



No. 08-040107- 00003-0000

Fecha: 2009-08-31 12:14:11 Day: 2029 NULCRACION:
Tia: 11 PALENTIYII Evt: 379 FASENACIONALII
Act: 400 OPOSIOBSERVIER Folios: 37

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICION A

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

②

Número del expediente: 08-040107

Solicitante: BAYER SCHERING PHARMA AKTIENGESELLSCHAFT

**SOLICITUD
PUBLICADA**

Apoderado: L IAN RAISBECK

Título de la nueva creación o denominación del signo: METODO PARA LA
ANTICONCEPCION HORMONAL PREVENTIVA BAJO DEMANDA

Gaceta: 604

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: GYNOPHARM S.A. Dirección: Carrera 14 N° 94-44 Piso 7 Torre b Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Teléfono: 2 36 84 95 Fax: E-mail:	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual Número: 802,006,279-4
REPRESENTANTE O APODERADO	Nombre: CIELO ANGELA PEÑA RODRIGUEZ Dirección: CARRERA 13 No. 119-95 Teléfono: (571)213 12 13 Fax: (571)612 19 79 E-mail: negocios@optimum-co.com	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual Número 51.940.252 TP 82701

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

Art 14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la
misma tal y como se demostrara en el capítulo "Fundamento de Hechos"

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: CIELO ANGELA PEÑA

FIRMA: 

C.C. 51.940.252

TP. 82701



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 040107

Asunto : Oposición a la solicitud de patente de Invención titulada
"METODO PARA LA ANTICONCEPCION HORMONAL
PREVENTIVA BAJO DEMANDA".

Solicitante : BAYER SCHERING PHARMA AKTIENGESELLSCHAFT

Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 604 del 29 de Mayo de 2009

Yo, *CIELO ANGELA PEÑA RODRIGUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *82701* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad *GYNOPHARM S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "METODO PARA LA ANTICONCEPCION HORMONAL PREVENTIVA BAJO DEMANDA", cuyo titular es BAYER SCHERING PHARMA AKTIENGESELLSCHAFT, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.



1. INTERÉS PARA ACTUAR ✓

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular formas farmacéuticas. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 21 de abril de 2008 reivindicando prioridad bajo la solicitud DE200510050729 del 2005-10-19; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 604 del 29 de Mayo de 2009, cuya publicación internacional corresponde a la WO2007045513 del 2007-04-26.
- 2.2. La solicitud colombiana 08 040107 objeto de la presente oposición, se refiere a un método de anticoncepción hormonal femenina controlada bajo demanda, caracterizado porque comprende administrar una preparación farmacéutica que comprende al menos un progestógeno por vía transdérmica, bajo demanda y en una sola ocasión, en anticipación del encuentro sexual.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren a un método de tratamiento y no a una composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: EP1541137 publicada el 15 de junio de 2005.

2.5. Además que la solicitud se refiere a un método terapéutico que expresamente no es objeto de patente bajo la norma Colombiana, tampoco es novedoso, dado que el documento D1, particularmente en la descripción revela un parche que comprende una capa que contiene un medicamento tal como gestodena y opcionalmente un estrógeno (p.ej. etinil estradiol) para ser administrado a una mujer, con niveles de plasma de al menos 1.0 ng/ml de gestodena, que son alcanzados en condiciones

estables sin la necesidad de penetración, aplicable para ser usado en la contracepción femenina. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud tampoco es novedosa pues lo revelado ya se encontraba en el estado de la técnica

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 040107 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”* A la fecha de prioridad, 19 de octubre de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un método terapéutico para contracepción, sobre el cual busca protección en el capítulo reivindicatorio.

2.7.2. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, las cláusulas reclaman un método terapéutico



y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*. La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Parente de invención denominada **“METODO PARA LA ANTICONCEPCION HORMONAL PREVENTIVA BAJO DEMANDA”**, cuyo titular es **BAYER SCHERING PHARMA AKTIENGESELLSCHAFT**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 604 del 29 de Mayo de 2009.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- DI: EP1541137 publicada el 15 de junio de 2005.



4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de GYNOPHARM S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- o DI: EP1541137 publicada el 15 de junio de 2005.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

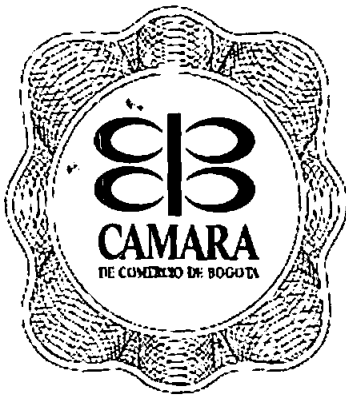
Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.



01



* 8 3 7 4 9 9 0 7 *



10

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/25

HORA: 08:55:03

OPERACION: 10PD30825015

PAGINA: 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A.-----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2047.

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/25

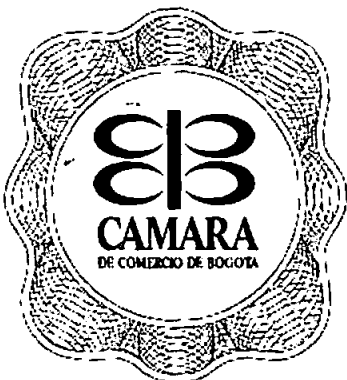
HORA: 08:55:03

OPERACION: 10PD30825015

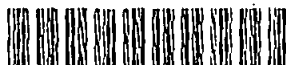
PAGINA: 2

uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal. c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto; comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en

*** CONTINUA ***



01



* 8 3 7 4 9 9 0 8 *



11

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/25

HORA: 08:55:03

OPERACION: 10PD30825015

PAGINA: 3

general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o lo de sus socios.-----

C E R T I F I C A

CAPITAL

Nro Acciones

Valor Accion

Autorizado

\$*****4,000,000,000 *****4,000,000 *****1,000

Suscrito

\$*****2,672,646,000 *****2,672,646 *****1,000

Pagado

\$*****2,672,646,000 *****2,672,646 *****1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le corres-

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/25

HORA: 08:55:03

OPERACION: 10PD30825015

PAGINA: 4

pondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal.-----

C E R T I F I C A

Que según Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:

GYNOPHARM S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Llobet Poal Manuel	CC.*****14,670,196
2. Zanatta Reheman Leonardo Andres	CC.*****2,760,271
3. Munoz Marroquin Diego	CC.*****7,688,292
4. Montealegre Gonzalez Andres Leonardo	CC.*****79,950,262

Suplentes

1. Agudelo Pelaez Luis Hernando	CC.*****14,238,997
2. Aroca Almanza Arleth Ayelina	CC.*****36,718,415
3. Penaranda Urbina Adriana Paola	CC.*****53,120,683
4. tovar Vasquez Ruth	CC.*****52,175,756

C E R T I F I C A

Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Gerente General.

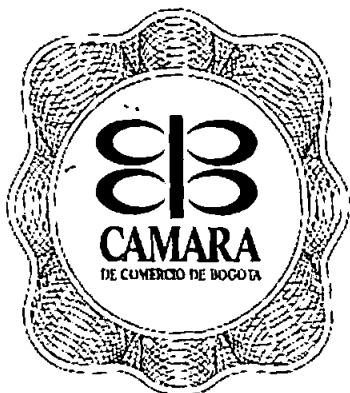
Palacios Aragon Luis Alberto✓

CE.*****319,788

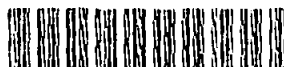
C E R T I F I C A

Que según Acta No. 49 del 03 de Marzo de 2008 correspondiente a la

*** CONTINUA ***



01



* 8 3 7 4 9 9 0 9 *



10

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/25

HORA: 08:55:03

OPERACION: 10PD30825015

PAGINA: 5

Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*****351,283

C E R T I F I C A

Que según Acta No. 19 del 30 de Abril de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el No. 149,314 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal.	
PENALOSA AUDITORES & ASOCIADOS S.A.	Ni.*****830,095,635

C E R T I F I C A

Que por Documento Privado del 11 de Mayo de 2009, otorgado en Bogota por Peñalosa Auditores & Asociados S.A. inscrito en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el Nro 149,315 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Designado: Revisor Fiscal Ppal	
Padilla Romero Ivan Dario	CC.*****80,025,798
Designado: Revisor Fiscal Suplente	
Gomez Preciado Clara Judith	CC.*****52,544,226

C E R T I F I C A

Que según Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Cámara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro respectivo, consta que el señor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representación de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/25

HORA: 08:55:03

OPERACION: 10PD30825015

PAGINA: 6

S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOFARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOFARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que por Escritura Pública No. 2,404 del 28 de Mayo de 2009, otorgada en la Notaria la. de Bogota cuya parte pertinente se inscribió en esta Cámara de Comercio, el 02 de Julio de 2009 bajo el No. 3,948 del libro respectivo,-----
consta que el señor LUIS ALBERTO PALACIOS ARAGON con CE No.319788, en su calidad de Representante Legal de GYNOPHARM S.A., manifesto que confiere poder general, amplio y suficiente a la Doctora -----
CAROLINA MARIA ROMERO CERON, identificada con cedula de ciudadanía numero 52.352.190, para que en nombre de la sociedad GYNOPHARM -----
S.A., promueva y defienda los intereses de la sociedad judicial y extrajudicialmente, en toda especie de gestiones y actuaciones ante las autooridades administrativas o jurisdiccionales en especial ----
para: a) Recibir notificaciones de cualesquiera tipo de actos -----
emanados de las autoridades administrativas o judiciales. b) -----
Presentar recursos por la via administrativa o judicial, renunciar a terminos, desistir, conciliar, transigir y modificar. c) Elevar peticiones y solicitar informacion a las autoridades -----
administrativas y jurisdiccionales. d) Presentar demandas ante las autoridades administrativas y judiciales.-----

C E R T I F I C A

*** CONTINUA ***



01



83749910



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/25

HORA: 08:55:03

OPERACION: 10PD30825015

PAGINA: 7

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2009.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles después de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

m. r. j. a.

14

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-040107- -00003-0000

Fecha 2009-08-31 12:14:19 Dep: 2020 NUECREACION
Tra 11 PATENTE Y L. Evt: 379 FASE NACIONAL
Act 400 OPOSTOBSERVTER Folia: 37

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 64,136
FECHA : AGOSTO 31 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
GYROPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	082754387	105300296	20/08/2009	1,435,000.00

***** CONCEPTO *****

CARGO. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEHAS COMERCIALES	287,000.00
	TOTAL :	\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

15

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **08 040.107**, titulada "**METODO PARA LA ANTICONCEPCION HORMONAL PREVENTIVA BAJO DEMANDA**", cuyo titular es **BAYER SCHERING PHARMA AKTIENGESELLSCHAFT**, publicada en la gaceta No. 604 del 29 de mayo de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 25 días del mes de 8 de 2009.

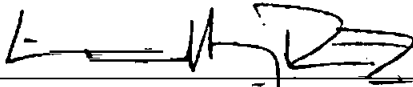
GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.

NIT: 802.006.2794

Representante Legal

Acepto:


CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.

RECONOCIMIENTO DE FIRMAS

Ante mí, LILIANA CONSTANZA BARBOSA PLATA,
Notaria Veintinueve del Circuito de Bogotá (E),
comparece

Señor Adolfo
Adolfo

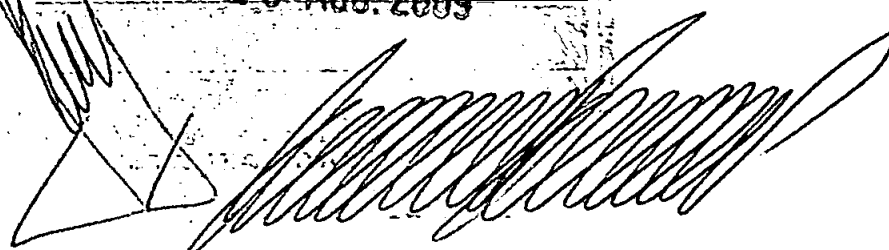
identificado con cédula de ciudadanía

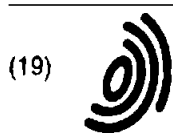
DEB 19788

y declara que la firma puesta en el presente
instrumento privado es suya y que el contenido
del mismo es cierto.

Bogotá, C.

26 AGO. 2009





(19)

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 541 137 A2

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
15.06.2005 Bulletin 2005/24

(51) Int Cl.7: **A61K 9/70**(21) Application number: **04078365.6**(22) Date of filing: **10.12.2004**

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR**
Designated Extension States:
AL BA HR LV MK YU

- Bracht, Stefan, Dr.
07751 (DE)
- Dittgen, Michael, Prof. Dr.
99510 Apolda (DE)
- Huber, Petra
80337 München (DE)
- Schenk, Drik
83623 Dietramszell (DE)

(30) Priority: **12.12.2003 EP 03078881**

(71) Applicant: **SCHERING AKTIENGESELLSCHAFT
13342 Berlin (DE)**

(74) Representative: **Plougmann & Vingtoft A/S
Sundkrogsgade 9
P.O. Box 831
2100 Copenhagen OE (DK)**

(72) Inventors:
• Langguth, Thomas
07751 Jena (DE)

(54) Transdermal delivery system of hormones without penetration enhancers

(57) The present invention relates to a patch comprising a drug-containing layer with low content of hormones, such as gestodene, and optionally an estrogen (e.g. ethinyl estradiol). Upon administering the patch to a woman, plasma levels of at least 1.0 ng/ml of Gestodene is achieved at steady state conditions without the need of incorporating penetration enhancers or permeation enhancers in the drug-containing layer. Satisfactorily plasma levels of the hormones is also achieved throughout a period of at least 1 week, making the patch applicable for being used in female contraception with the concept of administering the patch once weekly.

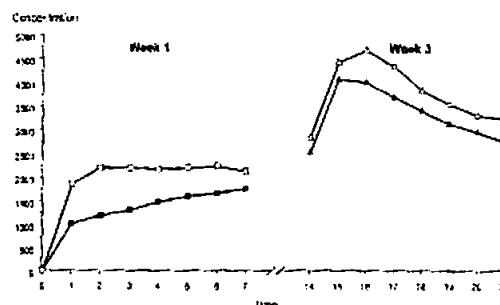


Fig. 1

Description

Field of invention

5 [0001] The present invention relates to the field of pharmaceutical formulation techniques. The invention provides a low dosage pharmaceutical composition for transdermal delivery of at least one hormone, preferably a progestin, such as a gestodene, and optionally an estrogen, so as to achieve plasma concentration profiles effective in inhibiting ovulation in a woman.

10 **Background**

[0002] Transdermal delivery of estrogens and progestins for providing contraception is a known concept (Sitruk-Ware, Transdermal application of steroid hormones for contraception, J Steroid Biochem Molec Biol, Volume 53, p 247-251). However, estrogens and progestins do generally poorly penetrate the skin, for which reason it is common, 15 in transdermal systems, to incorporate agents with skin penetrating enhancing effect.

[0003] The following documents describe a number of transdermal systems with a progestin and an estrogen present in the adhesive layer and wherein the need of penetration enhancers is emphasised:

20 WO 92/07590 describes compositions with penetration enhancers for the transdermal delivery of Gestodene and an estrogen so as to achieve maximal plasma levels of Gestodene of about 0.9 ng/ml.

WO 97/397443 relates to a transdermal system containing between 30 to 60% of penetration enhancers so as to deliver a contraceptively effective amount of an estrogen and a progestin.

25 WO 01/37770 relates to transdermal systems containing between 10 to 60 % of penetration enhancers for delivery of Ethinylestradiol and Levonorgestrel in contraceptively effective amounts.

30 US 5,512,292 is directed to compositions comprising a contraceptively effective amount of Gestodene and an estrogen, such as Ethinylestradiol, together with a suitable permeation enhancer. The amount of the estrogen co-delivered is kept at a constant and contraceptive effective rate while the amount of Gestodene co-delivered varies depending on the phase of the menstrual cycle.

[0004] In US 5,376,377 comparable studies between transdermal systems with and without penetration enhancers are shown. The studies include an adhesive layer made of ethylene vinyl acrylate and as the active ingredient, 35 Gestodene and an estrogen (ethinylestradiol). The study results indicate the need of incorporation penetration enhancers in the adhesive layer so as to achieve contraceptive effective amounts. Maximal plasma levels of about 0.8 ng/ml were achieved.

[0005] Finally, WO 90/04397 also discloses examples of compositions for transdermal delivery of gestodene, optionally in combination with an estrogen, such as Ethinylestradiol, wherein the composition further may comprise a penetration enhancer, such as 1,2-propandiol or isopropylmyristat. As adhesive layer is mentioned a number of various polymers. Examples on polar polymers (polyacrylates and silicones) in combination with a penetration enhancer are specifically disclosed. The resulting plasma levels of Gestodene at steady state conditions were approx. 250 to 337 40 pg/ml.

[0006] In addition to penetration enhancers, it is also suggested to add solubilising agents or the like to the drug-containing layer in order to increase the amount of dissolved drug or to add agents inhibiting the crystallisation of the drug in the layer. 45

[0007] For example, in US 6,521,250 is disclosed an adhesive layer that comprises a mixture of styrene-isoprene block copolymer and a hydrogenated resin acid or its derivatives, the amount of the resin being of 55-92%. Such an adhesive layer seems suitable for the transdermal delivery of estradiol in combination with a progestin in that such systems have a proper adhesive contact with the skin for long-term application and prevent crystallisation of the hormones. 50

[0008] US 5,904,931 relates to TTS systems containing in the drug-containing layer a steroid (such as Gestodene) and dimethyl isosorbide. The latter enhances the solubility of the steroid in the drug-containing layer. The concentration of the Gestodene in the drug-containing layer may vary from 1-40 % by weight of the layer and the drug-containing layer may consist of adhesives such as polyacrylates, silicones, styrene-butadiene co-polymers and polyisobutylenes. Especially, polar polymers, such as polyacrylates, are suitable. 55

[0009] DE 199 06 152 relates to a transdermal drug delivery system in which Gestodene is embedded in a polar polymer, such as polyvinylpyrrolidone, methylcellulose, ethylcellulose, and hydroxypropylcellulose, previous to being

EP 1 541 137 A2

added to an adhesive polymer, such as polyisobutylene. Thus, this transdermal drug delivery system is a twophase system and the drug-containing layer is not transparent because of the content of the polar polymers, which upon exposure to water will result in the presence of milky-white spots. The amount of Gestodene in the drug-containing layer is 5.1 % by weight of the drug-containing layer.

[0010] In WO 02/45701 it is emphasised that the addition of a resin ester in an amount up to 25% by weight to an adhesive layer may sufficiently suppress crystal formation of active agents such as for example hormones. The adhesive layer may include all non-toxic natural and synthetic polymers known and which are suitable for use in transdermal systems, for example polyacrylates, polysiloxanes, polyisobutylenes, styrene block copolymers and the like. Particularly, polyacrylates are emphasised. The TTS system is suitable for steroids (Gestodene), which may be incorporated in the adhesive layer in an amount substantially at or near or even above the saturation with respect to their concentration in the carrier composition rather than substantially at subsaturation. Preferably, the amount of the steroid is from about 0.1% to about 6% by weight, based on the dry weight of the total carrier composition.

[0011] Unfortunately, penetration enhancers may adversely affect the skin such as irritating the skin, which to some extent renders transdermal systems unacceptable for the user. Additionally, it is generally known that penetration enhancers may negatively affect the stability of active substances rendering long-term storage problematic. Furthermore, it is also recognised that the viscosity is reduced by incorporation of penetration enhancers resulting in the risk of formation of dark rings along the edges of the patch.

[0012] Therefore, there is a need for transdermal systems without the above-mentioned drawbacks, such as transdermal systems that do not require penetration enhancers for achieving therapeutically effective amounts of a steroidal hormone, such as Gestodene.

[0013] Gestodene is a known orally active synthetic progestin with a progesterone-like profile of activity (see, U.S. Pat. No. 4,081,537). It is used as an oral contraceptive in combination with certain estrogens.

Summary of the Invention

[0014] This invention relates to compositions suitably formulated for transdermal delivery of hormones, so that contraceptively effective levels are achieved without the need of incorporating penetration enhancers in the hormone-containing adhesive layer. The actual hormones are preferably steroidal hormones, such as progestins, such as a Gestodene, which optionally may be used in combination with an estrogen. Unlike the general knowledge in the art, the present inventors have provided transdermal systems comprising a limited number of ingredients. For example penetration enhancers and or permeation enhancers are not required in order to achieve high release rate and therapeutically effective plasma levels.

[0015] The present inventors have found that the selection of a drug-containing layer that has a solubility for the steroidal hormone (e.g. Gestodene) is critical for the successful achievement of therapeutically effective levels of a hormone in the blood. Example 2 herein shows the comparison of two Gestodene-containing layers with respect to their release rate of Gestodene. It is clearly demonstrated that a drug-containing layer of a polar polymer (polyacrylate) requires a concentration of Gestodene of 3.9 % by weight of this layer to achieve the desired high release rate. Surprisingly, and in contradiction to what has previously been known, the same high release rate can be achieved with a concentration of 1.9 % by weight of Gestodene in a drug-containing layer comprising a less polar polymer, such as polyisobutylene, even without the use of a penetration enhancer. Also in-vivo studies have revealed that drug-containing layers containing the more non-polar type of polymer such as the polyisobutylene in preference to the polyacrylates are better in terms of achieving high plasma AUC (Example 4)

[0016] Thus, the present inventors have found, unlike what could be expected, that the use of drug-containing layers preferably containing a apolar polymer, such as polyisobutylenes, and characterised by having a limited solubility with respect to Gestodene of no more than 3% by weight have a high release rate of Gestodene despite the actual load of Gestodene in the drug-containing layer is low. This is clearly an advantage over the previously known TTS systems in terms of decreasing the risk of skin irritation, decreasing the exposure of hormone to the user and to the environment.

[0017] A further advantage is that the drug-containing layer is a monophasic system and contains the drug evenly distributed throughout the layer. That is to say that the drug-containing layer is homogenous. In absence of polar polymers or other polar additives with tendency to absorb water or to retain water, the drug-containing layer is transparent. Thus, a transparent composition, wherein the skin can be visually inspected through the drug delivery system, has been provided by the present invention. Transparency of a transdermal drug delivery system is a clear advantage for the user because non-transparent systems are visible and thus indicate sickness, which is not the intention with a contraceptive patch.

[0018] Accordingly, a first aspect of the invention relates to compositions for transdermal delivery of a steroidal hormone, preferably a progestin, such as Gestodene or a derivative thereof (ester thereof), and optionally an estrogen. The composition comprises a drug-containing layer comprising said hormone and one or more pharmaceutically acceptable excipients or carriers, and the drug-containing layer having a solubility for said hormones (such as Gestodene)

EP 1 541 137 A2

of no more than 3% by weight of the drug-containing layer.

[0019] In a particular aspect thereof, the invention relates to a composition comprising a progestin, such as Gestodene or a derivative thereof, and a polymer in an amount of from about 15 to 99 % by weight of the drug-containing layer, the polymer being selected from the group consisting of hydrocarbon polymers, polysiloxanes, poly-acrylates and mixtures thereof that form a drug-containing layer having a solubility for Gestodene of no more than 3% by weight of the drug-containing layer.

[0020] In another particular aspect thereof, the invention relates to compositions comprising a drug-containing layer consisting essentially of a progestin such as Gestodene or a derivative thereof, a polymer in an amount of from about 15 to 99 % by weight of the drug-containing layer, a tackifier, such as a rosin ester in an amount of up to 85% by weight, such as in an amount in the range of 1-85% of the drug-containing layer, and optionally an estrogen.

[0021] In a still particular aspect, the invention relates to a composition for transdermal delivery comprising a drug-containing layer that comprises:

- i) a progestin, preferably a Gestodene or derivative thereof, such as an ester thereof; and
- ii) a polymer selected from the group consisting of polyisobutylenes, polybutenes, polyisoprenes, polystyrenes, styrene isoprene styrene block polymers, styrene butadiene styrene block polymers and mixtures thereof.

[0022] A still particular aspect of the invention relates to a transparent composition for transdermal delivery, the composition comprises a drug-containing layer that comprises a progestin, preferably a Gestodene or derivative thereof (such as an ester thereof) and the drug-containing layer has a solubility for Gestodene of no more than 3% by weight of the drug-containing layer.

[0023] It has surprisingly been found that relatively high plasma levels of Gestodene can be maintained for a prolonged period of time by administering a Gestodene formulated in a composition of the invention. The plasma profile and plasma levels of Gestodene, as resulting from the administration of a Gestodene and optionally an estrogen, are effective in inhibiting the ovulation in a woman.

[0024] Therefore compositions of the invention may be used for inhibiting ovulation or alternatively for the treatment of endometriosis, pre-menstrual syndrome, climacteric disorders, prevention of osteoporosis, regulating the menstrual cycle or stabilising the menstrual cycle.

[0025] Thus, in still further aspects, the invention relates to the use of a composition as described herein optionally in combination with an estrogen, for inhibition of ovulation in a female. When the composition is singly administered, then a plasma concentration-time curve of Gestodene is achieved characterised by having plasma levels of Gestodene in a concentration of at least 1.0 ng/ml, as determined at steady state conditions. In association herewith, the invention relates to a method for inhibiting ovulation in a female, such as a woman. The method comprises administering topically to the skin or mucosa an effective amount of Gestodene or a derivative thereof, optionally in combination with an estrogen, so as upon singly administering said Gestodene, then a plasma concentration-time curve of Gestodene is achieved characterised by having plasma levels of Gestodene in a concentration of at least 1.0 ng/ml, as determined at steady state conditions.

[0026] Finally, the invention relates to a kit comprising 1 to 11 dosage units, such as 9 or 3 dosage units, dependent on the length of the treatment period, formulated in a form for transdermal delivery of Gestodene or a derivative thereof, such in a form of a composition as described herein. The dosage form comprising a drug-containing layer comprising Gestodene and one or more pharmaceutically acceptable excipients or carriers, wherein the drug-containing layer has a solubility with respect to Gestodene of no more than 3% by weight of the drug-containing layer.

Detailed Description

[0027] The invention provides compositions for transdermal delivery of hormones (transdermal therapeutic system) that upon topical application to the skin or to a mucosa results in therapeutically effective amounts, such as contraceptively effective amounts of the hormones, although skin penetration enhancers are not necessarily incorporated in the drug-containing layer.

[0028] As used herein, the term "topical" or "topically" denotes the direct contact of the composition with a surface area of a mammal including skin and mucosa.

[0029] The term "mucosa" means any surface membrane on a mammal, which is not skin, such as a surface present in the buccal cavity, vagina, rectum, nose or eye. Thus, the mucosa may be buccal, vaginal, rectal, nasal or ophthalmic mucosa.

[0030] The compositions of the invention may be designed in several various application forms provided that the composition comprises a drug-containing layer, which is adapted to be placed near to or in direct contact with skin or mucosa upon topically administering the composition.

[0031] Therefore, in a preferred application form, the composition, e.g. the transdermal therapeutic system, consists

essentially of

- a) a backing layer;
- b) at least one drug-containing layer comprising said hormone or a mixture of said hormones and one or more pharmaceutically acceptable ingredients; and
- c) optionally a removable release liner or protective layer

[0032] Preferably, the backing layer, the drug-containing layer and the removable release liner (or protective layer) are transparent, which means that the skin is visible.

[0033] In case the drug-containing layer fails to exhibit sufficient self-tackiness to the skin or mucosa, it may be provided with an additional layer of a pressure-sensitive adhesive layer or with a pressure-sensitive adhesive edge or ring so as to ensure adherence of the composition to the skin over the whole application period. The pressure-sensitive adhesive layer may be located between the drug-containing layer and the skin and the adhesive ring may be located around or at the edge of the drug-containing layer. Optionally, the composition may also additionally comprise one or more membranes or adhesive layers. For example, a membrane for controlling the release of the hormones can be located between the drug-containing layer and the pressure sensitive layer or between the drug-containing layer and the skin.

[0034] The size of the drug-containing layer is selected from a variety of reasonable sizes. As used herein, a reasonable size is meant to be a surface area of from about 5 to 20 cm², preferably of from about 7 to 15 cm², most preferably of from about 8 to 12 cm², such as 10 cm². Notably, the surface area is the area that is in contact with or in close proximity to the skin or mucosa.

[0035] According to the invention it is found that a drug-containing layer with minimised solubility for the hormone provides sufficient skin penetration of a steroidal hormone. In the present invention, the drug-containing layer is characterised by defining its solubility for Gestodene. Notably, the skin penetration rate suffices without the need of incorporation of a skin penetration enhancer. For example, it is surprisingly found that the skin penetration of a steroidal hormone of the invention results in therapeutically effective amounts of the steroidal hormone in the circulating blood, such as contraceptively effective amounts of the hormone.

[0036] Accordingly, the invention relates in a first aspect to a composition for transdermal delivery of a steroidal hormone, such as a progestin, e.g. Gestodene or a derivative thereof. The composition comprises a drug-containing layer and one or more pharmaceutically acceptable excipients or carriers and the drug-containing layer has a solubility for Gestodene of no more than 3% by weight of the drug-containing layer. The composition may optionally comprise an estrogen.

[0037] In some embodiments thereof, the solubility of the drug-containing layer for Gestodene is no more than 2.5 % by weight of the drug-containing layer, preferably no more than 2.0 %, such as no more than 1.8%. In principle, the solubility could be very low, but it is considered that the critical level with respect to the lowest level of said solubility is about 0.1%, such as about 0.2%, 0.3%, 0.5%, 0.7%, 0.8%, 0.9% or 1% by weight of Gestodene in the drug-containing layer. It is generally considered that the solubility of the drug-containing layer for Gestodene is in the range between about 0.1% and 3%, such as about 0.2% and 3%, 0.4% and 3%, 0.5% and 3%, 0.8% and 3% or 1% and 3%. In further embodiments thereof, the upper limit in the range is not 3% by weight but lower, such as 2.5%, 2.2% or 2.0%.

[0038] As used herein, the term "a gestodene" is denoted to mean Gestodene (13 β -Ethyl-17 α -ethynyl-17 β -hydroxy-4,15-gonadien-3-one), a derivative thereof or a mixture thereof, such as mixtures of the derivatives or a mixture of Gestodene and a derivative. The derivative may be a derivative of the 17 β -hydroxy group, such as ether, ester, acetal or a pharmacologically acceptable salt thereof. For example an ester with 2 to 12 carbon atoms in the acyl radical, including alkanoates with 2 to 8 carbon atoms in the alkanoyl radical.

[0039] In preferably embodiments of the invention, an ester of Gestodene is Gestodene propionate, Gestodene valerate, and/or Gestodene capronate, which are described in US 5,858,394.

[0040] As mentioned, the inventors have found that a suitable drug-containing layer of the invention is one that has solubility for the steroidal hormone (e.g. Gestodene) of no more than 3% by weight of the drug-containing layer.

[0041] The phrase "solubility for a steroidal hormone, such as" a solubility for Gestodene, of no more than 3% by weight of the drug-containing layer" is meant to characterise the quantity of the steroidal hormone, such as Gestodene that can dissolve in a particular drug-containing layer yielding a visually clear solution. The term (a solubility for) should not be understood as meaning the actual concentration of hormone, such as Gestodene, in the drug-containing layer. As described below, the total concentration of hormone in the drug-containing layer may be above or below 3% by weight of the drug-containing layer. Furthermore, the total concentration of hormone in the drug-containing layer may give rise to a drug-containing layer comprising the hormone at saturated or sub-saturated levels.

[0042] In order to select drug-containing layers having the specified solubility for a hormone, such as Gestodene, the following test may be carried out in order to determine whether the hormone is completely dissolved and the resulting drug-containing layer is visually clear.

EP 1 541 137 A2

[0043] One test method is to determine whether the hormone is completely dissolved in that solid particles cannot be detected visually or by using a microscope having a magnification of 25X.

[0044] Another method is to actually determine the solubility of the drug-containing layer for the hormone by the following method. The method is based on the determination of the release rate constants of the hormone from a drug-containing layer comprising the hormone in completely dissolved form and from a drug-containing layer with the hormone partially dissolved.

The method includes the following steps:

[0045] Firstly, identical drug-containing layers, but with various, such as increasing, amounts of the hormone, are to be manufactured. As a rule, at least 3 of the various drug-containing layers should contain the hormone in a form completely dissolved in the drug-containing layer and at least 3 drug-containing layers should contain the hormone as partially dissolved, e.g. with the hormone in the form of solid particles.

[0046] As concerning the manufacturing process, the following steps can be followed. Any other method known in the art to manufacture adhesive layers may also be appropriate:

- The drug substance is dissolved or suspended in an appropriate solvent.
- The polymer, optionally the tackifier and other excipients are dissolved in an appropriate solvent.
- The two solutions are combined while stirring, so as to obtain a homogeneous mixture.
- The mixture is coated onto a release liner in an appropriate thickness and dried under heat to evaporate the solvents.
- The resulting laminate is covered with the backing foil.

Secondly, the release rate of the drug from the drug-containing layer is tested using the equipment and test conditions given in the relevant section of the European Pharmacopoeia (Ph.Eur. 2.9.4. Dissolution test for transdermal patches) or the United States Pharmacopoeia (USP 26, <724> DRUG RELEASE, apparatus 5 (Paddle over Disk)).

- A sample with a defined area is cut from the drug-containing layer.
- After removal of the release liner the sample is placed in a vessel (as described in the Pharmacopoeia mentioned above) which is previously filled with an appropriate dissolution media equilibrated at $32\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$. The drug-containing layer should be in contact with the dissolution media. Samples of the dissolution media are taken at pre-defined time intervals and the amount of hormone dissolved in the dissolution media is measured using HPLC or other appropriate quantification methods. The dissolution media can be selected from those ensuring sink conditions. For example, suitable dissolution media are aqueous solutions containing up to 30% by weight of organic solvents, such as ethanol, isopropanol and dioxane.

[0047] Thirdly, the release rate of hormones from the two types of drug-containing layers is determined as follows:

- the amount of hormone released per area unit of each of the drug-containing layer is calculated from the dissolution data mentioned above and the specific area of the drug-containing layer.
- the release rate constant for each drug-containing layer is determined as the slope obtained by the linear regression analysis of the at least three data points on the amount of hormone per area unit versus the square root of time.
- The release-rate constant for each of the drug-containing layers is plotted against the concentration of hormone in the drug-containing layer. Linear regression analysis is then carried out separately for the drug-containing layers with completely dissolved hormone and for drug-containing layers with partially dissolved hormone, i.e. with solid particles of hormone present. The two regression lines will cross each other at a point. The concentration of the hormone that can be read at the cross point of the two regression lines denotes the "solubility" of the hormone in the drug-containing layers.

[0048] The term "drug-containing layer" is meant to denote that part of the transdermal composition or system wherein the steroidal hormone is present. The drug-containing layer can be in semi-solid or solid form and comprises the hormone formulated directly in the layer. The hormone of the invention may be dispersed, partly dispersed, partly dissolved or fully dissolved in it dependent on the concentration and the physico-chemical properties of the hormone. The drug-containing layer is not meant to be in the form of a gel or a liquid. Intentionally, the drug-containing layer is meant to be in direct contact with the skin or mucosa. However, in some embodiments, there is an additional layer, a so-called no-drug-containing layer, located between the drug-containing layer and the skin or mucosa.

[0049] As said, compositions according to the invention do not necessarily comprise a skin penetration enhancer. Thus, in some embodiments of the invention, the drug-containing layer exclude the presence of a skin penetration rate enhancer, which means that the drug-containing layer consists essentially of ingredients not including a skin penetration

rate enhancer. This means that for example less than 2%, such as less than 1%, preferably less than 0.5%, such as less than 0.2%, such as less than 0.1% by weight of the drug-containing layer is composed of a skin penetration enhancer.

[0050] According to the present invention, the selection of the proper drug-containing layer effects the skin penetration. The proper drug-containing layer is preferably made of a polymer or mixtures of polymers. The polymers may have adhesive properties or may be without noticeable adhesive properties. In some embodiments, the drug-containing layer is a so-called pressure sensitive adhesive layer.

[0051] In principle any mixture of polymers resulting in the said solubility for Gestodene may be applied. Thus, in one embodiment of the invention the drug-containing layer comprises at least one polymer that may have adhesive properties or not. Typically, such polymers are biologically acceptable lipophilic polymers of the types of a hydrocarbon polymer, a polysiloxane, a poly-acrylate, or mixtures thereof. Preferably, the polymers may be selected from those hydrocarbon polymers, polysiloxanes and/or poly-acrylates that form a drug-containing layer having a solubility for Gestodene, of no more than 3% by weight of the drug-containing layer.

[0052] The amount of the polymer is to some extent a critical parameter. The proper amount may depend on the actual type of polymer and the steroidal hormone in use. In general, the amount of the polymer is at least 1% by weight of the drug-containing layer, such as at least 5%, 10%, 15% or 20%. However, preferably, the polymer is present in the drug-containing layer in an amount of at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or at least 80% by weight of the drug-containing layer. In other words, the polymer can be used in an amount of from about 1 to 99 % by weight of the drug-containing layer, such as from about 5 to 99%, 10 to 99 %, 15 to 99% or 20 to 99 %. Preferably, the polymer is present in the drug-containing layer in an amount ranging from about 15 to 99%, such as from about 15 to 90%, 15 to 85% or 15 to 80%, such as from about 20 to 85%, 20 to 75%, such as from about 25 to 85 %, 25 to 75% by weight of the drug-containing layer.

[0053] This being said, a particular aspect of the invention is directed to a composition for transdermal delivery of a steroidal hormone, such as a Gestodene or a derivative thereof, and optionally an estrogen, the composition comprising a drug-containing layer that comprises

- at least one steroidal hormone, such as a Gestodene or a derivative thereof and one or more pharmaceutically acceptable ingredients or carriers;
- a polymer or a mixture of polymers, preferably in an amount of from about 15 to 99 % by weight of the drug-containing layer,

wherein the polymer is being selected from the group consisting of hydrocarbon polymers, polysiloxanes, poly-acrylates and mixtures thereof that form a drug-containing layer having a solubility with respect to said steroidal hormone of no more than 3% by weight of the drug-containing layer.

[0054] As mentioned, it has been found that adhesive layers comprising the more non-polar types of polymers, such as the hydrocarbon polymers, have been shown to be superior to the polar type polymers, such as the polyacrylates (Example 2). Therefore in a preferred embodiment of the invention, the drug-containing layer comprises as the polymer a hydrocarbon polymer, which preferably may include polyisobutylenes, polybutenes, polyisoprenes, polystyrenes, styrene isoprene styrene block polymers, styrene butadiene styrene block polymers and/or mixtures thereof.

[0055] As mentioned above, in some embodiments of the invention, the drug-containing layer is adhesive. Preferentially, the polymer of the drug-containing layer has suitable adhesive properties so that no further sticky agent, such as a tackifier is required. Whenever it is considered necessary to improve the adhesive strength of the drug-containing layer, the layer further comprises a tackifier.

[0056] The term "tackifier" denotes an agent that improves the adhesive strength of the adhesive layer to the skin or mucosa.

[0057] Examples of tackifiers are selected from hydrocarbon resins, rosin resins and terpene resins. Examples of hydrocarbon resins are commercially available under the tradename Escorez® from ExxonMobil; Rogalite®, Piccotac® and Picco® from Eastman or Indopok® from BP. Examples of rosin esters suitable for transdermal systems according to the present invention include esters of hydrogenated wood rosin e.g. pentaerythritol ester of hydrogenated wood rosin, esters of partially hydrogenated wood rosin e.g. pentaerythritol esters of partially hydrogenated wood rosin, esters of wood rosin, esters of modified wood rosin, esters of partially dimerized rosin, esters of tall oil rosin, esters of dimerized rosin, and similar rosins, and combinations and mixtures thereof. Such rosin esters are commercially available under the tradenames Forak®, Foralyn®, Pentalyn®, Pernalyn® and Staybelite®.

[0058] In a preferred embodiment of the invention, the drug-containing layer comprises a tackifier in the form of a rosin ester such as pentaerythritol ester.

[0059] It is generally considered that the tackifier can be present in any suitable amount as long as the said critical solubility of the steroidal hormone in the drug-containing layer is not affected noticeably. Thus, a tackifier may be present in the drug-containing layer in an amount of from about 0.1 to 95 %, such as 0.5% to 95%, such as 1% to 95%

EP 1 541 137 A2

by weight of the drug-containing layer. That is to say that the tackifier can be present in an amount of from about 1% to 85%, 1 to 75 %, 1 to 65 %, 1 to 55 %, 1 to 50 %, 1 to 45 %, 1 to 40 % or more preferably of about 1 to 35 % such as preferably 1 to 30 %, more preferably 1 to 25%. Obviously, the amount of tackifier in the drug-containing layer may be critical to the solubility of the steroidal hormone in the drug-containing layer. Thus, in still other embodiments of the invention, the tackifier is present in the drug-containing layer in an amount of up to 35%, such as of up to 30%. More preferably, the amount of tackifier is up to 25%, such as up to 20% or 15%, more preferably of up to 10%, 7%, 5% by weight of the drug-containing layer.

[0060] It follows that a further particular aspect of the invention relates to a composition for transdermal delivery of Gestodene or an ester thereof, and optionally an estrogen, the composition comprising a drug-containing layer consisting essentially of:

- at least one steroidal hormone, such as a gestodene, and one or more pharmaceutically acceptable ingredient(s) and/or carrier(s) ;
- a polymer or a mixture of polymers, preferably in an amount of from about 15 to 99 % by weight of the drug-containing layer, the polymer is preferably selected from the group consisting of hydrocarbon polymers, polysiloxanes, poly-acrylates and mixtures thereof, most preferably hydrocarbon polymers (polyisobutylenes, polybutenes, polyisoprenes, polystyrenes, styrene isoprene styrene block polymers, styrene butadiene styrene block polymers and/or mixtures thereof). As mentioned the drug-containing layer has a solubility for Gestodene as mentioned above; and
- a tackifier in an amount of up to 85% by weight of the drug-containing layer; and
- optionally an estrogen.

[0061] As being said, the drug-containing layer is to be composed of ingredients forming a layer wherein the solubility criterion for Gestodene is met. Preferably, this criterion is met when the drug-containing layer is mainly composed of the hormones of the invention together with a polymer or a mixture of polymers and optionally a tackifier.

[0062] In some embodiments, it is found that a suitable polymer of the invention is lipophilic and essentially without any presence of free hydrophilic groups. Thus, any suitable hydrocarbon polymer, polysiloxane or poly-acrylate is selected from those polymers with a limited amount of functional groups in the side chains, such as free hydrophilic functional groups, such as carboxylic-, ester-, hydroxy-, amino-, amide, halogen- or sulfo- groups. Therefore, in some embodiments, the polymer essentially excludes poly-acrylates, of which some comprise free carboxylic and/or hydroxyl groups.

[0063] In preferred embodiments, the polymer is a hydrocarbon polymer, a poly-siloxane or a mixture of the two types of polymers. As mentioned, the hydrocarbon type polymers are of the non-polar type polymers essentially without free hydrophilic functional groups, such as carboxylic-, ester-, hydroxy-, amino-, amide, halogen- or sulfo- groups in the side chains. Therefore, in a most preferred embodiment, the polymer is a hydrocarbon polymer.

[0064] A plethora of hydrocarbon polymers exist of both high molecular weight and low molecular weight or mixtures thereof. Typically, the hydrocarbon polymers are in the form of polyisobutylenes, polybutenes, polyisoprenes, polystyrenes, styrene isoprene styrene block polymers, styrene butadiene styrene block polymers or mixtures thereof. The molecular weight of high molecular weight polymers (at least with respect to polyisobutylene) is usually within the range of 500,000 to 2,000,000 Da, whereas that of low molecular weight is of range from about 20,000 to 100,000 Da. Typically, such polymers comprise a mixture of high molecular weight polymers and low molecular weight polymers wherein the amount of the low molecular weight polyisobutylene in the total mixture is at least 50%.

[0065] In preferred embodiments, the hydrocarbon polymer is a polyisobutylene, polybutene, polyisoprene, most preferably polyisobutylene.

[0066] In some embodiments of the invention the polymer excludes isoprene co-polymers.

[0067] The poly-siloxanes are typically high molecular weight polydimethylsiloxanes with free silanol groups or end-capped silanol groups (Bio-PSA®).

[0068] Typical examples of poly-acrylates, which as mentioned above may be excluded or used in minimal amounts in some embodiments, include polymers selected from homopolymers of acrylic esters, copolymers of two or more types of acrylic ester units or copolymers of acrylic esters or other functional monomers. Acrylic esters include, but are not limited to, butyl methacrylate, pentyl methacrylate, hexyl methacrylate, heptyl methacrylate, octyl methacrylate, nonyl methacrylate, decyl methacrylate. For example ethylene/ethylacrylate copolymers, polymethacrylate polymers and polysiloxane-polymethacrylate copolymers. As mentioned, functional monomers containing a hydrophilic functional group may be excluded as a suitable polymer, such as hydroxyethyl methacrylate, hydroxypropyl methacrylate, etc. and monomers containing an amide group such as methacrylate, dimethylmethacrylamide.

[0069] Moreover, for the same reason polymers such as polyalkylenes (polyethylene, polypropylene, ethylene/propylene copolymers, chlorinated polyethylene, polytetrafluoroethylene), polyacetates (ethylene/vinyl acetate copolymers, vinyl chloride-vinyl acetate copolymer), polyvinylenes (polyvinylidene chloride, ethylene-vinyl alcohol copolymer,

EP 1 541 137 A2

ethylene-vinylxyethanol copolymer, polyvinylpyrrolidone) polycarbonates, cellulose polymers (methyl or ethyl cellulose derivatives, hydroxypropyl methyl cellulose and cellulose esters) may not be appropriate polymers according to the invention and are to be excluded or at least used in a restricted amount in some embodiments of the invention.. The exclusion does not however prevent the use of such polymers in other layers or parts of the composition.

[0070] Furthermore, in some embodiments, the drug-containing layer does not comprise, or at least only comprise a restricted amount of, a hydrophilic polymer, such as crystallisation inhibitors like polyvinylpyrrolidone, cellulose polymers, such as methyl or ethyl cellulose derivatives or hydroxypropyl methyl cellulose, or mixtures thereof.

[0071] Also in some embodiments a solubiliser, such as dimethyl-isosorbide, is not present in the drug-containing layer of at least only present in a restricted amount.

[0072] By the term "restricted amount" is meant that the polymer or solubiliser in question is present in a concentration in the drug-containing layer of less than 10%, such as less than 8, 5, 3, 2, 1, 0.5 or 0.2% by weight of the layer.

[0073] As mentioned, it has been possible to provide sufficient skin penetration of a steroidal hormone without incorporating a skin penetration enhancer and/or permeation enhancer. That is to say that in interesting embodiments of the invention, a skin penetration enhancer and/or permeation enhancer is excluded in the drug-containing layer or present in the drug-containing layer in a restricted amount, this amount being less than 5%, such as less than 4%, 3%, 2%, 1%, 0.5%, or 0.2% by weight of the drug-containing layer.

[0074] The terms "skin penetration enhancers" and "permeation enhancers" are in the present invention meant to be interchangeable terms and denotes compounds, which provide enhanced skin penetration/permeation to the active drugs when it is administered together with the drugs to the skin of a user. Penetration/permeation enhancers in transdermal formulations will change the thermodynamic activity of the drug in the drug-containing layer, and thereby lead to a positive or negative "push" effect. In addition, some penetration/permeation enhancers may conceivably penetrate into the highly ordered intercellular lipid structure of the stratum corneum and reduce its resistance by increasing lipid acyl chain mobility, thus providing a "pull" effect.

[0075] Any skin penetrating/permeation enhancing effect of a substance may be recognised upon testing identical formulations with and without penetration enhancer, for example by using nude mouse skin or the like. The skilled person knows such test methods.

[0076] Typical penetration/permeation enhancers are included in the group of compound listed below:

- Alcohols, such as monohydric alcohols having about 2 to 10 carbon atoms, such as ethyl, isopropyl, butyl, pentyl, octanyl decanyl and/or benzyl alcohols; dihydric alcohols such as 1,2-propanediol polyhydric alcohols such as glycerin, sorbitol and/or polyethylene glycol; saturated and unsaturated fatty alcohols with 8-18 carbon atoms, such as capryl-, decyl-, lauryl-, 2-lauryl-, myristyl-, cetyl-, stearyl-, oleyl-, linoleyl- and linolenylalcohol.
- Fatty acids, such as saturated or unsaturated fatty acids that may include 8-18 carbon atoms, for example, lauric acid, myristic acid, stearic acid, oleic acid, linoleic acid, linolenic acid and palmitic acid, triacetin, ascorbic acid, panthenol, butylated hydroxytoluene, tocopherol, tocopherol acetate, tocopheryl linoleate. Other fatty acids include but are not limited to valeric acid, capronic acid, caprylic acid, pelargonic acid, capric acid, isovaleric acid, neopentanoic acid, neopentanoic acid and/or isostearic acid.
- Esters such as aliphatic esters ethyl acetate, lower (C1 - C4) alkyl ester of lactic acid, fatty acid esters of the general formula $\text{CH}_3 - (\text{CH}_2)_n - \text{COOR}$, wherein n is a number from 8 to 18 and R is an alkyl residue of maximally 6 carbon atoms, such as fatty acid esters for example, those of lauric acid, myristic acid, stearic acid and palmitic acid, e.g., the methyl esters, ethyl esters, propyl esters, isopropyl esters, butyl esters, sec-butyl esters, isobutyl esters of these acids, or dicarboxylic acid diesters of the general formula $\text{R}'\text{OCO}(\text{CH}_2)_m \text{COOR}'$, wherein m is a number from 4 to 8 and R' in each case means an alkyl residue of maximally 6 carbon atoms, such as propyl oleate, decyl oleate, isopropyl palmitate, glycol palmitate, glycol laurate, dodecyl myristate, isopropyl myristate and glycol stearate, suitable dicarboxylic acid diesters are, for example, the diisopropyl adipate, diisobutyl adipate and diisopropyl sebacate.
- Ethers, such as polyethylene glycol ethers of aliphatic alcohols (such as cetyl, lauryl, oleyl and stearyl) including polyoxyethylene (4) lauryl ether, polyoxyethylene (2) oleyl ether and polyoxyethylene (10) oleyl ether.
- Alkanes, such as alkanes with chain lengths of 6 to 17 carbon atoms.
- Amides such as dimethyl acetamide, dimethyl formamide, dimethyl lauramide, dimethyl laurylamide and/or fatty acid amides and their derivatives.
- Amides, such as amides with long aliphatic chains, or aromatic amides, urea and urea derivatives such as cyclic

EP 1 541 137 A2

urea, dodecyl-urea, diphenyl-urea and/or allantoin.

- Amino acids.
- 5 - Amino acetates, such as derivatives of amino acetates such as dodecyl-N,N-dimethylaminoacetate and dodecyl-2-methyl-2-(N,N-methylaminoacetate), decyl-2-(N,N-dimethylamino)-propionat, decyl-2-(N,N-dimethylamino)-butyrat, octyl-2-(N,N-dimethylamino)-propionat, and/or dodecyl-(N,N-dimethylaminophenylacetate.
- Azone derivatives such as 1-dodecylazacycloheptane-2-one derivatives, azacycloalkane derivatives and/or
10 hexamethylenlauramid derivatives.
- Cyclodextrins such as alpha, beta, and gamma cyclodextrins.
- Glycerides, such as Monoglycerides, including glycerol monooleate, glycerol monolaurate and glycerol monolinoleate, polyethylene glycol-3-lauramide (PEG LR), polyethylene glycol monolaurate (PGML) glycerol monooleate (GMO), glycerol monolinoleate and/or glycerol monolaurate (GML).
- 15 - Glycols such as ethylene glycol, diethylene glycol, or propylene glycol dipropylene glycol and/or trimethylene glycol.
- 20 - Oils, such as mineral, vegetable, animal and fish fats and oils such as cotton seed, corn, safflower, olive and castor oils, squalene, and/or lanolin.
- Polyols such as propylen glycol.
- 25 - Pyrrolidones such as 2-pyrrolidone, N-methyl- 2-pyrrolidone, dodecyl-pyrrolidone, 2-pyrrolidon-5-carboxylic acid, N-hexyl-, N-lauryl-, 4-carboxy-, 4-carboxycarbon derivatives, 3-hydroxy-N-methyl-2-pyrrolidon, N-farnesyl-2-pyrrolidon, N-(2(decylthio)ethyl)-2-pyrrolidone and/or N-(2-hydroxyethyl)-2-pyrrolidone.
- 30 - Sulfoxides such as sulfoxide derivatives such as methyloctyl-sulfoxide, dimethylsulfoxide (DMSO), hexylmethyl-sulfoxide (hexyl-MSO) and/or decylmethyl-sulfoxide (decyl-MSO).
- Surface active agents such as cationic surfactants like cetyltrimethylammonium bromide, octadecyltrimethylammoniumchloride, cetylpyridiniumchloride and/or equivalent cationic compounds, anionic surfactants such as sulphate salts which include but are not limited to compounds such as sodium lauryl sulphate and/or sodium dodecyl
35 sulphate, and non-ionic surfactants such as esters of sorbitol and sorbitol anhydride which include but are not limited to polysorbate, sorbitan-monopalmitate and/or sorbitan-polyoleat.
- Terpenes, ketones and oxides.

40 **[0077]** In addition to the steroidal hormone, such as a progestin, the one or more polymers, the one or more tackifiers and the optional estrogen, the drug-containing layer or other parts of the composition also contain stabilisers, dyes, pigments, inert fillers, anti-ageing agents, anti-oxidants, elastomers, thermoplastics and other conventional components of transdermal compositions that are known in the art. Preferably, the composition, or at least the drug-containing layer, does not comprise or does only comprise in a restricted amount (less than 1%, 0.8%, 0.5%, 0.2% or 0.1% by weight of the drug-containing layer) polyvinylpyrrolidone, methylcellulose, ethyl cellulose, hydroxypropyl methylcellulose, and/or dimethyl-isosorbide.

45 **[0078]** It should be understood that compositions of the inventions are transparent or at least in very interesting embodiments transparent, which means that the skin can be visually inspected through the drug delivery system. That is to say that the drug-containing layer is a monophasic system in which the drug (here progestin) is completely dissolved in the drug-containing layer. The property as a monophasic system may be identified by mechanical stretching of the drug-containing layer by using a test method as described below.

50 **[0079]** The drug-containing layer is further characterised by being homogenous. The term "homogeneous" is used to describe a monophasic system, wherein the matrix is composed of one polymer phase. These systems can be distinguished from multiphasic systems, which are composed of at least two polymer phases. In most cases multiphasic systems can be detected visually by their opaque appearance. The opaque appearance is caused by the light diffraction due to differences in the diffraction index of the polymer phases. Other methods to detect monophasic systems are microscopic or rheological methods or by mechanical stretching thin polymer films. During mechanical stretching the thin polymer film composed of multiphasic systems turns opaque, as determined visually.

EP 1 541 137 A2

[0080] Thus, in summary it should be understood that interesting embodiments of the invention include:

a drug-containing layer that comprises:

- 5 i) a progestin such as Gestodene or an ester thereof; and
- ii) a polymer selected from the group consisting of polyisobutylenes, polybutenes, polyisoprenes, polystyrenes, styrene isoprene styrene block polymers, styrene butadiene styrene block polymers and mixtures thereof.

[0081] In further interesting embodiments thereof the drug-containing layer is characterised by the following parameters, which may be present as a single parameter or as mixture of parameters;

- The drug-containing layer has a solubility for Gestodene of no more than 3% by weight of the drug-containing layer;
- The drug-containing layer excludes dimethylisobutide or contains an amount of dimethylisobutide of less than 0.5% by weight of the layer;
- 15 • The drug-containing layer excludes polyvinylpyrrolidone, methylcellulose, ethylcellulose and/or hydroxypropylcellulose or contains an amount of less than 2% of polyvinylpyrrolidone, methylcellulose, ethylcellulose and/or hydroxypropylcellulose by weight of the layer;
- The drug-containing layer contains the progestin (Gestodene or an ester thereof) completely dissolved in the layer;
- The drug-containing layer comprises the Gestodene or an ester thereof in an amount of 0.5-3% by weight of the drug-containing layer;
- 20 • The drug-containing layer is transparent;
- The drug-containing layer is homogenous;
- The drug-containing layer is monophasic;
- The drug-containing layer excludes a skin penetration enhancer or contains an amount of less than 2% by weight of the layer;
- 25 • The drug-containing layer comprises said polymer in an amount of from about 15 to 99 % by weight of the layer;
- The drug-containing layer comprises a tackifier, such as a rosin ester, in an amount of up to 85% by weight of the drug-containing layer;

30 [0082] As mentioned above, the compositions of the invention are characterised by delivering an effective contraceptive amount of a steroidal hormone, such as a progestin, such as a gestodene, optionally in combination with an estrogen. In the embodiment, wherein the progestin is Gestodene or a derivative thereof the composition may be characterised by providing an in-vitro nude mouse skin permeation rate of Gestodene and/or a derivative thereof of at least 25 $\mu\text{g}/\text{cm}^2 \cdot 24\text{h}$. In other terms, the composition may be characterised by having a drug-containing layer delivering

35 Gestodene and/or a derivative thereof in an amount of from about 40 to 70 μg per day.
 [0083] Not only Gestodene or a derivative thereof may be used as a drug in the composition of the invention. Other progestins may be included in the drug-containing layer together with Gestodene or in place of a gestodene, such as dienogest, drospirenone, levonorgestrel, cyproteronacetate, tetrahydrodienogest, norethisterone, norethisteronacetate, desogestrel, 3-keto-desogestrel, norgestimate, lynestrenol, medroxy-progesteroneacetate, norgestrel, norethisteroneenanthate, trimegestone or alpha and beta-progesterone receptor ligands.

40 [0084] As mentioned, the composition is effective in inhibiting ovulation. In some instances, the composition further comprises an estrogen. The estrogen may be incorporated together with the progestin in the same drug-containing layer or be incorporated in a separate drug-containing layer free of the progestin.

45 [0085] The term "estrogen" includes both the natural 17 β -estradiol and the semi-synthetic estrogen derivatives such as esters of natural estrogen and 17-alkylated estrogens. Semisynthetic esters of natural estrogen include for example estradiol-17- β -enanthate, estradiol-17- β -valerate, estradiol-17- β -benzoate, estradiol-17- β -undecanoate, estradiol-16,17-hemisuccinate or estradiol-17- β -cypionate. Examples on 17-alkylated estrogens are Ethinylestradiol, Ethinylestradiol-3-isopropylsulphonate, quinestrol, mestranol or methyl estradiol. The term "estrogen" may also include a non-steroidal compound having estrogen activity, such as diethylstilbestrol, dienestrol, clomifen, chlorotrianesene or cyclofenil.

50 [0086] In a preferred embodiment, the estrogen is Ethinylestradiol.

[0087] To achieve the therapeutically effective amount of hormone in the blood, the actual concentration of the drug in the drug-containing layer may be adjusted. Generally speaking, the drug-containing layer should contain some hormone in excess of the amount of hormone to be absorbed for achieving the therapeutically effective amount of the hormone. Normally, this excess is small, such as the amount of hormone is less than 10 times the desired/required amount of hormone, preferably less than 5 fold, such as less than 2 fold. For example, it is also considered important to limit the amount of hormone so as to reduce the overall exposure of hormone to the user. Appropriate concentrations of a steroidal hormone, such as a progestin, such as Gestodene or a derivative thereof, in the drug-containing layer

EP 1 541 137 A2

is therefore from about 0.5 to 10% by weight of the drug-containing layer. In still more preferred embodiments, the concentration of said hormone is about 0.5 to 10%, such as from about 0.75 to 5%. As mentioned, the total concentration of hormone, such as Gestodene may result in drug-containing layers comprising the hormone in saturated or sub-saturated levels. In a very interesting embodiment, the concentration of a steroidal hormone, such as Gestodene or a derivative thereof, in the drug-containing layer is from about 1 to 3%, such as 1 to 2%.

[0088] Likewise, in some embodiments of the invention that further comprise an estrogen, the estrogen is present in the drug-containing layer in an amount of from about 0.5 to 10% by weight of the adhesive layer, preferably of from about 0.75 to 5%, more preferably of from about 1 to 3%, such as 1 to 2%.

[0089] Moreover, the said progestin, such as Gestodene or a derivative thereof is in a mass ratio to said estrogen in the range of from about 4 to 0.5, preferably 2 to 0.5 such as 1:1.

[0090] It has surprisingly been found that relatively high plasma levels of Gestodene can be maintained for a prolonged period of time by administering Gestodene or a derivative thereof formulated in a composition of the invention. Also surprisingly, it is found that the plasma profile and plasma levels of Gestodene, as resulting from the administration of Gestodene or a derivative thereof and optionally an estrogen, are effective in inhibiting the ovulation in a woman.

[0091] Therefore, further aspects of the invention relate to the use of a composition of the invention, optionally in combination with an estrogen, for the inhibition of ovulation in a female, such as a woman. When the medicament is singly administered, then a plasma concentration-time curve of Gestodene is achieved characterised by having plasma levels of Gestodene in a concentration of at least 1.0 ng/ml, as determined at steady state conditions. As follows, an aspect of the invention relates to a method for inhibiting ovulation in a female, such as a woman, comprising administering topically to skin or mucosa an effective amount of Gestodene or a derivative thereof, optionally in combination with an estrogen, so as upon singly administering said gestodene, then a plasma concentration-time curve of Gestodene is achieved characterised by having plasma levels of Gestodene in a concentration of at least 1.0 ng/ml, as determined at steady state conditions.

[0092] Alternatively, the uses and methods of the invention are for the treatment of other symptoms, disorders or symptoms which are normally treated by administering a progestin, such as Gestodene or a derivative thereof or a combination of a progestin and an estrogen.

[0093] Therefore, it should in general be understood that in some embodiments of the invention, the uses and methods are for the treatment of endometriosis, pre-menstrual syndrome, climacteric disorders, regulating menstrual cycle and/or stabilising menstrual cycle.

[0094] For example, administering a progestin without concurrent therapy with an estrogen can treat irregular bleeding and abnormal bleeding. As used herein, the term "irregular bleeding" characterises any uterine bleeding, outside the regular monthly menstrual periods of non-pregnant women. Uterine bleeding are irregular if menstrual cycles or menstrual periods are too short, too long, too frequent, too infrequent, or occur at irregular intervals which falls outside the regular 26-30 days menstrual cycle. The menstrual period is classified as too long when being delayed with 15 to 50 days or more to the expected onset of said bleeding. The term "abnormal bleeding" characterises heavy bleeding typically soaking through enough sanitary protection products to require changing more than every one or two hours, having a period that lasts over seven days. Abnormal bleeding does not include bleeding in women who have already reached menopause, abnormal uterine bleeding due to side effects of estrogen replacement therapy, abnormal bleeding as a symptom of uterine cancer, as a result of a consequence of abnormal blood clotting normally, an inherited bleeding disorder or because of a medical illness that affects levels of blood platelets.

[0095] In other embodiments, the progestin is administered in combination with an estrogen, such as by administering a medicament of the invention comprising the combination of a progestin, such as Gestodene or a derivative thereof, and an estrogen for the treatment of climacteric disorders, such as symptoms and diseases associated with menopause, such as hot flashes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence, loss of libido, poor concentration, diminished energy, diminished drive, irritability, urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition and/or osteoporosis. Most notably the treatment is directed to hot flashes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, urogenital atrophy, atrophy of the breasts or for the prevention or management of osteoporosis.

[0096] In connection with treatment of climacteric disorders, the estrogen may be selected from natural estrogens, such as estradiol and esters thereof, such as estradiol valerate, estradiol benzoate. Furthermore, natural estrogens include estrone, estriol, estriol succinate and conjugated estrogens, including conjugated equine estrogens such as estrone sulfate, 17 β -estradiol sulfate, 17 α -estradiol sulfate, equilin sulfate, 17 β -dihydroequilin sulfate, 17 α -dihydroequilin sulfate, equilenin sulfate, 17 β -dihydroequilenin sulfate and 17 α -dihydroequilenin sulfate or mixtures thereof.

[0097] In some embodiments of the invention, the plasma concentration-time curve of Gestodene at steady state conditions is characterised by having plasma levels of Gestodene in a concentration of at least 1.5 ng/ml, such as at least 2.0 ng/ml or at least 2.5 ng/ml. In other interesting embodiments, the plasma concentration-time curve of Gestodene at steady state conditions is characterised by having plasma levels of Gestodene in the range of 1 to 8 ng/

EP 1 541 137 A2

ml, preferably in the range of 1.5 to 6 ng/ml following the first 6 days after single administration of a composition of Gestodene or a derivative thereof, preferably in the form of a composition of the invention.

[0098] In still further embodiments, the plasma concentration-time curve of Gestodene at steady state conditions is characterised by having maximal plasma levels of Gestodene in the period of 18 to 60 hours following single administration of the medicament and/or having plasma levels of Gestodene at steady state conditions in the period of 5 to 7 days following single administration of the medicament in the order of at least 50% of the maximal plasma levels of Gestodene obtained during the first 18 to 60 hours following administration.

[0099] The gestodene is preferably administered repeatedly in cycles of 28 days such that within each cycle of 28 days, the gestodene/composition is administered with an interval of 7 days in a period of 21 days (3 weeks) followed by no administration of Gestodene or a derivative thereof for 7 days (one week). That is to say that the gestodene/composition is administered on day 1, 8 and 15 within each cycle of 28 days. Preferably, said day 1 may be the day of the start of menstruation, or any other suitable day, such as the first, second, third, fourth, fifth or sixth day following the day of start of menstruation. In another embodiment, the gestodene, optionally in combination with an estrogen, is administered repeatedly in cycles of 12 weeks such that within each cycle of 12 days, the gestodene/composition is administered with an interval of 7 days in a continuous period of 11 weeks followed by no administration of Gestodene or a derivative thereof for 7 days (one week).

[0100] To improve the contraceptive efficacy and security, an estrogen may be administered concomitantly with the gestodene. The estrogen may be selected from the estrogens mentioned above.

[0101] As may be understood, the uses and methods of the invention include the application of Gestodene or a derivative thereof, which may be in the form of a composition as defined herein. Thus, the term "medicament" includes a composition as defined herein. Furthermore, the term "medicament" is meant to include a kit of the invention.

[0102] In a still further aspect, the invention relates to a kit comprising 1 to 11 dosage units intended for a treatment period of 12 weeks formulated in a form for transdermal delivery of a progestin, such as of Gestodene or a derivative thereof, said dosage units comprise a drug-containing layer comprising gestodene and one or more pharmaceutically acceptable excipients or carriers and the drug-containing layer has a solubility with respect to said gestodene of no more than 3% by weight of the drug-containing layer. The dosage unit may comprise a composition as described herein. It is to be understood that in one embodiment thereof, 11 dosage units are administered continuously once weekly during a period of 11 weeks followed by one week of no administration of a dosage unit or administration of a placebo.

[0103] In other embodiments, the kit is intended for a treatment period of 12 weeks, but the kit comprises 1 to 9 dosage units. In one embodiment, 3-dosage units are administered weekly for a period of 3 weeks, followed by one week of no administration of a dosage unit or administration of a placebo. That is to say that the kit is intended for a treatment period of 4 weeks and the kit comprises 1-3 dosage units.

[0104] The dose of the progestin, such as of Gestodene or a derivative thereof in each dosage unit corresponds to a dose selected from a 6-day dose, 7-day dose, 8 day-dose, 14-day dose or 21-day dose. In one embodiment thereof, each dosage unit comprises Gestodene or a derivative thereof in a dose from about 0.5 to 5 mg, preferably 1 to 3 mg, more preferably 1.5 to 2.5 mg.

[0105] It is further to be understood that the kit may further comprise an estrogen as mentioned above. The estrogen may be combined together with the progestin, such as Gestodene or a derivative thereof, in the same dosage unit or provided in separate dosage units. The kit may for example further comprises 1 to 30 dosage units comprising an estrogen and no gestodene. The estrogen may be in a dosage form formulated for transdermal delivery, vaginal delivery or the like. Alternatively, the estrogen may be in the form of dosage units formulated for peroral delivery of an estrogen, such as in the form of a tablet, pill, capsule, powder, paste or granules.

[0106] The compositions of the invention may be fabricated using procedures known in the art. One example is included herein.

Figures

[0107] Figure 1. Mean serum levels of Gestodene (GSD) during two treatment cycles, week 1 and week 3, respectively. The legends are as follows:

■ cycle 1, week 1

□ cycle 2, week 1

▲ cycle 1, week 2

△ cycle 2, week 2

Examples

Example 1

5 Manufacturing of a patch

[0108] A composition of the invention is prepared as follows.

[0109] In a first step 380 g of Gestodene, and optionally 180 g of Ethinylestradiol, is dissolved in an appropriate solvent, such as 16,8 kg of dioxane. In a second step, about 57 kg of a mixture of polyisobutylene and rosin ester in heptane (Arcare® MA 24A) is weighed off. The hormone solution of the first step is transferred under stirring to the polymer solution and stirring is continued until a homogeneous solution is achieved. The thus obtained drug-containing solution is coated onto a release liner (such as FL 2000 75µm PET 1S; Fa Loparex) and dried under appropriate conditions. The dried drug-containing layer is then laminated with a backing foil/layer, such as Cotran®, 9720, 3M. The thus obtained laminate is divided into patches of the size of 10 cm² and the resulting patch has the following composition:

15

20

Gestodene:	1.9 mg
Optionally Ethinylestradiol:	0.9 mg
Polymer (In the form of polyisobutylene in combination with a tackifier e.g MA-24A®)	97,2 mg
Release liner:	10 cm ²
Backing layer:	10 cm ²

[0110] In another example, the resulting patch is similar to the above-mentioned but the amount of Ethinylestradiol is 0.6 mg.

25 In still another example, the resulting patch is similar to the above-mentioned but the adhesive is Duro-tak®, 10711, which is composed of a hydrocarbon polymer.

Example 2

30 Skin penetration rates of compositions with various polymers.

[0111] Six compositions (A-F) were manufactured with acrylate-vinylacetate polymers as the polymer in the drug-containing layer. Furthermore, composition G was made using polyisobutylene as the polymer in the drug-containing layer. The manufacturing was performed according to the process as described in Example 1. None of the compositions comprises a skin penetration enhancer.

35 [0112] Each of the compositions were tested in the in-vitro mouse skin permeation test. The test is performed using skin preparations of nude mouse skin (HsdCpb: NMRI-nu) available from Harlan Bioservice for Science GmbH, Wal-rode, Germany. The test formulation is attached on the outside of a skin specimen. Both are placed into the permeation cell with the inside in contact with the receptor media. HEPES buffered aqueous solution is used as receptor media. Sodium azide is added to prevent microbial growth. The receptor solution is maintained at 32°C. Samples are taken from the receptor solution at defined time intervals and the concentration of Gestodene (GSD) and Ethinylestradiol (EE) in the receptor media were analysed by HPLC. The flux rate was then calculated as the amount of drug released per area and time unit [µg/cm²·24h] using the calculated amounts of active substances.

40 [0113] Results on skin penetration rate in vitro:

45

Table 1.

Formulation	A	B	C	D	E	F	G
GSD (% w/w)	1.9	3.9	2.1	4.2	1.9	3.8	1.9
EE (% w/w)	1.0	2.0	1.1	2.1	1.0	1.9	0.9
Polymer	Acrylate - vinylacetate e.g. Durotak 387- 2051	Acrylate - vinylacetate e.g. Durotak 387- 2051	Acrylate - vinylacetate e.g. Durotak 387- 2825	Acrylate - vinylacetate e.g. Durotak 387- 2825	Acrylate - vinylacetate e.g. Durotak 87- 2097	Acrylate - vinylacetate e.g. Durotak 87- 2097	PIB e.g. MA- 24A

55

EP 1 541 137 A2

Table 1. (continued)

Formulation	A	B	C	D	E	F	G
GSD permeation $\mu\text{g}/\text{cm}^2 \cdot 24\text{h}$	14.8	32.8	12.6	14.3	13.5	16.7	30.9
EE permeation $\mu\text{g}/\text{cm}^2 \cdot 24\text{h}$	2.6	6.5	1.5	2.8	1.3	1.9	8.1

[0114] The results indicate that the permeation rate of Gestodone as well as of Ethinylestradiol from composition G (polyisobutylene) is superior to that from compositions A-F.

Example 3

Contraceptive effect and pharmacokinetic profile

[0115] The effect on ovulation inhibition, serum drug concentrations and safety of a patch of the invention was investigated in a selected population of women. The study design was based on the requirements of the EMEA guideline for clinical studies with contraceptive steroids (Committee for Proprietary Medicinal Products, CPMP/EWP 519/98).

Study design

[0116] The study has three phases: a pre-treatment phase including two washout cycles and one additional cycle to ensure that the selected women were ovulatory. Finally, the second phase is a treatment phase of two cycles, which was followed by a third phase consisting of one-cycle post-treatment phase.

[0117] Women enrolled in the study were required to be healthy, non-pregnant, non-smoking, non-lactating female volunteers aged between 18 and 35 years, with a normal body mass index of 18-26 kg/m^2 and a normal menstrual cycle length such as 28 days $\pm$ 4 days. Only women with light skin were included so that application sites could be easily and uniformly assessed.

[0118] The test patch is a patch comprising a drug-containing layer of 0.9 mg Ethinylestradiol and 1.0 mg Gestodone and Arcare MA-24A®, the drug containing layer has a size of 10 cm^2 . Arcare MA-24A® is a polyisobutylene based adhesive from Adhesive Research.

[0119] During the study, blood was drawn for the determination of endogenous hormones, such as estradiol, progesterone, follicle stimulating hormone, sex hormone binding protein, Ethinylestradiol, Gestodone. Transvaginal ultrasound examination were carried out to evaluate development of ovarian follicle-like structures. Patch adhesion, skin reactions at the application site and the woman's general health status was assessed. Vaginal bleeding was also evaluated.

[0120] During the pre-treatment cycle normal and spontaneous ovulation was established by assessment of serum progesterone values in that only women with an ovulatory pre-cycle and progesterone serum levels higher than 5 nmol/l were admitted to the treatment phase.

[0121] The treatment phase includes a period of two menstrual cycles. The first treatment in the first cycle began one day after the volunteers started menstruating in this cycle by application of a patch. A total of three test patches were applied in intervals of 7 days between, such as application at days 1, 8 and 15 of the first cycle - each at different application sites- during each treatment cycle. Each patch was worn for 7 days, then replaced with a new patch to complete a total of 21 days of continuous use. This was followed by a 7-day treatment-free interval before the next treatment period started with a total of three patches applied, each applied with an interval of 7 days. If the patches were lost or became more than 40% detached, a new patch was applied.

[0122] Patches were applied to the clean, dry intact and preferably hairless skin of the lower abdomen, below the navel, starting with the right side in the first treatment cycle, then alternating sides.

Determination of pharmacodynamic variables

[0123] The primary pharmacodynamic variable is the proportion of women with ovulation inhibited. In accordance with the so-called Hoogland method, ovulation requires follicular growth beyond 13 mm and subsequent ovarian rupture, plus a serum progesterone concentration $> 5 \text{ nmol}/\text{l}$ that concurs with the follicle rupture. As follows, the ovulation is said to be inhibited when the follicle is below 13 mm and the serum progesterone concentration is below 5 nmol/l at

EP 1 541 137 A2

the time of follicle rupture.

Determination of pharmacokinetic variables

[0124] Pharmacokinetic parameters such as area under the drug concentration time curve during the patch-wearing period $AUC_{(0-168h)}$, C_{max} , t_{max} , and accumulation factors within each cycle, such as determined by the $AUC_{(0-168h)}$ of 3rd patch/ $AUC_{(0-168h)}$ of 1st patch within cycle 1 or 2, or accumulation factors between two cycles, such as $AUC_{(0-168h)}$ of 3rd patch in cycle 2/ $AUC_{(0-168h)}$ of 3rd patch in cycle 1. The AUC was calculated according to the linear trapezoidal rule.

[0125] Serum concentrations of the estrogen and progestin, including Ethinylestradiol and Gestodene, were determined throughout the study to assess the pharmacokinetic characteristics of the patch. The sampling points were at the day 18 of the last pre-treatment cycle and days 1, 2, 3, 4, 5, 6, 7, 8, 15, 16, 17, 18, 19, 20, 21 and 22 of cycle 1 as well as days 1 (before application of new patch), 2, 3, 4, 5, 6, 7, 8, 15, 16, 17, 18, 19, 20, 21 and 22 of cycle 2.

[0126] The concentrations of Ethinylestradiol and Gestodene were determined by conventional methods known in the art. Specifically, the concentration of Ethinylestradiol was determined by gas chromatography using mass spectrometry in the chemical ionisation mode as the detection method following the extraction of Ethinylestradiol from acidified serum and consecutive derivatization. Gestodene concentrations were determined by radioimmunoassay using a rabbit antiserum and 3H-labelled Gestodene. After incubation and centrifugation, the resultant precipitate was redissolved with NaOH. The assay has a lower limit of quantification of approx. 250 pg/ml.

Results

[0127] The primary pharmacodynamic variable was the proportion of women with ovulation inhibition.

[0128] Ovarian activity was suppressed effectively, i.e.;

No Ovarian Activity:	cycle 1: 78%, cycle 2: 56%.
Potential Activity:	cycle 1: 15%, cycle 2: 22%.
Non-active FLS:	cycle 1: 4%, cycle 2: none;
Active FLS:	cycle 1: 4%, cycle 2: 22%

[0129] No cases of ovulation were found throughout the study. Ovulation inhibition, defined as a Hoogland score lower than 6 (ovulation), was sufficient for all volunteers in the per protocol data set throughout the study.

[0130] Progesterone concentrations were adequately suppressed below 2.5 nmol/l in each of the treatment cycles. Mean estradiol levels in the blood was under 20 pg/ml on all days on which a patch was applied.

Pharmacokinetic results

[0131] In all predose samples, Ethinylestradiol (EE) and Gestodene (GSD) serum concentrations were below the limit of quantitation (LOQ: 10pg/ml for EE, 250pg/ml for GSD). After administering the study medication, EE and GSD serum concentrations were quantifiable for at least 168 hours in all subjects. See results in Table 2 and 3 as well as in figure 1.

Table 2.

Mean pharmacokinetic parameters of ethinyl estradiol (EE)					
Pharmacokinetic parameter	Unit	Cycle 1		Cycle 2	
		Week 1	Week 3	Week 1	Week 3
C_{max}	pg/ml	45.6	50.4	45.2	48.0
T_{max}	h	48	24	48	48
$AUC_{(0-168h)}$	ng x h /ml	5.3	6.1	5.1	5.8

EP 1 541 137 A2

Table 3.

Mean pharmacokinetic parameters of gestodene (GSD)					
Pharmacokinetic parameter	Unit	Cycle 1		Cycle 2	
		Week 1	Week 3	Week 1	Week 3
C _{max}	pg/ml	1564	3896	2219	4416
T _{max}	h	144	48	96	48
AUC(0-168h)	ng x h / ml	194	524	302	598

Example 4

Comparison of polyisobutylene adhesive and acrylic formulation in human.

[0132] A randomized, cross-over study to determine the average daily delivery of Ethinylestradiol (EE) and gestodene (GSD) from three different transdermal patch formulations (A-C) in healthy postmenopausal volunteers following single administration was carried out. The aim was also to compare the transdermal application with that of intravenous injection.

The test formulations were as follows:

[0133]

Formulation A (Polyisobutylene)			
No.	Name of ingredient	Amount per 10 cm ² patch	Remark
1	Ethinylestradiol	0.95 mg	
2	Gestodene	1.9 mg	
3	Polyisobutylene Adhesive	97.15 mg	MA-24A

Formulation B (Polyisobutylene, 70% of Formulation A)			
No.	Name of ingredient	Amount per 10 cm ² patch	Remark
1	Ethinylestradiol	0.67 mg	
2	Gestodene	1.33 mg	
3	Polyisobutylene Adhesive	98.00 mg	MA-24A

Formulation C (Acrylate)			
No.	Name of ingredient	Amount per 10 cm ² patch	Remark
1	Ethinylestradiol	0.67 mg	
2	Gestodene	1.33 mg	
3	Acrylic Adhesive	73.5 mg	Gelva® 7883
4	Isopropyl myristate	5.0 mg	Permeability enhancer
5	Copovidone	15.0 mg	Crystallization inhibitor (Kollidon VA64, BASF, Germany)

[0134] The study was carried out according to the following parameters:

[0135] The patches were administered by single transdermal administration with a 7-day wearing period per test.

EP 1 541 137 A2

One week of washout was carried out after removal of patch at each test treatment. A dose of 60µg EE and 75µg of GSD was administered intravenously once.

[0136] Blood sampling for kinetic measurements was at 72 hours after intravenous administration and during a period of 12 days after transdermal administration as described in Example 3. Determination of blood levels of GSD and EE were carried out according to Example 3.

Results:

[0137] The maximum concentrations of gestodene are given in the following table indicating the difference of the polyisobutylene formulations A and B and the acrylic formulation. The figure shows the time course of the gestodene mean serum levels.

Parameter	Formulation A	Formulation B	Formulation C
C _{max} [pg/ml]:	2082	1995	1277
t _{max} (h):	168	144	156
AUC (0-7d): [h*ng/mL]	243	257	155

[0138] The results indicate that the drug delivery of Formulation C, which included a drug-containing layer of an acrylate in combination with a penetration enhancer, is significantly lower than the drug delivery from Formulations A and B.

Example 5

[0139] Drug-containing layers containing 1.9 mg of Gestodene and 0.9 mg of Ethinylestradiol and composed of different mixtures of polymers are shown (A to M).

EP 1 541 137 A2

Polymer Brand name	Polymer Chemical name	A	B	C	D	E	F	G
Foral 85E®	Pentaerythritol ester of hydrogenated rosin	20.0						
Foral 105E®	Glycerol ester of hydrogenated rosin		20.0				30.0	
Oppanol B10 N / SFN®	Polyisobutylene (MW about 40.000 Daltons)	57.2	57.2			67.2	55.2	
Oppanol B11 SFN®	Polyisobutylene (MW about 49.000)							62.2
Oppanol B12 SFN®	Polyisobutylene (MW about 55.000 dalton)			62.2	62.2			
Oppanol B30 SFN®	Polyisobutylene (MW about 200.000 dalton)							
Oppanol B100	Polyisobutylene (MW about 1.000.000 Dalton)	20.0	20.0	12.0	12.0	20.0	12.0	15.0
Oppanol B150	Polyisobutylene (MW about 2.600.000 Dalton)							
Indopol H300	Synthetic Polybutene (MW about 1.300 Dalton)					10.0		
Indopol H1900	Synthetic Polybutene (MW about 2.500 Dalton)			23.0				
Indopol H2100	Synthetic Polybutene (MW about 2.500 Dalton)				23.0			
Escorez 5300	cyclic aliphatic petroleum hydrocarbon resin							20.0
Staybelite Ester 3E	Ester of Hydrogenated Resin							
Staybelite Ester 5E JQ	glycerol ester of partially hydrogenated rosin							
Kraton D1161NU	styrene-isoprene-styrene block polymer							

EP 1 541 137 A2

Polymer Brand name	Polymer Chemical name	H	I	J	K	L	M
Foral 85E®	Pentaerythritol ester of hydrogenated rosin	10.0					
Foral 105E®	Glycerol ester of hydrogenated rosin		10.0				65.0
Oppanol B10 N / SFN®	Polyisobutylene (MW about 40.000 Daltons)	67.2	67.2		75.7	75.7	
Oppanol B11 SFN®	Polyisobutylene (MW about 49.000)						
Oppanol B12 SFN®	Polyisobutylene (MW about 55.000 dalton)			57.2			
Oppanol B30 SFN®	Polyisobutylene (MW about 200.000 dalton)	10.0	10.0				
Oppanol B100	Polyisobutylene (MW about 1.000.000 Dalton)	10.0	10.0	15.0			
Oppanol B150	Polyisobutylene (MW about 2.600.000 Dalton)				10.8	10.8	
Indopol H300	Synthetic Polybutene (MW about 1.300 Dalton)						
Indopol H1900	Synthetic Polybutene (MW about 2.500 Dalton)						
Indopol H2100	Synthetic Polybutene (MW about 2.500 Dalton)						
Escorez 5300	cyclic aliphatic petroleum hydrocarbon resin						
Staybelite Ester 3E	Ester of Hydrogenated Resin				10.8		
Staybelite Ester 5E JQ	glycerol ester of partially hydrogenated rosin			25.0		10.8	
Kraton D1161NU	styrene-isoprene-styrene block polymer						32.2

Claims

1. A composition for transdermal delivery comprising a drug-containing layer that comprises Gestodene or an ester thereof and one or more pharmaceutically acceptable excipients or carriers, wherein the drug-containing layer has a solubility for said Gestodene of no more than 3% by weight of the drug-containing layer.
2. The composition according to claim 1, wherein the one or more pharmaceutically acceptable carriers is at least one polymer selected from the group consisting of polyisobutylenes, polybutenes, polyisoprenes, polystyrenes,

EP 1 541 137 A2

styrene isoprene styrene block polymers, styrene butadiene styrene block polymers and mixtures thereof.

3. The composition according to any one of claims 1 to 2, wherein the drug-containing layer further comprises a tackifier selected from the group consisting of hydrocarbon resins, rosin resins and terpene resins.
4. The composition according to claim 3, wherein the tackifier is a rosin ester.
5. The composition according to any one of preceding claims, wherein the Gestodene or an ester thereof is completely dissolved in the layer.
6. The composition according to any one of preceding claims, wherein the drug-containing layer comprises less than 2% by weight of polyvinylpyrrolidone, methylcellulose, ethylcellulose and hydroxypropylcellulose.
7. The composition according to any one of preceding claims, wherein the drug-containing layer comprises less than 0.5% by weight of dimethylisobutylmaleate.
8. The composition according to any one of preceding claims, wherein the Gestodene or an ester thereof is in an amount ranging between 0.5 and 3% by weight of the drug-containing layer.
9. The composition according to any one of preceding claims, wherein the drug-containing layer is transparent.
10. The composition according to any one of preceding claims, wherein the drug-containing layer comprises less than 2% by weight of a skin penetration enhancer or a skin permeation enhancer.
11. The composition according to any one of preceding claims, further comprising an estrogen.
12. The composition according to claim 11, wherein the estrogen is Ethinylestradiol.
13. Use of a composition as defined by any one of claims 1 to 12 for the inhibition of ovulation in a female.
14. The use according to claim 13, wherein the plasma concentration-time curve of Gestodene after single administration of the composition is **characterised by** having plasma levels of Gestodene in a concentration of at least 1.0 ng/ml, as determined at steady state conditions.
15. The use according to claim 13, wherein the plasma concentration-time curve of Gestodene after single administration of the composition is **characterised by** having plasma levels of Gestodene in the range of 1 to 8 ng/ml, preferably in the range of 1.5 to 6 ng/ml following the first 6 days after administering the composition as a single administration.
16. A kit comprising 1 to 11 dosage units intended for a treatment period of 12 weeks formulated in a form for transdermal delivery of Gestodene or an ester thereof, said dosage unit comprises a composition as defined in any one of claims 1 to 12.
17. The kit according to claim 16, wherein the kit is intended for a treatment period of 12 weeks and the kit comprises 9 dosage units.
18. The kit according to claim 16, wherein the kit is intended for a treatment period of 4 weeks and the kit comprises 4 dosage units.
19. The kit according to any one of claims 16 to 18, wherein the gestodene is present in an effective dose corresponding to a dose selected from a 6-day dose, 7-day dose, 8 day-dose, 14-day dose or 21-day dose.
20. The kit according to any one of claims 16 to 18, wherein each dosage unit comprises a Gestodene in a dose from about 0.5 to 5 mg, preferably 1 to 3 mg, more preferably 1.5 to 2.5 mg.
21. The kit according to any one of claims 16 to 18, wherein the dosage unit further comprises an estrogen.



US006176323B1

(12) United States Patent
Weirich et al.**(10) Patent No.: US 6,176,323 B1**
(45) Date of Patent: Jan. 23, 2001**(54) DRILLING SYSTEMS WITH SENSORS FOR DETERMINING PROPERTIES OF DRILLING FLUID DOWNHOLE**WO 96/02734 * 2/1996 (WO).
WO 97/27381 * 7/1997 (WO).
WO 98/50680 11/1998 (WO).

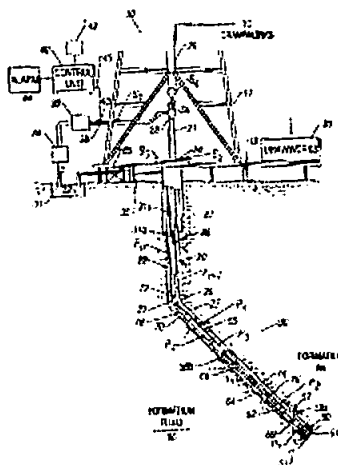
* cited by examiner

(75) Inventors: John B. Weirich, Spring; Ronald G. Bland, Houston; William W. Smith, Jr., The Woodlands, all of TX (US); Volker Krueger, Celle (DE); John W. Harrell, Waxahatchie, TX (US); Hatem N. Nasr; Valeri Papanyan, both of Houston, TX (US)**Primary Examiner—Robert E. Pezzuto****(74) Attorney, Agent, or Firm—Madan, Mossman & Sriram, P.C.****(73) Assignee:** Baker Hughes Incorporated, Houston, TX (US)**(*) Notice:** Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.**(21) Appl. No.: 09/111,368****(22) Filed: Jun. 26, 1998****Related U.S. Application Data****(60)** Provisional application No. 60/051,614, filed on Jun. 27, 1997.**(51) Int. Cl.⁷ E21B 47/00****(52) U.S. Cl. 175/40****(58) Field of Search 175/39, 40, 41, 175/42, 50, 45, 46, 44; 166/250; 73/152.03, 152.01, 152.52, 151, 152****(56) References Cited****U.S. PATENT DOCUMENTS**2,341,745 * 2/1949 Silverman et al.
2,588,210 * 3/1952 Crisman et al.

(List continued on next page.)

FOREIGN PATENT DOCUMENTS0 697 504 A2 2/1996 (EP).
2 307 684 6/1997 (GB).
WO
96/321420 * 10/1993 (WO).**(57) ABSTRACT**

The present invention provides a drilling system for drilling oilfield boreholes or wellbores utilizing a drill string having a drilling assembly conveyed downhole by a tubing (usually a drill pipe or coiled tubing). The drilling assembly includes a bottom hole assembly (BHA) and a drill bit. The bottom hole assembly preferably contains commonly used measurement-while-drilling sensors. The drill string also contains a variety of sensors for determining downhole various properties of the drilling fluid. Sensors are provided to determine density, viscosity, flow rate, clarity, compressibility, pressure and temperature of the drilling fluid at one or more downhole locations. Chemical detection sensors for detecting the presence of gas (methane) and H₂S are disposed in the drilling assembly. Sensors for determining fluid density, viscosity, pH, solid content, fluid clarity, fluid compressibility, and a spectroscopy sensor are also disposed in the BHA. Data from such sensors may be processed downhole and/or at the surface. Corrective actions are taken based upon the downhole measurements at the surface which may require altering the drilling fluid composition, altering the drilling fluid pump rate or shutting down the operation to clean wellbore. The drilling system contains one or more models, which may be stored in memory downhole or at the surface. These models are utilized by the downhole processor and the surface computer to determine desired fluid parameters for continued drilling. The drilling system is dynamic, in that the downhole fluid sensor data is utilized to update models and algorithms during drilling of the wellbore and the updated models are then utilized for continued drilling operations.

64 Claims, 9 Drawing Sheets

U.S. PATENT DOCUMENTS

U.S. PATENT DOCUMENTS			
		4,807,469	2/1989 Hoff .
		4,813,495	3/1989 Leach 175/6
2,805,346	9/1957 Piety .	4,833,915	5/1989 Radd et al. .
2,908,817	6/1959 McKay .	4,841,183	7/1989 Tolle .
3,327,527	6/1967 Anys .	4,941,951	7/1990 Sheppard et al. .
3,885,429	5/1975 Megyeri .	4,994,671	2/1991 Satinya et al. .
4,091,881	5/1978 Maus 175/7	5,327,984	7/1994 Rasi et al. .
4,195,349	3/1980 Balkandi .	5,351,532	10/1994 Hager .
4,297,880	11/1981 Berger .	5,435,176	7/1995 Mnachak, III .
4,454,756	6/1984 Sharp et al. 73/151	5,517,024	5/1996 Mullius et al. .
4,655,511	4/1987 Rodney et al. .	5,581,024	12/1996 Meyer, Jr. et al. .
4,683,944	8/1987 Cuilett .	5,679,894	10/1997 Kruger et al. .
4,765,183	8/1988 Coury .	5,715,895	2/1998 Champness et al. 175/17
4,805,449	2/1989 Das .		

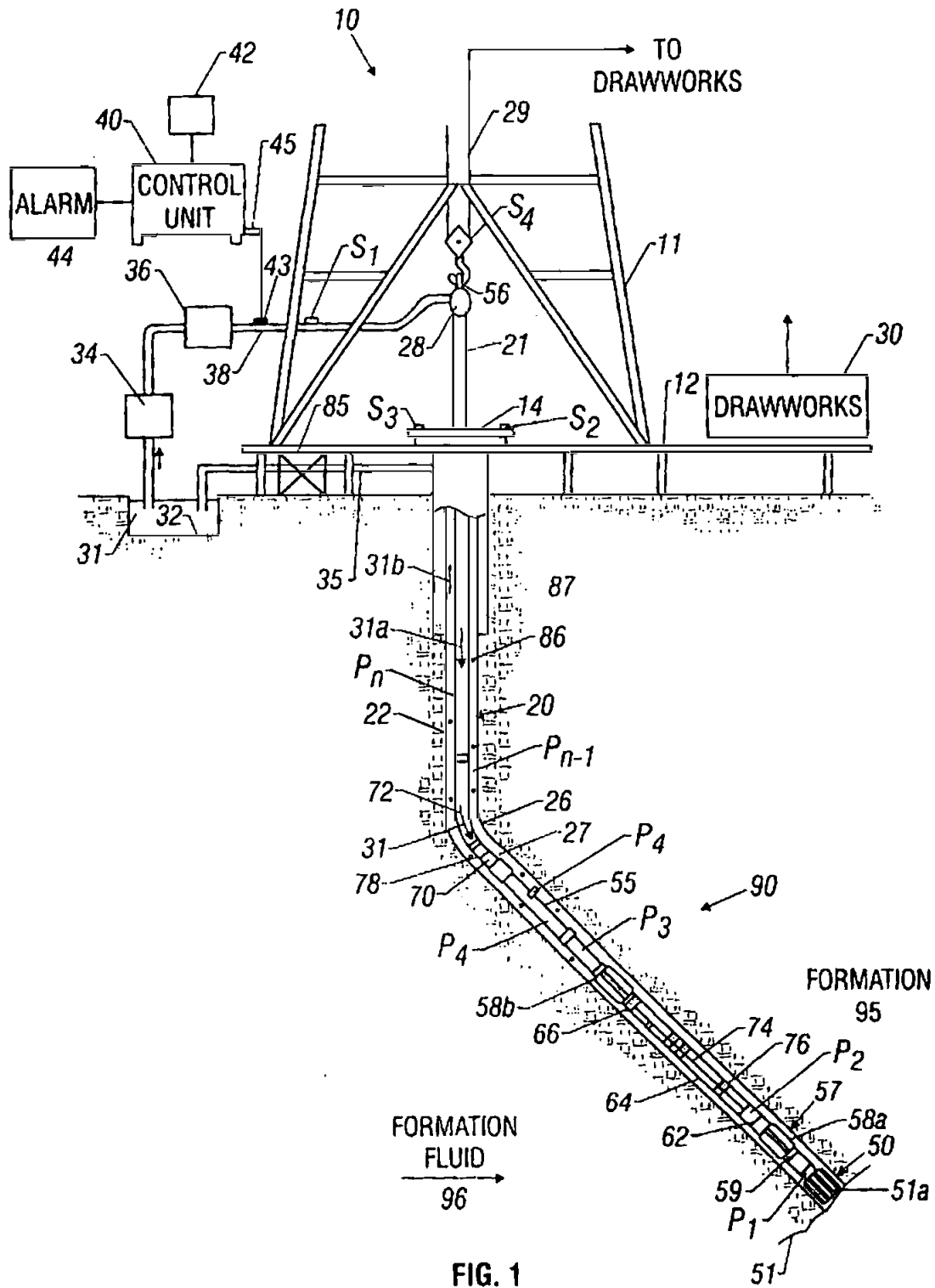


FIG. 1

DRILLING SYSTEMS WITH SENSORS FOR DETERMINING PROPERTIES OF DRILLING FLUID DOWNHOLE

CROSS-REFERENCE TO RELATED APPLICATION

This application takes priority from U.S. patent application Ser. No. 60/51,614 filed on Jun. 27, 1997.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates generally to drilling systems for forming or drilling wellbores or boreholes for the production of hydrocarbons from subsurface formations and more particularly to drilling systems utilizing sensors for determining downhole parameters relating to the fluid in the wellbore during drilling of the wellbores. The measured fluid parameters include chemical properties including chemical composition (gas, pH, H_2S , etc.), physical properties including density, viscosity, clarity, lubricity, color, compressibility, accumulation of cuttings, pressure and temperature profiles or distribution along wellbores. This invention further relates to taking actions based at least in part on the downhole measured fluid parameters, including adjusting the properties of the drilling fluid supplied from the surface, fluid flow rate, hole cleaning, and taking corrective actions when a kick is detected, thereby improving the efficiency and effectiveness of the drilling operations.

2. Description of the Related Art

To recover oil and gas from subsurface formations, wellbores (also referred to as boreholes) are drilled by rotating a drill bit attached at an end of a drill string. The drill string includes a drill pipe or a coiled tubing (referred herein as the "tubing") that has a drill bit at its downhole end and a bottomhole assembly (BHA) above the drill bit. The wellbore is drilled by rotating the drill bit by rotating the tubing and/or by a mud motor disposed in the BHA. A drilling fluid commonly referred to as the "mud" is supplied under pressure from a surface source into the tubing during drilling of the wellbore. The drilling fluid operates the mud motor (when used) and discharges at the drill bit bottom. The drilling fluid then returns to the surface via the annular space (annulus) between the drill string and the wellbore wall or inside. Fluid returning to the surface carries the rock bits (cuttings) produced by the drill bit as it disintegrates the rock to drill the wellbore.

In overburdened wellbores (when the drilling fluid column pressure is greater than the formation pressure), some of the drilling fluid penetrates into the formation, thereby causing a loss in the drilling fluid and forming an invaded zone around the wellbore. It is desirable to reduce the fluid loss into the formation because it makes it more difficult to measure the properties of the virgin formation, which are required to determine the presence and retrievability of the trapped hydrocarbons. In underbalanced drilling, the fluid column pressure is less than the formation pressure, which causes the formation fluid to enter into the wellbore. This invasion may reduce the effectiveness of the drilling fluid.

A substantial proportion of the current drilling activity involves directional boreholes (deviated and horizontal boreholes) and/or deeper boreholes to recover greater amounts of hydrocarbons from the subsurface formations and also to recover previously unrecoverable hydrocarbons. Drilling of such boreholes require the drilling fluid to have complex physical and chemical characteristics. The drilling

fluid is made up of a base such as water or synthetic material and may contain a number of additives depending upon the specific application. A major component in the success the drilling operation is the performance of the drilling fluid, especially for drilling deeper wellbores, horizontal wellbores and wellbores in hostile environments (high temperature and pressure). These environments require the drilling fluid to excel in many performance categories. The drilling operator and the mud engineer determine the type of the drilling fluid most suitable for the particular drilling operations and then utilize various additives to obtain the desired performance characteristics such as viscosity, density, gelation or thixotropic properties, mechanical stability, chemical stability, lubricating characteristics, ability to carry cuttings to the surface during drilling, ability to hold in suspension such cuttings when fluid circulation is stopped, environmental harmony, non-corrosive effect on the drilling components, provision of adequate hydrostatic pressure and cooling and lubricating impact on the drill bit and BHA components.

A stable borehole is generally a result of a chemical and/or mechanical balance of the drilling fluid. With respect to the mechanical stability, the hydrostatic pressure exerted by the drilling fluid in overburdened wells is normally designed to exceed the formation pressures. This is generally controlled by controlling the fluid density at the surface. To determine the fluid density during drilling, the operators take into account prior knowledge, the behavior of rock under stress, and their related deformation characteristics, formation dip, fluid velocity, type of the formation being drilled, etc. However, the actual density of the fluid is not continuously measured downhole, which may be different from the density assumed by the operator. Further, the fluid density downhole is dynamic, i.e., it continuously changes depending upon the actual drilling and borehole conditions, including the downhole temperature and pressure. Thus, it is desirable to determine density of the wellbore fluid downhole during the drilling operations and then to alter the drilling fluid composition at the surface to obtain the desired density and/or to take other corrective actions based on such measurements. The present invention provides drilling apparatus and methods for downhole determination of the fluid density during the drilling of the wellbores.

It is common to determine certain physical properties in the laboratories from fluid samples taken from the returning wellbore fluid. Such properties typically include fluid compressibility, rheology, viscosity, clarity and solid contents. However, these parameters may have different values downhole, particularly near the drill bit than at the surface. For example, the fluid viscosity may be different downhole than the viscosity determined at the surface even after accounting for the effect of downhole pressure and temperature and other factors. Similarly, the compressibility of the drilling fluid may be different downhole than at the surface. If a gas zone is penetrated and the gas enters the drilling fluid, the compressibility of drilling fluid can change significantly. The present invention provides drilling apparatus and methods for determining in-situ the above-noted physical parameters during drilling of the wellbores.

Substantially continuous monitoring of pressure gradient and differential pressure between the drill string inside and the annulus can provide indication of kicks, accumulation of cuttings and washed zones. Monitoring of the temperature gradient can qualitative measure of the performance of the drilling fluid and the drill bit. The present invention provides distributed sensors along the drill string to determine the pressure and temperature gradient and fluid flow rate at selected locations in the wellbore.

3

Downhole determination of certain chemical properties of the drilling fluid can provide on-line information about the drilling conditions. For example, presence of methane can indicate that the drilling is being done through a gas bearing formation and thus provide an early indication of a potential kick (kick detection). Oftentimes the presence of gas is detected when the gas is only a few hundred feet below the surface, which sometimes does not allow the operator to react and take preventive actions, such as closing valves or shutting down drilling to prevent a blow out. The present invention provides an apparatus and method for detecting the presence of gas and performs kick detection.

Corrosion of equipment in the wellbore is usually due to the presence of carbon dioxide, hydrogen sulphide (H_2S) and oxygen. Low pH and salt contaminated wellbore fluids are more corrosive. Prior art does not provide any methods for measuring the pH of drilling fluid or the presence of H_2S downhole. The returning wellbore fluid is analyzed at the surface to determine the various desired chemical properties of the drilling fluid. The present invention provides method for determining downhole certain chemical properties of the wellbore fluid.

As noted above, an important function of the drilling fluid is to transport cuttings from the wellbore as the drilling progresses. Once the drill bit has created a drill cutting, it should be removed from under the bit. If the cutting remains under the bit it is redrilled into smaller pieces, adversely affecting the rate of penetration, bit life and mud properties. The annular velocity needs to be greater than the slip velocity for cuttings to move uphole. The size, shape and weight of the cuttings determine the viscosity necessary to control the rate of settling through the drilling fluid. Low shear rate viscosity controls the carrying capacity of the drilling fluid. The density of the suspending fluid has an associated buoyancy effect on cuttings. An increase in density usually has an associated favorable affect on the carrying capacity of the drilling fluid. In horizontal wellbores, heavier cuttings can settle on the bottom side of the wellbore if the fluid properties and fluid speed are not adequate. Cuttings can also accumulate in washed-out zones. Prior art drilling tools do not determine density of the fluid downhole and do not provide an indication of whether cuttings are settling or accumulating at any place in the wellbore. The present invention utilizes downhole sensors and devices to determine the density of the fluid downhole and to provide an indication whether excessive cuttings are present at certain locations along the borehole.

In the oil and gas industry, various devices and sensors have been used to determine a variety of downhole parameters during drilling of wellbores. Such tools are generally referred to as the measurement-while-drilling (MWD) tools. The general emphasis of the industry has been to use MWD tools to determine parameters relating to the formations, physical condition of the tool and the borehole. Very few measurements are made relating to the drilling fluid. The majority of the measurements relating to the drilling fluid are made at the surface by analyzing samples collected from the fluid returning to the surface. Corrective actions are taken based on such measurements, which in many cases take a long time and do not represent the actual fluid properties downhole.

The present invention addresses several of the above-noted deficiencies and provides drilling systems for determining downhole various properties of the wellbore fluid during the drilling operations, including temperature and pressures at various locations, fluid density, accumulation of cuttings, viscosity, color, presence of methane and hydrogen

4

sulphide, pH of the fluid, fluid clarity, and fluid flow rate along the wellbore. Parameters from the downhole measurements may be computed by a downhole computer or processor or at the surface. A surface computer or control system displays necessary information for use by the driller and may be programmed to automatically take certain actions, activate alarms if certain unsafe conditions are detected, such as entry into a gas zone, excessive accumulation of cuttings downhole, etc. are detected. The surface computer communicates with the downhole processors via a two-way telemetry system.

SUMMARY OF THE INVENTION

The present invention provides a drilling system for drilling oilfield wellbores. A drilling assembly or bottom hole assembly (BHA) having a drill bit at an end is conveyed into the wellbore by a suitable tubing such as a drill pipe or coiled tubing. The drilling assembly may include a drill motor for rotating the drill bit. A drilling fluid is supplied under pressure from a source thereof at the surface into the tubing. The drilling fluid discharges at the drill bit bottom. The drilling fluid along with the drill cuttings circulates to the surface through the wellbore annulus. One or more shakers or other suitable devices remove cuttings from the returning fluid. The clean fluid discharges into the source.

In one embodiment, a plurality of pressure sensors are disposed, spaced apart, at selected locations in the drilling assembly and along the drill string to determine the pressure gradient of the fluid inside the tubing and in the annulus. The pressure gradient may be utilized to determine whether cuttings are accumulating within a particular zone. If the pressure at any point is greater than a predetermined value, or is approaching a leak off test (LOT) pressure or the pressure integrity test (PIT) pressure, the system provides a warning to the operator to clean the wellbore prior to further drilling of the wellbore. The pressure difference between zones determined from the distributed pressure sensor measurements also can provide an indication of areas or depths where the cuttings have accumulated. Any step change in the pressure gradient is an indication of a localized change in the density of the fluid. The distributed pressure measurements along the wellbore in conjunction with temperature measurements can also be utilized to perform reservoir modeling while the wellbore is being drilled instead of conducting expensive tests after the wellbore has been drilled. Such modeling at this early stage can provide useful information about the reservoirs surrounding the wellbore. Additionally, differential pressure sensors may be disposed at selected locations on the drill string to provide pressure difference between the pressure of the fluid inside the drill string and the fluid in the annulus.

Fluid flow measuring devices may be disposed in the drill string to determine the fluid flow through the drill string and the annulus at selected locations along the wellbore. This information may be utilized to determine the fluid loss into the formation in the zones between the flow sensor locations and to determine wash out zones.

A plurality of temperature sensors are likewise disposed to determine the temperature of the fluid inside the tubing and the drilling assembly and the temperature of the fluid in the annulus near the drill bit, along the drilling assembly and along the tubing. A distributed temperature sensor arrangement can provide the temperature gradient from the drill bit to any location on the drill string. Extreme localized temperatures can be detrimental to the physical and/or chemical properties of the drilling fluid. Substantially continuous

5

monitoring of the distributed temperature sensors provides an indication of the effectiveness of the drilling fluid.

In the embodiments described above or in an alternative embodiment, one or more acoustic sensors are disposed in the drill string. The acoustic sensors preferably are ultrasonic sensors to determine reflections of the ultrasonic signals from elements within the borehole, such as suspended or accumulated cuttings. The response of such sensors is utilized to determine the accumulation of cuttings in the wellbore during drilling. A plurality of ultrasonic sensors disposed around the drill string can provide an image of the wellbore fluid in the annulus. The depth of investigation may be varied by selecting a suitable frequency from a range of frequencies. A plurality of such sensor arrangements can provide discretely disposed along the drill string can provide such information over a significant length of the drill string.

The drill string also contains a variety of sensors for determining downhole various properties of the wellbore fluid. Sensors are provided to determine density, viscosity, flow rate, pressure and temperature of the drilling fluid at one or more downhole locations. Chemical detection sensors for detecting the presence of gas (methane), CO₂ and H₂S are disposed in the drilling assembly. Sensors for determining fluid density, viscosity, pH, solid content, fluid clarity, fluid compressibility, and a spectroscopy sensor are also disposed in the BHA. Data from such sensors is processed downhole and/or at the surface. Based upon the downhole measurements corrective actions are taken at the surface which may require altering the drilling fluid composition, altering the drilling fluid pump rate or shutting down the operation to clean the wellbore. The drilling system contains one or more models, which may be stored in memory downhole or at the surface. These models are utilized by the downhole processor and the surface computer to determine desired fluid parameters for continued drilling. The drilling system is dynamic, in that the downhole fluid sensor data is utilized to update models and algorithms during drilling of the wellbore and the updated models are then utilized for continued drilling operations.

Examples of the more important features of the invention thus have been summarized rather broadly in order that detailed description thereof that follows may be better understood, and in order that the contributions to the art may be appreciated. There are, of course, additional features of the invention that will be described hereinafter and which will form the subject of the claims appended hereto.

BRIEF DESCRIPTION OF THE DRAWINGS

For detailed understanding of the present invention, reference should be made to the following detailed description of the preferred embodiment, taken in conjunction with the accompanying drawings, in which like elements have been given like numerals and wherein:

FIG. 1 shows a schematic diagram of a drilling system having a drill string containing a drill bit, mud motor, measurement-while-drilling devices, downhole processing unit and various sensors for determining properties of the drilling fluid according to one embodiment of the present invention.

FIG. 2A shows a schematic diagram of a drilling assembly with a plurality of pressure sensors and differential pressure sensors according to the present invention.

FIG. 2B shows a schematic diagram of a drilling assembly with a plurality of temperature sensors according to one embodiment of the present invention.

6

FIG. 3 shows a schematic diagram of a sensor for determining the density of the drilling fluid.

FIG. 4 shows a schematic of a drill string with a plurality of acoustic devices for determining selected properties of drilling fluid according to the present invention.

FIG. 4A shows an arrangement of a plurality of acoustic sensor elements for use in the acoustic systems shown in FIG. 4.

FIG. 4B shows a display of the fluid characteristics obtained by an acoustic device of the system of FIG. 4.

FIG. 5 shows a schematic diagram of a sensor for determining the viscosity of the drilling fluid.

FIG. 6 shows a schematic diagram of a sensor for determining the compressibility of the drilling fluid.

FIG. 7 shows a schematic diagram of a sensor for determining the clarity of the drilling fluid.

FIG. 8 shows a schematic diagram of a fiber optic sensor for determining certain chemical properties of the drilling fluid.

FIG. 9 is a schematic illustration of a fiber optic sensor system for monitoring chemical properties of produced fluids;

FIG. 10 is a schematic illustration of a fiber optic sol gel indicator probe for use with the sensor system of FIG. 9;

FIG. 11 is a schematic illustration of an embodiment of an infrared sensor carried by the bottomhole assembly for determining properties of the wellbore fluid.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In general, the present invention provides a drilling system for drilling oilfield boreholes or wellbores utilizing a drill string having a drilling assembly conveyed downhole by a tubing (usually a drill pipe or coiled tubing). The drilling assembly includes a bottom hole assembly (BHA) and a drill bit. The bottom hole assembly preferably contains commonly used measurement-while-drilling sensors. The drill string also contains a variety of sensors for determining downhole various properties of the wellbore fluid. Sensors are provided to determine density, viscosity, flow rate, pressure and temperature of the drilling fluid at one or more downhole locations. Chemical detection sensors for detecting the presence of gas (methane), CO₂ and H₂S are disposed in the drilling assembly. Sensors for determining fluid density, viscosity, pH, solid content, fluid clarity, fluid compressibility, and a spectroscopy sensor are also disposed in the BHA. Data from such sensors may be processed downhole and/or at the surface. Corrective actions are taken based upon the downhole measurements at the surface which may require altering the drilling fluid composition, altering the drilling fluid pump rate or shutting down the operation to clean the wellbore. The drilling system contains one or more models, which may be stored in memory downhole or at the surface. These models are utilized by the downhole processor and the surface computer to determine desired fluid parameters for continued drilling. The drilling system is dynamic, in that the downhole fluid sensor data is utilized to update models and algorithms during drilling of the wellbore and the updated models are then utilized for continued drilling operations.

FIG. 1 shows a schematic diagram of a drilling system 10 having a drilling string 20 shown conveyed in a borehole 26. The drilling system 10 includes a conventional derrick 11 erected on a platform 12 which supports a rotary table 14 that is rotated by a prime mover such as an electric motor

(not shown) at a desired rotational speed. The drill string 20 includes a drill pipe 22 extending downward from the rotary table 14 into the borehole 26. A drilling assembly or borehole assembly (BHA) 90 carrying a drill bit 50 is attached to the bottom end of the drill string. The drill bit disintegrates the geological formations (rocks) when it is rotated to drill the borehole 26 producing rock bits (cuttings). The drill string 20 is coupled to a draw works 30 via a kelly joint 21, swivel 28 and line 29 through a pulley 23. During the drilling operations the draw works 30 is operated to control the weight on the bit, which is an important parameter that affects the rate of penetration. The operation of the draw works 30 is well known in the art and is thus not described in detail herein. FIG. 1 shows the use of drill pipe 22 to convey the drilling assembly 90 into the borehole 26. Alternatively, a coiled tubing with an injector head (not shown) may be utilized to convey the drilling assembly 90. For the purpose of this invention, drill pipe and coiled tubing are referred to as the "tubing". The present invention is equally applicable to both drill pipe and coiled tubing drill strings.

During drilling operations a suitable drilling fluid 31 (commonly referred to as the "mud" from a mud pit (source) 32 is supplied under pressure to the tubing 22 by a mud pump 34. The term "during drilling" herein means while drilling or when drilling is temporarily stopped for adding pipe or taking measurement without retrieving the drill string. The drilling fluid 31 passes from the mud pump 34 into the tubing 22 via a desurger 36, fluid line 38 and the kelly joint 21. The drilling fluid 31a travels through the tubing 22 and discharges at the borehole bottom 51 through openings in the drill bit 50. The drilling fluid 31b carrying drill cuttings 86 circulates uphole through the annular space (annulus) 27 between the drill string 20 and the borehole 26 and returns to the mud pit 32 via a return line 35. A shaker 85 disposed in the fluid line 35 removes the cuttings 86 from the returning fluid and discharges the clean fluid into the pit 32. A sensor S₁ preferably placed in the line 38, provides the rate of the fluid 31 being supplied to the tubing 22. A surface torque sensor S₂ and a speed sensor S₃ associated with the drill string 20 respectively provide measurements about the torque and the rotational speed of the drill string. Additionally, a sensor S₄ associated with line 29 is used to provide the hook load of the drill string 20.

In some applications the drill bit 50 is rotated by only rotating the drill pipe 22. However, in many applications, a downhole motor or mud motor 55 is disposed in the drilling assembly 90 to rotate the drill bit 50. The drilling motor rotates when the drilling fluid 31a passes through the mud motor 55. The drill pipe 22 is rotated usually to supplement the rotational power supplied by the mud motor, or to effect changes in the drilling direction. In either case, the rate of penetration (ROP) of the drill bit 50 for a given formation and the type of drilling assembly used largely depends upon the weight on bit (WOB) and the drill bit rotational speed.

The embodiment of FIG. 1 shows the mud motor 55 coupled to the drill bit 50 via a drive shaft (not shown) disposed in a bearing assembly 57. The mud motor 55 transfers power to the drive shaft via one or more hollow shafts that run through the resistivity measuring device 64. The hollow shaft enables the drilling fluid to pass from the mud motor 55 to the drill bit 50. Alternatively, the mud motor 55 may be coupled below the resistivity measuring device 64 or at any other suitable place in the drill string 90. The mud motor 55 rotates the drill bit 50 when the drilling fluid 31 passes through the mud motor 55 under pressure. The bearing assembly 57 supports the radial and axial forces

of the drill bit 50, the downthrust of the drill motor and the reactive upward loading from the applied weight on bit. Stabilizers 58a and 58b coupled spaced to the drilling assembly 90 acts as a centralizer for the drilling assembly 90.

A surface control unit 40 receives signals from the downhole sensors and devices (described below) via a sensor 43 placed in the fluid line 38, and signals from sensors S₁, S₂, S₃, hook load sensor S₄ and any other sensors used in the system and processes such signals according to programmed instructions provided to the surface control unit 40. The surface control unit 40 displays desired drilling parameters and other information on a display/monitor 42, which information is utilized by an operator to control the drilling operations. The surface control unit 40 contains a computer, memory for storing data, recorder for recording data and other peripherals. The surface control unit 40 also includes models or programs, processes data according to programmed instructions and responds to user commands entered through a suitable device. The control unit 40 is preferably adapted to activate alarms 44 when certain unsafe or undesirable operating conditions occur.

Still referring to FIG. 1, the drilling assembly 90 contains sensors and devices which are generally used for drilling modern boreholes, including formation evaluation sensors, sensors for determining borehole properties, tool health and drilling direction. Such sensors are often referred to in the art as the measurement-while-drilling devices or sensors. The drilling system 10 further includes a variety of sensors and devices for determining the drilling fluid 31 properties and condition of the drilling fluid during drilling of the wellbore 26 according to the present invention. The generally used MWD sensors will be briefly described first along with general description of downhole processor for processing sensor data and signals. The sensors used for determining the various properties or characteristics of the drilling or wellbore fluid are described thereafter.

The MWD sensors preferably include a device 64 for measuring the formation resistivity near and/or in front of the drill bit, a gamma ray device 76 for measuring the formation gamma ray intensity and devices 67 for determining drilling direction parameters, such as azimuth, inclination and x-y-z location of the drill bit 50. The resistivity device 64 is preferably coupled above a lower kick-off subassembly 62 and provides signals from which resistivity of the formation near or in front of the drill bit 50 is determined. The resistivity device 64 or a second resistivity device (not shown) may be utilized to measure the resistivity of the drilling fluid 31 downhole. An inclinometer 74 and gamma ray device 76 are suitably placed along the resistivity measuring device 64 for determining the inclination of the portion of the drill string near the drill bit 50 and the formation gamma ray intensity respectively. Any suitable inclinometer and gamma ray device, however, may be utilized for the purposes of this invention. In addition, an azimuth device, such as a magnetometer or a gyroscopic device, may be utilized to determine the drill string azimuth. A nuclear magnetic resonance (NMR) device may also be used to provide measurements for a number of formation parameters. The above-described devices are known in the art and therefore are not described in detail herein.

Still referring to FIG. 1, logging-while-drilling (LWD) devices, such as devices for measuring formation porosity, permeability and density, may be placed above the mud motor 64 in the housing 78 for providing information useful for evaluating and testing subsurface formations along borehole 26. Any commercially available devices may be utilized as the LWD devices.

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

2020
Bogotá, D.C.,

Abogado
LUIS FELIPE CASTILLO GISBONE

ASUNTO	Radicación	06-56831
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	011
	Folios	011 3907

Patente de Invención ☐ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/IB2004/052764
Fecha de Presentación Internal. 2004-12-11

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 4 a 23 como se radicó inicialmente

Reivindicaciones: Folios: 24 a 26 como se radicó inicialmente

Dibujos: Folio: 28 como se radicó inicialmente

Prioridad: Folio 1 (2003-12-12, 2004-12-10, US, N° 60/529161, 11/010116).

2. Objeto de la invención

La presente solicitud se titula "APARATO Y MÉTODO PARA LA MEDICIÓN DE SÓLIDOS EN UN POZO DE SONDEO", (folio N° 1).

El objeto de la presente solicitud de patente se relaciona con la medición de sólidos en un pozo y el monitoreo de la limpieza de los sólidos durante una operación de limpieza de un pozo de petróleo o gas.

De otra parte, el pliego reclama un método para detectar sólidos en un pozo de sondeo, relacionado en las reivindicaciones 1 a 17.

El objeto de la solicitud definido anteriormente se clasificó en la IPC E21B 47/10.

3. De la solicitud de patente.

3.1. Título

El título de la solicitud de la referencia no concuerda con la materia reclamada. El pliego reivindicatorio se limita a reclamar un método para la medición de sólidos en un pozo, mientras que el título se refiere a un método y adicionalmente a un aparato, donde este último no se encuentra ni especificado en las reivindicaciones ni en la descripción.

3.2. Reivindicaciones (artículo 30 D 486)

El pliego reivindicatorio calificado no es claro ni conciso por cuanto no define de manera correcta la materia que se desea proteger.

La reivindicación 1 no es clara en primer lugar porque en ningún aparte de la solicitud se ha aclarado como es el montaje de fondo de pozo (BHA), y en segundo lugar, porque las etapas mencionadas (movilizar un montaje y medir una característica indicativa) se refieren a la operación (uso) de un dispositivo, lo cual no constituye características técnicas válidas para definir una invención de procedimiento.

Adicionalmente, la reivindicación presenta como característica fundamental el medir una característica indicativa de los sólidos, sin establecer claramente que tipo de característica indicativa es la que se pretende medir. Igual situación ocurre con la reivindicación 2.

La reivindicación 10 no es clara por cuanto no se define que es lo que se ajusta en base a la característica medida.

Las reivindicaciones 14 a 17 se refieren al uso de un modelo de computadora. Esto no es una característica válida por cuanto el uso de un programa de computadora es un procedimiento rutinario que corresponde a la operación del dispositivo y no a una característica técnica de la invención.

Por los motivos anteriores, el pliego reivindicatorio calificado NO cumple con los requisitos de claridad exigidos en el artículo 30 de la Decisión 486.

4. Determinación del Estado de la Técnica

Considerando que la solicitud reclama prioridad del 12 de Diciembre de 2003, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta. Se realizó búsqueda de documentos relevantes dentro del estado de la técnica, entendiendo como estado de la técnica la definición provista en el Art. 16 D 486, y las excepciones fijadas en el Art. 17 de la misma.

No obstante, la solicitud presenta problemas en la definición de la materia, se realizó una búsqueda parcial la cual se complementará una vez se realicen los ajustes a la solicitud.

Se encontró como anterioridades los documentos relacionados a continuación que pueden afectar la patentabilidad del objeto de la presente solicitud

Nº	Documento*	Título	Fecha de publicación
D1	US6176323	DRILLING SYSTEMS WITH SENSORS FOR DETERMINING PROPERTIES OF DRILLING FLUID DOWNHOLE	2001-01-23

*los documentos mencionados se anexan al expediente

5. Análisis de patentabilidad (artículo 14 D486)

En cumplimiento del Art. 14 D486 se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicabilidad industrial, con el fin de establecer la patentabilidad de la invención reivindicada de la solicitud en estudio.

5.1. Novedad (artículo 16 D486)

El examen de novedad se realizó por medio de la comparación de las características técnicas de la solicitud con la materia encontrada en el estado del arte.

La reivindicación 1 se refiere a un método para detectar sólidos en un pozo que comprende las siguientes etapas:

- Movilizar un montaje de fondo de pozo BHA en un pozo de sondeo usando un medio de transporte. Donde el BHA comprende un montaje de detector.
- Medir una característica indicativa de los sólidos en el pozo de sondeo.

La anterioridad D1 se refiere a un método para detectar sólidos en un pozo utilizando un montaje de taladro que se transporta a través del pozo por medio de una tubería. El método incluye:

- Desplazar un montaje de fondo de pozo BHA 90 usando un transportador, donde el BHA 90 comprende un montaje de sensores 140a- 140c.
- Medir una característica indicativa de los sólidos en el pozo usando el montaje de sensores (col. 9 líneas 30 a 54)

Las reivindicaciones 2 a 13 presentan materia adicional que especifica las siguientes etapas:

- Descargar fluido al pozo a través de al menos un orificio en el BHA,
- Suspender los sólidos en el flujo del fluido
- Medir una característica de las partículas sólidas suspendidas en el fluido usando el montaje detector.
- Medir la característica según se mueve el BHA.
- Transmitir la característica vía un enlace de comunicaciones a la superficie.
- Generar una señal acústica del impacto de las partículas suspendidas en el fluido con el BHA.

La anterioridad D1 comprende las siguientes características similares a lo reclamado en las anteriores reivindicaciones:

- Descargar fluido al pozo a través una boquilla 50 (reivindicación 46)
- Medir las características indicativas de los sólidos suspendidos en el flujo de fluido a través usando el arreglo de sensores (col. 12 línea 52 a col. 13 línea 8).
- Donde la característica se mide a medida que se taladra, según se mueve el BHA (col 12 líneas 52 a 55).
- Donde las señales tomadas por los sensores son transmitidas a la unidad de

- control 40 de la superficie (col. 8 líneas 6 a 21).
- Generar una señal acústica de las partículas sólidas suspendidas en el fluido (col. 12 líneas 28 a 51).

Finalmente las reivindicaciones 14 a 17 se refieren a usar un modelo de computadora para generar los parámetros de trabajo.

El dispositivo presentado en D1 comprende uno o más modelos que se almacenan en la memoria, utilizados para diseñar los parámetros del fluido, donde los datos de los sensores son utilizados para actualizar los modelos y algoritmos durante la perforación del pozo (resumen).

Dados los argumentos anteriores, el objeto solicitado no presenta ninguna ventaja o efecto novedoso con respecto al estado del arte, por consiguiente se considera que el objeto de la solicitud no tiene Novedad y no cumple con los requisitos del artículo 14 de la decisión.

6. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US6176323	1 a 17	Novedad

Se recomienda, que tenga en cuenta que el replanteamiento de esos apartes NO podrá implicar una ampliación de la protección que correspondería a la divulgación contenida en la solicitud inicial, de acuerdo a lo que establece el artículo 34 de la Decisión 486.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2 Literal e) del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Directora Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
04 DIC. 2009

CONCEPTO TECNICO No. 3784	EXAMINADOR TECNICO Código No. 202082
---------------------------	---

JKCQ

REYES & REYES

A B O G A D O S

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-040107- -00005-0000

Fecha: 2009-11-24 16:06:45 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 37

SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 08 040.107

TÍTULO SOLICITADO: MÉTODO PARA LA ANTICONCEPCIÓN HORMONAL PREVENTIVA BAJO DEMANDA.

PUBLICACIÓN: Gaceta 604 de 29/05/2009, N° de publicación 241.

PRIORIDAD: DE 10 2005 050729.8 de 19/10/2005.

**SOLICITANTE: BAYER SCHERING PHARMA
AKTIENGESELLSCHAFT.**

APODERADO: J. IAN RAISBECK.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

Comendidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por

los artículos 14, 16, 18 y 20 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario, veamos:

En primer lugar, debe tenerse en cuenta el hecho que la solicitud colombiana en trámite incurre en una improcedencia directa de patentabilidad al reivindicar un método de tratamiento, tal y como se evidencia en las reivindicaciones 1 a 9 y 16 de dicha solicitud, en donde se menciona un método de anticoncepción hormonal femenina controlada bajo demanda. En efecto la Comunidad Andina de Naciones en su aparte d) del artículo 20 del capítulo I, acerca de los requisitos de patentabilidad, menciona literalmente que *"No serán patentables: d) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales."*

En un segundo aspecto, y esta vez refiriéndonos a la carencia de nivel inventivo de la solicitud colombiana en trámite, es importante resaltar que los sistemas de administración por vía percutánea, clase a la que pertenece el parche transdérmico que reivindica la solicitud colombiana en cuestión, son formulaciones farmacéuticas cuya técnica y aplicación están ampliamente descritos en el estado de la técnica. Cualquier persona medianamente versada en la materia debe reconocer que un sistema transdérmico está constituido por una serie de capas consecutivas, cada una de las cuales tiene funciones específicas. Según la presencia o no de una membrana que controle la liberación del principio activo, los sistemas transdérmicos pueden ser de tipo matricial (carentes de membrana) o de tipo reservorio¹. En este sentido resulta carente de nivel inventivo insertar cualquier tipo de principio activo en este tipo de formulaciones farmacéuticas, puesto que dicha inserción se resumiría a la aplicación de los respectivos ensayos de preformulación y formulación para conseguir las características de estabilidad, seguridad, eficacia y eficiencia que requieren este tipo de medicamentos.

De acuerdo con lo expuesto anteriormente, la versatilidad de este tipo de sistemas de entrega de fármaco también se puede hacer evidente a través de diversos documentos donde se exponen diversos tipos de tratamientos anticonceptivos de características similares a las reivindicadas por la solicitud colombiana en trámite, veamos:

¹ Vila Jato. J.L. Tecnología Farmacéutica. Volumen II. Páginas 416 a 422.

Publicación internacional WO 2005/058287 publicada el 30 de Junio de 2005 y titulada "TRANSDERMAL DELIVERY OF HORMONES WITHOUT THE NEED OF PENETRATION ENHANCERS" revela:

Field of Invention

The present invention relates to the field of pharmaceutical formulation techniques. The invention provides a low dosage pharmaceutical composition for transdermal delivery of at least one hormone, preferably a progestin, such as a gestodene, and optionally an estrogen, so as to achieve plasma concentration profiles effective in inhibiting ovulation in a woman.

Patente americana US 2004/0053901 publicada el 18 de marzo de 2004 y titulada "TRANSDERMAL HORMONE DELIVERY SYSTEM: COMPOSITIONS AND METHODS." revela:

A transdermal hormone delivery system (THDS) is disclosed. The THDS is useful for control of fertility and as therapy for a variety of diseases and conditions treatable by robust delivery of progestin and estrogen hormones, particularly the progestin, levonorgestrel. The THDS comprises a backing layer, an adjoining adhesive polymer matrix comprising an effective amount of at least a progestin hormone, delivery of which is enhanced by one or more skin permeation enhancing agents present in pre-determined amounts. The THDS is capable of providing effective daily doses of progestin and estrogen hormones from a small surface area in contact with the skin, e.g., less than 20 square centimeters. Methods of fertility control and various types of hormone replacement therapy utilizing the THDS are also disclosed.

Patente americana US 5512292 publicada el 30 de abril de 1996 y titulada "TRANSDERMAL CONTRACEPTIVE FORMULATIONS METHODS AND DEVICES" revela:

The present invention provides compositions and methods for the transdermal administration of a contraceptively effective amount of gestodene and estrogen, such as ethinyl estradiol, in combination, together with a suitable permeation enhancer. The amount of the estrogen codelivered is kept at an about constant and contraceptively effective rate while the amount of gestogen codelivered varies depending on the phase of the menstrual cycle but remains at a contraceptively effective rate. The size of the system may also vary depending on the amount of gestogen to be delivered.

Como se puede apreciar claramente, en este tipo de dispositivos transdérmicos, ya se habían incluido con anterioridad combinaciones hormonales entre gestágenos y progestágenos (específicamente levonorgestrel y etinilestradiol) para obtener terapias contraceptivas.

Finalmente, y teniendo en cuenta que la solicitud colombiana hace énfasis en la manera controlada "bajo demanda" del método contraceptivo que reivindica, es importante hacer evidente que este tipo de control bajo demanda en formulaciones que contienen métodos hormonales anticonceptivos, ya se había descrito con anterioridad en el mismo estado de la técnica. En efecto, existen documentos que exponen este mismo régimen de contracepción, veamos:

La publicación científica **"A Pre-Coital Pill? A Preliminary In Vitro Study²."** revela:

"The use of the progestogen-only pill as a 'pre-coital contraceptive' was tested by in vitro studies of sperm-mucus interaction. The results suggest that a single tablet of levonorgestrel 30 microg, or norethisterone 350 microg, was effective in preventing sperm migration in the cervical mucus about 12 hours later. This suggests that the progestogen-only pill may be effective as a morning before pill."

La patente Americana US 6143754 publicada el 07 de noviembre de 2000 y titulada **"COMPETITIVE PROGESTERONE ANTAGONIST FOR DEMAND-ORIENTED FEMALE BIRTH CONTROL"** revela:

This invention describes the novel use of dissociated competitive progesterone antagonists for the production of a pharmaceutical agent for demand-oriented female birth control (pill on demand), which can be used regardless of the point in the menstrual cycle, in a dosage unit that is to be administered on a one-time basis, whose dosage is below the ovulation-inhibiting dosage.

(...)

² Kovacs GT, Hendricks J, Summerbell D, Baker HW. Br J Fam Plann. 2000 Jul;26(3):165-6.

It has now been found, surprisingly enough, that nidation can be reliably prevented by even one-time administration only upon demand of a competitive progesterone antagonist (at a subovulation-inhibiting dosage), and in this respect a new type of oral contraceptive is available.

(...)

In addition, for local or topical use, for example, vaginal suppositories or transdermal systems such as skin plasters are available.

La publicación internacional 01/26603 publicada el 19 de abril de 2001 y titulada "MESOPROGESTINS (PROGESTERONE RECEPTOR MODULATORS) AS A COMPONENT OF FEMALE CONTRACEPTIVES" revela:

The use of a mesoprogesterin in a discontinuous, non-cyclical administration regime is the use as a so-called demand pill which has to be administered only around the time point of sexual intercourse for which contraception is desired. Preferably the administration is before sexual intercourse (i. medicinal condom). For details c.f. WO 93/23020.

(...)

In addition to oral administration of the estrogen and the mesoprogesterin, it is equally possible to administer one or both of the components transdermally, for example with a skin patch, which is best known for the administration of estrogen (Climara Patch).

Como se puede apreciar claramente, en estas anterioridades se hace mención de sistemas de administración de tratamientos contraceptivos, los cuales se administran bajo demanda, preferiblemente un tiempo adecuado y anterior al encuentro sexual. Al igual que en la solicitud colombiana en cuestión, dichos tratamientos se pueden incluir en sistemas transdérmicos y tan solo se requieren aplicar una sola vez.

En conclusión, la solicitud colombiana en trámite carece de los requerimientos fundamentales para concedérsele el privilegio de patente de invención, en primer lugar porque incurre en una improcedencia directa de patentabilidad al reivindicar un método de tratamiento, en segundo lugar porque carece de nivel inventivo al incluir combinaciones hormonales útiles en terapias anticonceptivas en formulaciones farmacéuticas ampliamente descritas en el estado de la técnica y

finalmente porque carece de novedad puesto que la manera o forma de dosificación "bajo demanda" de dichas formulaciones farmacéuticas también se encontraba descrita con anterioridad en el estado de la técnica para este tipo de terapia anticonceptiva.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS

- ❖ Vila Jato. J.L. Tecnología Farmacéutica. Volumen II. Páginas 416 a 422.
- ❖ Portadas y capítulos reivindicatorios de la Publicación internacional WO 2005/058287 publicada el 30 de Junio de 2005 y titulada "TRANSDERMAL DELIVERY OF HORMONES WITHOUT THE NEED OF PENETRATION ENHANCERS"; Patente americana US 5512292 publicada el 30 de abril de 1996 y titulada "TRANSDERMAL CONTRACEPTIVE FORMULATIONS METHODS AND DEVICES" y Patente americana US 2004/0053901 publicada el 18 de marzo de 2004 y titulada "TRANSDERMAL HORMONE DELIVERY SYSTEM: COMPOSITIONS AND METHODS."
- ❖ Abstract de La publicación científica "A Pre-Coital Pill? A Preliminary In Vitro Study ."
- ❖ La patente Americana US 6143754 publicada el 07 de noviembre de 2000 y titulada "COMPETITIVE PROGESTERONE ANTAGONIST FOR DEMAND-ORIENTED FEMALE BIRTH CONTROL" columnas 2 a 5.
- ❖ La publicación internacional 01/26603 publicada el 19 de abril de 2001 y titulada "MESOPROGESTINS (PROGESTERONE RECEPTOR MODULATORS) AS A COMPONENT OF FEMALE CONTRACEPTIVES" Paginas 3, 5 y 12.

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
30 June 2005 (30.06.2005)

PCT

(10) International Publication Number
WO 2005/058287 A2

(51) International Patent Classification⁷: **A61K 9/70**,
31/565

(74) Agent: **SCHOUBOE**, Anne; Ploumann & Vingtoft A/S,
P.O. Box 831, Sundkrogsvej 9, DK-2100 Copenhagen Ø
(DK).

(21) International Application Number:
PCT/IB2004/052752

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(22) International Filing Date:
10 December 2004 (10.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/528,718 12 December 2003 (12.12.2003) US
03078881.4 12 December 2003 (12.12.2003) EP

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CI, CG, CL, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): **SCHER-
ING AKTIENGESELLSCHAFT** [DE/DE]; Müller-
strasse 178, 13342 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BRACHT**, Stefan
[DE/DE]; Meisenweg 16, 07751 Jena (DE). **DITTGEN**,
Michael [DE/DE]; Heidenberg 35, 99510 Apolda (DE).
HUBER, Petra [DE/DE]; Lindwurmstrasse 72, 80337
München (DE). **LANGGUTH**, Thomas [DE/DE]; Am
Goethepark 2B, 07751 Jena (DE). **SCHENK**, Dirk
[DE/DE]; Ostenerfeldweg 5A, 83623 Diemtitz (DE).

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: **TRANSDERMAL DELIVERY OF HORMONES WITHOUT THE NEED OF PENETRATION ENHANCERS**

(57) Abstract: The present invention relates to a patch comprising a drug-containing layer with low content of hormones, such as gestodene, and optionally an estrogen (e.g. ethinyl estradiol). Upon administering the patch to a woman, plasma levels of at least 1.0 ng/ml of Gestodene is achieved at steady state conditions without the need of incorporating penetration enhancers or permeation enhancers in the drug-containing layer. Satisfactorily plasma levels of the hormones is also achieved throughout a period of at least 1 week, making the patch applicable for being used in female contraception with the concept of administering the patch ones weekly.

WO 2005/058287 A2

Claims

1. A composition for transdermal delivery comprising a drug-containing layer that comprises Gestodene or an ester thereof and one or more pharmaceutically acceptable excipients or carriers, wherein the drug-containing layer has a solubility for said Gestodene of no more than 3% by weight of the drug-containing layer.
2. The composition according to claim 1, wherein the one or more pharmaceutically acceptable carriers is at least one polymer selected from the group consisting of polyisobutylenes, polybutenes, polyisoprenes, polystyrenes, styrene isoprene styrene block polymers, styrene butadiene styrene block polymers and mixtures thereof.
3. The composition according to any one of claims 1 to 2, wherein the drug-containing layer further comprises a tackifier selected from the group consisting of hydrocarbon resins, rosin resins and terpene resins.
4. The composition according to claim 3, wherein the tackifier is a rosin ester.
5. The composition according to any one of preceding claims, wherein the Gestodene or an ester thereof is completely dissolved in the layer.
6. The composition according to any one of preceding claims, wherein the drug-containing layer comprises less than 2% by weight of polyvinylpyrrolidone, methylcellulose, ethylcellulose and hydroxypropylcellulose.
7. The composition according to any one of preceding claims, wherein the drug-containing layer comprises less than 0.5% by weight of dimethylisobutide.
8. The composition according to any one of preceding claims, wherein the Gestodene or an ester thereof is in an amount ranging between 0.5 and 3% by weight of the drug-containing layer.
9. The composition according to any one of preceding claims, wherein the drug-containing layer is transparent.
10. The composition according to any one of preceding claims, wherein the drug-containing layer comprises less than 2% by weight of a skin penetration enhancer or a skin permeation enhancer.

11. The composition according to any one of preceding claims, further comprising an estrogen.
12. The composition according to claim 11, wherein the estrogen is Ethinylestradiol.
- 5 13. Use of a composition as defined by any one of claims 1 to 12 for the inhibition of ovulation in a female.
14. The use according to claim 13, wherein the plasma concentration-time curve of
10 Gestodene after singly administration of the composition is characterised by having plasma levels of Gestodene in a concentration of at least 1.0 ng/ml, as determined at steady state conditions.
15. The use according to claim 13, wherein the plasma concentration-time curve of
15 Gestodene after singly administration of the composition is characterised by having plasma levels of Gestodene in the range of 1 to 8 ng/ml, preferably in the range of 1.5 to 6 ng/ml following the first 6 days after administering the composition as a single administration.
- 20 16. A kit comprising 1 to 11 dosage units intended for a treatment period of 12 weeks formulated in a form for transdermal delivery of Gestodene or an ester thereof, said dosage unit comprises a composition as defined in any one of claims 1 to 12.
17. The kit according to claim 16, wherein the kit is intended for a treatment period of 12
25 weeks and the kit comprises 9 dosage units.
18. The kit according to claim 16, wherein the kit is intended for a treatment period of 4 weeks and the kit comprises 4 dosage units.
- 30 19. The kit according to any one of claims 16 to 18, wherein the gestodene is present in an effective dose corresponding to a dose selected from a 6-day dose, 7-day dose, 8 day-dose, 14-day dose or 21-day dose.
20. The kit according to any one of claims 16 to 18, wherein each dosage unit comprises a
35 Gestodene in a dose from about 0.5 to 5 mg, preferably 1 to 3 mg, more preferably 1.5 to 2.5 mg.

21. The kit according to any one of claims 16 to 18, wherein the dosage unit further comprises an estrogen.
22. A method for inhibiting ovulation in a female, comprising administering topically to the skin or the mucosa an effective amount of Gestodene or an ester thereof derivative, optionally in combination with an estrogen, so that after singly administration of said Gestodene or an ester thereof, then a plasma concentration-time curve of Gestodene is achieved characterised by having plasma levels of Gestodene in a concentration of at least 1.0 ng/ml, as determined at steady state conditions.
23. The method according to claim 22, wherein the plasma concentration-time curve of Gestodene is characterised by having plasma levels of Gestodene in the range of 1 to 8 ng/ml following the first 6 days after single administration.
24. The method according to claim 23, wherein the Gestodene or an ester thereof is in a form of a composition as defined in claim 1.



United States Patent [19]
Gale et al.

[11] **Patent Number:** **5,512,292**
[45] **Date of Patent:** ***Apr. 30, 1996**

[54] **TRANSDERMAL CONTRACEPTIVE FORMULATIONS METHODS AND DEVICES**

[75] **Inventors:** **Robert M. Gale; Diane E. Nedberge,**
both of Los Altos; Linda E. Atkinson,
Portola Valley, all of Calif.

[73] **Assignee:** **ALZA Corporation, Palo Alto, Calif.**

[*] **Notice:** the term of this patent shall not extend beyond the expiration date of Pat. No. 5,376,377.

4,588,580	1/1989	Gale et al.	424/21
4,645,502	2/1987	Gale et al.	604/896
4,704,282	11/1987	Campbell et al.	424/424
4,746,515	5/1988	Cheng et al.	424/449
4,788,062	11/1988	Gale et al.	424/449
4,816,258	3/1989	Nedberge et al.	424/448
4,849,226	7/1989	Gale	424/448
4,863,738	9/1989	Taskovich	424/449
4,908,027	3/1990	Encore et al.	604/890.1
4,943,435	7/1990	Baker et al.	424/448
5,004,610	4/1991	Osborne et al.	424/448

FOREIGN PATENT DOCUMENTS

532388	10/1988	Australia	A61L 15/06
9004397	5/1990	WIPO	

[21] **Appl. No.:** **361,356**
[22] **Filed:** **Dec. 21, 1994**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 994,055, Dec. 17, 1992, Pat. No. 5,376,377, which is a continuation of Ser. No. 873,515, Apr. 20, 1992, abandoned, which is a continuation of Ser. No. 681,259, Apr. 8, 1991, abandoned, which is a continuation-in-part of Ser. No. 605,581, Oct. 29, 1990, abandoned.

[51] **Int. Cl.⁶** **A61F 13/02**
[52] **U.S. Cl.** **424/448; 424/449; 514/843; 514/947**
[58] **Field of Search** **424/448, 449; 514/843, 947**

OTHER PUBLICATIONS

Knepp et al., "Transdermal Drug Delivery: Problems and Possibilities," CRC Critical Reviews in Therapeutic Drug Carrier System, vol. 4, Issue 1, pp. 13-37 (1987).
Pannatier, et al., "The Skin as a Drug Metabolizing Organ," Drug Metabolism Reviews, vol. 8, No. 2, pp. 319-343 (1978).

Primary Examiner—J. Gabrielle Phelan
Attorney, Agent, or Firm—Michael J. Rafa; Steven F. Stone; Edward L. Mandell

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,598,122	8/1971	Zaffaroni et al.	128/268
3,598,123	8/1971	Zaffaroni	128/268
3,731,683	5/1973	Zaffaroni	128/268
3,797,494	3/1974	Zaffaroni	128/268
4,031,894	6/1977	Urquhart et al.	128/268
4,081,537	3/1978	Hofmeister et al.	424/238
4,201,211	5/1980	Chandrasekaran et al.	128/268
4,286,592	9/1981	Chandrasekaran	128/268
4,314,557	2/1982	Chandrasekaran	128/260
4,379,454	4/1983	Campbell et al.	604/897
4,435,180	3/1984	Leeper	604/896
4,559,222	12/1985	Encore et al.	424/28
4,568,343	2/1986	Leeper et al.	604/896
4,573,995	3/1986	Cheng et al.	604/896

[57] **ABSTRACT**

The present invention provides compositions and methods for the transdermal administration of a contraceptively effective amount of gestodene and estrogen, such as ethinyl estradiol, in combination, together with a suitable permeation enhancer. The amount of the estrogen co-delivered is kept at an about constant and contraceptively effective rate while the amount of gestodene co-delivered varies depending on the phase of the menstrual cycle but remains at a contraceptively effective rate. The size of the system may also vary depending on the amount of gestodene to be delivered.

31 Claims, 2 Drawing Sheets

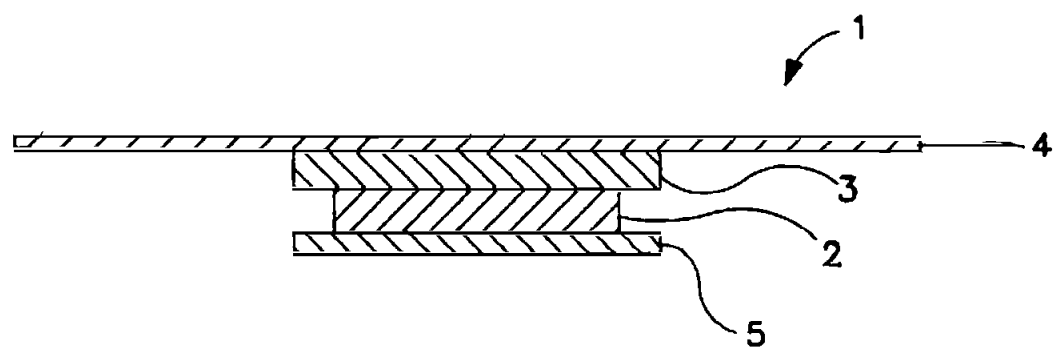


TABLE 3

Skin Donor	14.0 cm ² System					
	Experimental GTD mcg/day	Experimental EE ₂ mcg/day	Theoretical GTD mcg/day	Theoretical EE ₂ mcg/day	Theoretical Ratio GTD/EE ₂	Experimental Ratio GTD/EE ₂
1	52.7	28.9	100	50	2.0	1.83
2	118.6	58.9	100	50	2.0	2.01
3	108.3	54.3	100	50	2.0	1.99

A plot of the experiment ratios versus the theoretical for each of the examples is depicted in FIG. 4. As is shown in FIG. 4, the slope of the graph is approximately 1, thus indicating that the experimental ratios correspond to the theoretical ratios. Therefore, the systems were properly formulated to codeliver a constant amount of estrogen from various sizes of systems while the amount of gestodene codelivered varied as the system size increased.

This invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

What is claimed is:

1. A method for the transdermal coadministration of an estrogen and gestodene through the skin from a drug formulation comprised of ethinyl estradiol and gestodene, which method comprises:

- (a) placing a transdermal delivery device on the skin of a person, the device comprising:
 - (i) a reservoir comprising ethinyl estradiol, gestodene and a monoglyceride skin permeation enhancer,
 - (ii) a backing on the skin-distal surface of the reservoir, and
 - (iii) means for maintaining the reservoir in ethinyl estradiol-gestodene-and monoglyceride-transmitting relation with the skin,

whereby ethinyl estradiol and gestodene are coadministered through an area of skin at contraceptively effective rates, and said monoglyceride permeation enhancer is simultaneously coadministered to the area of skin at rates which are sufficient to substantially increase the permeability of the area to at least one of said ethinyl estradiol and gestodene.

2. A method according to claim 1 wherein the administration rate of ethinyl estradiol is maintained at a substantially constant rate of about 30-50 µg/day for a predetermined period of time while the administration rate of gestodene is varied between a first level of about 25 µg/day for a predetermined period of time, a second level of about 100 µg/day for a predetermined period of time, and a third level of about 50 µg/day for a predetermined period of time.

3. A method according to claim 2 wherein the administration rate of gestodene is increased by increasing the base surface area of the transdermal drug delivery device.

4. A method for providing contraception to a woman comprising:

- (a) placing a transdermal delivery device on an area of the woman's skin, the device comprising:
 - (i) a reservoir comprising ethinyl estradiol, gestodene and a monoglyceride skin permeation enhancer,
 - (ii) a backing on the skin-distal surface of the reservoir, and
 - (iii) means for maintaining the reservoir in ethinyl estradiol-gestodene-and monoglyceride-transmitting relation with the skin,

whereby ethinyl estradiol and gestodene are coadministered through the area of skin at contraceptively effective,

but not necessarily equal rates, and said monoglyceride permeation enhancer is simultaneously coadministered to the area of skin at rates which are sufficient to substantially increase the permeability of the area to at least one of said ethinyl estradiol and gestodene.

5. A method according to claim 4 wherein the administration rate of ethinyl estradiol is maintained at a substantially constant rate of about 30-50 µg/day for a predetermined period of time while the administration rate of gestodene is varied between a first level of about 25 µg/day for a predetermined period of time, a second level of about 100 µg/day for a predetermined period of time, and a third level of about 50 µg/day for a predetermined period of time.

6. A method according to claim 5 wherein the administration rate of gestodene is increased by increasing the base surface area of the transdermal drug delivery device.

7. A method according to claim 1 wherein the permeation enhancer is glycerol monooleate, glycerol monolinoleate or glycerol monolaurate.

8. A method according to claim 1 wherein the permeation enhancer is glycerol monooleate.

9. A method according to claim 8 wherein the ethinyl estradiol and gestodene are administered through the skin at equal rates.

10. A method according to claim 8 wherein the ethinyl estradiol and gestodene are administered through the skin at unequal rates.

11. A method according to claim 7 wherein the gestodene and ethinyl estradiol are administered through the skin at a rate of from about 30 µg/day to about 50 µg/day for a predetermined period of time.

12. A method according to claim 10 wherein the ethinyl estradiol is administered through the skin at a rate from about 30 µg/day to about 50 µg/day for a predetermined period of time and the gestodene is administered through the skin at a rate of about 100 µg/day for a predetermined period of time.

13. A method according to claim 10 wherein the ethinyl estradiol is administered through the skin at a rate from about 30 µg/day to about 50 µg/day for a predetermined period of time and the gestodene is administered through the skin at a rate of about 25 µg/day for a predetermined period of time.

14. A method according to claim 4, wherein the permeation enhancer is glycerol monooleate, glycerol monolinoleate or glycerol monolaurate.

15. A method according to claim 4 wherein the permeation enhancer is glycerol monooleate.

16. A method according to claim 14, wherein the ethinyl estradiol and gestodene are administered through the skin at equal rates.

17. A method according to claim 14 wherein the ethinyl estradiol and gestodene are administered through the skin at unequal rates.

18. A method according to claim 14, wherein the ethinyl estradiol and gestodene are administered through the skin at

15

a rate from about 30 µg/day to about 50 µg/day for a predetermined period of time.

19. A method according to claim 17, wherein the ethinyl estradiol is administered through the skin at a rate from about 30 µg/day to about 50 µg/day for a predetermined period of time and the gestodene is administered through the skin at a rate of about 100 µg/day for a predetermined period of time.

20. A method according to claim 17, wherein the ethinyl estradiol is administered through the skin at a rate from about 30 µg/day to about 50 µg/day for a predetermined period of time and the gestodene is administered through the skin at a rate of about 25 µg/day for a predetermined period of time.

21. A device for the transdermal coadministration of an estrogen and gestodene, at a contraceptively effective, but not necessarily equal rate, from a drug formulation comprised of ethinyl estradiol and gestodene, which device comprises:

- (a) a reservoir comprising a matrix containing an amount of each of the components of the drug formulation such that each component is delivered at a contraceptively effective, but not necessarily equal rate, and a skin permeation-enhancing amount of a monoglyceride permeation enhancer;
- (b) a backing on the skin-distal surface of the reservoir; and
- (c) means for maintaining the reservoir in ethinyl estradiol-gestodene-and monoglyceride-transmitting relation with the skin.

22. A device according to claim 21, wherein the permeation enhancer is, glycerol monooleate, glycerol monolinoleate or glycerol monolaurate.

16

23. A device according to claim 21 wherein the permeation enhancer is glycerol monooleate.

24. The device of claim 22 wherein the ethinyl estradiol and gestodene are administered through the skin at equal rates.

25. The device of claim 22 wherein the ethinyl estradiol and gestodene are administered through the skin at unequal rates.

26. A device according to claim 25, wherein the estradiol is administered through the skin at a rate from about 30 µg/day to about 50 µg/day for a predetermined period of time and the gestodene is administered through the skin at a rate of about 25 µg/day for a predetermined period of time.

27. A method according to claim 22, wherein the ethinyl estradiol is administered through the skin at a rate from about 30 µg/day to about 50 µg/day for a predetermined period of time and the gestodene is administered through the skin at a rate of about 50 µg/day for a predetermined period of time.

28. A method according to claim 25, wherein the ethinyl estradiol is administered through the skin at a rate from about 30 µg/day to about 50 µg/day for a predetermined period of time and the gestodene is administered through the skin at a rate of about 100 µg/day for a predetermined period of time.

29. A device according to claim 26 having a base surface area about 3.5 cm² in size.

30. A device according to claim 27 having a base surface area about 7.0 cm² in size.

31. A device according to claim 28 having a base surface area about 14.0 cm² in size.

* * * * *



US 20040053901A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0053901 A1****Chien**(43) **Pub. Date: Mar. 18, 2004**(54) **TRANSDERMAL HORMONE DELIVERY
SYSTEM: COMPOSITIONS AND METHODS****Publication Classification**(76) **Inventor: Te-Yen Chien, Neshanic Station, NJ
(US)**(51) **Int. CL⁷ A61K 31/56**
(52) **U.S. CL 514/171****Correspondence Address:**
WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE, 46TH FLOOR
1650 MARKET STREET
PHILADELPHIA, PA 19103 (US)(57) **ABSTRACT**(21) **Appl. No.: 10/621,711**(22) **Filed: Jul. 17, 2003****Related U.S. Application Data**(63) **Continuation-in-part of application No. 10/130,913,
filed on May 23, 2002, filed as 371 of international
application No. PCT/US00/32043, filed on Nov. 22,
2000.**(60) **Provisional application No. 60/167,535, filed on Nov.
24, 1999.**

A transdermal hormone delivery system (THDS) is disclosed. The THDS is useful for control of fertility and as therapy for a variety of diseases and conditions treatable by robust delivery of progestin and estrogen hormones, particularly the progestin, levonorgestrel. The THDS comprises a backing layer, an adjoining adhesive polymer matrix comprising an effective amount of at least a progestin hormone, delivery of which is enhanced by one or more skin permeation enhancing agents present in pre-determined amounts. The THDS is capable of providing effective daily doses of progestin and estrogen hormones from a small surface area in contact with the skin, e.g., less than 20 square centimeters. Methods of fertility control and various types of hormone replacement therapy utilizing the THDS are also disclosed.

TABLE 2-continued

		Serum Levels of Levonorgestrel and Ethinyl Estradiol in Clinical Trial Test Subjects During Four Cycles of Administration of THDS					
		Levonorgestrel (ng/ml)			Ethinyl Estradiol (pg/ml)		
Cycle	Day	15 cm ²	17.5 cm ²	20 cm ²	15 cm ²	17.5 cm ²	20 cm ²
	15	937.32 ± 176.32 (N = 2)	1775.66	2500.13 ± 752.94 (N = 4)	34.20 ± 17.42 (N = 2)	43.61	27.72 ± 6.83 (N = 4)
	17	947.81 ± 978.37 (N = 2)	7175.00	2911.94 ± 953.73 (N = 4)	31.08 ± 34.20 (N = 2)	87.21	25.34 ± 10.93 (N = 4)
	22	919.69 ± 115.95 (N = 2)	2274.46	2175.81 ± 1273.49 (N = 4)	22.17 ± 4.83 (N = 2)	34.89	29.26 ± 12.24 (N = 4)
4	1	49.00	ND	44.13 ± 59.57 (N = 2)	4.38	ND	3.30 ± 3.29 (N = 2)
	8	576.00	ND	1559.75 ± 392.09 (N = 2)	16.88	ND	34.51
	15	940.00	ND	2634.88 ± 1458.23 (N = 2)	10.63	ND	27.15 ± 4.91 (N = 2)
	22	1283.00		2588.50 ± 1693.89 (N = 2)	17.50	ND	23.01 ± 3.70 (N = 2)

[0095] The present invention is not limited to the embodiments described and exemplified above, but is capable of variation and modification within the scope of the appended claims.

What is claimed:

1. A skin permeation enhancer composition for enhancing absorption of a steroid hormone through the skin, wherein the composition comprises a combination of a pharmaceutically acceptable organic solvent, a fatty (C₆-C₂₀) alcohol ester of a hydroxy acid, a lower (C₁-C₄) alkyl ester of a hydroxy acid, and a C₆-C₁₈ fatty acid.

2. The composition of claim 1, wherein the pharmaceutically acceptable organic solvent is dimethyl sulfoxide.

3. The composition of claim 1, wherein the fatty alcohol ester of a hydroxy acid is a fatty alcohol ester of lactic acid.

4. The composition of claim 1, wherein the lower alkyl ester of a hydroxy acid is a lower alkyl ester of lactic acid.

5. The composition of claim 1, wherein the C₆-C₁₈ fatty acid is capric acid.

6. The composition of claim 1, comprising dimethyl sulfoxide, a fatty alcohol ester of lactic acid, a lower alkyl ester of lactic acid, and capric acid.

7. The composition of claim 6, wherein the dimethyl sulfoxide, fatty alcohol ester of lactic acid, lower alkyl ester of lactic acid, and capric acid, are present in a weight ratio of 2:1:1:0.8 to 6:1:1:0.8, respectively.

8. The composition of claim 7, wherein the dimethyl sulfoxide, fatty alcohol ester of lactic acid, lower alkyl ester of lactic acid, and capric acid, are present in a weight ratio of 3:1:1:0.8 to 4:1:1:0.8, respectively.

9. The composition of claim 6, wherein the fatty alcohol ester of lactic acid is lauryl lactate.

10. The composition of claim 6, wherein the lower alkyl ester of lactic acid is ethyl lactate.

11. The composition of claim 1, comprising one or more of a progestin, an estrogen and a testosterone hormone.

12. The composition of claim 11, wherein the progestin is levonorgestrel.

13. The composition of claim 11, wherein the estrogen is ethinyl estradiol or 17-β estradiol.

14. The composition of claim 1, comprising a progestin and an estrogen in a weight ratio of at least about 1.8:1.

15. The composition of claim 14, comprising a progestin and an estrogen in a weight ratio of at least about 2:1.

16. The composition of claim 1, comprising an estrogen in an amount less than about 1.5 percent by weight of the composition.

17. The composition of claim 1, comprising a testosterone.

18. The composition of claim 1, comprising a progestin, an estrogen and a testosterone.

19. The composition of claim 1, comprising dimethyl sulfoxide, lauryl lactate, ethyl lactate and capric acid in a weight ratio of about 3:1:1:0.8.

20. The composition of claim 19, comprising levonorgestrel and ethinyl estradiol in a weight ratio of about 1.8:1, wherein the ethinyl estradiol comprises less than about 1.5% by weight of the composition.

21. A polymer formulation for use in fabricating a transdermal hormone delivery system of a type comprising a backing layer and a polymer matrix in which is dispersed one or more steroid hormones to be transdermally delivered, wherein the formulation comprises a polymer and, on a weight percentage basis, from about 0% to about 5% humectant/plasticizer, and from about 10% to about 30% of a skin permeation enhancer composition comprising a combination of a pharmaceutically acceptable organic solvent, a fatty (C₆-C₂₀) alcohol ester of a hydroxy acid, a lower (C₁-C₄) alkyl ester of a hydroxy acid, and a C₆-C₁₈ fatty acid.

22. The formulation of claim 21, wherein the polymer is an adhesive polymer.

23. The formulation of claim 22, wherein the adhesive polymer is a polyacrylate adhesive copolymer.

24. The formulation of claim 23, wherein the polyacrylate adhesive copolymer comprises a 2-ethylhexyl acrylate monomer.

25. The formulation of claim 24, wherein the polyacrylate adhesive copolymer further comprises about 3% to about 60% w/w vinyl acetate.

26. The formulation of claim 21, wherein the humectant/plasticizer is a polyvinylpyrrolidone/vinyl acetate.

27. The formulation of claim 21, wherein the pharmaceutically acceptable organic solvent is dimethyl sulfoxide.

28. The formulation of claim 21, wherein the fatty alcohol ester of a hydroxy acid is a fatty alcohol ester of lactic acid.

29. The formulation of claim 21, wherein the lower alkyl ester of a hydroxy acid is a lower alkyl ester of lactic acid.

30. The formulation of claim 21, wherein the C₆-C₁₈ fatty acid is capric acid.

31. The formulation of claim 21, comprising dimethyl sulfoxide, a fatty alcohol ester of lactic acid, a lower alkyl ester of lactic acid, and capric acid.

32. The formulation of claim 31, wherein, prior to drying, the dimethyl sulfoxide, fatty alcohol ester of lactic acid, lower alkyl ester of lactic acid, and capric acid, are present in a weight ratio of 2:1:1:0.8 to 6:1:1:0.8, respectively.

33. The formulation of claim 32, wherein the dimethyl sulfoxide, fatty alcohol ester of lactic acid, lower alkyl ester of lactic acid, and capric acid, are present in a weight ratio of 3:1:1:0.8 to 4:1:1:0.8, respectively.

34. The formulation of claim 32 which, upon coating upon a backing layer and drying under conditions suitable to form an adhesive polymer matrix for delivering steroid hormones, comprises the dimethyl sulfoxide, fatty alcohol ester of lactic acid, lower alkyl ester of lactic acid, and capric acid in a weight ratio of about 4-8 parts dimethyl sulfoxide, about 4-8 parts fatty alcohol ester of lactic acid, about 1 part lower alkyl ester of lactic acid and about 3-6 parts capric acid.

35. The formulation of claim 34, wherein after the drying the dimethyl sulfoxide and the fatty alcohol ester of lactic acid are present in a weight ratio of between about 1.5:1 and about 1:1.5.

36. The formulation of claim 34, wherein the drying conditions are about 15 minutes at about 60° C.

37. The formulation of claim 31, wherein the fatty alcohol ester of lactic acid is lauryl lactate.

38. The formulation of claim 31, wherein the lower alkyl ester of lactic acid is ethyl lactate.

39. The formulation of claim 21, comprising a progestin.

40. The formulation of claim 39, wherein the progestin is levonorgestrel.

41. The formulation of claim 21, comprising a progestin and an estrogen.

42. The formulation of claim 41, wherein the progestin and the estrogen are present in a weight ratio of at least 1.8:1.

43. The formulation of claim 42, wherein the progestin and the estrogen are present in a weight ratio of at least 2:1.

44. The formulation of claim 41, wherein the estrogen comprises less than about 0.3% on a weight basis of the formulation.

45. The formulation of claim 41, wherein the progestin is levonorgestrel and the estrogen is ethinyl estradiol or 17 β-estradiol.

46. The formulation of claim 45, comprising, on a weight percentage basis, about 79.65% polyacrylate adhesive copolymer, about 1.25% polyvinylpyrrolidone/vinyl acetate, about 9.51% dimethyl sulfoxide, about 3.10% lauryl lactate, about 3.10% ethyl lactate, about 2.39% capric acid, about 0.58% levonorgestrel and about 0.28% ethinyl estradiol.

47. The formulation of claim 46 which, upon coating upon a backing layer and drying under conditions suitable to form an adhesive polymer matrix for delivering steroid hormones, comprises, on a weight percentage basis of the adhesive polymer matrix, from about 4% to about 12% dimethyl sulfoxide, from about 4.2% to about 12.6% lauryl lactate, from about 0.7% to about 2.3% ethyl lactate, and from about 3% to about 9% capric acid.

48. The formulation of claim 47, wherein the drying conditions are about 15 minutes at about 60° C.

49. The formulation of claim 41, which further comprises a testosterone.

50. The formulation of claim 21, comprising a testosterone.

51. A transdermal hormone delivery system comprising a backing layer that is substantially impermeable to skin permeation enhancing agents and one or more steroid hormones to be delivered transdermally, and an adhesive polymer matrix affixed to the backing layer, wherein the adhesive polymer matrix comprises an adhesive polymer and further comprises, on a final weight percentage basis of the adhesive polymer matrix:

a) from about 0% to about 5% of a humectant/plasticizer;

b) from about 12% to about 36% percent of a combination of skin permeation enhancing agents which is a mixture comprising from about 4% to about 12% pharmaceutically acceptable organic solvent, from about 4.2% to about 12.6% fatty (C₆-C₂₀) alcohol ester of a hydroxy acid, from about 0.7% to about 2.3% lower (C₁-C₄) alkyl ester of a hydroxy acid, and from about 3% to about 9% C₆-C₁₈ fatty acid; and

c) an amount of one or more steroid hormones effective to provide a pre-determined daily dose of the one or more hormones for between about one and about nine days.

52. The transdermal hormone delivery system of claim 51, comprising a progestin and an estrogen.

53. The transdermal hormone delivery system of claim 52, further comprising a testosterone.

54. The transdermal hormone delivery system of claim 51, comprising only a progestin.

55. The transdermal hormone delivery system of claim 51, comprising only a testosterone.

56. The transdermal hormone delivery system of claim 51, wherein the progestin is levonorgestrel.

57. The transdermal hormone delivery system of claim 51, wherein the estrogen is ethinyl estradiol or 17 β-estradiol.

58. The transdermal hormone delivery system of claim 51, wherein the humectant/plasticizer is a polyvinylpyrrolidone/vinyl acetate.

59. The transdermal hormone delivery system of claim 51, wherein the adhesive polymer comprises a polyacrylate copolymer.

60. The transdermal hormone delivery system of claim 59, wherein the polyacrylate copolymer comprises a 2-ethylhexyl acrylate monomer.

61. The transdermal hormone delivery system of claim 60, wherein the polyacrylate copolymer further comprises about 3 to 60% w/w vinyl acetate.

62. The transdermal hormone delivery system of claim 51, wherein the pharmaceutically acceptable organic solvent is dimethyl sulfoxide.

63. The transdermal hormone delivery system of claim 51, wherein the fatty alcohol ester of a hydroxy acid is a fatty alcohol ester of lactic acid.

64. The transdermal hormone delivery system of claim 51, wherein the lower alkyl ester of a hydroxy acid is a lower alkyl ester of lactic acid.

65. The transdermal hormone delivery system of claim 51, wherein the C₆-C₁₈ fatty acid is capric acid.

66. The transdermal hormone delivery system of claim 51, comprising dimethyl sulfoxide, a fatty alcohol ester of lactic acid, a lower alkyl ester of lactic acid, and capric acid.

67. The transdermal hormone delivery system of claim 66, wherein the fatty alcohol ester of lactic acid is lauryl lactate.

68. The transdermal hormone delivery system of claim 66, wherein the lower alkyl ester of lactic acid is ethyl lactate.

69. The transdermal hormone delivery system of claim 66, wherein the skin permeation enhancing agents are present in a weight ratio of about 4-8 parts dimethyl sulfoxide, about 4-8 parts fatty alcohol ester of lactic acid, about 1 part lower alkyl ester of lactic acid and about 3-6 parts capric acid.

70. The transdermal hormone delivery system of claim 66, wherein the dimethyl sulfoxide and the fatty alcohol ester of lactic acid are present in a weight ratio of between about 1.5:1 and about 1:1.5.

71. The transdermal hormone delivery system of claim 52, formulated for delivery of ethinyl estradiol and levonorgestrel, wherein the ethinyl estradiol is transdermally delivered at a rate of between about 10 μ g and 50 μ g per day for a term of about one day to about nine days, and the levonorgestrel is transdermally delivered at a rate of at least 20 μ g per day for a term of about one day to about nine days.

72. The transdermal hormone delivery system of claim 71, wherein the levonorgestrel is transdermally delivered at a rate of at least 30 μ g per day for a term of about one day to about nine days.

73. The transdermal hormone delivery system of claim 71, wherein the levonorgestrel is transdermally delivered in an amount sufficient to produce a steady state serum concentration of at least 1,000 pg/ml.

74. The transdermal hormone delivery system of claim 51, wherein the adhesive polymer matrix has a thickness of about 10 to about 300 μ m.

75. The transdermal hormone delivery system of claim 51, wherein the adhesive polymer matrix has a surface area of about 20 cm² or less.

76. The transdermal hormone delivery system of claim 75, wherein the adhesive polymer matrix has a surface area of about 17.5 cm² or less.

77. The transdermal hormone delivery system of claim 51, which further comprises an overlay layer, wherein the overlay layer is coated with an adhesive and extends beyond the perimeter of part or all of the backing layer and adhesive polymer matrix.

78. The transdermal hormone delivery system of claim 77, wherein the overlay layer is fabricated with the system, so as to be affixed to the non-dermal side of the backing layer.

79. The transdermal hormone delivery system of claim 77, wherein the overlay layer is fabricated separately from the system.

80. The transdermal hormone delivery system of claim 77, wherein a non-adhesive polymer is substituted for the adhesive polymer, and wherein skin adhesion is effected through the adhesive-coated overlay layer.

81. A method of making a transdermal hormone delivery system comprising a backing layer that is substantially impermeable to skin permeation enhancing agents and an

adhesive polymer matrix comprising one or more steroid hormones to be delivered transdermally, comprising the steps of:

a) formulating an adhesive polymer starting solution by combining an adhesive polymer with, on a weight percentage basis of the adhesive polymer starting solution:

1) from about 0% to about 5% of a humectant/plasticizer;

2) from about 10% to about 30% percent of a combination of skin permeation enhancing agents which is a mixture comprising a pharmaceutically acceptable organic solvent, a fatty (C₈-C₂₀) alcohol ester of a hydroxy acid, a lower (C₁-C₄) alkyl ester of a hydroxy acid, and a C₈-C₁₈ fatty acid; and

3) an amount of one or more of the steroid hormones effective to provide a pre-determined daily dose of the hormone for between about one and about nine days, thereby forming an adhesive polymer starting solution;

b) coating the adhesive polymer starting solution onto the backing layer; and

c) drying the coated backing layer for a time and at a temperature sufficient to produce a transdermal hormone delivery system wherein the adhesive polymer matrix is less than 300 μ m thick and wherein the skin permeation enhancing agents are present in amounts of from about 4% to about 12% pharmaceutically acceptable organic solvent, from about 4.2% to about 12.6% fatty (C₈-C₂₀) alcohol ester of hydroxy acid, from about 0.7% to about 2.3% lower (C₁-C₄) alkyl ester of hydroxy acid, and from about 3% to about 9% C₈-C₁₈ fatty acid.

82. The method of claim 81, wherein the adhesive polymer starting solution is coated onto the backing layer at a thickness of between about 300 μ m and about 800 μ m.

83. The method of claim 81, wherein the coated backing layer is dried for between about 5 minutes and about 25 minutes.

84. The method of claim 81, wherein the coated backing layer is dried at a temperature between about 40° C. and about 80° C.

85. The method of claim 81, wherein, following drying, the transdermal hormone delivery system is provided with a releasable liner affixed to the adhesive polymer matrix.

86. The method of claim 85, wherein, following drying, the transdermal hormone delivery system is provided with an overlay layer, wherein the overlay layer is coated with an adhesive and extends beyond part or all of the perimeter of the backing layer and adhesive polymer matrix.

87. The method of claim 86, wherein the overlay layer is fabricated separately from the transdermal hormone delivery system and provided with its own releasable liner.

88. The method of claim 86, wherein the overlay layer is fabricated together with the transdermal hormone delivery system, and the system with overlay provided with the releasable liner affixed to the adhesive of the overlay layer and the adhesive polymer matrix.

89. The method of claim 81, wherein the adhesive polymer starting solution is coated onto the backing layer at a thickness of between about 600 μ m and 700 μ m, and the

coated backing layer is dried for between about 13 and 17 minutes at about 55° C. -65° C.

90. A method of administering to a subject one or more of a progestin, estrogen or testosterone hormone, the method comprising applying to the skin of the subject desiring such treatment the one or more hormones dispersed within a skin permeation enhancer composition comprising a combination of a pharmaceutically acceptable organic solvent, a fatty (C₄-C₂₀ alcohol ester of a hydroxy acid, a lower (C₁-C₄ alkyl ester of a hydroxy acid, and a C₆-C₁₈ fatty acid.

91. The method of claim 90, wherein the pharmaceutically acceptable organic solvent is dimethyl sulfoxide.

92. The method of claim 90, wherein the fatty alcohol ester of a hydroxy acid is a fatty alcohol ester of lactic acid.

93. The method of claim 90, wherein the lower alkyl ester of a hydroxy acid is a lower alkyl ester of lactic acid.

94. The method of claim 90, wherein the C₆-C₁₈ fatty acid is capric acid.

95. The method of claim 90, comprising dimethyl sulfoxide, a fatty alcohol ester of lactic acid, a lower alkyl ester of lactic acid, and capric acid.

96. The method of claim 95, wherein the dimethyl sulfoxide, fatty alcohol ester of lactic acid, lower alkyl ester of lactic acid, and capric acid, are present in a weight ratio of 2:1:1:0.8 to 6:1:1:0.8, respectively.

97. The method of claim 96, wherein the dimethyl sulfoxide, fatty alcohol ester of lactic acid, lower alkyl ester of lactic acid, and capric acid, are present in a weight ratio of 3:1:1:0.8 to 4:1:1:0.8, respectively.

98. The method of claim 95, wherein the fatty alcohol ester of lactic acid is lauryl lactate.

99. The method of claim 96, wherein the lower alkyl ester of lactic acid is ethyl lactate.

100. A method of administering to a subject one or more of a progestin, estrogen or testosterone hormone, the method comprising applying to the skin of a subject desiring such treatment a transdermal hormone delivery system comprising a backing layer that is substantially impermeable to skin permeation enhancing agents and the one or more hormones to be delivered transdermally, and an adhesive polymer matrix affixed to the backing layer, wherein the adhesive polymer matrix comprises an adhesive copolymer and further comprises, on a final weight percentage basis of the adhesive polymer matrix:

- a) from about 0% to about 5% of a humectant/plasticizer;
- b) from about 12% to about 36% percent of a combination of skin permeation enhancing agents which is a mixture comprising from about 4% to about 12% pharmaceutically acceptable organic solvent, from about 4.2% to about 12.6% fatty (C₈-C₂₀) alcohol ester of hydroxy acid, from about 0.7% to about 2.3% lower (C₁-C₄) alkyl ester of hydroxy acid, and from about 3% to about 9% C₆-C₁₈ fatty acid; and
- c) an amount of the one or more progestin, estrogen or testosterone hormones, sufficient to provide an effective dose of the hormone.

101. The method of claim 100, wherein the effective dose is delivered for a period comprising a pre-determined number of days.

102. The method of claim 101, wherein the transdermal hormone delivery system is replaced once each period for successive periods extending as treatment is desired.

103. The method of claim 100, wherein the transdermal hormone delivery system delivers levonorgestrel.

104. The method of claim 100, wherein the transdermal hormone delivery system delivers ethinyl estradiol or 17 β-estradiol.

105. The method of claim 102, adapted for control of fertility, wherein the transdermal hormone delivery system provides a pre-determined fertility-controlling daily dose of a progestin and an estrogen for between about 1 and about 9 days, and the transdermal hormone delivery system is replaced once each week for three of four successive weeks of a menstrual cycle, for successive menstrual cycles extending as fertility control is desired.

106. The method of claim 105, wherein the transdermal hormone delivery system is formulated for delivery of ethinyl estradiol and levonorgestrel, wherein the ethinyl estradiol is transdermally delivered at a rate of between about 10 μg and 50 μg per day for a term of about one day to about one week, and the levonorgestrel is transdermally delivered at a rate of at least 20 μg per day for a term of about one day to about nine days.

107. The method of claim 106, wherein the levonorgestrel is transdermally delivered at a rate of at least 30 μg per day for a term of about one day to about nine days.

108. The method of claim 105, wherein the levonorgestrel is transdermally delivered in an amount sufficient to produce a steady state serum concentration of at least 1,000 pg/ml and the ethinyl estradiol is transdermally delivered in an amount sufficient to produce a serum concentration of between about 20 and about 80 pg/ml.

109. The method of claim 100, wherein the transdermal hormone delivery system is formulated for delivery of a progestin alone.

110. The method of claim 105, adapted for substantially eliminating menses, wherein the transdermal hormone delivery system is replaced once each week for a desired number of successive weeks, extending as fertility control and elimination of menses are desired.

111. A method of improving libido comprising applying to the skin of a subject desiring such treatment a transdermal hormone delivery system comprising a backing layer that is substantially impermeable to skin permeation enhancing agents and testosterone hormones to be delivered transdermally, and an adhesive polymer matrix affixed to the backing layer, wherein the adhesive polymer matrix comprises an adhesive copolymer and further comprises, on a final weight percentage basis of the adhesive polymer matrix:

- a) from about 0% to about 5% of a humectant/plasticizer;
- b) from about 12% to about 36% percent of a combination of skin permeation enhancing agents which is a mixture comprising from about 4% to about 12% pharmaceutically acceptable organic solvent, from about 4.2% to about 12.6% fatty (C₈-C₂₀) alcohol ester of hydroxy acid, from about 0.7% to about 2.3% lower (C₁-C₄) alkyl ester of hydroxy acid, and from about 3% to about 9% C₆-C₁₈ fatty acid; and
- c) an amount of a testosterone hormone, sufficient to provide an effective dose of the hormone.

112. The method of claim 111, wherein the effective dose is delivered for a period comprising a pre-determined number of days.

113. The method of claim 112, wherein the transdermal hormone delivery system is replaced once each period for successive periods extending as treatment is desired.

114. A transdermal hormone delivery system comprising a backing layer that is substantially impermeable to skin permeation enhancing agents and one or more hormones to be delivered transdermally, and an adhesive polymer matrix affixed to the backing layer and comprising a pre-determined amount of the hormones, wherein the adhesive polymer matrix has a surface area of about 20 cm² or less and a thickness of about 300 μ m or less and the delivery system is capable of delivering at least 20 μ g/day levonorgestrel for between about one and about nine days.

115. The transdermal hormone delivery system of claim 114, capable of delivering at least 30 μ g/day levonorgestrel for between about one and about nine days.

116. The transdermal hormone delivery system of claim 114, which further comprises an overlay layer, wherein the overlay layer is coated with an adhesive and extends beyond the perimeter of part or all of the backing layer and adhesive polymer matrix.

117. The transdermal hormone delivery system of claim 116, wherein the overlay layer is fabricated with the system, so as to be affixed to the non-dermal side of the backing layer.

118. The transdermal hormone delivery system of claim 116, wherein the overlay layer is fabricated separately from the system.

119. The transdermal hormone delivery system of claim 116, wherein a non-adhesive polymer is substituted for the adhesive polymer, and wherein skin adhesion is effected through the adhesive-coated overlay layer.

120. The transdermal hormone delivery system of claim 114, formulated for delivery of levonorgestrel.

121. The transdermal hormone delivery system of claim 120, which delivers an amount of levonorgestrel sufficient to impart a steady state serum concentration of levonorgestrel of at least 1,000 pg/ml.

122. The transdermal hormone delivery system of claim 120, formulated for delivery of levonorgestrel and an estrogen selected from the group consisting of ethinyl estradiol and 17 β -estradiol.

123. The transdermal hormone delivery system of claim 122, wherein the estrogen is ethinyl estradiol and the ethinyl estradiol is transdermally delivered at between 10 μ g and 50 μ g per day for between about one and about nine days.

124. The transdermal hormone delivery system of claim 114, formulated for delivery of a progestin alone.

125. The transdermal hormone delivery system of claim 114, formulated for delivery of a progestin, an estrogen and a testosterone.

126. The transdermal hormone delivery system of claim 114, formulated for delivery of a testosterone alone.

127. The transdermal hormone delivery system of claim 114, wherein the adhesive, polymer matrix comprises an adhesive polymer and further comprises, on a final weight percentage basis of the adhesive polymer matrix:

- a) from about 0% to about 5% of a humectant/plasticizer;
- b) from about 12% to about 36% percent of a combination of skin permeation enhancing agents which is a mixture comprising from about 4% to about 12% pharmaceutically acceptable organic solvent, from about 4.2% to about 12.6% fatty (C₈-C₂₀) alcohol ester of hydroxy

acid, from about 0.7% to about 2.3% lower (C₁-C₄) alkyl ester of hydroxy acid, and from about 3% to about 9% C₈-C₁₈ fatty acid; and

- c) an amount of the one or more progestin, estrogen or testosterone hormones, effective to provide a pre-determined daily dose of each hormone for between about one and about nine days.

128. The transdermal hormone delivery system of claim 127, wherein the humectant/plasticizer is a polyvinylpyrrolidone/vinyl acetate.

129. The transdermal hormone delivery system of claim 127, wherein the adhesive polymer comprises a polyacrylate copolymer.

130. The transdermal hormone delivery system of claim 129, wherein the polyacrylate copolymer comprises a 2-ethylhexyl acrylate monomer.

131. The transdermal hormone delivery system of claim 129, wherein the polyacrylate copolymer further comprises about 3 to 60% w/w vinyl acetate.

132. The transdermal hormone delivery system of claim 127, wherein the pharmaceutically acceptable organic solvent is dimethyl sulfoxide.

133. The transdermal hormone delivery system of claim 127, wherein the fatty alcohol ester of a hydroxy acid is a fatty alcohol ester of lactic acid.

134. The transdermal hormone delivery system of claim 127, wherein the lower alkyl ester of a hydroxy acid is a lower alkyl ester of lactic acid.

135. The transdermal hormone delivery system of claim 127, wherein the C₈-C₁₈ fatty acid is capric acid.

136. The transdermal hormone delivery system of claim 127, comprising dimethyl sulfoxide, a fatty alcohol ester of lactic acid, a lower alkyl ester of lactic acid, and capric acid.

137. The transdermal hormone delivery system of claim 136, wherein the fatty alcohol ester of lactic acid is lauryl lactate.

138. The transdermal hormone delivery system of claim 136, wherein the lower alkyl ester of lactic acid is ethyl lactate.

139. The transdermal hormone delivery system of claim 136, wherein the skin permeation enhancing agents are present in a weight ratio of about 4-8 parts dimethylsulfoxide, about 4-8 parts fatty alcohol ester of lactic acid, about 1 part lower alkyl ester of lactic acid and about 3-6 parts capric acid.

140. The transdermal hormone delivery system of claim 139, wherein the dimethyl sulfoxide and the fatty alcohol ester of lactic acid are present in a weight ratio of between about 1.5:1 and about 1:1.5.

141. A method of making a transdermal hormone delivery system comprising a backing layer that is substantially impermeable to skin permeation enhancing agents and an adhesive polymer matrix comprising one or more progestin, estrogen or testosterone hormones to be delivered transdermally, comprising the steps of:

- a) formulating an adhesive polymer starting solution by combining an adhesive polymer with, on a weight percentage basis of the adhesive polymer starting solution:

- 1) from about 0% to about 5% of a humectant/plasticizer;
 - 2) from about 10% to about 30% percent of a combination of skin permeation enhancing agents which is a mixture comprising a pharmaceutically acceptable organic solvent, a fatty (C_8 - C_{20}) alcohol ester of hydroxy acid, a lower (C_1 - C_4) alkyl ester of hydroxy acid, and a C_6 - C_{18} fatty acid; and
 - 3) an amount of the one or more progestin, estrogen or testosterone hormones effective to provide a pre-determined daily dose of each hormone for a period comprising a pre-determined number of days;
- h) coating the adhesive polymer starting solution onto the backing layer; and
- c) drying the coated backing layer for a time and at a temperature sufficient to produce a transdermal hormone delivery system wherein the adhesive polymer matrix has a surface area of about 20 cm^2 or less and a thickness of about $300\text{ }\mu\text{m}$ or less and the delivery system is capable of delivering at least $20\text{ }\mu\text{g/day}$ levonorgestrel for between about one and about nine days.
142. The method of claim 141, wherein the adhesive polymer matrix starting solution is coated onto the backing layer at a thickness of between about $300\text{ }\mu\text{m}$ and about $800\text{ }\mu\text{m}$.
143. The method of claim 141, wherein the coated backing layer is dried for between about 5 minutes and about 25 minutes.
144. The method of claim 141, wherein the coated backing layer is dried at a temperature between about 40° C . and about 80° C .
145. The method of claim 141, wherein, following drying, the transdermal hormone delivery system is provided with a releasable liner affixed to the adhesive polymer matrix.
146. The method of claim 145, wherein, following drying, the transdermal hormone delivery system is provided with an overlay layer, wherein the overlay layer is coated with an adhesive and extends beyond the perimeter of part or all the backing layer and adhesive polymer matrix.
147. The method of claim 146, wherein the overlay layer is fabricated separately from the transdermal hormone delivery system and provided with its own releasable liner.
148. The method of claim 146, wherein the overlay layer is fabricated together with the transdermal hormone delivery system, and the system with overlay provided with the releasable liner affixed to the adhesive of the overlay layer and the adhesive polymer matrix.
149. The method of claim 141, wherein the adhesive polymer matrix starting solution is coated onto the backing layer at a thickness of between about $600\text{ }\mu\text{m}$ and $700\text{ }\mu\text{m}$, and the coated backing layer is dried for between about 13 and 17 minutes at about 55° C . - 65° C .
150. A method of administering to a subject one or more of a progestin, estrogen or testosterone hormone, the method comprising applying to the skin of a subject desiring such treatment a transdermal hormone delivery comprising a backing layer that is substantially impermeable to skin

permeation enhancing agents and the hormones to be delivered transdermally, and an adhesive polymer matrix affixed to the backing layer and comprising the one or more progestin, estrogen or testosterone hormones, wherein the adhesive polymer matrix is of a maximum surface area of about 20 cm^2 and a maximum thickness of about $300\text{ }\mu\text{m}$ and the delivery system is capable of delivering at least $20\text{ }\mu\text{g/day}$ levonorgestrel for between about one and about nine days.

151. The method of claim 150, wherein the transdermal hormone delivery system is replaced periodically for successive periods extending as treatment is desired.

152. The method of claim 150, wherein the transdermal hormone delivery system delivers levonorgestrel.

153. The method of claim 150, wherein the transdermal hormone delivery system delivers ethinyl estradiol or $17\text{ }\beta$ -estradiol.

154. The method of claim 151, adapted for control of fertility, wherein the transdermal hormone delivery system provides a pre-determined fertility-controlling daily dose of a progestin and an estrogen for between about 1 and about 9 days, and the transdermal hormone delivery system is replaced once each week for three of four successive weeks of a menstrual cycle, for successive menstrual cycles extending as fertility control is desired.

155. The method of claim 154, wherein the transdermal hormone delivery system delivers levonorgestrel.

156. The method of claim 155, wherein the transdermal hormone delivery system delivers ethinyl estradiol or $17\text{ }\beta$ -estradiol.

157. The method of claim 154, wherein the transdermal hormone delivery system is formulated for delivery of ethinyl estradiol and levonorgestrel, wherein the ethinyl estradiol is transdermally delivered at a rate of between about $10\text{ }\mu\text{g}$ and $50\text{ }\mu\text{g}$ per day for a term of about one day to about one week, and the levonorgestrel is transdermally delivered at a rate of at least $20\text{ }\mu\text{g}$ per day for a term of about one day to about nine days.

158. The method of claim 157, wherein the levonorgestrel is transdermally delivered at a rate of at least $30\text{ }\mu\text{g}$ per day for a term of about one day to about nine days.

159. The method of claim 157, wherein the levonorgestrel is transdermally delivered in an amount sufficient to produce a steady state serum concentration of at least $1,000\text{ pg/ml}$ and the ethinyl estradiol is transdermally delivered in an amount sufficient to produce a serum concentration of between about 20 and about 80 pg/ml .

160. The method of claim 150, wherein the transdermal hormone delivery system is formulated for delivery of a progestin alone.

161. The method of claim 150, wherein the transdermal hormone delivery system is formulated for delivery of a testosterone in addition to the progestin and the estrogen.

162. The method of claim 154, adapted for substantially eliminating menses, wherein the transdermal hormone delivery system is replaced once each week for a desired number of successive weeks, extending as fertility control and elimination of menses are desired.

* * * * *

22

PubMed

U.S. National Library of Medicine
National Institutes of Health

Display Settings: Abstract

Br J Fam Plann. 2000 Jul;26(3):165-6.

A pre-coital pill? A preliminary in vitro study.

Kovacs GT, Hendricks J, Summerbell D, Baker HW.

Monash Medical School, Box Hill Hospital, Victoria, Australia.

The use of the progestogen-only pill as a 'pre-coital contraceptive' was tested by in vitro studies of sperm-mucus interaction. The results suggest that a single tablet of levonorgestrel 30 microg, or norethisterone 350 microg, was effective in preventing sperm migration in the cervical mucus about 12 hours later. This suggests that the progestogen-only pill may be effective as a 'morning before pill'.

PMID: 10920297 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources



US006143754A

United States Patent [19]

Chwalisz et al.

[11] **Patent Number:** 6,143,754[45] **Date of Patent:** Nov. 7, 2000

[54] **COMPETITIVE PROGESTERONE
ANTAGONIST FOR DEMAND-ORIENTED
FEMALE BIRTH CONTROL**

[75] **Inventors:** Kristof Chwalisz; Klaus Stockemann;
Karin Schmidt-Gollwitzer; Walter
Klemann, all of Berlin, Germany

[73] **Assignee:** Schering Aktiengesellschaft, Berlin,
Germany

[21] **Appl. No.:** 09/273,485

[22] **Filed:** Mar. 22, 1999

Related U.S. Application Data

[63] Continuation of application No. 08/817,535, Jul. 22, 1997,
abandoned.

[30] Foreign Application Priority Data

Oct. 24, 1994 [DE] Germany 44 38 820

[51] **Int. Cl.⁷** A61K 31/435; A61K 31/13

[52] **U.S. Cl.** 514/277; 514/579; 514/843

[58] **Field of Search** 514/277, 579,
514/843

[56] References Cited**U.S. PATENT DOCUMENTS**

5,439,913 8/1995 Chwalisz et al. 514/277

FOREIGN PATENT DOCUMENTS

9323020 11/1993 WIPO .

OTHER PUBLICATIONS

Experimental and Clinical Endocrinology, vol. 81, No. 2,
1983, pp. 122-136, Strecke, J. et al.

Journal of Steroid Biochemistry, vol. 11, No. 1C, 1979, pp.
963-969, Csapo, A.I. et al.

The New England Journal of Medicine, vol. 316, No. 4,
1987, pp. 187-191, Nieman, L.K. et al.

Human Reproduction, vol. 9, No. 2, Jun. 1994, pp. 11-21,
Lebeau, M.C. et al.

European Journal of Obstetrics, Gynaecology and Repro-
ductive Biology, vol. 4, No. 5, 1975, pp. 161-166, Baulieu,
E.E.

International Search Report for PCT/EP95/04191 mailed
Mar. 22, 1996.

Primary Examiner—Kevin E. Weddington

Attorney, Agent, or Firm—Millen, White, Zelano &
Branigan, P.C.

[57] ABSTRACT

This invention describes the novel use of dissociated com-
petitive progesterone antagonists for the production of a
pharmaceutical agent for demand-oriented female birth con-
trol (pill on demand), which can be used regardless of the
point in the menstrual cycle, in a dosage unit that is to be
administered on a one-time basis, whose dosage is below the
ovulation-inhibiting dosage.

10 Claims, No Drawings

COMPETITIVE PROGESTERONE ANTAGONIST FOR DEMAND-ORIENTED FEMALE BIRTH CONTROL

This application is a continuation of Ser. No. 08/817,535 filed Jul. 22, 1997; now abandoned.

This invention relates to the use of at least one competitive progesterone antagonist for the production of a pharmaceutical agent for demand-oriented female birth control ("pill on demand"), which can be used at any point in the menstrual cycle, in a dosage unit that is to be administered on a one-time basis, whose dosage is below the ovulation-inhibiting dosage.

Already all over the world, the use of oral contraceptives has developed into a business factor that cannot be ignored. Especially in view of the fact that the world population is continuing to shoot upward, further development of the hitherto proven methods for birth control is absolutely necessary.

The use of competitive progesterone antagonists in female birth control both in various animal species and in humans has been discussed for some years now, as can be found in the publications listed below, whereby especially the use of RU 486 (11- β -[4-N,N-(dimethylamino)phenyl]-17- β -hydroxy-17- α -propinyloestra-4,9(10)-dien-3-one; EP-A-0057115) has been cited in this connection:

Collins et al., Blockade of the Spontaneous Mid-Cycle Gonadotrophin Surge in Monkeys by RU 486: A Progesterone Antagonist or Agonist, *J. Clin. Metab.*, 63: 1270-1276 (1986);

Croxatto, H. B., Salvatierra 1990 Cyclic Use of Antigestagens for Fertility Control. *IIIrd International Symposium on Contraception*, Heidelberg, Jun. 19-23, 1990;

Danford et al., Contraceptive Potential of RU 486 by Ovulation Inhibition. III. Preliminary Observations on Once Weekly Administration. *Contraception* 40: 195-200 (1989);

Kekkonen et al., Lahteenmäki P 1990 Interference with Ovulation by Sequential Treatment with the Antiprogesterone RU 486 and Synthetic Progesterin. *Fertil Steril [Fertile Sterile]* 53: 4747 (1990);

Puri et al., Gonadal and Pituitary Responses to Progesterone Antagonist ZK 98 299 during the Follicular Phase of the Menstrual Cycle in Rhesus Monkeys. *Contraception* 39(2): 227-243 (1989);

Puri et al., Contraceptive Potential of a Progesterone Antagonist ZK 98 734: Effect on Folliculogenesis, Ovulation and Corpus Luteum Function in Rhesus Monkeys. In Moudgal et al., (eds) (1990).

In this connection, it should be mentioned that the dosage that exerts an ovulation-inhibiting effect depends to a great extent on the competitive progesterone antagonist that is used.

The class of 11 β -aryl- or 11 β ,19-arylene-substituted steroids is distinguished pharmacologically according to their strong progesterone- or glucocorticoid-antagonistic effect. Thus, RU 486 can be used, on the one hand, to bring about a therapeutically induced abortion (the human abortive dosage in combination with a prostaglandin is approximately 200-600 mg; EP-A 0 139 608), but also, on the other hand, via its antagonistic effect on a glucocorticoid receptor, to treat Cushing's syndrome.

Another possible use of competitive progesterone antagonists for female birth control, the so-called "LH+2" treatment, is proposed by Swahn et al. [The Effect of RU 486 Administration During the Early Luteal Phase on Bleeding Pattern, Hormonal Parameters and Endometrium, *Human Reproduction* 5(4): 402-408 (1990)], by an ovulation-

inhibiting RU 486 dosage unit being administered (luteal contraception) one time 2 days after the increase in the luteinizing hormone (LH) in the female menstrual cycle (this is generally on day 14, 15 or 16).

This process has no practical importance, however, since determining the LH peak in a simple and precise manner still represents a problem.

Glacier et al. (Mifepristone (RU 486) Compared with High-Dose Estrogen and Progestogen for Emergency Postcoital Contraception, *The New England J. of Med.* 327: 1041-1044 (1992)) also describes the use of RU 486 for postcoital contraception (emergency postcoital contraception). The method shows a low level of side effects in addition to high effectiveness. An extension of the cycle occurred in a high percentage of women in this study. This effect can be attributed primarily to the antioviatory effect of RU 486.

In addition, WO 93/23020 describes that competitive progesterone antagonists at a dose that lies both below the abortive and ovulation-inhibiting dosage can be used for female birth control. Here, however, generally weekly or repeated and thus regular administration is necessary to achieve the desired effect.

EP-A 0 219 447 also describes what effects the daily administration of a progesterone antagonist triggers with respect to the endometrial differentiation state during the follicular phase or optionally also the luteal phase of the female cycle in a period of up to 4 days at a dosage of 10-200 mg. The changes in the endometrium that result in this connection are used with respect to the time of nidation for in vitro fertilization.

Batista et al. [Daily Administration of the Progesterone Antagonist RU 486 Prevents Implantation in the Cycling Guinea Pig. *Am. J. Obstet. Gynecol.* 165:82-86 (1991)] also describes the use of RU 486 for female birth control, which in an ovulation-inhibiting dosage prevents nidation in guinea pigs by daily intake, precoitally and throughout the entire further cycle.

Kawano et al. (Effect of RU 486 on Glycogen Metabolism in Endometrium. *Acta Obstetrica et Gynaecologica Japonica*, 41: 1507-1511, (1989)) describes the influence of RU 486 at a dosage of 30 mg/kg of body weight on the endometrial glycogen metabolism in a rat model, so that successful implantation is disrupted. Administration is done, however, on day 2 or 4 of the pregnancy.

It has now been found, surprisingly enough, that nidation can be reliably prevented by even one-time administration only upon demand of a competitive progesterone antagonist (at a subovulation-inhibiting dosage), and in this respect a new type of oral contraceptive is available.

Previously, the use of competitive progesterone antagonists for contraception was possible only by repeated, regular intake.

Also, previous usage according to EP-A 0 219 447 is in contrast to this invention since here nidation should be made possible specifically by the administration of progesterone antagonist.

A so-called dissociated competitive progesterone antagonist is suitably used according to the invention.

In this connection, a dissociated, competitive progesterone antagonist is defined as a substance that at the dosage used exerts its action via the hypothalamic-ovarian axis not in terms of ovulation inhibition (central effect), but rather a local effect (peripheral selective effect) that is limited exclusively to the endometrium.

Right at a certain threshold dose, changes in the endometrium are observed while ovulation is not inhibited.

The quotient of ovulation-inhibiting and implantation-inhibiting dose (dissociation factor) can be used as a yardstick for the dissociation. Said quotient varies depending on the species.

In rats and in primates, all previously studied competitive progesterone antagonists show a dissociation between central and endometrial effects. The extent of this dissociation is substance-dependent. For a dissociated, competitive progesterone antagonist that is to be used according to the invention (found in the rat after peroral administration), the dissociation factor should preferably lie approximately at 30 or above.

RU 486 is an example of a slightly dissociated substance in primates. It inhibits ovulation even at low doses and thus results in cycle disruption.

Onapristone (11 β -[4-N,N-(dimethylamino)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -methyl-4,9(10)-gonadien-3-one; EP-A 0 129 499) is an example of a greatly dissociated progesterone-antagonistic compound that inhibits its ovulation in primates only at extremely high doses.

The endometrial effects of RU 486 and Onapristone occur, however, at comparable doses. This dissociation between central and endometrial effects makes it possible, when using a dissociated, competitive progesterone antagonist for the purposes of this invention, to increase its dosage and thus to ensure effective implantation inhibition after a single use.

In this respect, with the solution according to the invention, another requirement that is to be imposed on modern pharmaceutical agents is also that systemic loading of the organism by one-time administration be avoided by a locally differentiated mode of action.

The above statements make it clear that demand-oriented oral birth control was not possible until now.

Specifically for women who could not decide on the previously necessary, uniform intake of oral contraceptives or else for other, e.g., medicinal reasons, did not have the option of selecting this form of birth control, there now exists the alternative of opting for the one-time, demand-oriented intake of an oral contraceptive, without the organism having to be exposed to a hormonal control that continues throughout the entire menstrual cycle.

This invention has additional significant advantages, which certainly include the low dosage of the active ingredient.

Thus, the female menstrual cycle is in no way adversely affected in its cyclicality (as is caused by ovulation-inhibiting substances), and the organism is not stressed by unnecessarily large amounts of the competitive progesterone antagonist.

The use of such a progesterone antagonist further offers reliable contraception, i.e., the one-time intake of such a medicine prevents the nidation of the blastocysts.

According to this invention, the competitive progesterone antagonists are used in amounts of generally 1-400 mg of Onapristone or a biological equivalent dose of another competitive progesterone antagonist on a one-time basis.

Treatment with the competitive progesterone antagonist is generally performed regardless of the cycle time by the one-time, demand-oriented, i.e., generally precoital or else postcoital intake of a daily dosage unit.

Precoital intake of the medicine that is produced according to the invention is preferred. The time of intake can be up to 6 hours before or up to 24 hours after coitus.

In this case, intake is possible at any cycle time when a contraceptive measure is necessary, advisable, or desired.

As competitive progesterone antagonists, all compounds according to the invention that show a corresponding char-

acteristic affinity for the progesterone receptor and exert an endometrium-selective effect are suitable. Such progesterone antagonists show nidation inhibition at the dosage used without inhibiting the ovulation. Thus, for example, the following progesterone antagonists are suitable:

11 β -[4-N,N-(Dimethylamino)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -methyl-4,9(10)-gonadien-3-one (EP-A 0 129 499),

11 β -[4-acetylphenyl]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4,9(10)-estradien-3-one (EP-A 0 190 759),

11 β ,19-[4-(cyanophenyl)-*o*-phenylene]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-androsten-3-one,

11 β ,19-[4-(3-pyridinyl)-*o*-phenylene]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-andruten-3-one (both WO-A 93/23020),

17 α -hydroxy-17 β -(3-hydroxypropyl)-11 β -[4-(1-methylethenyl)-phenyl]-13 α -estra-4,9-dien-3-one,

11 β -[4-(3-furanyl)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -estra-4,9-dien-3-one (both EP-A 0 349 481),

(Z)-11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(3-hydroxyprop-1-enyl)estr-4-en-3-one (EP-A 0 404 283),

11 β -[4-[[[(acetyloxy)imino]methyl]phenyl]-17 β -methoxy-17 α -(methoxymethyl)estra-4,9-dien-3-one (EP-A 0 648 778, EP-A 0 648 779),

11 β -[4-[[[(ethoxycarbonyl)oxy]imino]methyl]phenyl]-17 β -methoxy-17 α -(methoxymethyl)estra-4,9-dien-3-one (EP-A 0 648 778, EP-A 0 648 779),

11 β -[4-(acetyl)phenyl]-19,24-dinor-17,23-epoxy-17 α -chola-4,9,20-trien-3-one,

(11 β ,17 α)-11-[4-(acetyl)phenyl]-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-one.

The competitive progesterone antagonists can be administered, for example, locally, topically, enterally, or parenterally.

For the preferred oral administration, especially tablets, coated tablets, capsules, pills, suspensions, or solutions that can be produced in the usual way with the additives and vehicles that are commonly used in galenicals are suitable.

The oral dosage unit that is to be administered on a one-time basis contains about 2 to 200 mg of Onapristone or the biologically equivalent dose (equivalent-action amount) of another dissociated competitive progesterone antagonist.

The dose that induces premature menstruation in *Cynomolgus* monkeys after one-time treatment on day 22 of the cycle but does not inhibit ovulation if administered on a one-time basis before the LH peak (LH-2) is considered an equivalent-action amount.

Particularly in the case of the preferred oral administration of the pharmaceutical agent that is produced according to the invention, it is desirable that a delayed release of the respective active ingredient occur. As a result, it is to be ensured that delayed implantation of the fertilized egg cannot occur.

Delayed release of the competitive progesterone antagonist can be achieved, for example, by formulating the dosage unit that is to be administered orally as a composite tablet or by providing the dosage unit that is to be administered orally with a timed-disintegration coating, as is readily known to one skilled in the art. The competitive progesterone antagonist that is used for the production of the pharmaceutical agent according to the invention can, by derivatization, for example, by esterification of a free hydroxy group in an effective precursor, also exhibit a longer half-life than this precursor. As a result, a prolonged effect is also achieved. This principle is implemented in, for example, the esters of

11 β -[4-N,N(dimethylamino)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -methyl-4,9(10)-gonadien-3-one (Onapristone) described in EP-A 0186 834, which are therefore preferably used within the scope of this invention. The following can be mentioned as representatives:

17 β -(3-Acetoxypropyl)-11 β -[4-N,N-(dimethylamino)phenyl]-17 α -hydroxy-13 α -methyl-4,9(10)-gonadien-3-one and

17 β -(3-benzoyloxypropyl)-11 β -[4-N,N-(dimethylamino)phenyl]-17 α -hydroxy-13 α -methyl-4,9(10)-gonadien-3-one.

In addition, for local or topical use, for example, vaginal suppositories or transdermal systems such as skin plasters are available.

The dosage unit that is to be administered on a one-time basis contains an amount of Onapristone or a biologically equivalent dose of another competitive progesterone antagonist for this special form of administration such that over a period of 4 to 72 hours, 1 to 400 mg of this competitive progesterone antagonist is released.

The examples below are to explain the formulation of a competitive progesterone antagonist, which is of special relevance for use within the scope of this invention.

EXAMPLE 1

Composition of a tablet with 10.0 mg of 11 β -[4-N,N-dimethylamino)-phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -methyl-4,9-gonadien-3-one for oral administration

10.0 mg of 11 β -[4-N,N-dimethylamino)-phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -methyl-4,9-gonadien-3-one

140.5 mg of lactose

69.5mg of corn starch

2.5mg of poly-N-vinylpyrrolidone

2.0mg of aerosil

0.5mg of magnesium stearate

225.0mg total weight of the tablet

EXAMPLE 2

Composition of a tablet with 50.0 mg of 11 β ,19-[4-(cyanophenyl)-o-phenylene]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-androsten-3-one for oral administration

50.0 mg of 11 β ,19-[4-(Cyanophenyl)-o-phenylene]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-androsten-3-one

140.5 mg of lactose

69.5 mg of corn starch

2.5 mg of poly-N-vinylpyrrolidone

2.0 mg of aerosil

0.5 mg of magnesium stearate

265.0 mg total weight of the tablet

The tablets are produced in a known way on a tablet press and are provided with a timed-disintegration coating.

Pharmacological Observations

The suitability especially of dissociated competitive progesterone antagonists for the production of a pharmaceutical agent for demand-oriented female birth control ("pill on demand"), which can be administered on a one-time basis in a non-ovulation-inhibiting dosage of the competitive progesterone antagonist, follows from the animal-experimental and human-pharmacological observations described below:

Cyclic female monkeys (body weight about 4-5 kg) are treated one time over 3 cycles in the late follicular phase of the cycle (1-2 days before ovulation) with 10 or 30 mg/kg s.c. or 30 mg/kg p.o. of Onapristone.

Then, the monkeys are paired up. Because of the progesterone determination in the luteal phase, it was noted that ovulation occurred and that the course of the luteal phase was normal. Bleeding (menstruation) occurred as expected on days 27-31 of the cycle. In the case of the treated animals, no pregnancy was noted, but in the case of the control animals, which were treated only with a vehicle, one pregnancy was noted after the pairing.

Other monkeys are treated in the earlier luteal phase (days 1-3 after ovulation) over 3 cycles one time with 10 or 30 mg of Onapristone/kg s.c. or 30 mg/kg p.o. After pairing was completed, no pregnancies were to be observed even after this treatment pattern in the animals that were treated with Onapristone.

Test subjects that exhibit a normal cycle are treated orally on a one-time basis with 100 or 400 mg of Onapristone on the second day before ovulation (LH-2). The hormone profiles (estradiol, progesterone, LH) confirm that ovulation was not inhibited. No significant shortening or lengthening of the cycle was proven.

Other test subjects are orally treated one time with 100 or 400 mg of Onapristone 2 days after ovulation (LH+2). Then, a biopsy of the endometrium is performed 4 and 6 days after ovulation. Histology revealed pronounced changes in the case of the treated females in terms of desynchronization of the endometrium.

Clinical experiments with infertile females indicate that a successful implantation is regarded as improbable especially because of such changes of the endometrium and thus successful implantation is also not to be expected in the case of the females of the treatment group.

What is claimed is:

1. A method for demand-oriented female birth control, comprising administering a single dose of a competitive progesterone antagonist at any point in the menstrual cycle, said dosage being below the ovulation-inhibiting dosage and being effective for birth control.

2. A method of claim 1, wherein the competitive progesterone antagonist is:

11 β -[4-N,N-Dimethylamino)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -methyl-4,9(10)-gonadien-3-one,

11 β -[4-(acetylphenyl)-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4,9(10)-estradien-3-one,

11 β ,19-[4-(cyanophenyl)-o-phenylene]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-androsten-3-one,

11 β ,19-[4-(3-pyridinyl)-o-phenylene]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-androsten-3-one,

17 α -hydroxy-17 β -(3-hydroxypropyl)-11 β -[4-(1-methylethenyl)-phenyl]-13 α -estra-4,9-dien-3-one,

11 β -[4-(3-furanyl)-phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -estra-4,9-dien-3-one,

(Z)-11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(3-hydroxyprop-1-enyl)estra-4-en-3-one

11 β -[4-[[[(acetyloxy)imino]methyl]phenyl]-17 β -methoxy-17 α -(methoxymethyl)estra-4,9-dien-3-one

11 β -[4-[[[(ethoxycarbonyloxy)imino]methyl]phenyl]-17 β -methoxy-17 α -(methoxymethyl)estra-4,9-dien-3-one

11 β -[4-(acetylphenyl)-19,24-dinor-17,23-epoxy-17 α -chole-4,9,20-trien-3-one, or (11 β , 17 α)-11-[4-(acetylphenyl)-17,23-epoxy-19,24-dinorchole-4,9,20-trien-3-one.

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

(19) World Intellectual Property Organization
International Bureau



INTERNATIONAL PATENT COOPERATION TREATY (PCT)

(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/26603 A2

- (51) International Patent Classification¹: A61K Berlin (DE). SCHUBERT, Gerd [DE/DE]; Kaeche-Kollwitz-Strasse 13, 07753 Jena (DE).
- (21) International Application Number: PCT/IB00/02053
- (22) International Filing Date: 31 August 2000 (31.08.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
09/386,133 31 August 1999 (31.08.1999) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/386,133 (CIP)
Filed on 31 August 1999 (31.08.1999)
- (71) Applicants (for all designated States except US): SCHERING AKTIENGESELLSCHAFT (DE/US); 13342 Berlin (DE). JENAPHARM GMBH & CO. KG (DE/DE); Otto-Schott-Strasse 15, 07745 Jena (DE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): CHWALISZ, Kristof [DE/DE]; Lobber Steig 7a, 13503 Berlin (DE). ELGER, Walter [DE/DE]; Schorlemmerallee 12B, 14195
- (84) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/26603 A2

(54) Title: MESOPROGESTINS (PROGESTERONE RECEPTOR MODULATORS) AS A COMPONENT OF FEMALE CONTRACEPTIVES

(57) Abstract: The present invention relates to the use of mesoproggestins for the production of a pharmaceutical for female contraception, to a pharmaceutical preparation for female contraception and to a method of female contraception administering effective amounts of a mesoproggestin in a female desiring contraception. Optionally the mesoproggestin can be used in combination with an estrogen. Mesoproggestins are defined as compounds possessing both agonistic and antagonistic activities at the progesterone receptor (PR) in vivo. They stabilize the function of PR at an intermediate level of agonistic and antagonistic. Corresponding functional states cannot be achieved with progestins or antiproggestins. J867, J912, J956 and J1042 are the mesoproggestins preferred according to the invention.

According to one aspect of the present invention mesoprogestins are used as a component for the production of a pharmaceutical for female contraception.

They can be used either as single pharmaceutically active principle in female contraceptives or they can be used together with an estrogen.

According to one aspect of the invention the mesoprogestins, either alone or in combination with estrogens, are used in a regular, cyclical administration regime. This shall mean that the mesoprogestins are administered in identical and repeating administration cycles as long as contraception is desired.

A cycle starts with the administration of a mesoprogestin or mesoprogestin / estrogen containing dosage unit followed daily by further dosage units thereof. Each cycle is completed by a period in which no active dosage units („pill-free" days) or in which placebos are administered.

Alternatively in case of mesoprogestin / estrogen administration the administration cycle can be completed by further administration of estrogen only containing dosage units.

A new application cycle starts on the first day after completion of the „pill free" or placebo phase, respectively or after the phase in which estrogen only containing dosage units have been administered.

In all cases day 1 in the first administration cycle is the first day of bleeding in the female's menstrual cycle in which the contraceptive treatment starts.

One embodiment of the mesoprogestin only administration provides for administering the mesoprogestin containing dosage units up to day 180 at the maximum. Under the continuous daily treatment (1 to 25 mg mesoprogestin/day) a reversible amenorrhoea is induced and maintained. The contraceptive effect is due to endometrial effects (endometrial suppression) of the mesoprogestin. Consequently the endometrium is not prepared for implantation of a fertilized egg. To achieve the contraceptive effect it is sufficient to administer the mesoprogestin in dosages to prevent nidation. The dose of the mesoprogestin can also be ovulation inhibiting but this is not essential to achieve the contraceptive effect and to induce and maintain amenorrhoea.

Preferably the mesoprogestin only administration takes place for 3 months at the maximum (this allows to check the contraceptive reliability of the method).

Compared to other contraceptive regimes which use progestins only the above described administration regime leads to a better bleeding behavior. Compared to the minipill

as to complete a 28 day long administration cycle. On the next day the next cycle starts with the administration of a mesoprogesterin/estrogen containing dosage unit, etc.

The estrogen is used in a daily amount of 10 to 30 µg ethinyl estradiol or a bioequivalent amount thereof.

Mesoprogesterins can be used sequentially with a progestin. In this contraceptive regimen the mesoprogesterin component prevents breakthrough bleeding which is usually associated with chronic progestin treatment. The progestin component at a dose used in so called "mini pill regimen" is administered for a period of 30-180 days, whereas the mesoprogesterin component is administered for a period of 1-30 days.

During mesoprogesterin treatment menstrual bleeding may or may not occur. As a result of sequential progestin/mesoprogesterin treatment the number of unscheduled bleeding is, however, markedly reduced.

The regular, cyclical administration regimes of a mesoprogesterin, optionally in combination with an estrogen, are illustrated in detail in Figure 2.

The use of a mesoprogesterin in a discontinuous, non-cyclical administration regime is the use as a so-called demand pill which has to be administered only around the time point of sexual intercourse for which contraception is desired. Preferably the administration is before sexual intercourse („medicinal condom"). For details c.f. WO 93/23020.

A further aspect of the invention refers to a pharmaceutical combination product (composition) containing a mesoprogesterin together with an estrogen.

A further aspect of the invention refers to a pharmaceutical combination product (composition) containing a mesoprogesterin together with a progestin.

Yet another aspect of the invention deals with pharmaceutical preparations for female contraception comprising daily dosage units of a mesoprogesterin.

All the aspects of the pharmaceutical preparation according to the invention are apparent from claims 25 to 38.

As mesoprogesterins i.a. compounds disclosed in DE 43 32 283 and in DE 43 32 284 are suitable for the purposes of the invention.

In such a dosage unit that is to be administered once a week, the mesoprogesterin should preferably be prepared in a formulation that results in a delayed release of the active ingredient.

A delayed release of the mesoprogesterin can be achieved, for example, by formulating the dosage unit that is to be administered orally as a composite tablet or by providing the dosage unit that is to be administered orally with a timed-disintegration coating, as is readily known to one skilled in the art.

By derivatization, for example by esterification of a free hydroxy group in an effective precursor, the mesoprogesterin that is used for the production of the pharmaceutical agent according to the invention can also have a longer half-life than this precursor. As a result, a longer-lasting action is also achieved.

For the purposes of this invention, the formulation of the mesoprogesterin and optionally the estrogen is done in a completely conventional manner, as is already known for the formulation of these compounds for their individual use as described for J867 in DE 43 32 283 and for estrogen therapy, for example Cyclo-Progynova.

In particular, reference is also made to the information that is contained in the mentioned prior art documents.

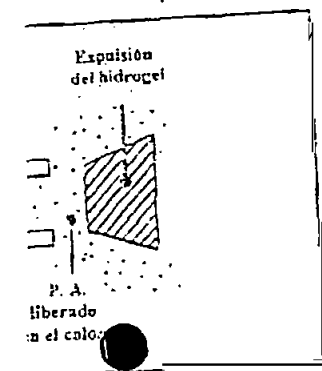
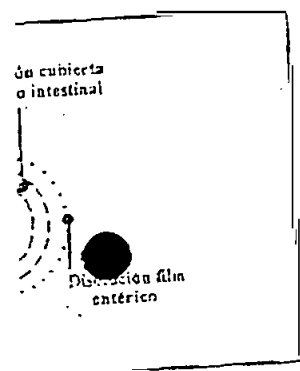
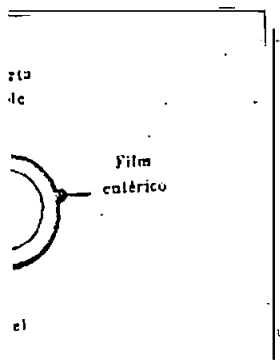
In addition to oral administration of the estrogen and the mesoprogesterin, it is equally possible to administer one or both of the components transdermally, for example with a skin patch, which is best known for the administration of estrogen (Climara Patch).

In addition, administration can be done using an intrauterine release system (c.f. Mirena), but this variant is not preferred within the scope of this invention.

The administration of one or both components as a depot formulation is also possible.

Finally, all above-mentioned types of administration can be combined. For example, the estrogen can be administered transdermally with a skin patch, and the progesterone antagonist can be administered daily orally or one or more times as a depot formulation.

ADMINISTRACIÓN DE MEDICAMENTOS



amiento del sistema Pulsincap®.

los enlaces azo, de tal forma que las azorreductasas se encargan de su degradación. Como ejemplos se podrían citar el copolímero del estireno y del 2-hidroxietilmetacrilato, reticulado con divinilazobenceno, utilizado como recubrimiento de capsulas de gelatina, o bien copolímeros sintetizados a partir del 2-hidroxietilmetacrilato y del metilmetacrilato (HEMA-co-MMA) en presencia de diferentes azocompuestos.

Otro tipo de sistemas degradables únicamente a nivel colónico son los hidrogeles sintéticos que contienen co-monómeros ácidos y enlaces azoaromáticos degradables enzimáticamente. En el medio ácido del estómago, su grado de hinchamiento es muy bajo, lo que evita la posible degradación de moléculas activas, pero a medida que se incrementa el pH en el intestino delgado, el grado de hinchamiento aumenta como resultado de la ionización y repulsión de cargas. Al llegar al colon el grado de hinchamiento alcanza un valor que permite el acceso de las azorreductasas a las uniones azo, produciéndose una expansión del gel y la difusión de la macromolécula incorporada. La velocidad de degradación depende de distintos factores, como la estructura y la longitud del agente reticulante y el grado de hinchamiento del hidrogel. Los más utilizados son termopolímeros del ácido acrílico N-t-butilacrilamida y N,N-dimetilacrilamida, reticulados con diferentes compuestos azoaromáticos como el 4-4'-di(metacrililoilamino) azobenceno.

8.1.3. Sistemas administrados por vía percutánea

La administración de medicamentos a través de la piel, con la finalidad de conseguir un efecto sistémico, ha conducido al desarrollo de unas formas de dosificación conocidas con el nombre de sistemas transdérmicos, o TTS (*transdermal therapeutic systems*). Esta nueva forma de administración ha sido definida como un sistema destinado a su aplicación sobre una zona determinada de la piel, que sirve de soporte o vehículo para uno o varios principios activos destinados a ejercer un efecto general después de su liberación y paso a través de la piel.

Contrariamente a las clásicas formas tópicas, los sistemas transdérmicos permiten un control de la posología y el mantenimiento constante de los niveles plasmáticos del medicamento durante el tiempo de aplicación del sistema. Por ello, resultan particularmente interesantes para aquellos medicamentos que se utilizan en tratamientos prolongados, que requieren unos bajos niveles plasmáticos que deben mantenerse constantes durante largos períodos de tiempo. Por estas características, los sistemas transdérmicos han encontrado aplicación terapéutica en la administración de medicamentos como la nitroglicerina, la clonidina, la escopolamina, el estradiol, etc., y en un futuro constituirán una interesante forma de administración de algunos analgésicos y analgésicos antiinflamatorios no esteroídicos.

Un sistema transdérmico está constituido por una serie de capas consecutivas, cada una de las cuales posee una función específica:

- Cubierta externa protectora, impermeable al agua y a los componentes del sistema.
- Reservorio de principio activo en forma de gel, suspensión, emulsión, film rígido, etc.
- Membrana (facultativa) porosa o no porosa que controla la liberación del principio activo contenido en el reservorio.
- Capa adhesiva hipoalérgica que puede estar presente en toda superficie del sistema, sólo en los bordes o no existir en el caso de que los componentes del reservorio de principio activo posean propiedades adhesivas.
- Lámina protectora interna, que se retira antes de aplicar el sistema sobre la piel.

En la actualidad se señalan, para los sistemas transdérmicos, algunas de las siguientes ventajas:

- Evita los riesgos y los inconvenientes derivados de una administración i.v.
- Incrementa la biodisponibilidad y eficacia de muchos medicamentos que sufren un efecto de primer paso por vía oral.
- Mantiene de forma prolongada y constante los niveles plasmáticos dentro de rangos terapéuticos.
- Permite una excelente colaboración por parte del paciente.
- Posibilita el cese de la administración del medicamento tras la retirada del sistema de la piel.

Según la existencia o no de una membrana que controle la liberación del principio activo, los sistemas transdérmicos pueden ser de tipo matricial (carentes de membrana) o de tipo reservorio.

A) Sistemas matriciales

Los sistemas tipo matricial, pueden ser clasificados en sistemas matriciales con difusión controlada, con gradiente de difusión controlada y sistemas microrreservorios con disolución controlada.

1. Sistemas matriciales con difusión controlada

Estos sistemas están constituidos por una matriz adhesiva a base de butilacrilatos de peso molecular entre 45.000 y 65.000 daltons y ácido acrílico, adicionándose un espesante (poliacrilato sódico) y un agente de reticulación (trialquilamina). A la masa así obtenida se le incorpora el principio activo. Estos sistemas son utilizados para la preparación de TTS que contengan nitroglicerina y dinitrato de isosorbida.

permeable al agua y a los componentes

en forma de gel, suspensión, emulsión,

o no porosa que controla la liberación

reservorio.

puede estar presente en toda superficie

existir en el caso de que los componentes

o posean propiedades adhesivas.

se retira antes de aplicar el sistema sobre

os sistemas transdérmicos, algunas de

entes derivados de una administración

l y eficacia de muchos medicamentos

por vía oral.

y constante los niveles plasmáticos de

ción por parte del paciente.

ación del medicamento tras la retirada del

nbra que controle la liberación de

pueden ser de tipo matricial (carentes

ser clasificados en sistemas matriciales

ifusión controlada y sistemas micro

1 controlada

r una matriz adhesiva a base de butil

000 daltons y ácido acrílico, adiciona

gente de reticulación (trialquilamina)

ncipio activo. Estos sistemas son utiliza

an ni

licerina y dinitrato de isosorb

La velocidad de liberación de un principio activo a partir de estos sistemas es función de la raíz cuadrada del tiempo, por lo que el mantenimiento de niveles plasmáticos sensiblemente constantes sólo se consigue durante la liberación de un pequeño porcentaje de la dosis inicial de medicamento. Este hecho se puede apreciar a la vista de los resultados que se recoge en el cuadro 8.1, referentes a un sistema que contiene nitroglicerina.

CUADRO 8.1

Características de liberación de un sistema transdérmico matricial que contiene nitroglicerina

Superficie (cm ²)	5	10	15	20	30
Contenido total de nitroglicerina (mg)	20	40	60	80	120
Nitroglicerina liberada en 24 h	2,5	5	7,5	10	15
Flujo nitroglicerina in vivo (mg/cm ² /24h)	0,05	0,05	0,05	0,05	0,05

rendimiento: 12,5%

2. Sistemas matriciales con gradiente de difusión controlada

Para obviar el inconveniente de una liberación no constante, en este sistema se crea un gradiente de concentración de principio activo en el seno de la matriz polimérica, tal y como se puede observar en la figura 8.29.

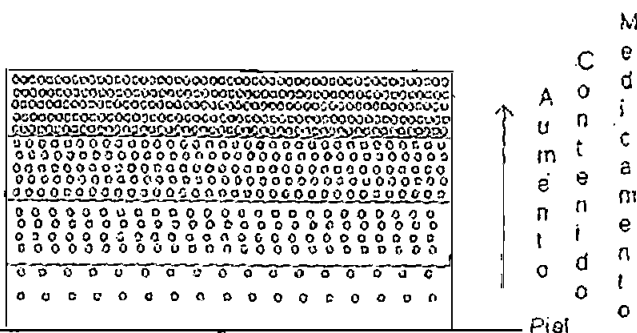


FIGURA 8.29. Sistema transdérmico con gradiente de difusión controlada.

Los estudios realizados con este sistema que contiene nitroglicerina como principio activo demuestran que la velocidad de liberación es más lenta que en el sistema anterior, pero más constante, lo que permite que en 24 horas se libere un mayor porcentaje de nitroglicerina (aproximadamente un 30% frente al 12,5%).

3. Sistema microrreservorio con disolución controlada

Está constituido este sistema por multitud de microcompartimentos hidrófilos (de tamaño entre 10 y 40 μm) dispersados en una matriz polimérica hidrófoba (figura 8.30). El proceso de liberación del principio activo es más complejo que en los sistemas anteriores, ya que inicialmente debe difundir del compartimento acuoso a la matriz polimérica y de ésta a la piel. El ejemplo más característico de estos sistemas es el que se conoce con el nombre de Nitrodisc, que contiene nitroglicerina como principio activo.

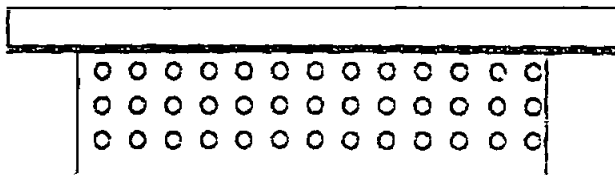


FIGURA 8.30. Sistema transdérmico microrreservorio con disolución controlada. Cada círculo representa un microrreservorio hidrófilico.

Basándose en el mismo principio, se ha desarrollado un sistema que libera simultáneamente una combinación de un progestágeno y un estrógeno; cada medicamento se libera a velocidad diferente pero constante durante un tiempo de 7 días y se emplea como dispositivo anticonceptivo transdérmico.

B) Sistemas de tipo reservorio

Los sistemas reservorio pueden diferir en su estructura según estén diseñados para contener un reservorio de medicamento sólido o líquido pero, en cualquier caso, es característica la existencia de una membrana que controla la liberación del principio activo (figura 8.31).

Como ejemplos de un sistema con reservorio para medicamentos sólidos se pueden citar el Scopoderm, que contiene escopolamina, y el Catapress, que contiene el antihipertensivo clonidina. El primero permite administrar por vía transdérmica una cantidad de 1,5 mg de escopolamina durante 3 días; el sistema debe colocarse en el lóbulo de la oreja, ya que la absorción transdérmica del medicamento varía según la zona de aplicación. El sistema Catapress libera clonidina durante 7 días, y aunque la dosis total administrada es aproximadamente la mitad que la requerida por vía oral, es frecuente la intolerancia dérmica, lo cual obliga a suspender el tratamiento por vía transdérmica.

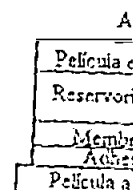


FIGURA 8.31. Sistema transdérmico de tipo reservorio.

Como representante de sistema Transderm-Nitro y de nitroglicerina que se libera a velocidad constante, seguidamente se coloca la película de vinilo-etileno. A continuación se aplica a la piel, y puesto que la membrana controla la pequeña liberación de principio activo para cubrir el período entre el reservorio de medicamento y la piel.

El sistema Estraderm es un sistema de liberación de principio activo es el estradiol, que se utiliza en la menopausia. El sistema se aplica durante tres semanas.

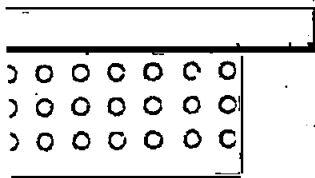
Muchos principios activos se liberan a velocidad lo suficientemente elevada, por lo que, en estos casos, se emplea la piel y particularmente el estradiol como siguientes alternativas: empleo de la absorción e iontoforesis.

1. Empleo de promedicamentos

En el caso de la administración de un medicamento por vía transdérmica (por tanto poco permeable) y éste, después de su absorción, origina nuevamente la necesidad de empleo de promedicamentos. Muchos han demostrado que los 3-4 días han demostrado que los 3-4 días mejor a través de la piel que se ha demostrado que la constante correspondiente al grupo en 17, por lo

olución controlada

ltitud de microcompartimentos hidro
sados en una matriz polimérica hidro
l principio activo es más complejo
te debe difundir del compartimento
el. El ejemplo más característico de
ore de Nitrodisc, que contiene nitro



vacío con disolución controlada. Cada círculo
reservorio hidrofílico.

ha desarrollado un sistema que liber
progestágeno y un estrógeno, cada uno
to constante durante un tiempo de
ivo transdérmico.

en su estructura según estén diseñad
ento sólido o líquido pero, en cualquier
membrana que controla la liberación

servorio para medicamentos sólidos
escopolamina, y el Catapress, que
nero permite administrar por vía tra
lamina durante 3 días; el sistema de
absorción transdérmica del medicame
na Catapress libera clonidina duran
es aproximadamente la mitad que
oleran transdérmica, lo cual obliga a su

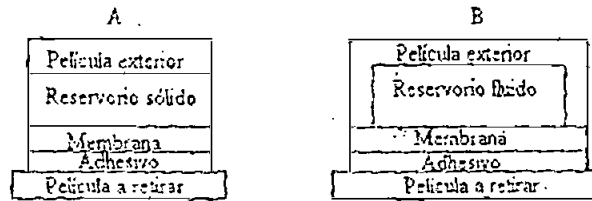


FIGURA 8.31. Sistema transdérmico tipo reservorio. A: medicamento sólido; B: medicamento líquido o fluido.

Como representante de un sistema reservorio para líquidos se pueden citar el sistema Transderm-Nitro y el Estraderm. El primero contiene una suspensión fluida de nitroglicerina que se deposita en las oquedades de una lámina de aluminio; seguidamente se coloca la membrana, que en este caso es de copolímero acetato de vinilo-etileno. A continuación se coloca la capa adhesiva para fijar el sistema a la piel, y puesto que la membrana es permeable a la nitroglicerina se produce una pequeña liberación de principio activo, lo cual asegura una dosis de ataque suficiente para cubrir el período de latencia que se presenta al existir una membrana entre el reservorio de medicamento y la piel.

El sistema Estraderm es análogo al Transderm-Nitro, pero en este caso el principio activo es el estradiol, que se utiliza para paliar el déficit hormonal durante la menopausia. El sistema se mantiene sobre la piel durante 3-4 días y el tratamiento se hace durante tres semanas, seguidas de otra de descanso.

Muchos principios activos no se pueden absorber a través de la piel a una velocidad lo suficientemente elevada como para alcanzar concentraciones terapéuticas, por lo que, en estos casos, es necesario disminuir la resistencia que ofrece la piel y particularmente el estrato córneo. Con esta finalidad se han propuesto las siguientes alternativas: empleo de promedicamentos, empleo de promotores de la absorción e iontoforesis.

1. Empleo de promedicamentos

En el caso de la administración a través de la piel, un principio activo poco lipófilo (por tanto poco permeable) puede transformarse en otro compuesto más lipófilo y éste, después de su absorción, sufre en las capas internas de la piel una transformación que origina nuevamente el principio activo. Como ejemplo de las posibilidades de empleo de promedicamentos, se puede citar el caso del estradiol. Diversos estudios han demostrado que los 3-17 diésteres del estradiol son más lipófilos y se absorben mejor a través de la piel que el estradiol. Los estudios de hidrólisis enzimática han demostrado que la constante correspondiente al grupo en 3 es mayor que la correspondiente al grupo en 17, por lo que el 17 acetato de estradiol podría considerarse

CAPÍTULO 8: NUEVAS FORMAS DE ADMINISTRACIÓN DE MEDICAMENTOS

como un promedimento intermedio entre el diéster administrado y el estradiol que pasa a la circulación sanguínea.

2. Empleo de promotoras

La permeabilidad de la piel puede incrementarse de forma muy notable por medio de promotores de la absorción, los cuales afectan a la resistencia que ofrece el estrato córneo. Son muchas las sustancias capaces de modificar la estructura del estrato córneo, pero en la práctica sólo algunos cumplen, al menos parcialmente, las siguientes condiciones:

- Ser inactivos farmacológicamente.
- No ser tóxicos ni irritantes y no provocar reacciones alérgicas.
- El agente promotor debe reducir la resistencia cutánea en una sola dirección, de tal forma que no permita la pérdida de electrólitos ni sustancias endógenas.
- Deben ser física y químicamente compatibles con la gran mayoría de los principios activos y excipientes utilizados en las preparaciones dermatológicas.
- Deben ser excelentes disolventes de los principios activos.
- Deben carecer de olor, color y sabor.

El paso de los medicamentos a través del estrato córneo puede realizarse por las células que lo constituyen (ruta transcelular o polar) o bien por las separaciones existentes entre los queratinocitos (ruta paracelular o apolar); ello justifica que promotores de absorción que actúan esencialmente sobre la ruta apolar, no tengan influencia sobre principios activos cuya ruta de absorción es transcelular.

Los promotores que afectan a la ruta polar actúan por hidratación e hinchamiento de la queratina, lo que provoca cambios conformacionales en su estructura y una disminución de su resistencia. El agua actúa como promotor por este mecanismo, aunque también produce una solvatación de las regiones polares de las ceramidas y glucoesfingolípidos (componentes lipídicos del estrato córneo).

Los agentes tensioactivos presentan probablemente un doble mecanismo, ya que afectan a la estructura terciaria de las proteínas, pudiendo incluso producir su desnaturalización, y favorecen la disolución de los lípidos del estrato córneo. Los agentes tensioactivos tienen, en su estructura, una región polar y una cadena apolar, y se ha comprobado que los que poseen una cadena de 12 carbonos, en el caso de los alquilsulfatos, son los que mejor actúan como promotores, puesto que son lo suficientemente lipófilos como para disolver los lípidos del estrato córneo, y lo suficientemente hidrófilos como para modificar la estructura de la queratina.

Es bastante frecuente recurrir al empleo de sistemas binarios que actúan tanto sobre la ruta polar como sobre la no polar. Uno de los mejores sistemas está

422 PARTE I: FORMAS FARMACÉUTICAS

constituido por un ácido graso in diol, como el propilenglicol. Otro laurocapram y propilenglicol.

El uso de los promotores de absorción de nuevos sistemas como los que se ven en un reservorio con el principio activo, una que controla el paso del principio activo a través de la membrana adhesiva que permite la limitación de que el promotor que está en contacto con la piel. En los bordes del sistema; la capa que promotor y de principio activo sufren también una membrana que controla el principio activo que se encuentran en



FIGURA 8.32. Esquema de dos sistemas de liberación controlada.

3. Iontoforesis

Es una técnica que permite utilizar la vía transdérmica de la piel cuando se aplica una corriente eléctrica. Esta técnica, conocida a principios de siglo, ya que permite de forma segura, sencilla, cargadas o no, a través de la piel. El atractivo de la iontoforesis aparece en la iontoforesis transdérmica.

8.1.4. Sistemas de liberación controlada

La utilización de la vía parenteral presenta una serie de ventajas, como:

como un promedimento intermedio entre el diéster administrado y el estradiol, que pasa a la circulación sanguínea.

2. Empleo de promotoras

La permeabilidad de la piel puede incrementarse de forma muy notable por medio de promotores de la absorción, los cuales afectan a la resistencia que ofrece el estrato córneo. Son muchas las sustancias capaces de modificar la estructura del estrato córneo, pero en la práctica sólo algunos cumplen, al menos parcialmente, las siguientes condiciones:

- Ser inactivos farmacológicamente.
- No ser tóxicos ni irritantes y no provocar reacciones alérgicas.
- El agente promotor debe reducir la resistencia cutánea en una sola dirección, de tal forma que no permita la pérdida de electrolitos ni sustancias endógenas.
- Deben ser física y químicamente compatibles con la gran mayoría de los principios activos y excipientes utilizados en las preparaciones dermatológicas.
- Deben ser excelentes disolventes de los principios activos.
- Deben carecer de olor, color y sabor.

El paso de los medicamentos a través del estrato córneo puede realizarse por las células que lo constituyen (ruta transcelular o polar) o bien por las separaciones existentes entre los queratinocitos (ruta paracelular o apolar); ello justifica que promotores de absorción que actúan esencialmente sobre la ruta apolar, no tengan influencia sobre principios activos cuya ruta de absorción es transcelular.

Los promotores que afectan a la ruta polar actúan por hidratación e hinchamiento de la queratina, lo que provoca cambios conformacionales en su estructura y una disminución de su resistencia. El agua actúa como promotor por este mecanismo, aunque también produce una solvatación de las regiones polares de las ceramidas y glucoesfingolípidos (componentes lipídicos del estrato córneo).

Los agentes tensioactivos presentan probablemente un doble mecanismo, ya que afectan a la estructura terciaria de las proteínas, pudiendo incluso producir su desnaturalización, y favorecen la disolución de los lípidos del estrato córneo. Los agentes tensioactivos tienen, en su estructura, una región polar y una cadena apolar, y se ha comprobado que los que poseen una cadena de 12 carbonos, en el caso de los alquilsulfatos, son los que mejor actúan como promotores, puesto que son lo suficientemente lipófilos como para disolver los lípidos del estrato córneo, y lo suficientemente hidrófilos como para modificar la estructura de la queratina.

Es bastante frecuente recurrir al empleo de sistemas binarios que actúan tanto sobre la ruta polar como sobre la no polar. Uno de los mejores sistemas está

constituido por un ácido graso in diol, como el propilenglicol. Otro laurocapram y propilenglicol.

El uso de los promotores da lugar a nuevos sistemas como los que se muestran en un reservorio con el principio activo que controla el paso del principio activo a través de la membrana adhesiva que permite la limitación de que el promotor pueda estar en contacto con la piel. En los bordes del sistema, la capa que contiene el promotor y de principio activo sufre también una membrana que controla el paso del principio activo que se encuentran en el



FIGURA 8.32. Esquema de dos sistemas de liberación controlada.

3. Iontoforesis

Es una técnica que permite introducir fármacos en la piel cuando se aplica una corriente eléctrica. Esta técnica, conocida a principios del siglo XX, ya que permite de forma segura, sencilla, cargadas o no, a través de la piel, el atractivo de la iontoforesis aparece en la transdérmica.

8.1.4. Sistemas de liberación controlada

La utilización de la vía parenteral presenta una serie de ventajas, como:



Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Ian Raisbeck Llinas
Apoderado

Oficio N°: 13875

ASUNTO:	Radicación PCT N°	08-40107
	Trámite	011
	Evento	379
	Actuación	440
	Folios	043

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado del Laboratorio Franco Colombiano S.A. Lafranco! S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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



ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

El anterior oficio fue notificado por fijación en lista de fecha, 04 DIC. 2009.

202021



Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor
Ian Raisbeck Llinas
Apoderado

Oficio N°: 3876

ASUNTO:

Radicación PCT N°	08-40107
Trámite	011
Evento	379
Actuación	440
Folios	007

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Cielo Ángela Peña Rodríguez, en su calidad de apoderada de Gynopharm S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

04 DIC. 2009

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

202021