



No. 10-074973-00003-0000

Fecha: 2011-09-16 12:08:40 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 30

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN 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: 10-074 973

Solicitante: BAYER SCHERING PHARMA OY

SOLICITUD
PUBLICADA

Apoderado: MONICA WOLF WASSERMAN

Título de la nueva creación o denominación del signo: "SISTEMA, DISPOSITIVO Y MÉTODO MEJORADOS PARA ADMINISTRAR VAGINALMENTE SUSTANCIAS TERAPEÚTICAMENTE ACTIVAS O SUS PROFARMACOS"

Gaceta: 629

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A.	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78b-201	C.C. ☐	Nit ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual <u> </u>	
	Telefono: 371 99 00 Fax: 373 0815	Número 890.106.527-5	
	E-mail: <u> </u>		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 104 N°119-95 OF 104	C.C. ☒	NIT ☐
	Telefono: 2131213 Fax: 6121979	C.E. ☐	Otro ☐
	E-mail: negocios@optimum-co.com	Cual <u> </u>	
		Número 51.975.664 TP 83823	

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 demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. 11-0091258

Fecha 18/09/2011

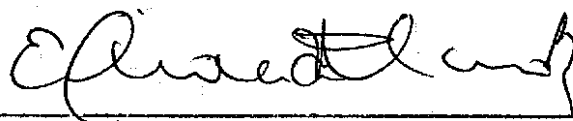
⑥ ANEXOS

- ☒ 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: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA:



C.C. 51.975.664

TP. 83823



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señor Director,

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 10 C74973

Asunto : Oposición a la solicitud de patente de Invención titulada
"SISTEMA, DISPOSITIVO Y MÉTODO MEJORADOS
PARA ADMINISTRAR VAGINALMENTE SUSTANCIAS
TERAPEUTICAMENTE ACTIVAS O SUS
PROFARMACOS"

Solicitante : BAYER SCHERING PHARMA OY.

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 629 del 20 de junio de 2011

Yo, *ELLANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *83823* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad PROCAPS 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 "SISTEMA, DISPOSITIVO Y MÉTODO MEJORADOS PARA ADMINISTRAR VAGINALMENTE SUSTANCIAS TERAPEUTICAMENTE ACTIVAS O SUS PROFARMACOS", cuyos titulares son BAYER SCHERING PHARMA OY, 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 DROSPIRENONA. 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 22 de junio de 2010 reivindicando prioridad bajo la solicitud EP20070397042 del 2007-11-22; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 629 del 20 de junio de 2011, cuya publicación internacional corresponde a la WO 2009066006 del 2009-05-28.

2.2. La solicitud colombiana 10 074973 objeto de la presente oposición se refiere a un sistema de administración intravaginal para la liberación controlada de drospirenona y un estrógeno y, opcionalmente, también una o más sustancias terapéuticamente activas o promotoras de la salud capaces de brindar y/o mejorar la protección contra infecciones bacterianas y fúngicas, y/o mejorar la protección contra enfermedades de transmisión sexual. El sistema de administración comprende uno o más compartimientos, cada uno de los cuales comprende un núcleo y una membrana que recubre el núcleo, dicho núcleo y dicha membrana están compuestos esencialmente por la misma composición de polímero o una composición de polímero diferente, donde al menos un compartimiento comprende drospirenona y al menos un compartimiento, que puede ser igual o diferente del que comprende drospirenona, comprende un estrógeno o una mezcla de drospirenona y un estrógeno, y donde la membrana o la superficie de la membrana o al menos uno de los núcleos comprende dicha sustancia terapéuticamente activa o promotora de la salud.

2.3. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: *“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”*, tenemos que 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 afectan la patentabilidad de la presente solicitud:

- D1: US 2007141102 publicada el 21 de junio de 2007.

2.4. Ahora bien, el documento D1, describe un sistema de administración de fármacos que consta de uno o varios compartimentos y que comprende un compuesto progestágeno disuelto en un copolímero de acetato de vinilo de polietileno termoplástico. También se describe un kit de anticonceptivos o terapia hormonal de reemplazo que comprende el sistema de administración de fármacos, y una preparación de combinación que proporciona simultáneamente la anticoncepción y el tratamiento de una enfermedad de transmisión sexual que comprende el sistema de administración de fármacos. Dicho documento D1 menciona que un sistema que comprende al menos un compartimento, donde dicho compartimento comprende un núcleo y una membrana que encierra el núcleo, donde dicho núcleo y membrana consisten esencialmente de la misma o diferente composición de polímeros, donde por lo menos un compartimento contiene drospirenona y al menos uno que puede ser igual o diferente contiene un estrógeno.

2.5. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 10 074973 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.6.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención*

tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”. A la fecha de prioridad, 22 de noviembre de 2007, a partir del documento D1, un experto en la materia sabiendo que es obvio considerar cambiar o probar otros polímeros, puede llegar de manera evidente a un sistema de administración intravaginal para la liberación controlada de drospirenona y un estrógeno y, opcionalmente, también una o más sustancias terapéuticamente activas o promotoras de la salud capaces de brindar y/o mejorar la protección contra infecciones bacterianas y fúngicas, y/o mejorar la protección contra enfermedades de transmisión sexual, donde el sistema de administración comprende uno o más compartimientos, cada uno de los cuales comprende un núcleo y una membrana que recubre el núcleo, dicho núcleo y dicha membrana están compuestos esencialmente por la misma composición de polímero o una composición de polímero diferente, donde al menos un compartimiento comprende drospirenona y al menos un compartimiento, que puede ser igual o diferente del que comprende drospirenona, y que comprende un estrógeno o una mezcla de drospirenona y un estrógeno, y donde la membrana o la superficie de la membrana o al menos uno de los núcleos comprende dicha sustancia terapéuticamente activa o promotora de la salud; sobre el cual busca protección en el capítulo reivindicatorio.

2.7. 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 uno de los tres requisitos necesarios para su protección.

2.8. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada “SISTEMA, DISPOSITIVO Y MÉTODO MEJORADOS PARA ADMINISTRAR VAGINALMENTE SUSTANCIAS TERAPEUTICAMENTE

ACTIVAS O SUS PROFARMACOS", cuyos titulares son BAYER SCHERING PHARMA OY, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 629 del 20 de junio de 2011.

3. PRUEBAS

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

- D1: US 2007141102 publicada el 21 de junio de 2007.

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 PROCAPS S.A.
 3. Recibo de caja del respectivo pago de tasa.
 4. Copias de los documentos:
- D1: US 2007141102 publicada el 21 de junio de 2007.



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 Director,

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0091258

Bogotá D.C., Septiembre 16 de 2011 - 11:34:47

RECIBIDO DE : PROCAPS S.A.

NI 890.106.527

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	382192473	27/07/2011	2.432.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	VR. UNDITARIO	VR. CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	12	MARCAS Y LEMAS COMERCIALES
			304.000.00	304.000.00
				\$304.000.00

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-074973- -00003-0000

Fecha: 2011-09-16 12:08:40 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 400 OPOSIOBSERVTER Folios: 30

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Septiembre 16 de 2011 - 11:34:48



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, 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 **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 10 074.973, titulada "**SISTEMA, DISPOSITIVO Y MÉTODO MEJORADOS PARA ADMINISTRAR VAGINALMENTE SUSTANCIAS TERAPÉUTICAMENTE ACTIVAS O SUS PROFÁRMACOS**", cuyo titular es **BAYER SCHERING PHARMA OY**, publicada en la gaceta No. 629 del 20 de Junio de 2011.

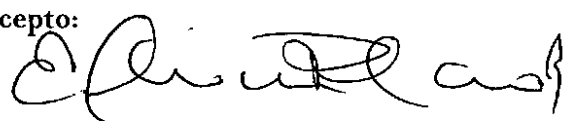
Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativamente 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 8 días del mes de Septiembre de 2011.


PROCAPS S.A.
C.C. N° 16'251.923
NIT: 890.106.527-5
Representante Legal

APROBADO
- 8 SET. 2011
PROCAPS S.A.

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

NOTARIA
2,300

NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO

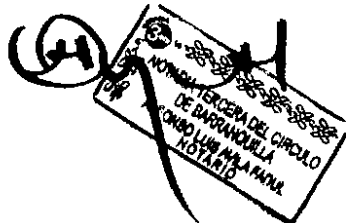
Ante el Notario Tercero de Barranquilla se presento:
WALTER TANAZA YATOKAWA

identificado con: CC 16.81.923 PALMERO

Y declaro que el contenido del anterior Documento es cierto
y suya la firma que lo refrenda.

Barranquilla: 12 SET. 2011

[Handwritten signature]





***** Pag. 1

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

05*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

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. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

***** C O N T I N U A *****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996,
otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta
Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del
libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS 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
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

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:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

***** C O N T I N U A *****



***** Pag. 2

CAMARA DE COMERCIO
DE BARRANQUILLA

05*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

Correo

electrónico:

mlozada@procaps.com.co

Pagina Web:

Telefono:

3719272

C E R T I F I C A

DURACION: Que la sociedad no se halla disuelta y su término de duración se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A D E

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de Capsulas y otros 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, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) 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. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) 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 cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion,

***** C O N T I N U A *****

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costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, 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 apoderados en el pais y en el exterior y, en 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 la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

C E R T I F I C A D O
DE EXISTENCIA

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,298,000,000	*****1,298,000	*****1,000
Pagado		
\$*****1,298,000,000	*****1,298,000	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representa-

***** C O N T I N U A *****



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 CAMARA DE COMERCIO
 DE BARRANQUILLA
 05*****

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cion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. 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. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. 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. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos

***** CONTINUA *****

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o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades 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), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

DE BARRANQUILLA
C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	.*****

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3. Minski Sharon

PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A
DE BARRANQUILLA

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

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S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal. Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 158 del 17 de Junio de 2011 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 23 de Junio de 2011 bajo el No. 170,929 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Suplente Rodriguez Rey Jose Luis	CC.*****72,001,912

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ----
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y ----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organó Social, otorga los siguientes poderes: Otorgar poder ----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO ----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que ----
representen a la sociedad PROCAPS S.A, ante todo tipo de ----
autoridades administrativas y jurisdiccionales, en asuntos de ----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar ----
pruebas, recibir, notificarse, ejercer la accion de tutela, ----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de ----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, ----
transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo

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C A M A R A D E C O M E R C I O
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ante la DIAN, de tal forma que en ningún momento quede sin -----
representación legal de la sociedad. PODERES ESPECIALES: a.- Se ----
confiere poder especial amplio y suficiente a las personas que se ----
determinan seguidamente, que conforman el grupo A y B, para, para
que conjuntamente suscriban contratos de suministros de mercancías
y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS
MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), -----
liquidados a la tasa representativa del mercado vigente en el día
que se realice la respectiva transacción. Grupo A. WALTER NANAKA
TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----
VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA -----
DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -----
CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME
FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----
amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA -----
CC.No.8.715.941, para que en nombre y representación de PROCAPS ----
S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a
que este obligada la sociedad, en el giro normal de sus negocios y
operaciones sociales, por tanto, quedan facultados para firmarlas,
como también los demás documentos relacionados con ellas, -----
notificarse, aportar y solicitar las pruebas que sean necesarias.
c.- Otorgar poder especial amplio y suficiente al señor MARLON ----
TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
CERRA CC.No.8.715.941, para que en nombre y representación de ----
PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
documento relacionado con los trámites o registros de Comercio ----
Exterior y o cualquier entidad del Estado que haga sus veces: d)
Otorgar poder especial amplio y suficiente a la doctora CARMEN ----
ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ----
representación de PROCAPS S.A.; endosen los títulos valores de la
sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
(1.000.000.000.00) M.L. CUARTO: El representante legal de la ----
sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta
que la presente reforma fue aprobada por la Asamblea General ----
Extraordinaria de Accionista de PROCAPS S.A., con observancia de
las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008,
otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente
se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008
bajo el No. 3,748 del libro respectivo,-----

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Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condicion de Presidente y Representante Legal de la Sociedad PROCAPS S.A., confiere por medio de este instrumento ----- publico Poder especial Amplio y Suficiente a la doctora MILENA ----- ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y ----- representacion de PROCAPS S.A., suscriba declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad en el giro normal de sus negocios y operaciones sociales, por tanto queda ----- facultada para firmar, como tambien los demas documentos ----- relacionados con ellas, notificarse, aportar y solicitar las ----- pruebas que sean necesarias.-----

C E R T I F I C A

Que por Documento Privado del 09 de Abril de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 20 de Abril de 2010 bajo el Nro 4,201 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ---- quien obra en el caracter de Presidente y/o Representante legal de la sociedad PROCAPS S.A., que por medio de este instrumento ----- publico, otorga Poder Especial Amplio y Suficiente a la Doctora ---- MONICA DE HART DE OCHOA, identificada con C.C. No. 32.676.025, para que en nombre y representacion de la sociedad, Endose las Facturas Nacionales e Internacionales hasta por la suma de UN MIL MILLONES DE PESOS (\$1.000.000.000.00)M.L. La doctora Monica de Hart de Ochoa, queda facultada para realizar todo acto o trámite necesario para el cabal cumplimiento del presente mandato.-----

C E R T I F I C A
DE BARRANQUILLA

Que por Documento Privado del 10 de Junio de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 13 de Julio de 2010 bajo el Nro 4,228 del libro respectivo,-----
consta que el señor RUBEN MISNKI GONTOVNIK, cc. No. 7.463.982 en su condicion de Presidente y representante legal de PROCAPS S.A., ---- confiere poder especial, amplio y suficiente al señor RICARDO DORADO HURTADO cc. No. 79.715.772 para que represente a la sociedad, ante el INVIMA, Fondo Nnacional de estupefacientes e ICA, con el fin que gestione, tramite o presente las diferentes solicitudes y ----- peticiones de la empresa, segun la competencia de estas entidades.
Por lo anterior, el Señor RICARDO DORADO HURTADO, queda facultado para presentar, gestionar, tramitar y firmar las diferentes ----- solicitudes y peticiones de la empresa, segun la competencia de ---- estas entidades, como tambien presentar y firmar todo los ----- documentos relacionados con estas solicitudes, notificarse de ----- cualquier acto administrativo que expidan, aportar y solicitar las pruebas que sean necesarias, desistir, y en general a realizar todo tramite o acto necesario de tal forma que la sociedad en ningun ---- momento quede sin representacion legal ante estas entidades, en ---- cumplimiento fiel al mandato otorgado.-----

C E R T I F I C A

***** C O N T I N U A *****



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C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

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PROCAPS S.A.-----

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Que por Documento Privado del 03 de Agosto de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 24 de Agosto de 2010 bajo el Nro 4,258 del libro respectivo,-----
consta que RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta vecindad, identificado con la cédula de ciudadanía No.7.463.982, expedida en Barranquilla, en mi condición de Representante legal y/o Presidente de la sociedad PROCAPS S. A., conforme a las -----
facultades otorgadas por los Estatutos Sociales, todo lo cual -----
demuestro con el certificado de existencia y representación legal expedido por la Cámara de Comercio de Barranquilla, que adjunto a este escrito, me permito manifestarles que confiero poder especial, amplio y suficiente al señor MARIO LÓPEZ LEON, varón, mayor de -----
edad, de esta vecindad, identificado con la cédula de ciudadanía No.72.311.558, expedida en Puerto Colombia (Atlántico), para que en nombre y representación de la sociedad, realice los siguientes -----
actos: 1. Endosar las Facturas Nacionales e Internacionales de esas compañías hasta por la suma de UN MIL MILLONES DE PESOS -----
(\$1.000.000.000.00) Moneda Legal. 2. Suscribir Declaraciones -----
Cambiarias, Aduaneras y Tributarias a las que esta obligada la -----
sociedad en el giro ordinario de sus negocios, quedando facultado para notificarse, aportar y solicitar pruebas relacionados con las declaraciones Cambiarias. El señor MARIO LÓPEZ LEÓN, queda -----
facultado para notificarse, aportar y solicitar pruebas, presentar escritos en caso que resulte necesario en general a realizar todo acto, diligencia o tramite que considere indispensable para el -----
cabal cumplimiento del presente mandato.-----

C E R T I F I C A

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 2011.

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 despues de la correspondiente inscripción, siempre

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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. Rojas





US 20070141102A1

17

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0141102 A1**
De Graaff et al. (43) **Pub. Date: Jun. 21, 2007**

(54) **DRUG DELIVERY SYSTEM BASED ON
POLYETHYLENE VINYLACETATE
COPOLYMERS**

(86) PCT No.: PCT/EP05/51189

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(57) **ABSTRACT**

Disclosed herein is a drug delivery system consisting of one or more compartments and comprising a progestogenic compound dissolved in a thermoplastic polyethylene vinylacetate copolymer. Also disclosed are a contraceptive kit or hormone-replacement therapy kit comprising the drug delivery system, and a combination preparation that simultaneously provides contraception and treatment of a sexually transmitted disease comprising the drug delivery system.

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Figure 1:
In-vitro release rates of etonogestrel for a number of drug delivery systems described in examples 2-14 according to the invention and two comparative examples.

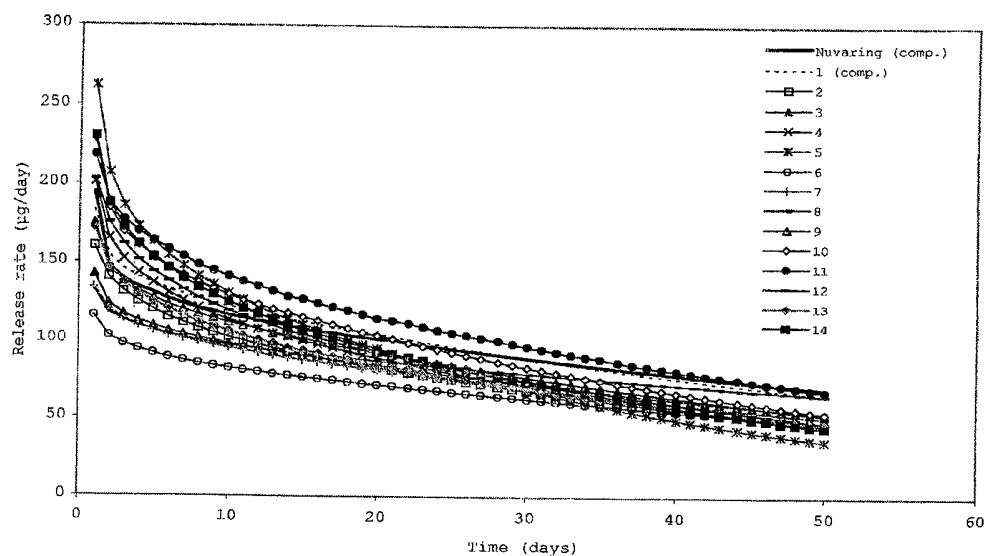
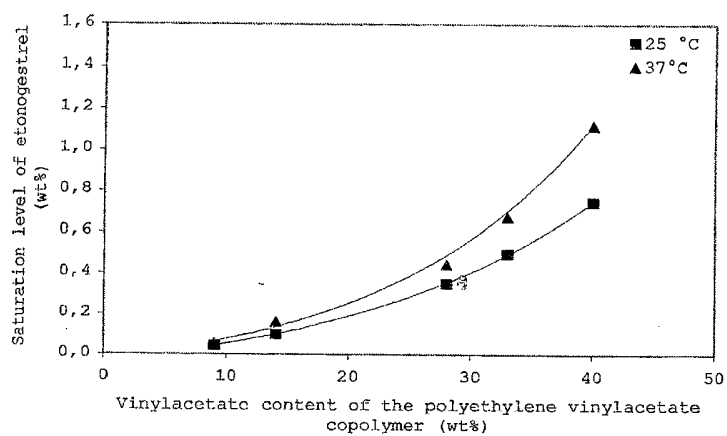


Figure 2:
Curve fit of the vinylacetate content of polyethylene vinylacetate copolymers summarized in table II
versus the saturation level of etonogestrel in these same copolymers at 25°C and at 37°C.



DRUG DELIVERY SYSTEM BASED ON POLYETHYLENE VINYLACETATE COPOLYMERS

FIELD OF THE INVENTION

[0001] The present invention relates to the field of female contraception and hormone replacement therapy.

[0002] The invention relates to a drug delivery system, its manufacture and its use, to make a kit or a combination preparation.

BACKGROUND TECHNOLOGY

[0003] Drug delivery systems, especially those intended for intravaginal use are known in the art.

[0004] U.S. Pat. No. 3,995,633 and U.S. Pat. No. 3,995,634 describe separate, preferably spherical or cylindrical, reservoirs containing different active substances, which are assembled in specially constructed holders.

[0005] U.S. Pat. No. 4,237,885 describes a tube or coil of polymeric material which is divided into portions by means of a plurality of "spacers" provided in the tube, after which each of the separate tube portions is filled with a different active substance in a silicone fluid and the two ends of the tube are subsequently connected to one another. In this release system, however, transport (diffusion) of active material from one reservoir to the other takes place through the wall of the tube, especially upon prolonged storage, so that the pre-set fixed release ratio between the active substances in question will change over a period of time.

[0006] EP-A-0050867 discloses a two-layered vaginal ring which comprises a pharmacologically acceptable supporting ring covered by two layers preferably of silicone elastomers whereby the inner layer is a silicone elastomer loaded with an active substance.

[0007] A ring-shaped silicone vaginal delivery system has been described in U.S. Pat. No. 4,292,965. The use of silicone elastomers is nowadays considered to be less safe and is clearly no longer the material of choice.

[0008] U.S. Pat. No. 4,596,576 describes a two-compartment vaginal ring wherein each compartment contains a different active substance. To achieve a suitable ring with a constant release ratio between the various active substances, the end portions of the compartments are joined by glass stoppers.

[0009] Drug delivery systems for intravaginal use, and in particular vaginal rings, prepared of polyethylene vinylacetate (EVA) copolymers are also known in the art.

[0010] For example, J. A. H. van Laarhoven et al., International Journal of Pharmaceutics 232 (2002) pages 163-173, describes the use of EVA copolymers for the preparation of a vaginal ring.

[0011] WO-A-97/02015 describes a two-compartment device: a first compartment consisting of an EVA copolymer core, an EVA copolymer etonogestrel-loaded middle layer and an EVA copolymer non-medicated outer layer; and a second compartment consisting of an EVA copolymer core, loaded with both etonogestrel and ethinyl estradiol, and an EVA copolymer non-medicated outer layer. The preparation

of the two-compartment device requires the cutting of fibres in the required lengths and the assembly of the pieces to a ring-shaped device.

[0012] EP-A-876815 describes a one-compartment vaginal ring comprising an EVA copolymer core comprising ethinyl estradiol and etonogestrel; and a non-medicated EVA copolymer skin. The progestogenic steroid etonogestrel is dissolved in the EVA copolymer core material in a concentration above the saturation level.

[0013] Among the above disclosures, EP-A-876815 clearly sets a standard; it involves a one-compartment design, it obviates the need for silastic polymer by using EVA combinations, and it releases two or more active substances in a substantially constant ratio to one another over a prolonged period in time. Although the vaginal ring described in EP-A-876815 fulfills its purpose and provides contraception, the design can still be improved upon. The drug delivery device disclosed in EP-A-876815 is physically stable only when stored below room temperature. It requires storage and transport below room temperature, which is expensive and requires a lot of attention. As indicated in EP-A-876815 the progestogen may eventually crystallize out on the exterior surface of the vaginal ring. Such a crystallization of progestogen onto the skin of the device may lead to uncontrolled and high burst release.

[0014] It is therefore desirable to avoid the possibility of crystallization of the progestogen on the exterior surface of the vaginal ring when it is stored on or above room temperature (i.e. about 25° C.). At the same time, however, the amounts of progestogen released and release rate should remain unchanged, to ensure a sufficient pharmaceutical effect for use in contraception and/or Hormone Replacement Therapy (HRT).

[0015] An improved drug delivery device, easy to prepare, whilst avoiding the possibility of exterior crystallization of the progestogenic compound and still providing sufficient amounts and rates of release of the progestogenic compound for use in contraception and/or HRT has now been found.

SUMMARY OF THE INVENTION

[0016] Accordingly, the present invention provides a drug delivery system consisting of one or more compartments and comprising a progestogenic compound dissolved in a thermoplastic polyethylene vinylacetate copolymer whereby,

[0017] if the delivery system consists of one compartment, the compartment

comprises

[0018] (i) a core of a thermoplastic polyethylene vinylacetate copolymer comprising the progestogenic compound, such progestogenic compound being dissolved in the polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., and an estrogenic compound; and

[0019] (ii) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, said skin being permeable for both compounds;

[0020] if the delivery system consists of more than one compartment, only

one compartment comprises

[0021] (iii) the progestogenic compound, such progestogenic compound being dissolved in a core of a thermoplastic polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., and an estrogenic compound; and

[0022] (iv) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, said skin being permeable for both compounds.

[0023] The improved drug delivery system is physically stable under room temperature conditions (about 25° C.) and thus does not need special storage and transportation conditions at a temperature below room temperature. Moreover the drug delivery system is easy to prepare and still provides sufficient amounts and rates for release of the progestogenic compound for use in contraception and/or HRT.

[0024] FIG. 1:

[0025] In-vitro release rates of etonogestrel for a number of drug delivery systems described in examples 2-14 according to the invention and two comparative examples.

[0026] FIG. 2:

[0027] Curve fit of the vinyl acetate content of polyethylene vinylacetate copolymers summarized in Table II versus the saturation level of etonogestrel in these same copolymers at 25° C. and at 37° C.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The advantages of the invention are obtained by designing the drug delivery system as described above. The drug delivery system comprises at least one compartment, which consists of two layers, i.e. a core and a skin. The skin is directly covering the core, giving the drug delivery system an uncomplicated design such that it can be prepared by an economically attractive preparation process.

[0029] In one embodiment the progestogenic compound is present in a concentration such that the core comprises the progestogenic compound being dissolved in the polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C. In another embodiment the concentration of the progestogenic compound below the saturation level at 25° C. in the core can be obtained by using polyethylene vinylacetate copolymer with a relatively high concentration of vinylacetate, that is, a copolymer containing in the range from 30 to 50 wt % vinylacetate copolymer. In a further embodiment the polyethylene vinylacetate copolymer in the core comprises in the range from 32 to 45 wt % vinylacetate. Use of such a polyethylene vinylacetate copolymer with a relatively high concentration of vinylacetate was found to result in decreased release of progestogenic compound from the core.

[0030] In one embodiment polyethylene vinylacetate copolymer has a wt % vinylacetate of 32 to 50% and in an even further embodiment has a wt % vinylacetate of 35 to 50%. The use of a polyethylene vinylacetate copolymer having such a high vinylacetate content for the core provides a system with an advantageous flexibility.

[0031] In another embodiment the skin is prepared from polyethylene vinylacetate copolymer comprising 1 to 15 wt

% vinylacetate, and in an even further embodiment from polyethylene vinylacetate copolymer comprising 5 to 15 wt % vinylacetate.

[0032] In an even further embodiment a polyethylene vinylacetate content in the range of 1 to 15 wt % can advantageously be used in a drug delivery system having a skin with a thickness in the range from 10 to 110 μ m. Such a skin thickness of less than about 110 μ m is advantageous to obtain a good flexibility of the overall pharmaceutical delivery device. Furthermore the use of such skin thickness and vinylacetate content results in an advantageous low burst release.

[0033] In another embodiment polyethylene vinylacetate copolymer has a vinylacetate content of 14 to 28 wt % for the skin. Such vinylacetate content can advantageously be used in a pharmaceutical delivery device having a skin thickness in the range from 70 to 250 μ m, for which it is especially easy to obtain a very good process consistency. A skin of polyethylene vinylacetate copolymer with a vinylacetate content of about 14 to 28 wt % is further advantageous, because it results in an advantageously low extent of aging of the material. Such aging can be chemical or physical. It is herein noticed that, without wishing to be bound to any kind of theory, aging can result in a gradual change in time of the release profile (properties) due to physical changes in the polymeric structure of the copolymer. The above embodiment thus results in an advantageously low extent of change of the release profile of the active ingredients after long-term storage.

[0034] The polyethylene vinylacetate copolymer can independently for core and skin be any commercially available polyethylene vinylacetate copolymer, such as for example the products available under the trade names: Elvax®, Evatane®, Lupolen V®, Movrion®, Ultrathene®, Ateva® and Vestypar® and further polyethylene vinylacetate copolymers marketed by for example Dupont (e.g. Dupont 760), Equistar (e.g. Equistar UE637-000), Huntsman (e.g. Huntsman PE1903) and Exxon Mobil (E100309). Suitable polyethylene vinylacetate copolymers for the core include the commercially available Ateva® 4030, Ateva® 3325, Evatane® 33-25 and Evatane® 40-55. Suitable polyethylene vinylacetate copolymers for the skin include the commercially available Ateva® 1070, Ateva® 1231 en Ateva® 1525, Evatane® 1020 VN3, Evatane® 1040 VN4 and Evatane® 1080 VN5.

[0035] The progestogenic compound of the subject invention can be any progestogen. In a further embodiment, the progestogenic compound is a steroidal progestogenic compound. Examples of suitable progestogenic compounds include compounds such as desogestrel, etonogestrel, levonorgestrel, norgestimate, gestodene, drospirenone or any other compound with progestogenic activity. In a particular embodiment the progestogenic compound is etonogestrel (3-keto desogestrel).

[0036] In a further embodiment, when the progestogenic compound is etonogestrel, such etonogestrel is present in the core in a concentration below the saturation level at 25° C. between 0.1 and 1.0 wt %, based on the weight of the core, and in an even further embodiment in a concentration between 0.3 and 0.8 wt %. In a particular embodiment such etonogestrel is present in the core in a concentration in the range of 0.4 to 0.7 wt %.

[0037] The estrogenic compound can be any estrogen. In a further embodiment, the estrogenic compound is a steroidal estrogenic compound. Examples of suitable estrogenic compounds include compounds such as estradiol, estriol, mestranol, estradiol-valerate and ethinyl estradiol. In a particular embodiment the estrogenic compound is ethinyl estradiol. In a further embodiment such ethinyl estradiol is present in the core in a concentration between 0.01 and 0.5 wt %, based on the weight of the core, and in an even further embodiment in a concentration between 0.05 and 0.2 wt %. In a particular embodiment such ethinyl estradiol is present in the core in a concentration in the range of 0.07 to 0.15 wt %.

[0038] In addition to the progestogenic compound and the estrogenic compound the drug delivery system can contain other drugs, e.g. anti-microbials. Such anti-microbials can be used for example to concomitantly treat and/or prevent sexually transmitted diseases (STD's) such as AIDS, chlamydia, herpes and gonorrhoea. The anti-microbial drug can be any anti-bacterial drug such as any antibiotic, any anti-viral agent, any anti-fungal agent or any anti-protozoal agent. An example of an anti-microbial drug contemplated to be incorporated into the vaginal ring of the subject invention is mandelic acid condensation polymer (Zanefeld et al. (2002), *Fertility and Sterility* 78(5): 1107-1115). Another example is dapivirine (4-[[4-[2,4,6-trimethylphenyl]amino-2-pyrimidinyl]amino]benzonitrile).

[0039] The improved drug delivery system according to the invention provides sufficient amounts and rates of release of the progestogenic compound for use in contraception and/or HRT. By these sufficient amounts and rates for release is understood that throughout the release period at each point in time a safe and sufficient effective amount of the progestogenic compound is released. In particular the release profile of the progestogenic compound may not be too steep. The mean release required is dependent on the use. In an even further embodiment for use in contraception the mean release may also not be too low. In one practical embodiment, when the progestogenic compound is etonogestrel, sufficient amounts and rates of release of etonogestrel for use in contraception are amounts and rates of release similar to those of Nuvaring®. In one embodiment the release of etonogestrel of such a drug delivery device on day 21 (R_{21}) is 80 $\mu\text{g/day}$ or more. In a further embodiment the mean release of etonogestrel of such a drug delivery device lies in the range from 96 to 144 $\mu\text{g/day}$. In a further embodiment, the release of etonogestrel in such a drug delivery device is reflected by releases at R_2 and/or R_{21} , wherein R_2 lies in the range from 122-181 $\mu\text{g/day}$; and/or R_{21} lies in the range from 82 to 121 $\mu\text{g/day}$. In an even further embodiment, the release of etonogestrel in such a drug delivery device is reflected by releases at R_2 and/or R_{21} , wherein R_2 lies in the range from 135-165 $\mu\text{g/day}$; and/or R_{21} lies in the range from 85 to 115 $\mu\text{g/day}$. In a still even further embodiment, the release of etonogestrel in such a drug delivery device is reflected by releases at R_2 and/or R_{21} , wherein R_2 lies in the range from 140-160 $\mu\text{g/day}$; and/or R_{21} lies in the range from 90 to 110 $\mu\text{g/day}$. In an even further embodiment, when the progestogenic compound is etonogestrel, R_2 is about 150 $\mu\text{g/day}$ and/or R_{21} is about 100 $\mu\text{g/day}$.

[0040] In one embodiment the drug delivery system according to the invention is a cylindrical fibre, consisting of

a cylindrical core and a skin covering this core. In a particular embodiment the cross sectional diameter of such a cylindrical fibre is between about 2.5 and 6 mm, in a specific embodiment between about 3.0 and 5.5 mm, and in another embodiment between about 3.5 and 4.5 mm and in yet another embodiment is 4.0 or 5.0 mm. In one embodiment, the surface of the core body is more than 800 mm^2 , and in another embodiment more than 1000 mm^2 and in a further embodiment in the order of 1700-2200 mm^2 . Significantly larger surfaces are possible, provided that the design (physical dimensions) of a drug delivery system intended for vaginal use prevents inconvenience for the subject.

[0041] The drug delivery system according to the invention can have several shapes, including but not limited to a spiral shape, a T-shape or a ring shape. In a specific embodiment the drug delivery system according to the invention is ring-shaped, i.e. is an annular drug delivery system. In one particular embodiment, the drug delivery system is a ring-shaped drug delivery system having an outer circumference of the ring of between 50 and 60 mm and in another embodiment between 52 and 56 mm.

[0042] The drug delivery system comprises at least one compartment having the characteristics as specified in the claims. In addition to this compartment one or more additional compartments can be present, making a total of for example two or three compartments. For example, an additional compartment can be added which is a placebo compartment or a compartment loaded with one or more other drugs. Such an extra compartment can be advantageous for example in practicing hormonal replacement therapy, where the ratio between progestogen and estrogen is different from the ratio suitable for contraception. Such an extra compartment can also be advantageous to administer, in addition to the progestogenic and estrogenic compounds, anti-microbial drugs to treat and/or prevent STD's such as AIDS, chlamydia, herpes and gonorrhoea, as suggested hereinabove.

[0043] In a specific embodiment, however, the drug delivery system consists of only one compartment, such compartment having the characteristics as specified in the claims.

[0044] In one specific embodiment the drug delivery system consisting of one or more compartments and comprising a progestogenic compound dissolved in a thermoplastic polyethylene vinylacetate copolymer whereby,

[0045] if the delivery system consists of one compartment, the compartment comprises

[0046] (i) a core of a thermoplastic polyethylene vinylacetate copolymer, said copolymer containing 30 to 50 wt % vinylacetate, and said core comprising a progestogenic compound, said progestogenic compound being dissolved in the polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., and an estrogenic compound; and

[0047] (ii) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, said copolymer containing 1 to 15 wt % vinylacetate, said skin being permeable for both compounds, and said skin having a thickness in the range of 10 to 110 μm ;

[0048] if the delivery system consists of more than one compartment, only one compartment comprises

[0049] (iii) the progestogenic compound, such progestogenic compound being dissolved in a core of a thermoplastic polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., said copolymer containing 30 to 50 wt % vinylacetate, and an estrogenic compound; and

[0050] (iv) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, said copolymer containing 1 to 15 wt % vinylacetate, said skin being permeable for both compounds, and said skin having a thickness in the range of 10 to 110 μm .

[0051] In a further embodiment the concentration of progestogenic compound in the core lies in the range of 0.3 to 0.8 wt %. In an even further embodiment said skin has a thickness in the range of 20 to 100 μm . In a still further embodiment said skin has a thickness in the range of 30 to 70 μm . In a still even further embodiment the copolymer of the skin contains 1 to 14 wt % vinylacetate. In an even further embodiment the copolymer of the skin contains 1 to 12 wt % vinylacetate. Such drug delivery system has the further advantage that an advantageous low burst release can be obtained.

[0052] In another specific embodiment of the invention the drug delivery system consisting of one or more compartments and comprising a progestogenic compound dissolved in a thermoplastic polyethylene vinylacetate copolymer whereby,

[0053] if the delivery system consists of one compartment, the compartment comprises

[0054] (i) a core of a thermoplastic polyethylene vinylacetate copolymer, said copolymer containing 30 to 50 wt % vinylacetate, and said core comprising a progestogenic compound, such progestogenic compound being dissolved in the polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., and an estrogenic compound; and

[0055] (ii) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, said copolymer containing 14 to 28 wt % vinylacetate, said skin being permeable for both compounds, and said skin having a thickness of 70 to 250 μm ;

[0056] if the delivery system consists of more than one compartment, only one compartment comprises

[0057] (iii) the progestogenic compound, such progestogenic compound being dissolved in a core of a thermoplastic polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., said copolymer containing 30 to 50 wt % vinylacetate, and an estrogenic compound; and

[0058] (iv) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, said copolymer containing 14 to 28 wt % vinylacetate, said skin being permeable for both compounds, and said skin having a thickness of 70 to 250 μm .

[0059] In a further embodiment the concentration of progestogenic compound in the core lies in the range of 0.3 to 0.8 wt %. In a still further embodiment the thickness of said skin is in the range from 75 to 250 μm , and in an even further embodiment the thickness of said skin is in the range

from 80 to 180 μm . In a still further embodiment the thickness of said skin is 100 to 250 μm . And in a further embodiment the thickness of said skin is 110 to 250 μm . In an even further embodiment the vinylacetate content of the thermoplastic skin lies in the range from 14 to 28 wt % vinylacetate. And in a still further embodiment the vinylacetate content of the skin is from 16 to 25 wt %.

[0060] Such drug delivery system shows an improved stability in that the release profile is less and in some cases not or nearly not influenced by the aging of the skin copolymer.

[0061] The drug delivery system of the subject invention can be manufactured by any known process of extrusion, such as co-extrusion and/or blend-extrusion. For example, the drug-loaded core and the non-medicated outer layer can be co-extruded. The fibres thus obtained can be cut into pieces of the required length and each piece can be assembled to, for example, a ring-shaped device in any suitable manner. In one embodiment the fibres are cut into pieces with a length in the range from 135 to 185 mm and in a further embodiment into pieces with a length in the range 155 to 159 mm, and in one further embodiment into pieces with a length of about 157 mm. Subsequently the pieces are assembled into a ring-shaped device. The assembly into a ring-shaped device can be carried out in any manner suitable for this purpose. For example the ends of the fibre can be joined together with an adhesive; or by placing the fibre in a mould at an elevated temperature (e.g. a temperature of above about 40° C.) and injecting molten high density polyethylene in between the fibre ends, whereafter the prepared ring is cooled; or by joining the fibre ends together by welding. In one embodiment a ring-shaped drug delivery system is prepared by welding the fibre ends together at a welding temperature of 130° C. and a welding time of 15 to 20 seconds, on a TWI mono-welding unit.

[0062] The present invention hence also provides a method of manufacturing a drug delivery system in the shape of a ring comprising the steps of:

[0063] (i) producing a medicated homogenous polyethylene vinylacetate copolymer core granulate, comprising a progestogenic and an estrogenic compound;

[0064] (ii) co-extruding the core granulate with a polyethylene vinylacetate copolymer skin granulate, resulting in a copolymer fibre comprising a core covered by a skin;

[0065] (iii) assembling the fibre into a ring.

[0066] As indicated above the loaded (medicated) homogenous polymer can be a suitable polyethylene vinylacetate copolymer loaded with a suitable progestogenic compound and a suitable estrogenic compound. The polymer for the skin can be another suitable polyethylene vinylacetate copolymer.

[0067] The thermoplastic polyethylene vinylacetate copolymer core granulate can be prepared by grounding the polyethylene vinylacetate copolymer for the core; dry powder mixing the grounded polymer for the core with the progestogenic and/or estrogenic compound to be loaded in the core; blend extruding the resulting powder mixture; and cutting the resulting loaded polymer strands into granules, thereby obtaining a core granulate. The core granulate can

be lubricated with a lubricant. Suitable lubricants include for example irgawax, talc, aerosil and stearates such as magnesium stearate.

[0068] The prepared rings can for example be packed in a suitable sachet, such as described in e.g. EP-A-1037812, optionally after being sterilized or disinfected.

[0069] The drug delivery system according to the invention is especially suitable for use in the field of female contraception and hormone replacement therapy. The drug delivery system can advantageously be used for the simultaneous controlled release of a progestogenic compound and estrogenic compound. The drug delivery system may—as already indicated above—also be used to concomitantly provide contraception and combat microbial disease. The microbial infection to be treated and/or prevented can be any bacterial, viral, fungal or protozoal infection. Specifically, sexually transmitted diseases such as HIV, chlamydia, gonorrhoea, or herpes may be treated by incorporation of an anti-microbial agent into the ring of the subject invention.

[0070] The invention further provides a method of contraception which comprises the steps of a) positioning a drug delivery system of the subject invention within the female vaginal tract and b) retaining the system within the vaginal tract for at least approximately 21 days. In addition the invention provides a method of concomitantly providing contraception whilst simultaneously treating or preventing a sexually transmitted disease which comprises the steps of positioning a drug delivery system of the subject invention within the female vaginal tract and retaining the system within the vaginal tract for at least approximately 21 days.

[0071] In one embodiment, the drug delivery system is removed after about 21 days for an approximate one week period to permit menstruation. In other embodiments, the drug delivery system is removed after about 42, 63, 84, 105, 126, 147, 186, 189, 210, 231, 252, 273, 294, 315, 336 or 357 days or after each month for an approximate one week period to permit menstruation. After the approximate week to allow for menstruation, a new drug delivery system of the subject invention is inserted into the female vagina to provide contraception in the next female cycle or cycles.

[0072] In another embodiment, the drug delivery system is removed after about 21 days and a subsequent drug delivery system is inserted directly after the previous drug delivery system has been removed, i.e. without an approximate one week period to permit menstruation. In other embodiments, the drug delivery system is removed after about 42, 63, 84, 105, 126, 147, 186, 189, 210, 231, 252, 273, 294, 315, 336 or 357 days or after each month.

[0073] In a further embodiment this invention provides the use of the drug delivery system described above for the manufacture of a contraceptive kit or kit for hormone-replacement therapy.

[0074] In a still further embodiment this invention provides the use of the drug delivery system described above for the manufacture of a combination preparation to provide contraception whilst simultaneously to treat and/or prevent a sexually transmitted disease.

[0075] The invention is further illustrated by the following non-limiting examples.

Preparation of the Examples

[0076] Examples of ring-shaped drug delivery systems, comprising the polyethylene vinylacetate copolymer mate-

rials for skin and core, the dimensions and the concentrations of active ingredients as indicated in Table I, were prepared as follows:

[0077] Etonogestrel (a progestogenic compound) and ethinyl estradiol (an estrogenic compound) were mixed homogeneously through the copolymer used for the core.

[0078] The mixing of the core material of examples 1-10 was performed by dry powder mixing the micronized compounds and copolymer powder in a stainless steel drum using a Rhönrad (Barrel-hoop principle) with a fixed rotation speed of approximately 46 rpm for 15 minutes.

[0079] The mixing of the core material of examples 12-14 was performed by dry powder mixing the micronized compounds and copolymer powder in a stainless steel drum using a Rhönrad (Barrel-hoop principle) with a fixed rotation speed of approximately 26 rpm for 60 minutes.

[0080] For preparing the core material of example 11, the micronized compounds were mixed with copolymeric granulate instead of powder. Mixing was carried out in a stainless steel drum using a Rhönrad (Barrel-hoop principle) with a fixed rotation speed of approximately 26 rpm for 60 minutes.

[0081] Subsequently the homogenized mixture was blend extruded using a 25 mm co-rotating double screw blend extruder and the resulting medicated polymer strands were cut into granules using an Scheer granulator. According to this process a drug-loaded core granulate was manufactured.

[0082] After granulation the drug-loaded core granulate for examples 11-14 was sieved. The drug-loaded core granulate for all examples was lubricated with magnesium stearate in order to facilitate the next processing step (co-extrusion). In examples 1-10 the drug loaded core granulate was co-extruded with the copolymer used for the skin in a Plastic Maschinenbau co-extruder. In examples 11-14 the drug loaded core granulate was co-extruded with the copolymer used for the skin in a Fourné 35-22 co-extruder. The skin and core materials were combined in a self-centering spinning block from which two co-extruded fibres were produced. For each fibre, 2 separate spinning pumps (to control the volume flow rate (melt flow) of each layer) were applied. The capillaries applied had a diameter of 3.6 mm and all fibres were extruded at an extrusion temperature of 110° C.

[0083] The drug loaded fibers of examples 1-10 were processed at an extrusion speed of 1 m/min; the drug loaded fibres of examples 12-14 were processed at an extrusion speed of 6.7 m/min; and the drug loaded fiber of example 11 was processed at an extrusion speed of 2.0 m/min

[0084] Upon leaving the spinnerette, the skin-core fibre was led through air and subsequently through a water bath (10-20° C.) by means of a take-off unit. The outer diameter of the fibre was measured on-line continuously using a laser micrometer. Hereafter the fibres were cut into pieces of about 157 mm. For examples 1-10 the ends of the fibre pieces were subsequently glued together with Loctite® acrylate glue. The ends of the fibre pieces for examples 11-14 were welded together at 130° C. for 17 seconds to form a ring. The characteristics of the materials that were used for skin and core of each example have been taken up in Table II.

[0085] Determination of Saturation Level

[0086] To determine the saturation level of etonogestrel of the polyethylene vinylacetate copolymers used, films of about 200 nm were prepared by film extrusion. The films were cut in pieces of 5×5 cm and subsequently immersed in saturated aqueous solutions of etonogestrel at 25° C. After 6 weeks of incubation, equilibrium was reached and the films were analyzed for the content of etonogestrel. The pieces were extracted with methanol for 20 hours at a temperature of 70° C. and subsequently the concentration of etonogestrel was assessed by HPLC, using a Novapak C18 column of 3.9×150 mm at column temperature of 30° C., a mobile phase of methanol/water/THF (46/48/6 v/v%), a flow rate of 1.5 ml/min, and an injection volume of 40 µl. Detection was carried out by UV detection at 210 nm.

[0087] Fibre Dimension

[0088] The fibre dimensions (outer diameter and skin thickness) were determined directly after processing. The outer diameter was determined by means of laser thickness gauge (Mitutoyo). The skin thickness was determined using a microscope (Jena).

[0089] Vinylacetate Content of the Copolymer

[0090] The vinylacetate content for the copolymers used in the examples 2-14 as specified in II, IV, V and VI was determined by 1H NMR in a DRX600 NMR spectrometer (Bruker Spectrospin, Switzerland). For the NMR method 15-20 mg of slices of about 3-5 mg originating from different parts of the sample were mixed with 0.7 ml of tetrachloroethane-d₂. Subsequently the NMR tube was heated in an oil bath during 15-18 hours at 100° C. Hereafter a proton spectrum was acquired at 90-100° C. with 128 scans and a D1 of 5 seconds to assure complete relaxation. The spectrum was processed by applying an exponential multiplication of 0.3 Hz followed by Fourier transformation. The spectrum was integrated and the integral of the CHO(C=O)CH₃ group was set at 1. The vinylacetate content was calculated with formula I:

$$vinylacetate(\%) = \frac{y \cdot M_{VA}}{[(x - 2 \cdot y) / 4] \cdot M_{CH_2-CH_2} + y \cdot M_{VA}} \cdot 100 \quad (I)$$

wherein:

[0091] x=integral CH₂

[0092] y=integral CHO(C=O)CH₃

[0093] M_{VA}=molecular weight VA (86)

[0094] M_{CH₂-CH₂}=molecular weight MCH₂-CH₂ (28)

[0095] With y set at 1 (see above) the formula is reduced to formula II:

$$vinylacetate(\%) = \frac{86}{(x - 2) \cdot 7 + 86} \cdot 100 \quad (II)$$

[0096] The measurement was performed in duplicate using two different samples. The vinylacetate content was calculated from the obtained spectrum.

[0097] In-Vitro Release Rate

[0098] The in-vitro release rate of etonogestrel for examples 1-14 was determined by immersing the samples in 200 ml water of 37° C. under continuous stirring at 750 rpm. In order to maintain sink conditions the water in the containers was refreshed daily by an auto-sampler. The etonogestrel concentration was determined daily by HPLC, using a Novapak C18 column of 3.9×150 mm at column temperature of 30° C., a mobile phase of acetonitril:water (30/70 v/v%), a flow rate of 1.5 ml/min, and an injection volume of 10 µl. Detection was carried out by UV detection at 205 nm. (see also the article of J. A. H. van Laarhoven et al., International Journal of Pharmaceutics 232 (2002) pages 163-173).

Stability

[0099] The dimensions and the concentrations of active ingredients of the examples are summarized in Table I and the characteristics of the material used is summarized in Table II. An overview of the release profiles of etonogestrel for examples 1-14 and for the commercially available Nuvaring®, which is a product according to EP-A-0876815, are depicted in FIG. 1.

[0100] Because of the concentration above the saturation level at 25° C., etonogestrel in the samples of Nuvaring® and comparative example 1 may eventually crystallize out onto the skin of the device, which is undesirable.

[0101] As illustrated by Table III and FIG. 1, examples 2-14 show that with drug delivery systems according to the invention, which have a concentration below saturation level at 25° C., a similar and sufficient release profile of etonogestrel for use in contraception and/or HRT is still obtained.

TABLE I

Description of the materials, concentrations and variables used in examples 1-14.						
Example	Core material	Skin material	Fibre diameter (cm)	Skin thickness (cm)	Etonogestrel (wt %)	Ethinyl estradiol (wt %)
Nuvaring®	Evatane® 28-25	Evatane® 1020	0.4	0.011	0.69	0.16
Comparative 1	Evatane® 33-25	Evatane® 1020	0.4	0.0083	0.69	0.13
2	Evatane® 33-25	Evatane® 1020	0.4	0.0042	0.4	0.075

TABLE I-continued

Description of the materials, concentrations and variables used in examples 1-14.						
Example	Core material	Skin material	Fibre diameter (cm)	Skin thickness (cm)	Etonogestrel (wt %)	Ethinyl estradiol (wt %)
3	Evatane® 33-25	Evatane® 1020	0.5	0.0061	0.4	0.075
4	Evatane® 33-25	Evatane® 1040	0.4	0.0091	0.4	0.075
5	Evatane® 33-25	Evatane® 1080	0.4	0.0134	0.4	0.075
6	Evatane® 40-55	Evatane® 1020	0.4	0.0059	0.69	0.13
7	Evatane® 40-55	Evatane® 1020	0.4	0.0047	0.6	0.11
8	Evatane® 40-55	Evatane® 1020	0.5	0.0057	0.6	0.11
9	Evatane® 40-55	Evatane® 1040	0.4	0.0099	0.6	0.11
10	Evatane® 40-55	Evatane® 1080	0.4	0.0152	0.6	0.11
11	Ateva® 4030	Ateva® 1525	0.4	0.0084	0.6	0.10
12	Ateva® 3325	Ateva® 1070	0.4	0.0035	0.4	0.075
13	Ateva® 3325	Ateva® 1231	0.4	0.0065	0.4	0.075
14	Ateva® 3325	Ateva® 1525	0.4	0.0099	0.4	0.075

[0102]

TABLE II

Description of the characteristics of the materials used in examples 1-14.			
Material	Vinylacetate ¹⁾ (wt %)	Saturation level of etonogestrel at 25° C. (wt %)	Saturation level of etonogestrel at 37° C. (wt %)
Evatane® 28-25	±28	0.35	0.44
Evatane® 33-25	±33	0.50	0.67
Evatane® 40-55	±40	0.75	1.12
Evatane® 1020	±9	0.046	0.055
Evatane® 1040	±14	0.10	0.161
Evatane® 1080	±18	0.16*	0.21*
Ateva® 1070	±9	0.045*	0.066*
Ateva® 1231	±12	0.078*	0.107*
Ateva® 1525	±15	0.12*	0.155*

TABLE II-continued

Description of the characteristics of the materials used in examples 1-14.			
Material	Vinylacetate ¹⁾ (wt %)	Saturation level of etonogestrel at 25° C. (wt %)	Saturation level of etonogestrel at 37° C. (wt %)
Ateva® 4030	±40	0.75*	1.126*
Ateva® 3325	±33	0.50*	0.701*

¹⁾Vinylacetate content taken from product specification of the supplier
*these saturation levels were obtained by interpolation from curve fit of the vinylacetate content of the material versus saturation level as shown in FIG. 2.

[0103]

TABLE III

Release rates for examples 1-14					
Example	Concentration above/below saturation level	Vinylacetate content of the core (wt %)	Vinylacetate content of the skin (wt %)	R2 (µg/day)	R21 (µg/day)
Nonvarying Comparative	Above	28 ¹⁾	9 ¹⁾	151.0	99.3
Comparative 1	Above	34	10	154.5	102.6
2	Below	34	10	143.7	81.3
3	Below	34	10	124.0	82.8
4	Below	34	15	165.2	86.9

TABLE III-continued

Release rates for examples 1-14					
Example	Concentration above/below saturation level	Vinylacetate content of the core (wt %)	Vinylacetate content of the skin (wt %)	R2 (µg/day)	R21 (µg/day)
5	Below	34	20	207.3	91.9
6	Below	40	10	102.9	70.5
7	Below	40	10	119.9	80.1
8	Below	40	10	117.9	86.1
9	Below	40	15	146.4	90.8
10	Below	40	20	184.4	101.1
11	Below	42	15	188.1	113
12	Below	32	9	175.3	90
13	Below	32	11	147.0	82
14	Below	32	15	187.5	92

R2 and R21 represent the release rates on day 2 and day 21 respectively.
¹Vinylacetate content for this sample was based on product specification of the supplier

Burst Release

[0104] The extent of burst release is indicated by the burst release factor. The burst release factor was determined at t=0 with formula III:

$$\left(\frac{R_1 - R_2}{R_1}\right) \cdot 100$$

(III)

wherein

[0105] R₁ is release of the sample on day 1

[0106] R₂ is release of the sample on day 2.

[0107] The burst release factor of examples 1-14 was determined at t=0. The results are shown in Table IV.

[0108] To exclude influence of the material of the core, only examples with a similar etonogestrel and vinylacetate content in the core were compared. As illustrated in table IV, a drug delivery system with a relatively thin polyethylene vinylacetate copolymer skin having a relatively low vinylacetate content results in an advantageously low burst release.

Flexibility

[0109] Furthermore the flexibility of examples 1-14 was determined and compared with the flexibility of Nuvaring®. The flexibility was determined by means of a press-pull apparatus (LR 5K, Lloyd Instruments). The entire ring-shaped drug delivery system in a relaxed state was fixed in two V-shaped holders. The distance between the corners of the V-shaped profiles is 54 mm. Subsequently the holders were pressed towards each other with a predetermined speed

TABLE IV

Results on the burst release at t = 0 of examples 1-14					
Example	Etonogestrel (wt %)	Vinylacetate content of the core (wt %)	Vinylacetate content of the skin (wt %)	Skin thickness (cm)	Burst release factor at t = 0 ⁽¹⁾ (%)
Nuvaring	0.69	28 ⁽²⁾	9 ⁽²⁾	0.011	33.5
Comparative	0.69	34	10	0.0083	18.6
1	0.4	34	10	0.0042	13.9
3	0.4	34	10	0.0061	15.0
4	0.4	34	15	0.0091	21.7
5	0.4	34	20	0.0134	25.3
6	0.69	40	10	0.0059	12.3
7	0.6	40	10	0.0047	11.7
8	0.6	40	10	0.0057	12.7
9	0.6	40	15	0.0099	19.4
10	0.6	40	20	0.0152	24.0
11	0.6	42	15	0.0084	16.1
12	0.4	32	9	0.0036	16.1
13	0.4	32	11	0.0065	17.1
14	0.4	32	15	0.0099	22.9

⁽¹⁾The burst release factor of Nuvaring, samples 1-10 and samples 11-14 was based on the mean burst release factor of respectively 4, 3 and 6 samples.
⁽²⁾Vinylacetate content for this sample was based on product specification of the supplier

of 50 mm/min until the distance between the corners of the V-shaped profiles was 21 mm. The force in Newton that was applied to the ring-shaped drug delivery system to bring about a certain deformation of the ring was measured at predetermined spots. That is, it was measured when the deformation comprised 10 mm (i.e. at a distance of 44 mm), 20 mm (i.e. at a distance of 34 mm), 30 mm (i.e. at a distance of 24 mm) and 33 mm (i.e. at a distance of 21 mm). The results are summarized in Table V.

The extent of aging of the copolymer is indicated by the Aging factor. The Aging factor was determined with formula IV:

$$\text{Aging} = \left(1 - \frac{R_{2,\text{after storage}}}{R_{2,t=0}} \right) \times 100\%$$

(IV)

TABLE V								
Flexibility tests for examples 1-14								
Exmpls	Vinylacetate content of the core (wt %)	Vinylacetate content of the skin (wt %)	Fibre diameter (cm)	Skin thickness (cm)	Force at 10 mm(N)	Force at 20 mm(N)	Force at 30 mm(N)	Force at 33 mm(N)
Nuvaring 28 ²⁾		9 ²⁾	0.4	0.011	1.10	2.00	4.00	5.10
1	32	10	0.4	0.0083	0.78	1.37	2.90	3.82
2	34	10	0.4	0.0042	0.61	1.13	2.43	3.25
3*	34	10	0.5	0.0061	1.34	2.56	5.79	7.56
4	34	15	0.4	0.009	0.71	1.28	2.71	3.60
5	34	20	0.4	0.0134	0.72	1.30	2.82	3.73
6	40	10	0.4	0.0059	0.43	0.73	1.42	1.84
7	40	10	0.4	0.0047	0.40	0.69	1.35	1.75
8*	40	10	0.5	0.0057	0.77	1.37	2.81	3.76
9	40	15	0.4	0.0059	0.54	0.96	1.78	2.20
10	40	20	0.4	0.0152	0.56	1.05	2.14	2.78
11	42	15	0.4	0.0084	0.32	0.55	1.07	1.37
12	32	9	0.4	0.0036	0.54	1.02	2.34	3.17
13	32	11	0.4	0.0065	0.69	1.27	2.82	3.74
14	32	15	0.4	0.0059	0.67	1.24	2.78	3.73

*Examples 3 and 8 show a relatively low flexibility due to the fact that the cross-sectional diameter of these fibres is 0.5 cm.
For the fibres having the same cross-sectional diameter of 0.4 cm it can be concluded that the ring-shaped drug delivery systems comprising a core with a higher vinylacetate content show a much higher flexibility when compared to Nuvaring®.
²⁾Vinylacetate content for this sample was based on product specification of the supplier.

Ring Shaped Drug Delivery Systems Comprising a Skin Prepared from Polypolyethylene Vinylacetate Copolymer with a High Vinylacetate Content

[0110] During storage, the polyethylene vinylacetate copolymer ages. During this aging process crystalline and amorph domains in the polyethylene vinylacetate copolymer rearrange. As a result of the aging of the copolymer, the release of active ingredients, here etonogestrel, can change.

wherein

[0111] $R_{2,t=0}$ = Release on day 2 at t=0

[0112] $R_{2,\text{after storage}}$ = Release on day 2 after the indicated storage time

[0113] The aging behaviour for examples 1-10 and 11-14 has been tested under real-time conditions (i.e. storage for 8 months at 20 ° C. respectively 3 months at 25° C.) and under accelerated conditions (i.e. storage for 5 months respectively 3 months at 40° C.). After storage the release of etonogestrel on day 2 was determined and the aging factor calculated. The results are given in Table VI.

TABLE VI							
Aging for examples 1-10 after 5 months storage at 40° C.							
Example	Etonogestrel (wt %)	Vinylacetate content of the core (wt %)	Vinylacetate content of the skin (wt %)	Skin thickness (cm)	$R_{2,t=0}$ (µg/day sample)	$R_{2, 1-5 \text{ mod}}$ (µg/day sample)	Aging factor (%)
1	0.69	34	10	0.0083	154.5	140.8	8.8
2	0.4	34	10	0.0042	140.7	130.4	7.5
3	0.4	34	10	0.0061	124.0	117.4	5.3
4	0.4	34	15	0.0091	155.2	159.2	3.7
5	0.4	34	20	0.0134	207.3	207.6	0
6	0.69	40	10	0.0059	102.9	91.5	11.3
7	0.6	40	10	0.0047	119.9	108.8	9.2
8	0.6	40	10	0.0057	117.9	105.6	10.5

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TABLE VI-continued

Aging for examples 1-10 after 5 months storage at 40° C.							
Example	Etonogestrel (wt %)	Vinylacetate content of the core (wt %)	Vinylacetate content of the skin (wt %)	Skin thickness (cm)	R _{2, 1-3} (µg/day/ sample)	R _{2, 1-5 months} (µg/day/ sample)	Aging factor (%)
9	0.5	40	15	0.0099	146.4	136.3	6.9
10	0.5	40	20	0.0152	184.4	183.3	0.6

[0114] To exclude influence of the material of the core, only examples with a similar etonogestrel and vinylacetate content in the core are to be compared. The results in Table VI illustrate that after 5 months storage at 40° C., drug delivery systems with a relatively thick polyethylene vinylacetate copolymer skin having a relatively high vinylacetate content show less aging.

1. A drug delivery system consisting of one or more compartments and comprising a progestogenic compound dissolved in a thermoplastic polyethylene vinylacetate copolymer whereby,

if the delivery system consists of one compartment, the compartment comprises

- (i) a core of a thermoplastic polyethylene vinylacetate copolymer comprising the progestogenic compound, the progestogenic compound being dissolved in the polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., and an estrogenic compound; and
- (ii) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, the skin being permeable for both compounds;

if the delivery system consists of more than one compartment, only one compartment comprises

- (iii) the progestogenic compound, such the progestogenic compound being dissolved in a core of a thermoplastic polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., and an estrogenic compound; and
- (iv) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, and the skin being permeable for both compounds.

2. A drug delivery system according to claim 1, wherein the progestogenic compound is a steroidal progestogenic compound and/or the estrogenic compound is a steroidal estrogenic compound.

3. A drug delivery system according to claim 1, wherein the polyethylene vinylacetate copolymer of the core is a copolymer containing 30 to 50 wt % vinylacetate.

4. A drug delivery system consisting of one or more compartments and comprising a progestogenic compound dissolved in a thermoplastic polyethylene vinylacetate copolymer whereby,

if the delivery system consists of one compartment, the compartment comprises

- (i) a core of a thermoplastic polyethylene vinylacetate copolymer, the copolymer containing 30 to 50 wt %

vinylacetate, and the core comprising a progestogenic compound, the progestogenic compound being dissolved in the polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., and an estrogenic compound; and

- (ii) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, the copolymer containing 1 to 15 wt % vinylacetate, the skin being permeable for both compounds, and the skin having a thickness in the range of 10 to 110 µm;

if the delivery system consists of more than one compartment, only one compartment comprises

- (iii) the progestogenic compound, the progestogenic compound being dissolved in a core of a thermoplastic polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., the copolymer containing 30 to 50 wt % vinylacetate, and an estrogenic compound; and
- (iv) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, the copolymer containing 1 to 15 wt % vinylacetate, the skin being permeable for both compounds, and the skin having a thickness in the range of 10 to 110 µm.

5. A drug delivery system consisting of one or more compartments and comprising a progestogenic compound dissolved in a thermoplastic polyethylene vinylacetate copolymer whereby,

if the delivery system consists of one compartment, the compartment comprises

- (i) a core of a thermoplastic polyethylene vinylacetate copolymer, the copolymer containing 30 to 50 wt % vinylacetate, and the core comprising a progestogenic compound, the progestogenic compound being dissolved in the polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C., and an estrogenic compound; and
- (ii) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, the copolymer containing 14 to 28 wt % vinylacetate, the skin being permeable for both compounds, and the skin having a thickness of 70 to 250 µm;

if the delivery system consists of more than one compartment, only one compartment comprises

- (iii) the progestogenic compound, the progestogenic compound being dissolved in a core of a thermoplastic polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C.,

the copolymer containing 30 to 50 wt % vinylacetate, and an estrogenic compound; and

(iv) a skin of a thermoplastic polyethylene vinylacetate copolymer covering the core, said the copolymer containing 14 to 28 wt % vinylacetate, the skin being permeable for both compounds, and the skin having a thickness of 70 to 250 μm .

6. A drug delivery system according to claim 1, wherein the progestogenic compound is etonogestrel.

7. A drug delivery system according to claim 6 wherein the release on day 21 of etonogestrel of the drug delivery system is 80 $\mu\text{g/day}$ or more.

8. A drug delivery system according to claim 1, wherein the estrogenic compound is ethinyl estradiol.

9. A drug delivery system according to claim 1, wherein the system is ring-shaped.

10. A drug delivery system according to claim 1, wherein the drug delivery system consists of one compartment.

11. A drug delivery system according to claim 1, wherein the drug delivery system is a drug delivery system for intravaginal use.

12. A drug delivery system according to claim 1, wherein the drug delivery system does not need special storage and transportation conditions at a temperature below room temperature.

13. A method of manufacturing a drug delivery system according to claim 9 comprising the steps of:

(i) producing a medicated homogenous polyethylene vinylacetate copolymer core granulate, comprising a progestogenic and an estrogenic compound;

(ii) co-extruding the core granulate with a polyethylene vinylacetate copolymer skin granulate, resulting in a copolymer fiber comprising a core covered by a skin;

(iii) assembling the fibre into a ring.

14. A method according to claim 13, wherein the core granulate in step (i) is lubricated with a lubricant.

15. A contraceptive kit or kit for hormone-replacement therapy comprising the drug delivery system according to claim 1.

16. A combination preparation to provide contraception whilst simultaneously to treat and/or prevent a sexually transmitted disease comprising the drug delivery system according to claim 1.

* * * * *