tablets were measured at room temperature using the apparatus reported by Nogami et al. [13] (n = 3). The amount of water absorbed into a tablet was determined by measuring the weight change before and after the test, and the swelling ratio was estimated by measuring the change in the tablet thickness caused by water absorption. These measurements were carried out after establishing apparent equilibrium.

3. Results and discussion

3.1. Characterization of pulverized materials

Intact MCC, MCC pulverized with a vibrational rod mill, and MCC pulverized with a Jet mill are abbreviated as I-MCC, R-MCC, and J-MCC, respectively, in the following sentences. Table 1 shows the mean particle diameters and the degree of crystallinity of I-MCC, R-MCC and J-MCC.

The mean particle diameter and the degree of crystallinity of I-MCC were 44 μm and 65.5%, respectively. Those of R-MCC were reduced to 30–15 μm and 54.6–12.1% with grinding time. Decrease in crystallinity is due to a mechanochemical effect as previously reported by Nakai et al. [14]. However, the particle diameter of J-MCC was as small as that of R-MCC ground for 30 min, but the degree of crystallinity scarcely changed by grinding. The reason for the difference of the degree of crystallinity between R-MCC milled by a vibrational rod mill for 30 min and J-MCC milled by a jet mill was presumed that the grinding mechanism between a vibrational rod mill and a Jet mill is different. The main mechanism of a vibrational rod mill is the friction while that of a Jet mill is the collision. Therefore, the reduction in crystallinity has to be higher for a vibrational rod mill.

Fig. 1 shows SEM photographs of I-MCC and R-MCC. The shape of the MCC was also changed by pulverization, that is, R-MCC particles were almost round in shape, while I-MCC particles were fibrous.

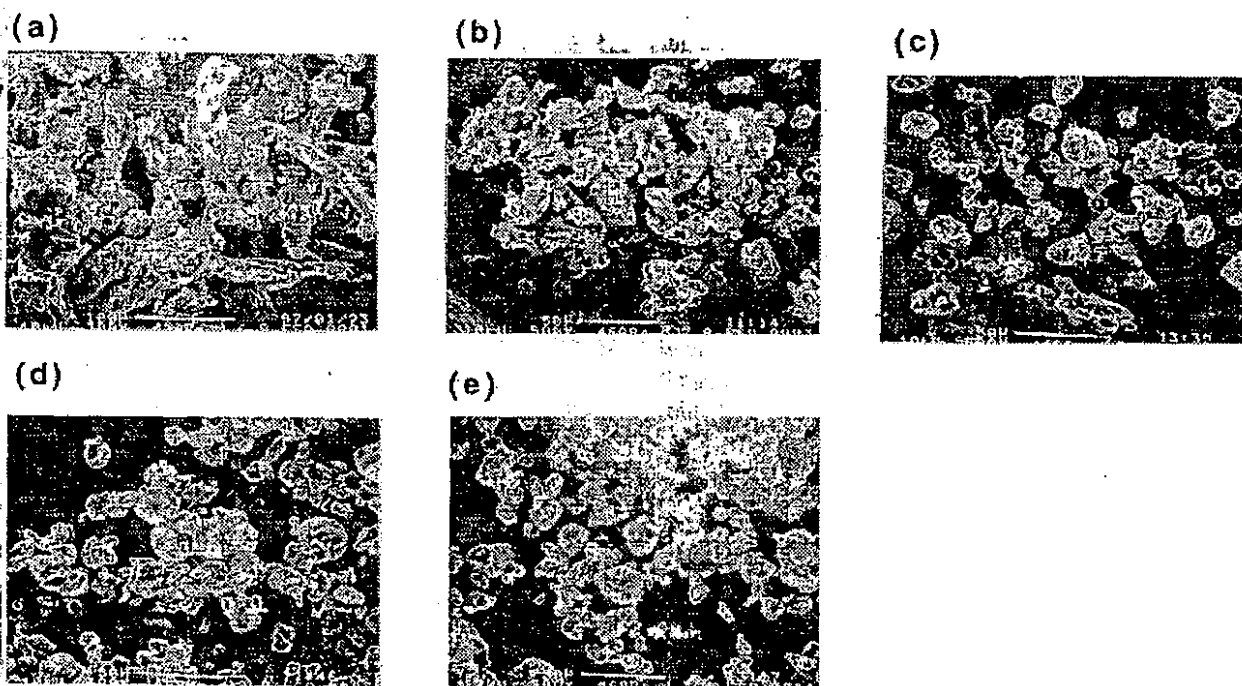


Fig. 1. Scanning electron micrographs of I-MCC and R-MCC (a) I-MCC (b) R-MCC pulverized for 5 min (c) R-MCC pulverized for 10 min (d) R-MCC pulverized for 20 min (e) R-MCC pulverized for 30 min.

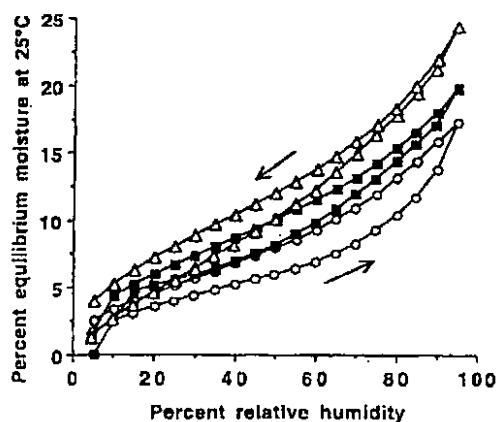


Fig. 2. Water vapor adsorption curves of MCC with various degrees of crystallinity at 25°C. Degree of crystallinity: I-MCC: (O) 65.5%; R-MCC: (■), 37.6%; (Δ) 25.8%.

The equilibrium moisture curves of MCC with various degree of crystallinity are shown in Fig. 2. The amount of water adsorbed by MCC at a constant relative humidity increased with a decrease in the degree of crystallinity. This phenomenon was caused due to the fact that the amorphous region is more hydrophilic than the crystalline region.

3.2. Compactability of MCC

The parameter of compactability was changed among the samples. Fig. 3 shows the relationship between the parameters of compactability and the degree of crystallinity of MCC.

The stress transmission from the upper punch to the lower punch was almost at the same level among the MCC samples. However, the compression energy was lowered with a decrease in the degree of crystallinity of the MCC samples. A Heckel plot analysis was performed in order to obtain information regarding the roles of the crystalline region and the amorphous region in MCC to the crushing strength of tablets. A Heckel plot analysis is often applied to evaluate the compactability of MCC with different bland-names. However, to the authors' knowledge, no report has been published to estimate the compactability of ground MCC using a Heckel plot.

Table 2 shows the results of calculation of the parameters. The B value mainly expresses the magnitude of fracture of the particles caused after densification by movement and reorientation of particles, and yield pressure ($1/K$ in the Heckel equation) is mainly related to the plastic deformation of particles during compression. It was found that these values were lowered as the degree of crystallinity of MCC became smaller. The results suggested that the crystalline region and the amorphous region in the MCC particles may be fractured and deformed plastically during compression, respectively. The reason why compression energy was proportional to the degree of crystallinity as shown in Fig. 3 was considered as follows: the crystalline region with a hard

Table 2

Results of Heckel plot analysis of MCC with various degrees of crystallinity

Degree of crystallinity (%)	B^a	Yield pressure (MPa) ^b
I-MCC		
65.5	0.1415	232.0
R-MCC		
54.6	0.0899	194.1
48.2	0.0811	191.8
37.6	0.0751	178.4
25.8	0.0697	174.0
12.1	0.0663	148.5

^aDifference between the relative density at the point where measurable force was applied and the relative density calculated from the intercept of the Heckel plot linear portion.

^bThe reciprocal of the slope in Heckel plot linear portion which would reflect plasticity of the sample.

structure required considerable energy to be fractured; however, the amorphous region with a soft structure required relatively small energy compared to crystalline region, because it only deformed plastically. Table 3 shows the crushing strength of tablets compressed at 155.6 MPa, it was recognized that the crushing strength reduced as the decreasing the degree of crystallinity of MCC. Fig. 4 shows the relationship between compression energy and the crushing strength of tablets. The crushing strength of tablets was almost proportional to the compression energy. These results suggest that compression energy may mainly consume to fracture the crystal region in MCC, and that fractured crystal region may contribute to increase the crushing strength of tablets. In addition, MCC might be collapsed by strong impact of a rod during pulverization. Therefore, the number of contact points among R-MCC particles each other in a tablet may decrease with pulverization time. As the results of this, the decrease in crushing strength of R-MCC tablets may be observed.

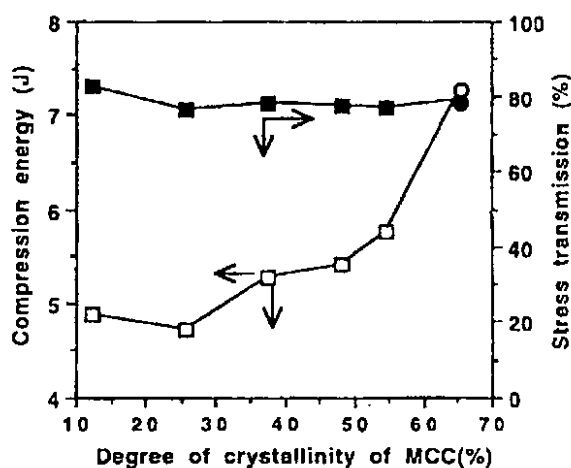


Fig. 3. Effect of crystallinity on compression energy and stress transmission of MCC, (O), (●): I-MCC; (□), (■): R-MCC.

Table 3

Crushing strength of tablets compressed at 155.6 MPa

Degree of crystallinity of MCC (%)	Crushing strength (kg/mm ²)
I-MCC	
65.5	0.44
R-MCC	
54.6	0.34
48.2	0.32
37.6	0.28
25.8	0.23
12.1	0.22

In previous studies [5,9], the characteristics of MCC were compared among different brand-named MCCs. However, the effect of the degree of crystallinity of MCC on the compactability could not be detected clearly, because the differences of the degree of crystallinity among various brand-named MCCs were very small. In our study, the relationship between the degree of crystallinity of MCC and the compactability could be clarified by changing the degree of crystallinity in wide range for the same brand-named MCC. Duberg and Nyström investigated the effect of the particle size of on the characterization of a Heckel plot using several numbers of excipients sieved to a small and a large fraction [14]. They reported that the difference in parameters of a Heckel plot between a small fraction and a large fraction of excipients was scarcely observed. These results in their study supported that the difference in parameters of Heckel plot among MCC samples may be mainly caused by the difference of degree of crystallinity rather than that of the particle size.

3.3. Effect of crystallinity on dissolution of tablets

Fig. 5 shows the dissolution profiles of MCC tablets containing acetaminophen.

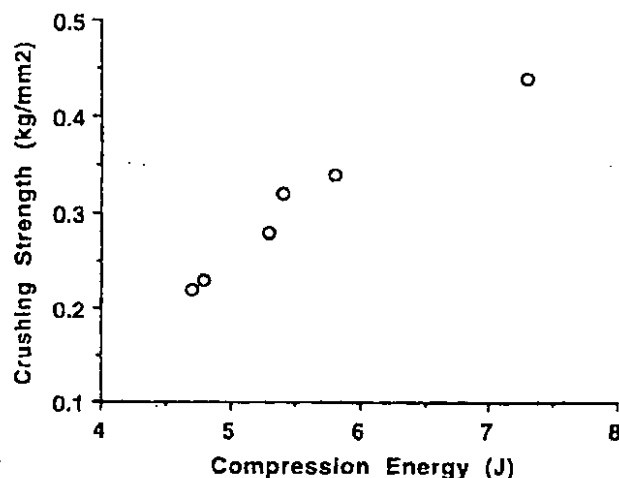


Fig. 4. The relationship between compression energy and the crushing strength of tablets.

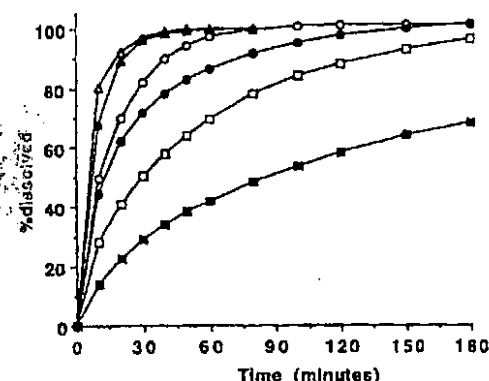


Fig. 5. Dissolution profiles of acetaminophen from tablets containing MCC with various degrees of crystallinity. Crystallinity of MCC in tablets: I-MCC: (○), 65.5%; R-MCC: (●), 54.6%; (□), 48.2%; (■), 37.6%; (△), 25.8%; (▲), 12.1%.

Disintegration was not observed in each tablet except for the I-MCC tablet during the dissolution test, though the tablets containing R-MCC exhibited swelling.

The dissolution rate was decreased as the degree of crystallinity decreased from 65.5 to 37.6%. However, the dissolution rates for tablets with a low degree of crystallinity from 25.8 to 12.1% markedly increased. Similarly, the amount of water absorbed into the tablets and the swelling ratio of the tablets changed with the degree of crystallinity of MCC as shown in Fig. 6.

The crushing strength of a tablet decreased with the reduction of the degree of crystallinity of MCC as shown in Table 3. In general, the crushing strength of a tablet is closely correlated with the dissolution rate. The dissolution tests, therefore, were performed for tablets whose crushing strength was adjusted within the range from 0.27 kg/mm² to 0.32 kg/mm² as shown in Table 4. The compression force was set at 77.8 MPa for I-MCC, 155.6 MPa for R-MCC ground for 5 min and 233.4 MPa for R-MCC ground for 20 min, respectively. Fig. 7 shows the dissolution pro-

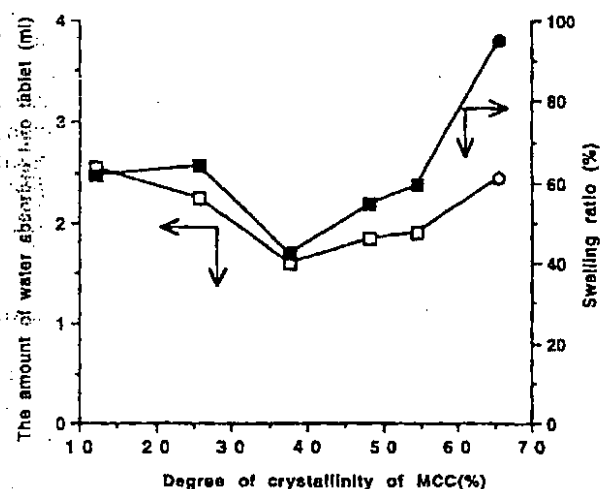


Fig. 6. Effect of crystallinity of MCC on the amount of water uptake and swelling ratio of MCC tablets. (○), (●): I-MCC; (□), (■): R-MCC.

Table 4

Crushing strength of tablets compressed at various compression force

Degree of crystallinity of MCC (%)	Compression force (MPa)	Crushing strength (kg/mm ²)
I-MCC		
65.5	77.8	0.30
R-MCC		
48.2	155.6	0.32
25.8	233.4	0.27

files for tablets with equivalent crushing strength. The order of the dissolution rates among these tablets was the same as Fig. 5, i.e. R-MCC ground for 20 min > I-MCC > R-MCC ground for 5 min.

The dissolution testing for tablets made of J-MCC was carried out to evaluate the effect of the particle size of MCC on the dissolution rate. Although the degree of crystallinity of J-MCC and I-MCC were almost equal each other, the particle size of J-MCC was apparently smaller than that of I-MCC. Compression force at 50.6 MPa was applied to prepare J-MCC tablets in order to adjust its crushing strength to I-MCC tablets compressed at 155.6 MPa, because the tablet hardness will often affect the dissolution rate. Fig. 8 shows the result of dissolution test. The dissolution profiles of these tablets were almost the same.

These results suggest that the dissolution rate of acetaminophen from MCC tablets depend upon the crystallinity of MCC, and that it is not affected by the particle size of MCC.

As is evident from the results, the degree of crystallinity of MCC may become a dominant factor in controlling the dissolution rate of directly compressed tablets including MCC. We should, therefore, pay attention to the degree of crystallinity of MCC during pulverization process, because it may affect the dissolution properties of tablets. However, drug dissolution rate from the MCC tablet did not linearly changed with the degree of crystallinity of MCC. Further studies will be required to clarify this phenomenon.

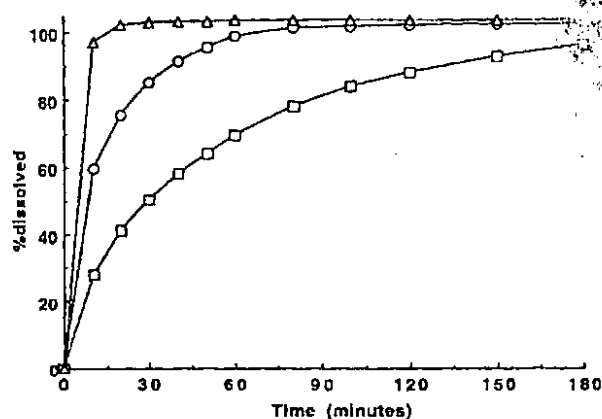


Fig. 7. Dissolution profiles for acetaminophen tablets with a equivalent crushing strength. Crystallinity of MCC in tablets: I-MCC: (O), 65.5%; R-MCC: (□), 48.2%; (Δ), 25.8%.

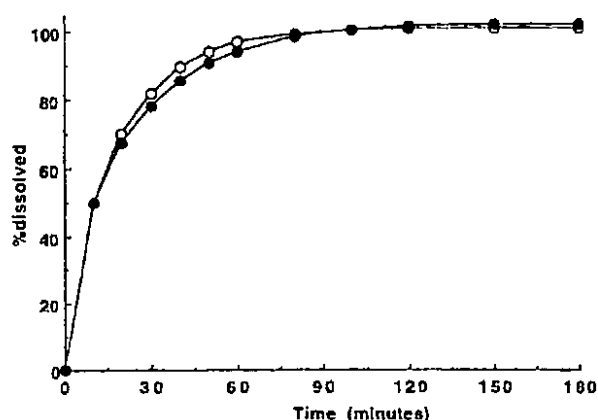


Fig. 8. Dissolution profiles for acetaminophen tablets consist of MCC pulverized with a vibrational rod mill or a Jet mill. (O), R-MCC; (●), J-MCC.

Acknowledgements

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MATERIAL SAFETY DATA SHEET

Avicel® PH Microcrystalline Cellulose

FMC BioPolymer

MSDS Ref. No.: 9004-34-6
Date Approved: 01/31/2008
Revision No.: 9

This document has been prepared to meet the requirements of the U.S. OSHA Hazard Communication Standard, 29 CFR 1910.1200 and Canada's Workplace Hazardous Materials Information System (WHMIS) requirements.

1. PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME: Avicel® PH Microcrystalline Cellulose
CHEMICAL FAMILY: Carbohydrate
SYNONYMS: Microcrystalline cellulose (INCI name): MCC, cellulose gel
ALTERNATE PRODUCT NAME(S): Avicel PH 101, 102, 103, 105, 112, 200, 113, 301, 302, 200LM

MANUFACTURER

FMC BioPolymer
1735 Market Street
Philadelphia, PA 19103
(800) 526-3649 (General Information)
msdsinfo@fmc.com (Email - General Information)

FMC Europe NV
Avenue Mounier 83
1200 Brussels, Belgium
353 21 435 4133 (General Information - Cork, Ireland)

EMERGENCY TELEPHONE NUMBERS

(302) 451-0100 (FMC Plant - Newark, Delaware)
(303) 595-9048 (Medical - U.S. - Call Collect)

For leak, fire, spill, or accident emergencies, call:
(800) 424-9300 (CHEMTREC - U.S.A. & Canada)
(703) 527-3887 (CHEMTREC - Collect - All Other Countries)

2. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW:

- White free-flowing, odorless powder.
- Powder becomes slippery when wet.
- Accumulation of overhead settled dust may form explosive concentrations in air when disturbed and dispersed.

POTENTIAL HEALTH EFFECTS: No significant health hazard expected.

ADDITIONAL EXPOSURE LIMITS:

MCC:

Australia (TWA) 10 mg/m³Belgium (TWA) 10 mg/m³ (inhalable dust)China (STEL): 25 mg/m³China (TWA): 10 mg/m³Hong Kong (TWA): 10 mg/m³Ireland (TWA): 10 mg/m³ (inhalable dust)Korea (TWA): 10 mg/m³New Zealand (TWA): 10 mg/m³ (respirable dust with no asbestos and less than 1% free silica)Singapore (PEL): 10 mg/m³Switzerland (TWA): 3 mg/m³ (respirable dust)United Kingdom (STEL): 10 mg/m³ (total inhalable dust)United Kingdom (TWA): 10 mg/m³ (total inhalable dust); 4 mg/m³ (respirable dust)

9. PHYSICAL AND CHEMICAL PROPERTIES

ODOR:	Odorless
APPEARANCE:	White, free-flowing powder
AUTOIGNITION TEMPERATURE:	Not applicable
BOILING POINT:	Not applicable
COEFFICIENT OF OIL / WATER:	(Kow) Not applicable
EVAPORATION RATE:	(Butyl acetate = 1) Not applicable
FLASH POINT:	Not applicable
MELTING POINT:	Not applicable
OXIDIZING PROPERTIES:	Not applicable
PERCENT VOLATILE:	Typically 1 - 5 % water, by weight
pH:	(In solution) 5.0 - 7.0 (11% solids dispersion)
SOLUBILITY IN WATER:	(% by weight) Insoluble
SPECIFIC GRAVITY:	(H ₂ O = 1) Bulk density, 0.2 - 0.5 g/cc
VAPOR DENSITY:	(Air = 1) Not applicable
VAPOR PRESSURE:	Not applicable

COMMENTS:

EXPLOSIVE PROPERTIES: Microcrystalline cellulose: St-1

MINIMUM IGNITION TEMPERATURE: Microcrystalline cellulose: 420°C