



No. 06-110229- -00002-0000

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Act. 400 OPOS/OBSERVTER Folios: 58

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

Numero del expediente: 06-110229

Solicitante: SCHERING AKTIENGESSELLSCHAFT

**SOLICITUD
PUBLICADA**

Apoderado: J. IAN RAISBECK

Título de la nueva creación o denominación del signo: "PREPARACIÓN
FARMACÉUTICA PARA APLICAR SOBRE LA PIEL QUE CONTIENE DROSPIRENONA."

Gaceta: 579

③ **OPOSICION PRESENTADA POR:**

SOLICITANTE	Nombre: <u>PROCAPS S.A</u>	IDENTIFICACION	
	Dirección: <u>CALLE 80 No. 78B -201</u>	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: <u>COLOMBIA</u>	C.E. ☐	Otro ☐
	Lugar de Constitución: <u>BARRANQUILLA</u>	Cual <u> </u>	
	Teléfono: <u>(571)3719900</u> Fax: <u>(571)3730818</u>	Número <u>890.106.527-5</u>	
	E-mail: <u> </u>		
REPRESENTANTE O APODERADO	Nombre: <u>LAURA CATALINA SILVA BARRERA</u>	IDENTIFICACION	
	Dirección: <u>CARRERA 13 No. 119-95 OF: 104</u>	C.C. ☐	NIT ☒
	Teléfono: <u>(571) 2131213</u> Fax: <u>(571) 6121979</u>	C.E. ☐	Otro ☐
	E-mail: <u>negocios@optimum-co.com</u>	Cual <u> </u>	
		Número <u>52.455.803</u> TP <u>147399</u>	

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

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

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. _____

Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: LAURA CATALINA SILVA BARRERA

FIRMA: Laura Catalina Silva B.

C.C. 52.455.803

TP. 147399

3
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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 06-110229

Asunto : Oposición a la solicitud de patente de Invención titulada
"PREPARACIÓN FARMACÉUTICA PARA APLICAR
SOBRE LA PIEL QUE CONTIENE DROSPIRENONA"

Solicitante : SCHERING AKTIENGESELLSCHAFT.

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 579 del 31 de agosto de 2007

Yo, **LAURA CATALINA SILVA BARRERA**, abogada con tarjeta profesional N° 147399 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 "**FORMA DE DOSIS FARMACEUTICA SÓLIDA**", cuyo titular es **ABBOTT LABORATORIES**, 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 y etinilestradiol. 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 30 de octubre de 2006, reivindicando prioridad bajo la solicitud DE200410016779 del 1 de abril de 2004, y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 579 del 31 de agosto de 2007 página 546 y N° publicación 300, cuya publicación internacional corresponde a la WO2005/097196 del 2005-10-20.

2.2. la solicitud colombiana 06-110229 objeto de la presente oposición, se refiere a una preparación farmacéutica para aplicar sobre la piel que contiene drospirenona caracterizada porque la cantidad de drospirenona contenida en la preparación en su estado inicial no es superior a la de solubilidad saturada y después de ser aplicada sobre la piel, la solubilidad saturada de la drospirenona es superada por desprendimiento de componentes activadores de la disolución, donde la solubilidad saturada de la drospirenona de la preparación es superada durante su

aplicación en al menos un factor 5, preferentemente al menos en un factor 10, donde la solubilidad saturada de la drospirenona de la preparación durante la aplicación es superada, al cabo de 1 hora, en al menos el factor 2, preferentemente en al menos el factor 5, donde presenta un contenido de etanol o isopropanol, y donde contiene un aditivo inhibidor de la cristalización referido a la drospirenona.

- 2.3. En primera instancia, se debe advertir que las reivindicaciones definen una preparación farmacéutica caracterizadas por su uso o método de aplicación. Según el preámbulo, estas se refieren a una preparación farmacéutica, pero al caracterizar la misma, estas definen como una cantidad de medicamento administrado, después de ser aplicado sobre la piel, como la sustancia comienza a actuar en el organismo. Como tal, esto es una característica de su uso y a todas luces se refiere es a un método de tratamiento, dado que se refiere a la forma en la que el cuerpo la absorbe y no a las características del medicamento como tal, aquello que incluye o lo conforma de manera que se considere novedoso para ser objeto de patente.
- 2.4. Por lo tanto, estas se refieren es a un método de tratamiento y no a la composición farmacológica caracterizado por sustancias o compuestos en combinación o a un método de fabricación que mediante pasos o etapas se obtiene un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...) "*, los usos no están contemplados como patentables; y, Artículo 20.- *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, la presente no sería patentable.
- 2.5. Ahora bien, en materia del activo, es importante recordar que esta solicitud de patente esta incurso en los impedimentos que consagra el artículo 21 de la Decisión 486 de la CAN, el cual indica: *"los productos o procedimientos ya patentados,*

comprendidos en el estado de la técnica de conformidad con el artículo 16 de la presente decisión, no serán objeto de nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial". Esto significa que en Colombia a la fecha no se conceden patente para los segundos usos. La drospirirona como tal es una sustancia activa que fue patentada en 1978 (ver D1) y cuya primera indicación fue como antiandrógeno, lo mismo puede decirse de los estrógenos sintéticos empleados lógicamente como hormonas femeninas.

2.6. Este mismo artículo 14 se refiere a 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 novedad y el nivel inventivo de la presente solicitud:

- D1: US4129564, Publicada el 12 de diciembre de 1978.
- D2: WO 9507081 publicada el 16 de marzo de 1995.
- D3: US5352457 publicada el 4 de octubre de 1994.
- D4: EP0267051 publicada el 11 de mayo de 1988.

2.7. El arte previo a la solicitud Colombiana se remonta hacia 1978 en el documento D1, donde se revela un procedimiento para la preparación, así como la descripción del gestageno de drospirenona (DRSP) (Véase Reivindicaciones del D1). Por lo tanto, tratar de proteger la una preparación farmacéutica cuyo activo es la drospirenona no es novedoso.

2.8. Ahora bien, desde el punto de vista de aplicación sobre la piel, el documento anterior D2 se refiere al empleo de estrógeno tal como el estradiol y drospirirona en cantidades que van desde 0,2 hasta 3,0 mg/día en la preparación de un medicamento para tratar padecimientos, desordenes y síntomas asociados con

niveles endógenos insuficientes de estrógeno, donde particularmente en la página 4, líneas 17 a 18, se afirma que su preparación también puede comprender presentaciones transdérmicas entre otras tales como la oral, parenteral o en forma de un dispositivo implantable. Por lo tanto el objeto que se revela en la presente solicitud como es una composición farmacéutica de aplicación transdérmica, que tiene como agente activo la drospirirona en una cantidad suficiente, NO es nueva frente al documento D1.

2.9. Ahora bien, la entrega transdérmica de un ingrediente activo es ampliamente conocida en el medio. De hecho el documento D3, particularmente en la descripción, revela un método de preparar una forma farmacéutica para la entrega transdérmica de un ingrediente activo que es sólido en la temperatura ambiente y en el cual la parte o todo el ingrediente activo están presentes en una solución saturada o supersaturada. Particularmente a partir de la columna 2, línea 28, este documento D3, revela como el ingrediente activo puede ser absorbido por la piel a partir de una dispersión del compuesto sólido, donde el grado de respuesta puede ser controlado si el agente está en una solución supersaturada, en particular donde el solvente tiene una capacidad adecuada para el ingrediente activo. De igual forma, el documento D4, revela un método, la composición, y el empleo en la administración transdérmica particularmente el uso en la piel para la administración sistémica de una composición. Particularmente, esta anterioridad D4, revela a partir de la página 2, línea 62, que los solventes que pueden ser usados en la anterioridad son solventes orgánicos no polares permanentes, en particular aquellos teniendo el dieléctrico constante de menos de 4 y un punto de ebullición por encima de 150 C°. De hecho las cláusulas de este documento D4, revela que la composición está adaptada para el contacto con la piel humana para proporcionar una administración sistémica. Así las cosas, a partir de estos documentos D3 y D4, combinados con lo revelado en los documentos D1 y D2, cualquier persona

versada en la materia puede llegar a deducir una preparación farmacéutica para aplicar sobre la piel que contiene drospirenona caracterizada porque la cantidad de drospirenona contenida en la preparación en su estado inicial no es superior a la de solubilidad saturada.

2.10. Por lo tanto, este documento objeto de oposición a la luz del documento D1 y D2 carece evidentemente de NOVEDAD y a partir de estos documentos D3 y D4, combinados con lo revelado en los documentos D1 y D2, carece de ALTURA INVENTIVA.

2.11. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 06-110229 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los tres requisitos necesarios para su protección.

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

2.12.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”*. A la fecha de prioridad, 1 de abril de 2004 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1 y D2, una composición farmacéutica que tiene como agente activo la drospirirona y de aplicación transdérmica, sobre el cual busca protección en el capítulo reivindicatorio.

2.12.2. 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, 1 de abril de 2004, a partir de los documentos D3 y D4, combinados con lo revelado en los documentos D1 y D2, es posible deducir una composición farmacéutica de aplicación transdérmica que tiene como agente activo la drospirirona sobre el cual busca protección en el capítulo reivindicatorio.

2.12.3. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.13. 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 los tres requisitos de patentabilidad.

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2.14. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMA DE DOSIS FARMACÉUTICA SÓLIDA"**, cuyo titular es **ABBOTT LABORATORIES**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 579.

3. PRUEBAS

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

- D1: US4129564, Publicada el 12 de diciembre de 1978.
- D2: WO 9507081 publicada el 16 de marzo de 1995.
- D3: US5352457 publicada el 4 de octubre de 1994.
- D4: EP0267051 publicada el 11 de mayo de 1988.

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: US4129564, Publicada el 12 de diciembre de 1978.
- D2: WO 9507081 publicada el 16 de marzo de 1995.
- D3: US5352457 publicada el 4 de octubre de 1994.
- D4: EP0267051 publicada el 11 de mayo de 1988.

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6. NOTIFICACIONES

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

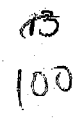
Señor Superintendente,

Laura Catalina Silva Barrera

LAURA CATALINA SILVA BARRERA

C.C. 52'455.803 de Bogotá

T.P.A. 147399 del C.S. de la J.



PODER ESPECIAL

CALLE 80 No. 78B-201 • A.A. 50330 • P.B.X.: (575) 3530783 - 3789000 - 3719900 • FAX: (575) 3533949 - 3558434 - 3533681 - 3532997
BARRANQUILLA - COLOMBIA • INT.: 890.106.527-5

NOTARIA QUINCE (15) DEL CIRCULO DE BOGOTA

EL ANTERIOR ESCRITO FUE PRESENTADO
PERSONALMENTE POR SU SIGNATARIO

Laura Catalina Silva Barrera

QUIEN SE IDENTIFICO CON LA C.C.

NUMERO 52 455.803

DE Bj Y T.P. DE ABOGADO

NO 147.399 DEL C.S.J.

RECONOCE SU CONTENIDO COMO CIERTO Y

MANIFIESTA QUE LA FIRMA FUE PUESTA

POR EL

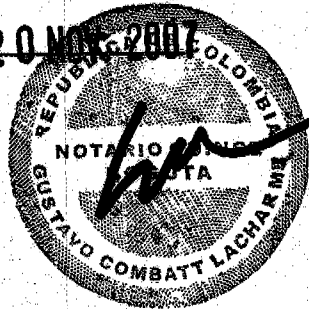
FIRMA :

Laura Catalina Silva Barrera

BOGOTA:

20 NOV 2007

FL NOTARIO QUINCEI





***** Pag. 1
CAMARA DE COMERCIO
DE BARRANQUILLA
07*****

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

***** CONTINUA *****

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.	32,909	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

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 E R T I F I C A



***** Pag. 2
CAMARA DE COMERCIO
DE BARRANQUILLA
07*****

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

PROCAPS S.A.

NIT: 890.106.527-5

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-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 y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos (terminados; d)-La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e)-La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f)- 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; g)- Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista,

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socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en 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 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

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000.000 *****	2,000,000 *****	*****1,000
Suscrito		
\$*****1,224,500.000 *****	1,224,500 *****	*****1,000
Pagado		
\$*****1,224,500.000 *****	1,224,500 *****	*****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 transaccion. 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 representacion 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

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



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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 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

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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.

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
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

CC.*****7,463,982

CC.*****7,461,324

CC.*****8,671,834

Suplentes

1. Minski Zilberblum Elliot
2. Minski Deitel Daniel
3. Minski Sharon

CC.*****72,219,541

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
Presidente.

Identificación

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NIT: 890.106.527-5

Minski Gontovnik Ruben
Suplente del Presidente

CC.*****7,463,982

Minski Minski Abraham
Vicepresidente

CC.*****802,575

Minski Gontovnik Meyer
Suplente del vicepresidente

CC.*****7,461,324

Minski Gontovnik Jose

CC.*****8,671,834

C E R T I F I C A

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 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 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. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

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

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PROCAPS S.A.-----
NIT: 890.106.527-5.

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:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal. Lozada Villareal Milena	CC.*****32,748,111

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Cámara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el artículo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendrán las funciones que a continuación se indican en razón de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los señores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representación de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que esté obligada la sociedad, así como para que responda todo tipo de requerimiento o solicitudes de información de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente a los siguientes señores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. GRUPO A: CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. GRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requerirá por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIRLES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210, para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios, pedir la práctica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebración de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantía, los Apoderados deberán aportar la autorización escrita del Representante Legal de la sociedad. Los Apoderados podrán presentar solicitudes de devolución y/o

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compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No. 1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A., confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A., en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No. 2.290 del libro respectivo, el señor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribir en el giro normal de sus negocios y operaciones socia-

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

10/11/2007 15:35:42 NIT: 890.106.527-5 PROCAPS S.A.

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

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les. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado para firmar las declaraciones comabiarías y demás documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado.-

C E R T I F I C A

Que segun documento privado del 22 de Febrero de 2005, inscrito en esta Camara de Comercio el 28 de Marzo de 2.005, bajo el No. 2.820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C.C. 16.251-923 de Palmira, quien actua como representante legal de la sociedad PROCAPS S.A., otorga Poder Especial, Amplio y Suficiente al señor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de informacion de las autoridades aduaneras en los ordenes distrital, departamental y nacional.-----

C E R T I F I C A

Que por Escritura Pública No. 2.011 del 10 de Octubre de 2006, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Dic/bre de 2006 bajo el No. 3.183 del libro respectivo,-----

Consta que RUBEN MINSKI GONTOVNIK CC.No.7.463.928, quien manifesto que en su condicion de Presidente y Representante Legal de la ----- Sociedad PROCAPS S.A., confiere poder especial amplio y suficiente a los siguientes señores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancías y servicios con entidades oficiales, hasta por la suma de ochocientos mil dolares de los Estados Unidos de America (US\$800.000.00), ---- liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. Grupo A: IVAN VILLAREAL CAMACHO CC.No.91.201.749. FERNANDO RINCON RIVERA CC.No.79.484.187. CLAUDIA TANGARIFE CASTILLO CC.No.41.660.293. Grupo B. WALTER TANAKA TATEKAWA CC.No.16.251.923. CARMEN ALICIA FLOREZ DE LA ROTA ----- CC.No.22.434.044. RICARDO DORADO HURTADO CC.No.79.715.772.-----

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: 20 de Marzo de 2007.

La información sobre embargos de establecimiento se suministra en

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



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Certificados de Matrícula, la de contratos sujetos a registro, en
Certificados Especiales.

m. l. j. e. o.



CONFIDENTIAL

20
107

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-110229- -00002-0000
Fecha 2007-11-27 13:49:29 Dep. 2020 NUECREACIONE
Tra 11 PATENTEYII Lvs 378 FASENACIONALI
Act. 400 OPOSIOBSERVIER Folios: 58

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 70,360
FECHA : AGOSTO 31 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	50770490	10/08/2007	1,024,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LENAS COMERCIALES	256,000.00
		TOTAL :	\$ 256,000.00

SOM: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXO 1

United States Patent [19]

Wiechert et al.

[11]

4,129,564

[45]

Dec. 12, 1978

[54] SPIROLACTONES

[75] Inventors: Rudolf Wiechert; Dieter Bittler;
Ulrich Kerb; Jorge Casals-Stenzel;
Wolfgang Losert, all of Berlin, Fed.
Rep. of Germany

[73] Assignee: Schering, A.G. Patentabteilung,
Berlin, Fed. Rep. of Germany

[21] Appl. No.: 850,524

[22] Filed: Nov. 11, 1977

[30] Foreign Application Priority Data

Nov. 16, 1976 [DE] Fed. Rep. of Germany 2652761

[51] Int. Cl.² A61K 31/58; C07J 1/00

[52] U.S. Cl. 260/239.57; 424/241

[58] Field of Search 260/239.57;
/Machine Searched Steroids

[56] References Cited

U.S. PATENT DOCUMENTS

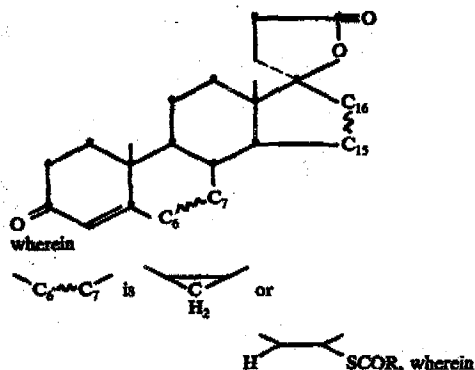
3,257,390 6/1966 Patchett 260/239.55
3,900,467 8/1975 Irmischer et al. 260/239.57

Primary Examiner—Elbert L. Roberts
Attorney, Agent, or Firm—Millen & White

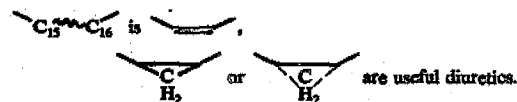
[57]

ABSTRACT

New spirolactones of the formula



R is a lower alkyl of up to 5 carbon atoms, and

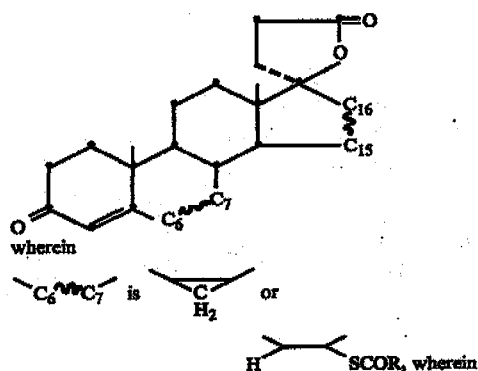


19 Claims, No Drawings

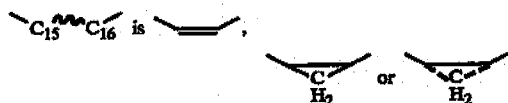
SPIROLACTONES

SUMMARY OF THE INVENTION

The present invention provides novel spirolactones of Formula I

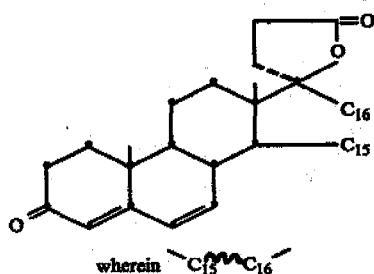


R is a lower alkyl of up to 5 carbon atoms, and



DETAILED DISCUSSION

The spirolactones of Formula I can be prepared by conventionally introducing the methylene group or the thiacyl group into the Δ^6 -unsaturated spirolactones of Formula II



is as defined above.

The methylene group is introduced into the compounds of Formula II in accordance with conventional methods, for example, by reaction of the compounds with dimethyl sulfoxonium methylide in an aprotic solvent, such as dimethyl sulfoxide, dimethylformamide, dioxane, or a mixture of dimethyl sulfoxide and tetrahydrofuran. See for reference, E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc. 84 (1962)867 and ibid. 84 (1962)3782.

This process is advantageously conducted at 20°-40° C. under a protective gas atmosphere, such as nitrogen.

The dimethyl sulfoxonium methylide is suitably prepared by reaction of trimethyl sulfoxonium iodide or chloride with a base, such as sodium hydride, sodium

hydroxide, potassium tert-butyrate, or sodium methylate.

The dimethyl sulfoxonium methylide is prepared in a conventional manner (see for reference, L. F. Fieser & M. Fieser, Reagents for Organic Synthesis, J. Wiley & Sons, Inc., N.Y., 1967, p. 315).

The thiacyl group is also introduced into the compounds of Formula II in accordance with known procedures. Especially suitable is the reaction of the compounds with the corresponding thio acid in the presence of a protonic solvent, such as methanol or ethanol, optionally in a mixture thereof with water, while heating. For reference, see process described in U.S. Pat. No. 3,013,102.

The preferred temperature range is that from above room temperature up to the boiling point of the reaction mixture.

It is also possible to conduct the thiacylation without a solvent.

The three starting materials of Formula II which are required for preparation of all compounds of Formula I in accordance with the foregoing procedures, i.e.,

Starting Material	$\text{---C}_6\text{---C}_7\text{---}$
3-oxo-4,6,15-androstatriene-[17-(β -1')-spiro-5']perhydrofuran-2'-one	
15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one	
15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one	

can be prepared as follows:

3-oxo-4,6,15-androstatriene-[17-(β -1')-spiro-5']perhydrofuran-2'-one

20.0 g. of 3 β -hydroxy-5,15-androstadiene-17-one is combined in 280 ml. of absolute tetrahydrofuran with 4.34 g. of freshly pressed lithium wire. Then, 36 ml. of 1-bromo-3-dimethoxypropane is added dropwise under ice cooling within 30 minutes. After 1.5 hours of agitation at ice-bath temperature, the mixture is filtered off from the unreacted lithium, and the filtrate is stirred into ice water. The precipitate is filtered off, washed with water, and taken up in methylene chloride.

After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 19.9 g. of 17 α -(3'-dimethoxypropyl)-5,15-androstadiene-3 β ,17 β -diol in the form of an oil.

19.9 g. of 17 α -(3'-dimethoxypropyl)-5,15-androstadiene-3 β ,17 β -diol is combined in 500 ml. of acetone under ice cooling with 1.0 g. of p-toluenesulfonic acid and stirred for 15 minutes under cooling. The mixture is then introduced under agitation into ice water which contains sodium bicarbonate; the precipitate is filtered off, washed, and taken up in methylene chloride. After drying and evaporation, 9.2 g. of crude 3 β -hydroxy-5,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2' ξ -methyl ether is obtained in the form of an oil.

19.2 g. of 3 β -hydroxy-5,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2' ξ -methyl ether is combined in 394 ml. of absolute toluene and 39.4 ml. of cyclohexanone with 3.94 g. of aluminum isopropylate in 40 ml. of

absolute toluene and heated for 45 minutes under gradual distillation. The mixture is then diluted with methylene chloride, washed with dilute sulfuric acid and water, dried, and evaporated. The residue is chromatographed on silica gel, thus obtaining 17.5 g. of 3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -methyl ether in the form of an oil.

UV: $\epsilon_{239} = 16,200$.

17.5 g. of 3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -methyl ether is combined in 350 ml. of acetone under ice cooling with 35 ml. of chromosulfuric acid (prepared from 267 g. of CrO_3 , 400 ml. of water, and 230 ml. of concentrated sulfuric acid, replenished with water to obtain 1 liter); the mixture is stirred for 30 minutes under cooling in an ice bath. The mixture is then stirred into ice water, the precipitate is filtered off, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 11.8 g. of 3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one. A sample recrystallized from diisopropyl ether/acetone melts at 189.5°–191.5° C.

UV: $\epsilon_{240} = 17,300$.

10.0 g. of 3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is combined in 100 ml. of absolute dioxane with 10 ml. of triethyl orthoformate and 10 ml. of dioxane/concentrated sulfuric acid (produced from 13.5 ml. of absolute dioxane and 0.48 ml. of concentrated sulfuric acid). The mixture is stirred for 30 minutes at room temperature, combined with 2 ml. of pyridine, and diluted with ether. The ether phase is washed with water, dried, and evaporated. The residue is triturated with pyridine-containing methanol, the thus-separated crystals are vacuum-filtered. Yield: 8.9 g. of 3-ethoxy-3,5,15-androstatriene-[17(β -1')-spiro-5']perhydrofuran-2'-one, m.p. 153.5°–159° C.

UV: $\epsilon_{240} = 19,800$.

8.9 g. of 3-ethoxy-3,5,15-androstatriene-[17(β -1')-spiro-5']perhydrofuran-2'-one is dissolved in 201 ml. of acetone, cooled in an ice bath, and combined with 1.38 ml. of pyridine, 6.36 g. of sodium acetate, and 63.6 ml. of water. Then, 4.72 g. of N-bromosuccinimide is added thereto, and 6.36 ml. of acetic acid is added dropwise over a period of 15 minutes. The mixture is further stirred for 45 minutes under ice cooling, diluted with ether, and washed neutral with water. After drying and evaporation, 10.35 g. of 6 β -bromo-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is obtained in the form of an oil.

UV: $\epsilon_{245} = 12,700$.

10.35 g. of 6 β -bromo-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is stirred in 103.5 ml. of dimethylformamide with 4.67 g. of lithium carbonate and 5.37 g. of lithium bromide for 18 hours at 100° C. The mixture is then introduced into ice water under agitation, the precipitate is filtered off, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed. After recrystallization from diisopropyl ether/acetone, 6.5 g. of 3-oxo-4,6,15-androstatriene-[17(β -

1')-spiro-5']perhydrofuran-2'-one is obtained, m.p. 182.5°–184.5° C.

UV: $\epsilon_{284} = 27,100$.

15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one

15 g. of 3 β -hydroxy-15 α ,16 α -methylene-5-androstene-17-one (produced, for example, according to DOS [German Unexamined Laid-Open Application] 2,109,555) is combined in 150 ml. of absolute tetrahydrofuran under ice cooling with 3.6 g. of lithium and thereafter 30 ml. of 1-bromo-3-dimethoxypropane is added dropwise within 30 minutes. After agitation for 2.5 hours at ice bath temperature, the mixture is separated from the unreacted lithium, and the filtrate is stirred into ice water. The thus-obtained precipitate is filtered off, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 16.8 g. of 17 α -(3'-dimethoxypropyl)-15 α ,16 α -methylene-5-androstene-3 β ,17 β -diol. A sample recrystallized from diisopropyl ether/acetone melts at 153°–159° C.

16.5 g. of 17 α -(3'-dimethoxypropyl)-15 α ,16 α -methylene-5-androstene-3 β ,17 β -diol is agitated in 410 ml. of 70% acetic acid for 18 hours at room temperature. The mixture is then stirred into ice water, and the thus-obtained precipitate filtered off, taken up in chloroform, and washed with sodium bicarbonate solution and water. After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 11.5 g. of 3 β -hydroxy-15 α ,16 α -methylene-5-androstene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -ol. A sample recrystallized from diisopropyl ether/acetone melts at 194°–202° C.

10.5 g. of 3 β -hydroxy-15 α ,16 α -methylene-5-androstene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -ol is combined in 210 ml. of absolute toluene with 21 ml. of cyclohexanone and 2.1 g. of aluminum isopropylate in 20 ml. of absolute toluene, and then heated for 45 minutes under gradual distillation. The mixture is then diluted with methylene chloride, washed with 2N sulfuric acid and water, dried, and evaporated. Yield: 11.5 g. of crude 15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-ol as an oil. A sample purified by preparative layer chromatography and recrystallization from diisopropyl ether/acetone melts at 259°–268° C.

UV: $\epsilon_{241} = 16,500$.

10.5 g. of 15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -ol is combined in 100 ml. of acetone under ice cooling with 10 ml. of chromosulfuric acid (prepared from 267 g. of CrO_3 , 400 ml. of water, and 230 ml. of concentrated sulfuric acid, replenished to a volume of 1 liter with water). The mixture is agitated for 1 hour, then stirred into ice water, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 8.2 g. of 15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one. A sample recrystallized from diisopropyl ether/acetone melts at 180°–181° C.

UV: $\epsilon_{240} = 16,600$.

4,129,564

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7.2 g. of 15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one is combined in 72 ml. of absolute dioxane and 7.2 ml. of triethyl orthoformate with a solution of 7.2 ml. of absolute dioxane and 0.26 ml. of concentrated sulfuric acid. The mixture is stirred for 30 minutes at room temperature. Then, 2 ml. of pyridine is added thereto, the mixture is diluted with ether, washed with water, and dried. After evaporation, 8.5 g. of crude 3-ethoxy-15 α ,16 α -methylene-3,5-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is obtained.

UV: ϵ_{241} = 15,700.

8.5 g. of 3-ethoxy-15 α ,16 α -methylene-3,5-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is dissolved in 192 ml. of acetone, cooled in an ice bath, and combined with 1.32 ml. of pyridine, 6.08 g. of sodium acetate, and 60.8 ml. of water; then, 4.51 g. of N-bromosuccinimide is added thereto and within 10 minutes, 6.08 ml. of acetic acid is added dropwise to the reaction mixture. The mixture is further stirred for 1 hour at ice bath temperature, diluted with ether, washed with water, and dried. After evaporation, 9.6 g. of crude 6 β -bromo-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one is obtained.

9.6 g. of 6 β -bromo-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one is stirred in 96 ml. of dimethylformamide with 3.75 g. of lithium carbonate and 4.4 g. of lithium bromide for 18 hours at 100° C. The mixture is then stirred into ice water, the thus-obtained precipitate is filtered off, taken up in methylene chloride, washed with 2N sulfuric acid and water, and dried. After evaporation, the residue is chromatographed on silica gel, thus obtaining 6.5 g. of 15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one. A sample recrystallized from diisopropyl ether melts at 180.5°-182.5° C.

UV: ϵ_{283} = 26,300.

15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one

15 g. of 3 β -hydroxy-15 β ,16 β -methylene-5-androstene-17-one (produced, for example, according to German Pat. No. 1,593,500) is reacted in 150 ml. of absolute tetrahydrofuran with 3.27 g. of lithium and 29 ml. of 1-bromo-3-dimethoxypropane for 2 hours at ice bath temperature and for 4 hours at room temperature. The mixture is filtered off from the unreacted lithium, the filtrate is stirred into ice water, the precipitate is filtered off and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed on silica gel. Yield: 17.4 g. of 17 α -(3'-dimethoxypropyl)-15 β ,16 β -methylene-5-androstene-3 β ,17 β -diol.

17.0 g. of 17 α -(3'-dimethoxypropyl)-15 β ,16 β -methylene-5-androstene-3 β ,17 β -diol is agitated in 340 ml. of 70% acetic acid for 18 hours at room temperature. The mixture is then stirred into ice water; the thus-obtained precipitate is filtered off and taken up in methylene chloride. The methylene chloride phase is washed with sodium bicarbonate solution and water, dried, and evaporated, thus obtaining 13.8 g. of 3 β -hydroxy-15 β ,16 β -methylene-5-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-ol as a crude product.

8.8 g. of 3 β -hydroxy-15 β ,16 β -methylene-5-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-ol is combined in 176 ml. of absolute toluene and 17.6 ml. of cyclohexa-

6

none with 1.76 g. of aluminum isopropylate in 50 ml. of absolute toluene and heated for 3 hours under gradual distillation. The mixture is then diluted with ether, washed with 2N sulfuric acid and water, dried, and evaporated. The residue is chromatographed on silica gel, thus obtaining 4.3 g. of 15 β ,16 β -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one. A sample recrystallized from diisopropyl ether/acetone melts at 178.5°-179.5° C.

UV: ϵ_{241} = 16,500.

4.2 g. of 15 β ,16 β -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 84 ml. of tert.-butanol with 4.2 g. of chloranil for 18 hours. The solvent is distilled off under vacuum, and the residue is chromatographed on silica gel. For purposes of additional purification, preparative layer chromatography is employed. Yield: 1.1 g. of 15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one as an oil.

UV: ϵ_{284} = 25,700.

For each starting material, after the preparative reaction is terminated, the reaction mixture is worked up in a conventional fashion to obtain the desired compound, e.g., by precipitation, extraction, recrystallization, and/or chromatography.

The compounds of this invention possess valuable pharmacological properties. They are, inter alia, diuretics of the aldosterone antagonist type, i.e., they reverse the effect of desoxycorticosterone on the excretion of sodium and potassium. Unexpectedly, the compounds of this invention display superior activity in comparison with the conventional diuretic, spironolactone. This effect can be determined using the test model of Hollman (G. Hollmann et al., "Tubuläre Wirkungen und renale Elimination von Spirolactonen" (Tubular Effects and Renal Elimination of Spirolactones), Naunyn-Schmiedeberg's Arch. Exp. Path. Pharmac. 247, 419 (1964); P. Marx, "Renal Effects of d-Aldosterone and Its Antagonist Spironolactone," dissertation of the Medical Faculty, Berlin Free University, 1966).

The compounds of Formula I can be administered to mammals, including humans, e.g., parenterally or enterally (orally) in accordance with fully conventional procedures, e.g., those used in the administration of spironolactone. Thus, suitable dosages as a diuretic are 20-500 mg/day for human patients.

The pharmacologically active compounds of Formula I can be processed in accordance with conventional methods of galenic pharmacy to produce medicinal agents, especially for oral administration. Conventional excipients include pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral or topical application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, vegetable oils, polyethylene glycols, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy-methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influenc-

ing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages.

For enteral application, particularly suitable are tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

Generally, the compounds of this invention are dispensed in unit dosage form comprising 10-100 mg in a pharmaceutically acceptable carrier per unit dosage.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

EXAMPLE 1

1.5 g. of 3-oxo-4,6,15-androstatriene-[17(β -1')-spiro5']perhydrofuran-2'-one is refluxed in 22.5 ml. of methanol with 1.5 ml. of thioacetic acid for 2 hours. The mixture is then diluted with ether, washed with water, sodium bicarbonate solution, and water, dried, and evaporated. The residue is chromatographed on silica gel, thus obtaining 1.05 g. of 7 α -acetylthio-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, m.p. 317°-319° C. (decomposition).

UV: ϵ_{238} = 19,800.

EXAMPLE 2

1.0 g. of 3-oxo-4,6,15-androstatriene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 15 ml. of methanol with 1 ml. of thiopropionic acid for 16 hours. The mixture is worked up and purified as described in Example 1, thus obtaining 670 mg. of 3-oxo-7 α -propionylthio-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one.

UV: ϵ_{238} = 18,500.

EXAMPLE 3

4.13 g. of trimethyl sulfoxonium iodide is agitated in 75 ml. of dimethyl sulfoxide with 512 mg. of 80% sodium hydride oil suspension for 2 hours under nitrogen. The almost clear solution is combined with 3.0 g. of 3-oxo-4,6,15-androstatriene-[17(β -1')-spiro-5']perhydrofuran-2'-one and agitated for 24 hours at room temperature. The mixture is then stirred into ice water, the precipitate is filtered off, washed with water, and taken up in ether. After drying and evaporation, the residue is chromatographed on silica gel and then further purified by preparative layer chromatography, thus obtaining 520 mg. of 6 β ,7 β -methylene-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one.

UV: ϵ_{266} = 18,100.

EXAMPLE 4

1.4 g. of 15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 22.5 ml. of methanol with 3 ml. of thioacetic acid for 17 hours. The mixture is then diluted with ether, washed with sodium bicarbonate solution and water, dried, and evaporated. The residue is purified by way of preparative layer chromatography and recrystallized from diisopropyl ether/acetone. Yield: 1.08 g. of 7 α -acetylthio-15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, m.p. 214.5°-217.5° C.

UV: ϵ_{238} = 19,100.

EXAMPLE 5

500 mg. of 15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 5 ml. of methanol with 1 ml. of thiopropionic acid for 32 hours. The mixture is worked up and purified as described in Example 4. Yield: 220 mg. of 15 α ,16 α -methylene-3-oxo-7 α -propionylthio-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one.

UV: ϵ_{238} = 18,700.

EXAMPLE 6

2.75 g. of trimethyl sulfoxonium iodide is stirred in 57 ml. of dimethyl sulfoxide with 341 mg. of 80% sodium hydride oil suspension for 2 hours at room temperature. The almost clear solution is combined under nitrogen with 2.0 g. of 15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one and agitated for 24 hours at room temperature. The mixture is then stirred into ice water, the thus-obtained precipitate is filtered off, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is purified by repeated preparative layer chromatography, thus obtaining 520 mg. of 6 β ,7 β ,15 α ,16 α -dimethylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one.

UV: ϵ_{266} = 18,000.

EXAMPLE 7

1.0 g. of 15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 15 ml. of methanol with 1 ml. of thioacetic acid for 2 hours. The mixture is then taken up in ether, washed with sodium bicarbonate solution and water, dried, and evaporated. The residue is chromatographed on silica gel. Recrystallization from diisopropyl ether/acetone yields 590 mg. of 7 α -acetylthio-15 β ,16 β -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, m.p. 242-247° C. (decomposition).

UV: ϵ_{238} = 19,300.

EXAMPLE 8

750 mg. of 15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 7.5 ml. of methanol with 0.75 ml. of thiopropionic acid for 18 hours. The mixture is worked up as described in Example 4, and the residue is purified by preparative layer chromatography, thus obtaining 320

mg. of 15 β ,16 β -methylene-3-oxo-7 α -propionylthio-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one as an oil.

UV: $\epsilon_{238} = 18,700$.

EXAMPLE 9

1.4 g. of trimethyl sulfoxonium iodide is stirred in 25 ml. of dimethyl sulfoxide with 170 mg. of 80% sodium hydride oil suspension for 1.5 hours under nitrogen. The almost clear solution is combined with 1.0 g. of 15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, dissolved in 10 ml. of dimethyl sulfoxide. After 24 hours of agitation at room temperature, the mixture is stirred into ice water, the precipitate is filtered off, taken up in ether, washed with water, and dried. The residue obtained after evaporation is purified by repeated preparative layer chromatography, thus producing 170 mg. of 6 β ,7 β ,15 β ,16 β -dimethylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one in the form of an oil.

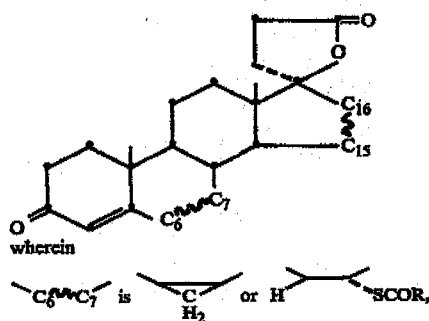
UV: $\epsilon_{266} = 18,400$.

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

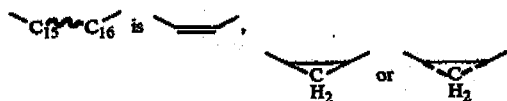
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

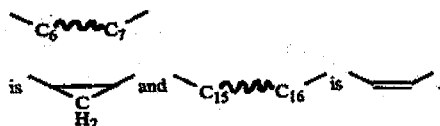
1. A spirolactone of the formula



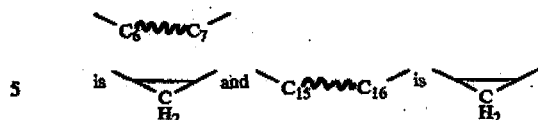
wherein R is lower alkyl of up to 5 carbon atoms, and



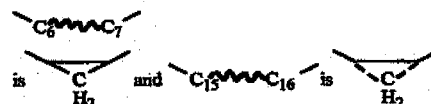
2. The spirolactone of claim 1 wherein



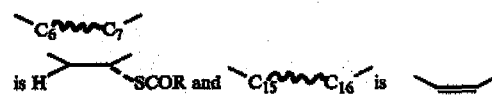
3. The spirolactone of claim 1 wherein



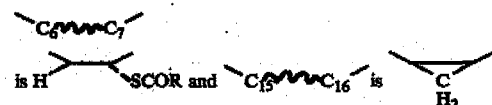
4. The spirolactone of claim 1 wherein



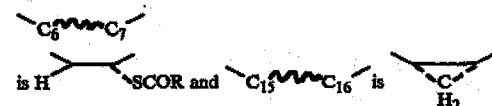
5. The spirolactone of claim 1 wherein



6. The spirolactone of claim 1 wherein



7. The spirolactone of claim 1 wherein



8. The spirolactone of claim 1 wherein R is methyl or ethyl.

9. 7 α -Acetylthio-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

10. 3-Oxo-7 α -propionylthio-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

11. 6 β ,7 β -Methylene-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

12. 15 α ,16 α -Methylene-3-oxo-7 α -propionylthio-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

13. 6 β ,7 β ,15 α ,16 α -Dimethylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

14. 7 α -Acetylthio-15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

15. 7 α -Acetylthio-15 β ,16 β -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

16. 15 β ,16 β -Methylene-3-oxo-7 β -propionylthio-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

17. 6 β ,7 β ,15 β ,16 β -Dimethylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

18. A pharmaceutical composition which comprises a diuretically effective amount of a spirolactone of claim 1 and a pharmaceutically acceptable adjuvant.

19. The method of achieving diuretic effects in mammals which comprises administering a diuretically effective amount of a spirolactone of claim 1.

* * * * *

ANEXO 2

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PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/57, 31/565	A1	(11) International Publication Number: WO 95/07081 (43) International Publication Date: 16 March 1995 (16.03.95)
(21) International Application Number: PCT/EP94/02997 (22) International Filing Date: 8 September 1994 (08.09.94) (30) Priority Data: 9301562 9 September 1993 (09.09.93) NL (71) Applicant (for all designated States except US): SATURNUS AG [LU/LU]; 11, rue Aldringen, L-2960 Luxembourg (LU). (72) Inventor; and (75) Inventor/Applicant (for US only): KONINCKX, Philippe, Robert, Marie, Wilhelmus, Ghislain [BE/BE]; Vuilenbos 2, B-3360 Bierbeek (BE). (74) Agent: PRINS, Hendrik, Willem; Arnold & Siedsma, Sweel-inkplein 1, NL-2517 GK The Hague (NL).		(81) Designated States: AM, AT, AU, BE, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PREPARATION FOR SUBSTITUTION THERAPY, CONTAINING AT LEAST ONE PROGESTOGEN AND AT LEAST ONE ESTROGEN (57) Abstract The invention relates to a preparation for substitution therapy and oral contraception comprising at least one progestogen and at least one estrogen in which the estrogen dose varies with a periodicity such that blood loss is substantially avoided, wherein the periodicity is preferably less than 10 days, more preferably less than 7 days, such as preparations containing the progestogen and/or estrogen in an oral, transdermal, parenteral and/or implantable application form.		

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PREPARATION FOR SUBSTITUTION THERAPY, CONTAINING AT LEAST ONE PROGESTOGEN
AND AT LEAST ONE ESTROGEN.

The present invention relates to a preparation for substitution therapy and for oral contraception. More particularly the present invention on the one hand relates to relieving the effects which occur because the ovaries
5 decrease or stop production of female hormones, for instance during the menopause. The substitution therapy is mainly intended to induce amenorrhoea with negligible blood loss.

During and after the menopause these effects comprise hot flushes and nocturnal sweating, atrophy of the vagina
10 which can result in sexual difficulties, bone decalcification, increase in heart and blood vessel disorders and psychic symptoms with a causal connection that is usually difficult to demonstrate.

Up to the present different types of substitution
15 therapy have been applied comprising a hormone treatment with one or more oestrogens and one or more progestogens.

According to a first therapy, low doses of oestrogens and progestogens are administered, but such a treatment is ineffective in respect of the decalcification and heart and
20 blood vessel disorders.

In another therapy the natural cycle of oestrogen and progestogen is followed as closely as possible. This treatment inevitably results in menstruation and has the advantage of a reduced risk of cancer of the uterus.

25 According to yet another therapy only oestrogens are administered in a dose which lies below the threshold for menstrual bleeding. This treatment has the drawback however of an increased risk of cancer of the uterus.

According to a most recently known therapy oestrogens
30 and progestogens are administered continuously such that the endometrium does not proliferate. This therapy has the drawback however of an unacceptably high incidence of slight, irregular blood loss.

2+
1/9

The present invention has for its object to provide a substitution therapy wherein the above described drawbacks occur to a much lesser extent, with the objective of inducing amenorrhoea with negligible blood loss over a long period
5 (many months to years).

On the other hand, the present invention relates to preparations designed for oral contraception with substantially continuous application.

In continuous application of oral contraceptive
10 frequently intermediate bleedings occur. The preparations according to the present invention are designed to induce menstrual bleeding with a regular menstrual bleeding, with an extended cycle or eventually a constant amenorrhoea, but characterized by an optimal (cycle) control and/or by a
15 substantially reduced occurrence of intermediate bleeding.

EP-A-559 240 discloses preparations for substitution therapy and oral contraception in which the estrogen dose is constant and the progestagen dose is periodically alternated.

However, the improvement in inhibiting endometrium
20 bleeding is minor. Above that, since the use of higher progestagen doses provided better results than lower doses it appears illogical to use periodically varying estrogen doses.

The present invention is based on the finding that surprisingly when using periodically varying estrogen doses
25 the occurrence of blood loss and intermediate bleeding is substantially avoided. The estrogen dose is herein oscillated such that estrogen-dominant and progestogen-dominant periods occur alternately with a sufficiently short periodicity. This short periodicity in the estrogen dose is necessary to
30 avoid blood loss.

Purely by administering a dose of progestogen or estrogen substantially constant in time and an estrogen or progestogen varying in time between at least two dose levels, it was possible to induce the desired amenorrhoea while no
35 blood loss occurred over a longer period.

The invention therefore relates to a preparation for substitution therapy and for oral contraception comprising at least one progestogen and at least one estrogen in which the

estrogen dose varies with a periodicity such that blood loss is substantially avoided.

It is noted that the preparation is formulated such that a substantially constant blood concentration is obtained for progestogen or estrogen, while the estrogen concentration in the blood varies between two blood concentrations. The periodicity must be sufficiently short and is generally less than 10 days. The periodicity is usually less than 7 days. The periodicity generally lies between 2-9 days, preferably between 2-6 days. It will however be apparent that the periodicity is dependent on the estrogens and progestogens used and the applied doses. Both the periodicity and concentrations of estrogen and progestogen are easy to determine by routine experimentation.

According to an embodiment of the invention the preparation contains a constant progestogen dose, while the estrogen dose oscillates between two levels. This preparation is recommended because there is a greater certainty of avoiding blood loss over a longer period.

According to another embodiment the preparation contains oscillating doses of progestogen and estrogen, in varying ratios however such that blood loss is avoided and amenorrhoea is induced.

Use can be made in general of all known progestogens, such as

	progesterone	300-900 mg/day
	norethisterone acetate	2-5 mg/day
	medroxyprogesterone acetate	1-5 mg/day
	d-norgestrel	30-150 µgr/day
30	desogestrel	30-150 µgr/day
	norgestimate	30-150 µgr/day
	cyproterone acetate	0.2-2 mg/day,
	gestodene	10-150 µg/day
	3-ketodesogestrel	10-150 µg/day
35	drospirenon	0.2-3.0 mg/day

or combinations thereof. It is noted that the preparation can contain one or more progestogens and estrogens.

It will be apparent that the quantity of progestogen and estrogen depends on the person (constitution and age),

the progestogen(s) and estrogen(s), anti-progestogen and anti-estrogen for use and the form of administering same.

The progestogen and estrogen can each be present in an oral, transdermal, parenteral or implantable application form for substitution therapy. The preparation can for instance
5 comprise an application form which contains the progestogen and estrogen, and a second like application form which contains the progestogen and an increased dose of estrogen. The progestogen and estrogen can of course be present in like
10 but separate forms of application or in mutually differing forms of application. The progestogen can for instance be an implantable application form while the oestrogen is administered orally, transdermally or parenterally in a dose which takes account of the required time period according to
15 the invention.

The oral application form to be used comprises tablets, capsules, syrup, solutions. The transdermal forms of application comprise gels, plasters. Strips can for instance be used wherein tablets with progestogen and oestrogen in the
20 desired ratio and periodicity are arranged in time sequence. The parenteral application form comprises injection fluid and the like. The implantable application form comprises for example a known implantable sustained release preparation.

The preparations for oral contraceptive comprise
25 estrogens and progestogens in common form.

Preparations according to the invention were administered over a period of 3-12 months to 40 women in the menopause. By making use of the combination preparations according to the invention a constant amenorrhoea could be
30 obtained in the case of more than 90% of the women, wherein the clinical tolerance was perceived as optimal, wherein the woman did not discern any subjective difference between a fixed or changing oestrogen dose with a periodicity of about one week.

35 Using the preparations according to the invention as oral contraceptive intermediate bleeding will be substantially reduced.

Example 1

A preparation according to the invention comprised tablets of the type A which contained 10 gamma aethinyl-estradiol, 1 mg estradiol valerianate and 0.5 mg norethisterone, and tablets of the type B which contained 15 gamma instead of 10 gamma aethinyl-estradiol. By alternately administering the tablets A and B over a time period of 7 days an amenorrhoea could be induced without blood loss for a very long period of time.

10 Example 2

A preparation according to the invention contained 1 mg norethisterone or 0.5 mg cyproterone acetate and 2 mg estradiol valerianate. The preparation moreover contained tablets of the type B having 3 mg instead of 2 mg estradiol valerianate. By using the preparation with alternate administering (4-5 days) of the tablets A and B or B and A an amenorrhoea could be induced without blood loss for a longer period of time.

Example 3

20 A preparation according to the invention comprised tablets of the type A which contained 15 gamma aethinyl-estradiol and 1 mg oestradiol valerianate and 1 mg norethisterone. The preparation moreover contained tablets of the type B having 1.5 mg instead of 1 mg norethisterone. By 25 alternately administering the tablets A and B with a periodicity of 4-7 days an amenorrhoea could be induced without blood loss for a very long period of time.

Example 4

A preparation according to the invention for oral contraceptive with optimal cycle control comprises tablets of type A comprising 20 µg aethinyl-estradiol and 75 µg gestoden. The preparation contained tablets of type B comprising 30 µg instead of 20 µg aethinyl-estradiol. Tablets A and B are used in four alternating periods of six days.

Example 5

A preparation according to the invention for oral contraceptive with optimal cycle control comprises tablets of type A comprising 15 µg aethinyl-estradiol and 75 µg gestoden, and tablets of type B comprising 25 µg instead of 15 µg aethinyl-estradiol. Tablets A and B are used in six alternating periods of four days.

In example 4 and 5 only aethinyl-estradiol is used in order to use a estrogen dose which is as low as possible. However, higher estrogen doses may be used. Instead of using a constant progestogen dose fluctuating doses may be use fluctuating simultaneously and/or progressively in view of the varying estrogen dose.

Example 6

A preparation for oral contraceptive according to the invention comprises tablets of type A comprising 20 µg aethinyl-estradiol and 75 µg gestoden, and tablets of type B comprising 30 µg aethinyl-estradiol and 75 µg gestoden and 50 µg onapristone. The tablets A and B are used in four alternating periods of each six days. After four periods the whole cycle is repeated without allowing a free period.

Example 7

A preparation according to the invention for hormone substitution treatment comprises tablets of type A comprising 2 µg estradiol valerianate and 50 µg gestoden. The tablets of type B comprised 3 µg estradiol valerianate and 25-100 µg onapristone. By alternatingly admininstering the tablets A and B over a time period of seven days amenorrhoea could be induced without blood loss for a very long period of time.

It is obvious for a skilled person in the examples in association with intermittently given antiprogestogen or anti-estrogen can be alternated alone or simultaneous with estrogens and/or progestagens. For instance, the antiprogestagen is added in a constant dose to the actual and the above mentioned combinations of estrogens and

progestagens in products for hormone replacement therapy and
for contraception.

CLAIMS

1. Preparation for substitution therapy and for oral contraception comprising at least one progestogen and at least one estrogen in which the estrogen dose varies with a periodicity such that blood loss is substantially avoided.

5 2. Preparation as claimed in claim 1, wherein the periodicity is less than 10 days, preferably less than 7 days.

3. Preparation as claimed in claim 1 or 2, wherein the periodicity amounts to 2-9 days, preferably 2-6 days.

10 4. Preparation as claimed in claims 1-3, wherein the dose of progestogen is substantially constant and the dose of oestrogen oscillates.

5. Preparation as claimed in claims 1-3, wherein the dose of progestogen and the dose of estrogen oscillate in
15 such a dose ratio, that blood loss is substantially avoided.

6. Preparation as claimed in claims 1-5, wherein the progestogen comprises

	progesterone	300-900 mg/day
	norethisterone acetate	0.2-5 mg/day
20	medroxyprogesterone acetate	1-5 mg/day
	d-norgestrel	30-150 µgr/day
	desogestrel	30-150 µgr/day
	norgestimate	30-150 µgr/day
	cyproterone acetate	0.2-2 mg/day,
25	gestodene	10-150 µg/day
	3-ketodesogestrel	10-150 µg/day
	drospirenon	0.2-3.0 mg/day

or combinations thereof.

7. Preparation as claimed in claims 1-6, wherein the
30 oestrogen comprises

	aethinylestradiol	5-15 gamma/day
	oestradiol valerianate	1-4 mg/day
	oestradiol	1-2 mg/day
	conjugated oestrogen	0.3-1.25 mg/day

oestriol 1-4 mg/day,
or combinations thereof.

8. Preparation as claimed in claims 1-7, comprising anti-progestogen.

5 9. Preparation as claimed in claim 1-8, comprising anti-estrogen.

10. Preparation as claimed in claims 1-9, containing the progestogen and/or estrogen in an oral, transdermal, parenteral and/or implantable application form.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 94/02997

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 559 240 (JENCAP RESEARCH LIMITED) 8 September 1993 cited in the application see column 12, line 49 - column 14, line 44	1-7,10
A	EP,A,0 275 716 (RUTGERS, THE STATE UNIVERSITY) 27 July 1988 see claims 1,36	1-7,10
A	EP,A,0 279 977 (ALZA CORPORATION) 31 August 1988 see claims	1-7,10
A	EP,A,0 346 014 (IMPERIAL CHEMICAL INDUSTRIES PLC) 13 December 1989 see abstract	9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.

PCT/EP 94/02997

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0559240	08-09-93	CA-A- 1332227	04-10-94
		CA-A- 1332228	04-10-94
		AU-B- 630334	29-10-92
		AU-A- 2276088	06-04-89
		AU-A- 3044892	11-02-93
		DE-D- 3888269	14-04-94
		DE-T- 3888269	07-07-94
		EP-A- 0309263	29-03-89
		JP-A- 1132523	25-05-89
		US-A- 5108995	28-04-92
		US-A- 5276022	04-01-94
		US-A- 5256421	26-10-93
EP-A-0275716	27-07-88	AU-A- 1242388	19-07-89
		WO-A- 8905663	29-06-89
		US-A- 4906169	06-03-90
		US-A- 5023084	11-06-91
		ZA-A- 8709729	23-06-88
EP-A-0279977	31-08-88	US-A- 4788062	29-11-88
		AU-A- 7998187	01-09-88
		JP-A- 63225318	20-09-88
		ZA-A- 8707420	14-04-88
EP-A-0346014	13-12-89	AT-T- 109351	15-08-94
		AU-B- 622184	02-04-92
		AU-A- 3592389	07-12-89
		DE-D- 68917219	08-09-94
		DE-T- 68917219	15-12-94
		ES-T- 2057124	16-10-94
		IL-A- 90410	31-07-94
		US-A- 5183814	02-02-93

ANEXO 3

41
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US005352457A

United States Patent [19]
Jenkins

[11] **Patent Number:** **5,352,457**
[45] **Date of Patent:** **Oct. 4, 1994**

[54] **TRANSDERMAL DEVICE**
[75] **Inventor:** **Anthony W. Jenkins, Comberton, United Kingdom**
[73] **Assignee:** **Ethical Pharmaceuticals Limited, Ely, United Kingdom**

[21] **Appl. No.:** **30,265**
[22] **PCT Filed:** **Oct. 4, 1991**
[86] **PCT No.:** **PCI/GB91/01730**
§ 371 **Date:** **Apr. 5, 1993**
§ 102(e) **Date:** **Apr. 5, 1993**
[87] **PCT Pub. No.:** **WO92/05811**
PCT Pub. Date: **Apr. 16, 1992**

[30] **Foreign Application Priority Data**
Oct. 5, 1990 [GB] **United Kingdom** 9021674.8
[51] **Int. Cl.⁵** **A61F 13/02**
[52] **U.S. Cl.** **424/448; 424/449**
[58] **Field of Search** **424/448, 449**

[56] **References Cited**
U.S. PATENT DOCUMENTS
4,031,894 9/1986 Urquhart et al. 128/268
4,746,509 5/1988 Haggiage et al. 424/449
4,769,028 9/1988 Hoffmann 424/443

FOREIGN PATENT DOCUMENTS
0013606 7/1980 European Pat. Off. .
0156080 10/1985 European Pat. Off. .
0201828 11/1986 European Pat. Off. .
0209121 1/1987 European Pat. Off. .
0272562 6/1988 European Pat. Off. .
0272987 6/1988 European Pat. Off. .
0275716 7/1988 European Pat. Off. .
0279982 8/1988 European Pat. Off. .
0318385 5/1989 European Pat. Off. .
0328806 8/1989 European Pat. Off. .

0332010 9/1989 European Pat. Off. .
0371496 6/1990 European Pat. Off. .
2086224 5/1982 United Kingdom .
2146526 4/1985 United Kingdom .
2185187 7/1987 United Kingdom .
86/06281 11/1986 World Int. Prop. O. .
87/06144 10/1987 World Int. Prop. O. .
88/01497 3/1988 World Int. Prop. O. .
WO8907959 9/1989 World Int. Prop. O. .

OTHER PUBLICATIONS

Patent Abstracts of Japan, vol. 12, No. 333 (C-526), Sep. 8, 1988.
Patent Abstracts of Japan, vol. 12, No. 159 (C-495), May 14, 1988.

Primary Examiner—D. Gabrielle Phelan
Attorney, Agent, or Firm—Bacon & Thomas

[57] **ABSTRACT**

The invention pertains to a method of preparing a device for transdermal delivery of an active ingredient which is solid at room temperature and in which part or all of the active ingredient is present in a saturated or supersaturated solution. In the first step, a mixture is prepared which includes at least a polymer adhesive, a vehicle for the polymer adhesive, an active ingredient and a solvent mixture for the active ingredient which solvent mixture comprises at least two solvents having different boiling points. The mixture is then formed into a film and dried. The vehicle for the polymer adhesive and at least one of the solvents and the solvent mixture have boiling points below the drying temperature of the film, while at least one of the solvents in the solvent mixture has a boiling point above the drying temperature of the film. Thus, at least one of the solvents remains in the film after drying and the solubility of the active ingredient contained in the remaining solvent is greater than 10%.

29 Claims, 3 Drawing Sheets

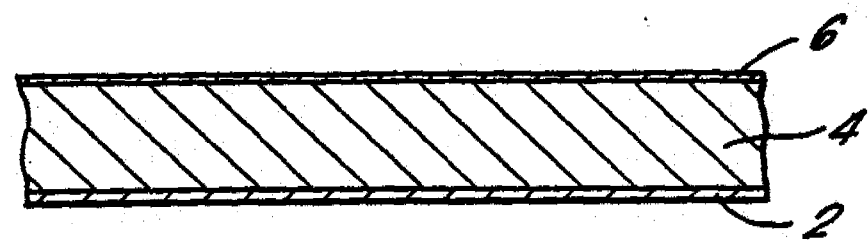


FIG. 1.

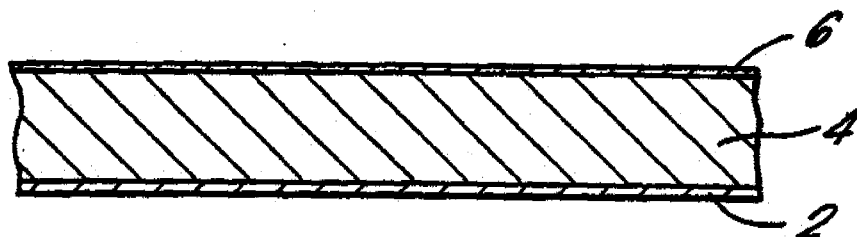


FIG. 2.

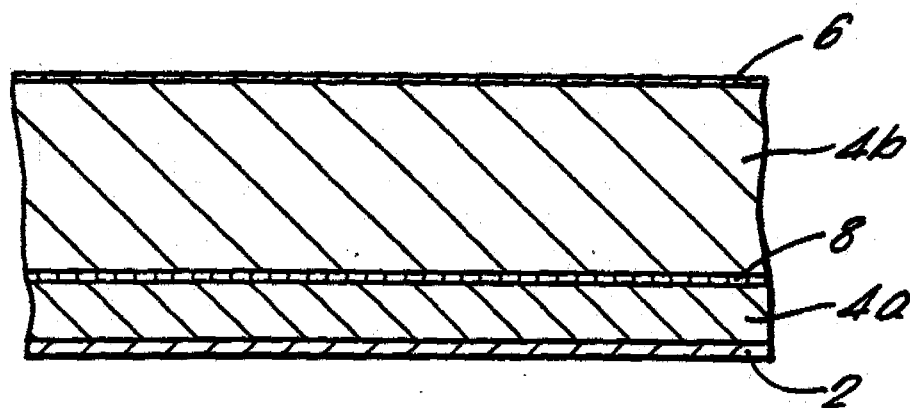
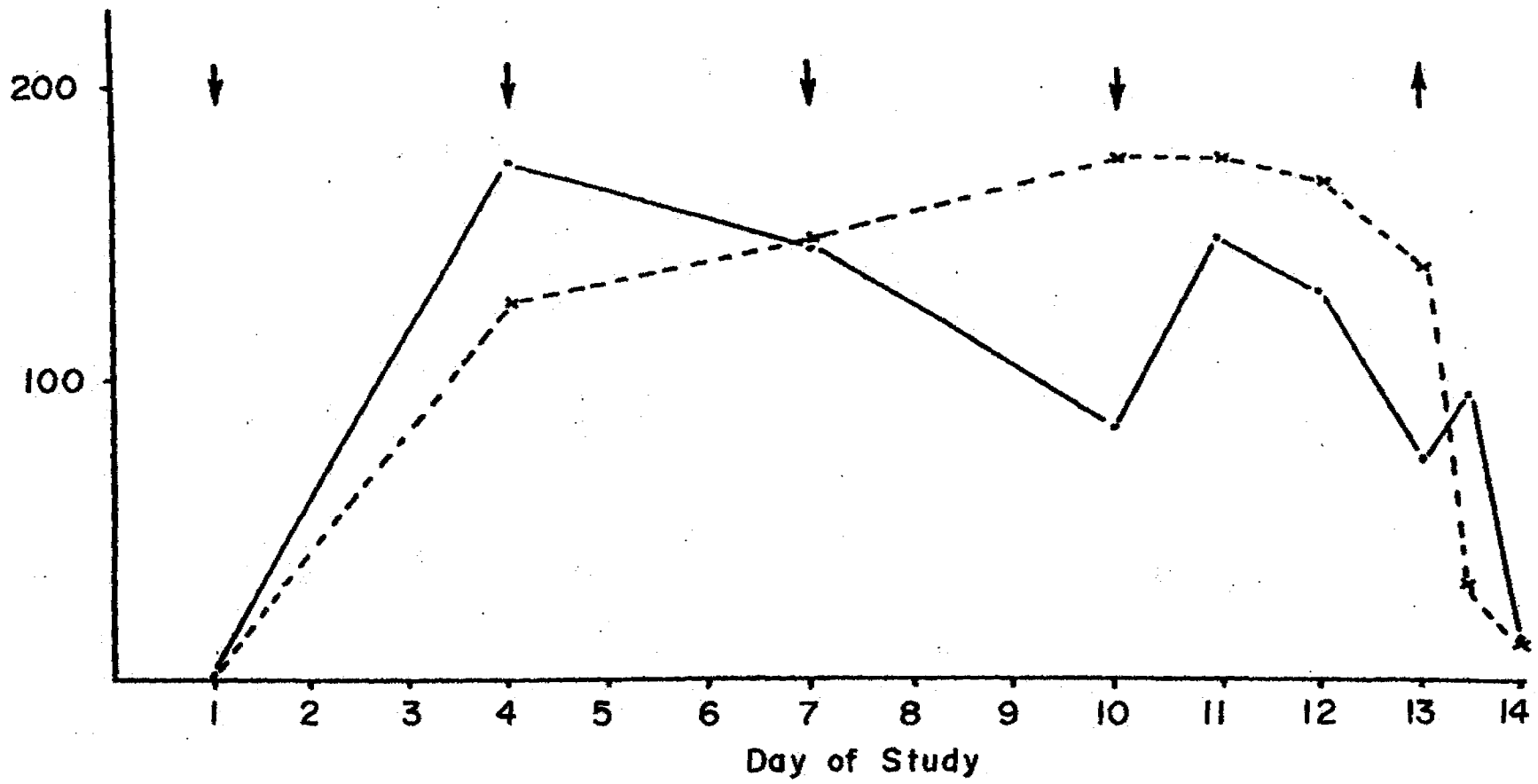


FIG. 3.

Norethisterone
concentration
pg/ml

Patches changed at Δ



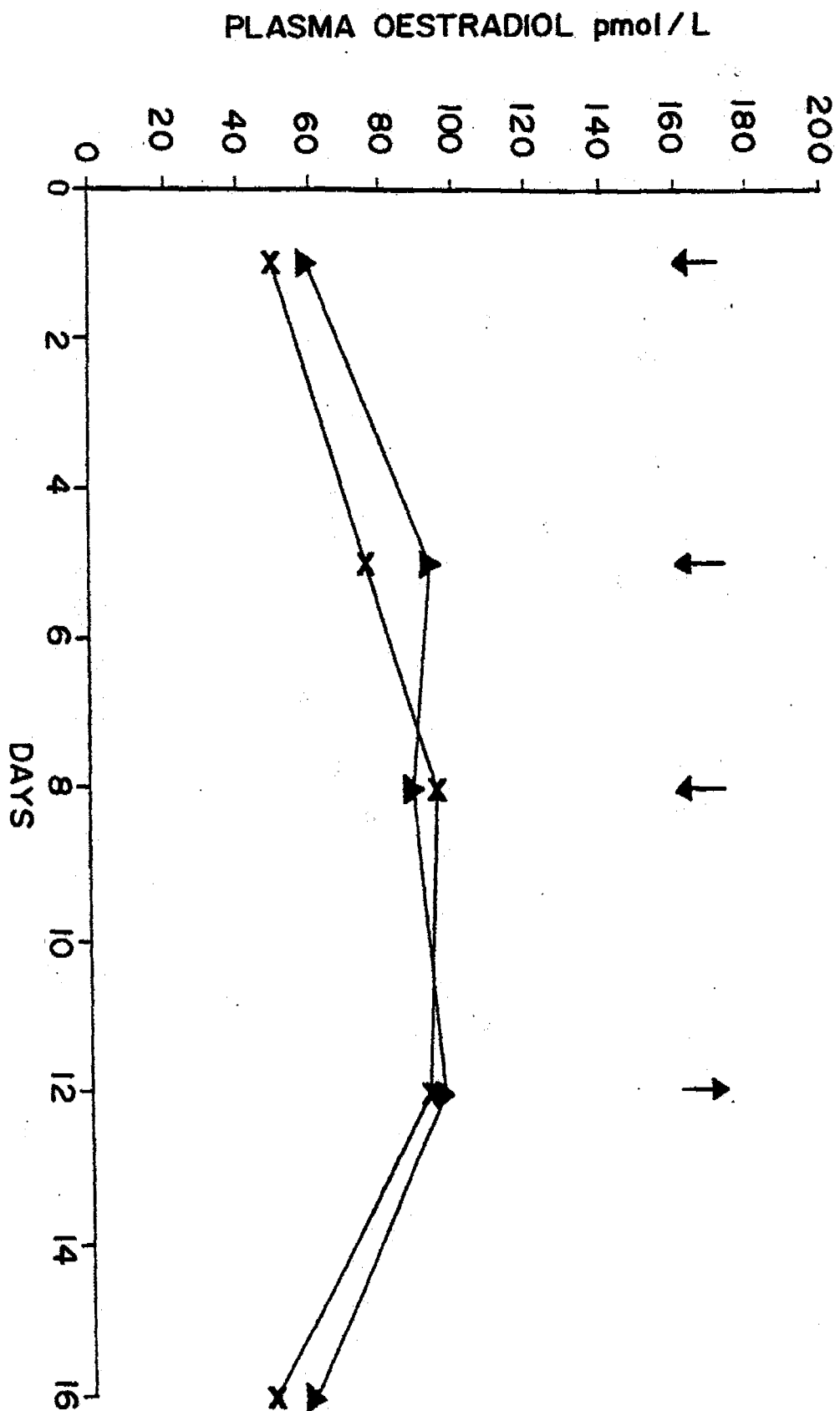


FIG. 4.

TRANSDERMAL DEVICE

The invention relates to a method of preparing a device for transdermal delivery of an active ingredient and to transdermal devices prepared by that method.

The administration of drugs through the skin is a concept which is now well established and this route has several advantages over more conventional forms of drug delivery such as injection or oral ingestion. A particular advantage is that transdermal drug delivery devices can provide a sustained and controlled release of the active ingredient over a prolonged period so that the resulting blood levels remain constant. This is in contrast to other forms of administration where surges of the agent occur in the bloodstream immediately after administration and then drop away rapidly until the next dose is given. In the case of oral administration the blood level is further influenced by contents of the intestines and therefore difficult to control. Transdermal administration permits direct access to the bloodstream without first passage through the gastrointestinal tract and liver and also without the inherent problems associated with injection such as risk of infection and need for sterile administration equipment.

Because of the advantage of transdermal administration, in recent years a very large number of devices have been developed and described for the transdermal administration of a variety of pharmaceuticals. The devices are usually in the form of a patch or plaster to be attached to the skin. Early devices such as for example, that described in U.S. Pat. No. 3,598,122 comprised a reservoir containing the active ingredient, either in solid or liquid form. The reservoir walls were composed of a material permeable to that ingredient and it was stuck to the skin by a thin layer of adhesive which was also permeable to the active ingredient. The outer surface of the reservoir was covered with a backing material impermeable to the active ingredient. Such devices were bulky and solvents in which the active agent was dissolved tended to interfere with the ability of the adhesive to stick to the skin.

With improvements in adhesives available it was soon found possible, and indeed preferable, to prepare transdermal devices in which the adhesive layer itself provided the drug reservoir. Thus more modern transdermal devices usually comprise at least an impermeable backing material, a layer of drug-containing adhesive attached to the backing material and a release liner on the other adhesive surface which is removed for application of the device to the skin. Additional membranes are sometimes included within the device to regulate the rate of passage of the active agent from the adhesive to the skin.

Various methods have been used to achieve suitable drug/adhesive mixtures in which the active ingredient is dispersed in the adhesive without affecting the ability of the adhesive to stick to the skin. One of the earliest drugs to be administered by a transdermal device was nitroglycerin which is used in the treatment of angina pectoris and congestive cardiac failure. Nitroglycerin is well absorbed by the skin and therefore particularly amenable to transdermal administration. Conveniently it is a liquid at room temperature and so the approach that has been taken is to absorb it on to a solid such as lactose which is then dispersed in a polymer adhesive. Such devices are described in, for example U.S. Pat. No. 4,776,850, G.B. 2,081,582, and others. One or more

other "solvents" are sometimes present in the nitroglycerin adhesive mixtures either as permeation enhancers, or for the purpose of "solvent casting" the mixture onto a backing layer.

Where the active ingredient to be incorporated into a transdermal device is a solid any solvent for the agent must be carefully chosen to be compatible with the adhesive. In WO86/00814 for example the problem is overcome by choosing a single solvent which is both a solvent for the drug and a solvent for the adhesive. However such a method restricts severely the number of different drugs which are compatible with a particular adhesive and also the type of adhesive which can be used.

Alternative methods have therefore been used in which a drug/adhesive mixture is prepared which includes a solvent for the drug and a solvent for the adhesive. The mixture is spread onto an appropriate backing material and then dried to evaporate the solvents leaving the drug dispersed in the adhesive in particulate form. A variation of the method is described in WO89/07951 in which the solvents for the adhesive are evaporated during a drying stage leaving the drug, in this case oestrogen, dispersed in particulate form in very high boiling point solvents which do not significantly evaporate on drying but which have a low capacity for the drug.

While the active ingredient can be taken up by the skin from a dispersion of the solid compound, the rate of uptake can be far better controlled if the agent is in a supersaturated solution, particularly where the solvent has an adequate capacity for the active ingredient. As the ingredient is taken up by the skin more will become dissolved in solution so maintaining a concentration gradient over a prolonged period which drives uptake through the skin. Transdermal devices are known which contain saturated drug solutions. They are described for example in G.B. 2,156,215 and U.S. Pat. No. 4,201,211. However these documents fail to describe a way in which the level of saturation can be precisely controlled to produce a supersaturated solution.

The present invention provides an improved method for preparing transdermal devices which contain supersaturated solutions of an active ingredient within an adhesive layer by use of a carefully selected mixture of solvents and selective evaporation of a particular solvent or solvents by drying at a temperature above the boiling points thereof, to influence the final concentration of the solution of active ingredient in the device.

In accordance with the invention a method of preparing a device for transdermal delivery of an active ingredient which is a solid at room temperature and in which part or all of the active ingredient is present in a supersaturated solution comprises the steps of:

- (a) preparing a mixture comprising at least
 - (i) a polymer adhesive
 - (ii) a vehicle for the polymer adhesive
 - (iii) the active ingredient
 - (iv) a solvent mixture for the active ingredient which comprises at least two solvents;
- (b) forming the mixture prepared in step (a) into a film, and
- (c) drying the film prepared in step (b) wherein the vehicle for the polymer adhesive and at least one of the solvents in the solvent mixture for the active ingredient have boiling points below the drying temperature and at least one of the solvents in the solvent mixture for the active ingredient has a boil-

ing point above the drying temperature and wherein the solubility of the active ingredient in the said solvent or solvents having a boiling point above the drying temperature is greater than 10%.

The above method provides a very precise way of preparing an adhesive/active ingredient mixture which contains a supersaturated solution of the ingredient after drying.

It is to be understood herein that the term "active ingredient" is intended to mean a single active agent or a combination of more than one active agent.

Dissolving the active ingredient in a mixture of solvents and then drying at a temperature which facilitates the evaporation of the vehicle for the adhesive and one of the solvents for the active ingredient, because it is above their boiling points, leaves the active ingredient in a supersaturated solution in the solvent or solvents that remain. Supersaturated solutions are particularly advantageous from the point of view of transdermal administration because they assist in controlling the rate of migration of the active ingredient through the skin as previously mentioned.

The choice of particular solvents, adhesives and drying temperatures is dictated by the solubility of the particular active ingredient in the solvent or solvents remaining in the device after drying. Thus with careful selection of all the components the method of the invention can provide transdermal devices which can administer a very wide range of drugs. The solubility of the active ingredient in the solvent or solvents having a boiling point above the drying temperature needs to be greater than 10%.

The polymer adhesive may be a polyisobutylene or silicone adhesive although acrylate polymer adhesives are particularly preferred. Suitable vehicles for the acrylate adhesives are for example methanol, ethanol, industrial methylated spirits (IMS), isopropanol and water. Suitable vehicles which may be used with polyisobutylene are toluene, xylene and methylene chloride. Suitable vehicles for silicone adhesives are chlorofluorocarbons such as, for example, trichlorotrifluoroethane. For acrylate adhesives aqueous dispersions are preferred. In this latter case drying temperatures used in drying the film must always be in excess of 100° C. at normal atmospheric pressures. Where the vehicle for the adhesive is a lower boiling solvent such as methanol (bp 65° C.), ethanol (bp 78.5° C.) or isopropanol (bp 82.4° C.), a lower drying temperature may be used providing it is above the boiling point of the low boiling solvent included in the solvent mixture for the active ingredient.

In one embodiment of the invention the vehicle for the adhesive and the solvent to be evaporated during drying from the solvent mixture for the active ingredient both are chosen to have a boiling point below that of ethanol. A drying temperature can thus be chosen which allows the ethanol to be maintained within the device. This is advantageous because ethanol is a useful skin permeation enhancer for some drugs. For acrylate systems a suitable solvent which may be evaporated while ethanol is retained is methanol. For non-aqueous systems ether or chlorofluorocarbons may be used.

In another embodiment of the invention the solvent in the solvent mixture for the active ingredient which is evaporated on drying may be ethanol, isopropanol, industrial methylated spirits (IMS) or water.

High boiling point solvents suitable for forming the saturated or supersaturated solutions of the active ingre-

dient in the transdermal device are those having boiling points in excess of 110° C. Preferred solvent mixtures include one or more of diethylene glycol, propylene glycol, propylene carbonate, glycerol, lower molecular weight polyethylene glycols, propylene glycol esters, polyol fatty acid esters, fatty alcohol derivatives, oleic acid, iso-octyl stearate, iso-propyl myristate, isopropyl palmitate, ethyl oleate, diisopropyl adipate, diethylsuccinate, hexylaurate, triglycerides of caprylic or capric acids, diethyltoluamide, laurocapram, n-methylpyrrolidone and diethylene glycol monoether. Also suitable as solvents which are not evaporated from the device on drying are essential oils such as eucalyptus oil, tea-tree oil and lavender oil. Preferably at least one of the solvents which remains in the device will also act as a permeation enhancer to assist uptake by the skin of the active ingredient. Preferred solvent systems are propylene glycol-diethyltoluamide, n-methylpyrrolidone-diethyltoluamide, propylene glycol - diethylene glycol monoethyl ether and diethyltoluamide-diethylene glycol monoethyl ether - tea tree oil.

Among the active agents which may be included in transdermal devices produced by the method of the invention are anti-histamines such as, for example, clenastine fumarate, steroid hormones such as oestradiol, progestins such as norethisterone acetate, norgestrel, ethynodiol diacetate, medroxy progesterone acetate, gestodene and desogestrel, vasodilators such as nifedipine and diltiazem, antihypertensives such as clonidine and propranolol, bronchodilators such as salbutamol and clenbuterol, anti-tumour agents such as methotrexate and 5-fluorouracil, alkaloids such as physostigmine and analgesics such as fentanyl, sufentanil, buprenorphine and hydromorphone. The device may contain an active ingredient which is a combination of more than one of the above active agents, for example an oestrogen with a progestin.

While the solvents to be used in the method of the invention must be selected in order that a supersaturated solution is produced on drying, solvents may also be selected which modify the properties of the adhesive so that it possesses the required degree of adhesion and tackiness to stick to the skin for the required period, which could be several days, but at the same time can be easily removed as required. The method of the present invention allows polymer adhesives which are normally too aggressive to be used in transdermal devices to be rendered suitable by choice and incorporation of an appropriate solvent mixture.

The assembly of a transdermal device prepared in accordance with the method of the present invention will now be described by way of example with reference to FIGS. 1 and 2 of the accompanying drawings and Examples 1 to 4.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a vertical section through a first embodiment of the invention without the inclusion of a rate control membrane.

FIG. 2 is a vertical section through a second embodiment of the invention including a rate control membrane.

FIG. 3 shows mean plasma concentration time curves following transdermal administration of norethisterone acetate to four post menopausal women using a transdermal device prepared in accordance with the method of the invention — results from samples assayed by RIA at Liverpool University. x—x results from same

samples assayed by RIA at Hammersmith Hospital. ↑ transdermal patches applied or replaced. ↓ transdermal patches removed.

FIG. 4 shows mean plasma concentration time curves following transdermal administration of oestadiol using the devices of Example 4 (▲—▲) and known product Estraderm 50 (X—X). The arrows indicate patches applied, replaced or removed as above.

As already described, a mixture is formed which comprises a polymer adhesive in a suitable vehicle, the active ingredient to be administered, and a solvent mixture for the active ingredient which comprises at least two solvents one of which must have a boiling point above the drying temperature and one below. Preferably the active ingredient is first dissolved in the solvent mixture and the solution slowly added to the adhesive polymer previously dispersed in a suitable vehicle. Depending on the coating technique and adhesive used the addition of an adhesive thickener may be required. The mixture of adhesive polymer and active ingredient is formed into a film, preferably by coating onto a flexible sheet material. A typical embodiment of a device formed in accordance with the method of the invention is shown in FIG. 1. The adhesive mixture is formed into a layer 4 on a siliconised release paper 2. The layer is preferably about 5 to 500 μm thick. The coated release paper is dried at the appropriate temperature to drive off the necessary solvents and then laminated to a backing material 6 impermeable to the active ingredient. Suitable siliconised release liners are 3M Health Care Type 660 or 1360, Daubert HDPE 164Z or L. Stace types 635/6. Preferable backing materials include polyester film laminate (e.g. 3M Health Care Type 1012 or 1220), metalised polyester laminate (e.g. 3M Health Care Type 1109) and co-extruded high barrier films either clear (e.g. BXL Plastics Hybar) or skin-tone (e.g. Grace-Cryovac MF200). Backings having higher oxygen and water vapour transmission rates are preferred for devices intended for treatment for more than 24 hours. A suitable backing material in these circumstances is Semex polyester-urethane film type MF 4387-00.

The reverse manufacturing method is also possible and in some cases advantageous i.e. spreading the adhesive/solvent mixture onto the backing material and then laminating it to the release liner.

FIG. 2 shows a second embodiment of the invention in which the adhesive/active ingredient layer is divided by a rate control membrane 8. The layer 4a which, in use, is in direct contact with the skin provides an initial loading dose of the active ingredient. As this migrates into the skin the consequent concentration difference between layer 4a and 4b causes the layer 4a to be replenished with active ingredient from the layer 4b at a rate dictated by the rate control membrane. Thus the inclusion of such a membrane provides a further means to control the rate of uptake for a pre-determined period, firstly by selection of the appropriate membrane and secondly by varying the thickness of the layers 4a and 4b on either side of the membrane. Suitable materials for forming the rate control membrane include polypropylene film (e.g. Celgard microporous film), polyvinyl acetate film (e.g. Mowiol film (Hoechst) and ethyl vinyl acetate film (e.g. controlled caliper MSP series films obtained from 3M Health Care Speciality Division). The thickness of the layer 4a may be in the range 5 to 50 μm and the thickness of the layer 4b may be in the range 50 to 500 μm .

The device of FIG. 2 is formed as previously described except that when using conventional coating/drying equipment the process becomes two stages. The backing material 6, coated with adhesive layer 4b is laminated to rate control membrane 8. The second stage is the lamination of this laminate to the adhesive layer 4a which has been coated on to the release paper 2. Alternative manufacturing methods are possible and more than one rate control membrane can be incorporated at any location within a multilayer device. Preferably all of the above described layers are assembled on a single large sheet which is die cut into transdermal devices of the appropriate size.

EXAMPLE 1

Transdermal Device Containing Norethisterone Acetate Without A Rate Control Membrane

A mixture of acrylate polymer adhesive and the active ingredient norethisterone acetate is formed containing the following:

Component	Quantity (g)
Norethisterone acetate (micronised)	395
Propylene glycol	2125
Diethyltoluamide	1000
Ethanol (95%) or IMS	1500
Primal N560 (acrylate adhesive dispersion in water)	44500
Acrysol ASE 60 (thickener for adhesive diluted 50:50)	480
Total	50 Kg

The norethisterone acetate is dissolved in propylene glycol, diethyltoluamide and ethanol by sonication or warming. This solution is added slowly to the aqueous acrylate adhesive dispersion (Primal N560, Rohm & Hass) with mixing. An adhesive thickener (Acrysol ASE 60) is then added to the mixture as a 50% solution/water mix sufficient to produce a thicker spreading solution of around 800 cP (Brookfield) for reverse roll coating or 60,000 cP to suit knife over roll coating.

The mixture is coated on the backing polyester (3M Health Care Type 1109) at about 100 μm wet coating thickness and dried at about 105° C. to drive off the water and the ethanol or IMS from the acrylate adhesive. The resulting dried adhesive layer is about 55 μm thick. The release liner (Stace type 636) is laminated to the adhesive layer. The final sheet is die-cut to form transdermal devices of about 19 or 28.5 cm^2 each containing 1.5 or 2.25 mg norethisterone acetate respectively, which are packaged individually.

EXAMPLE 2

Transdermal Device Containing Oestradiol With Rate Control Membrane

A mixture is prepared containing the following:

Component	Quantity (g)
17 β Oestradiol	87.5
Propylene glycol	400
Diethyltoluamide	100
95% Ethanol or IMS	100
Polysorbate 20	12.5
Primal N560 (acrylate adhesive dispersion)	4262.5
Acrysol ASE 60 (thickener for adhesive) 50:50 water	37.5

-continued

Component	Quantity (g)
Total	5000 g

The oestradiol is dissolved in the solvent mixture and slowly added to the aqueous adhesive to which an Acrysol ASE 60 thickener is also added in a similar way to Example 1. The mixture is coated onto a siliconised release liner (3M Health Care Type 660) to give a 50 μ m wet coating which is dried at 105° C. as described above. When dried the adhesive layer and liner are laminated to a rate control membrane sheet material (3M ethyl vinyl acetate membrane, MSP 987192) which is then coated with a 250 μ m wet coating of the same adhesive mixture and dried as before. The adhesive layers are then laminated to the clear polyester film laminate backing material as described. The sheets are cut into 20 cm² transdermal devices each containing 10.5 mg oestradiol and individually packaged for use.

EXAMPLE 3**Transdermal Device Containing Oestradiol Without A Rate Control Membrane**

A mixture is prepared containing the following:

Component	Quantity (g)
17 β oestradiol	440
Diethyltoluamide	2250
Isopropanol	60
Primal N560	47000
Acrysol ASE 60:water (50:50)	250
Total	50 Kg

The devices are prepared and assembled as described in Example 1. The release liner is coated to a wet-coat thickness of 100 μ m and after drying and laminating the laminate is die cut to 28.5 cm² devices each containing 2.5 mg oestradiol.

EXAMPLE 4**Transdermal Device Containing Oestradiol Without A Rate Control Membrane**

A mixture is prepared containing the following:

Component	Quantity (g)
17- β Oestradiol (micronised)	30
Diethyltoluamide	100
Diocetyl sodium sulphosuccinate	3
Isopropanol/water 50:50	2
Primal N560	655
Primal N582	200
Acrysol ASE 60:water 50:50	q.s. 10
Total	1000 g

The devices are prepared and assembled as described in Example 1 except that the devices are cut to 20 cm². Results obtained in a 4 subject pharmacokinetic study in comparison with an existing product (Estraderm 50) are shown in FIG. 4.

EXAMPLE 5**Transdermal Device Containing Buprenorphine Without A Rate Control Membrane**

A mixture is prepared containing the following:

Component	Quantity (g)
Buprenorphine	42
Ethanol or IMS	100
Diethyltoluamide	150
Diethylene Glycol Monoethyl ether	150
Tea Tree oil	100
Primal N560	3908
Primal N582	500
Acrysol ASE 60:water 50:50	50
Total	5000 g

The devices are prepared and assembled as described in Example 1 except that the release liner is coated to a wet coat thickness of 150 μ m and after drying the laminate is cut to 20 and 50 cm² devices containing 2.5 mg/20 cm² or 6.3 mg/50 cm² buprenorphine respectively.

It is to be noted that the terms Hybar, Cryovac, Celgard, Mowiol, Contran, Primal, Acrysol, Brookfield, Triton and Estraderm, used in the specification are Registered Trade Marks.

I claim:

1. A method of preparing a device for transdermal delivery of an active ingredient which is a solid at room temperature and in which part or all of the active ingredient is present in a supersaturated solution comprising the steps of:

(a) preparing a mixture comprising at least:

(i) a polymer adhesive which is selected from the group consisting of acrylate polymer adhesives, polyisobutylene adhesives, and silicone adhesives;

(ii) a vehicle for the polymer adhesive, which vehicle is selected from the group consisting of water, ethanol, industrial methylated spirits, isopropanol, toluene, xylene, methylene chloride, and chlorofluorocarbon;

(iii) the active ingredient;

(iv) a solvent mixture for the active ingredient which comprises at least two solvents having different boiling points;

(b) forming the mixture prepared in step (a) into a film, and

(c) drying the film prepared in step (b), wherein the vehicle for the polymer adhesive and at least one of the solvents in the solvent mixture for the active ingredient have boiling points below the drying temperature, and at least one of the solvents in the solvent mixture for the active ingredient has a boiling point above the drying temperature, and wherein the solubility of the active ingredient in the said solvent or solvents having a boiling point above the drying temperature is greater than 10%.

2. A method as claimed in claim 1 wherein the vehicle for the polymer adhesive is a solvent having a boiling point below that of ethanol.

3. A method as claimed in claim 2 wherein the vehicle for the polymer adhesive is methanol.

4. A method as claimed in claim 1 wherein the vehicle for the polymer adhesive is water.

5. A method as claimed in claim 1 wherein the solvent in the solvent mixture for the active ingredient with a boiling point below the drying temperature is selected from the group consisting of ethanol, industrial methylated spirits, isopropanol and water.

6. A method as claimed in claim 2 wherein the solvent in the solvent mixture for the active ingredient with a

boiling point below the drying temperature is a solvent having a boiling point below that of ethanol.

7. A method as claimed in claim 6 wherein the solvent in the solvent mixture for the active ingredient with a boiling point below the drying temperature is methanol.

8. A method as claimed in claim 1 wherein the solvent mixture for the active ingredient comprises at least one solvent having a boiling point above the drying temperature selected from the group consisting of diethylene glycol, propylene glycol, propylene carbonate, glycerol, lower molecular weight polyethylene glycols, propylene glycol esters, polyol fatty acid esters, fatty alcohol derivatives, oleic acid, iso-octyl stearate, isopropyl myristate, isopropyl palmitate, ethyl oleate, diisopropyl adipate, diethylsuccinate, hexylaurate, triglycerides of caprylic or capric acids, diethyl toluamide, laurocapram, n-methylpyrrolidone, diethylene glycol monoethyl ether and essential oils.

9. A method as claimed in claim 1 wherein the drying step (c) is carried out at or above 100° C.

10. A method as claimed in claim 1 wherein the drying step (c) is carried out at a temperature below the boiling point of ethanol.

11. A method as claimed in claim 1 wherein the active ingredient comprises at least one active agent selected from the categories antihistamines, steroid hormones, progestins, vasodilators, antihypertensives, bronchodilators, anti-tumor agents, alkaloids and analgesics.

12. A method as claimed in claim 1 wherein the film prepared in step (b) is formed by coating the mixture prepared in step (a) onto a thin flexible sheet material.

13. A method as claimed in claim 12 wherein the thin flexible sheet material is a siliconised release liner.

14. A method as claimed in claim 12 wherein the flexible sheet material is a backing material impermeable to the active ingredient.

15. A method as claimed in claim 12 wherein the film formed in step (b) is between 5 μ m and 500 μ m thick.

16. A method as claimed in claim 13 wherein the coated surface of the release liner is laminated to a backing material impermeable to the active ingredient.

17. A method as claimed in claim 14 wherein the coated surface of the impermeable backing material is laminated to a siliconised release liner.

18. A method as claimed in claim 13 wherein the coated surface of the release liner is laminated to a rate control membrane the free surface of which is further coated with the mixture prepared in step (a).

19. A method as claimed in claim 14 wherein the coated surface of the backing material is laminated to a rate control membrane, the free surface of which is further coated with the mixture prepared in step (a).

20. A method as claimed in claim 18 wherein the coated rate control membrane is laminated to a further rate control membrane or to a backing material impermeable to the active ingredient.

21. A method as claimed in claim 18 wherein the coated rate control membrane is laminated to a further rate control membrane or to a siliconised release liner.

22. A method as claimed in claim 18 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the rate of migration across the membrane.

23. A method as claimed in claim 19 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the rate of migration across the membrane.

24. A method as claimed in claim 18 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the proportion or amount of active ingredient immediately available adjacent to the skin for absorption.

25. A method as claimed in claim 19 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the proportion or amount of active ingredient immediately available adjacent to the skin for absorption.

26. A method as claimed in claim 14 wherein the backing material impermeable to the active ingredient is selected from the group consisting of a polyester film laminate, metalised polyester laminate co-extruded high barrier film and an air and water permeable polyurethane.

27. A method as claimed in claim 18 wherein the rate control membrane is selected from the group consisting of polypropylene film, a polyvinyl acetate film and an ethylvinyl acetate film.

28. A method as claimed in claim 19 wherein the rate control membrane is selected from the group consisting of polypropylene film, polyvinyl acetate film and ethylvinyl acetate film.

29. A device for transdermal delivery of an active ingredient prepared by the method as claimed in claim 1.

* * * * *

ANEXO 4

(12)

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(54) **Transdermal administration of amines.**

(57) Transdermal or percutaneous administration of systemic dosages of physiologically active amines to humans is accomplished at an increased rate by diluting the amine or a salt of said amine by dissolving it in a nonpolar nonvolatile solvent before bringing it into contact with the skin. The dilution may be applied to the skin from a supply absorbed in a polymeric matrix or sponge.

Description

TRANSDERMAL ADMINISTRATION OF AMINES

This invention relates to a method, composition, and article for use in transdermal or percutaneous administration to humans of a physiologically active amine and pertains more specifically to a method, composition and article for application to skin for systemic administration from a composition comprising said amine or a salt thereof, preferably a salt with a fatty acid having 8 to 20 carbon atoms, diluted with a nonpolar nonvolatile solvent.

It has long been known that various medicaments can be transported through the skin of a human to provide systemic and prolonged administration of the medicament. In the case of physiologically active amines, however, application of the pure amine to the skin frequently causes irritation, whereas application of the commonly used amine salts such as the hydrochloride, maleate or tartrate suppresses irritation but results in a relatively low rate of transport or penetration through the skin.

It has now been found that diluting physiologically active amines, whether irritating to the skin or not, or salts thereof which are soluble in nonpolar liquids, with nonpolar nonvolatile solvents enhances the rate of transport or flux of the amine through the skin with which it is placed in contact so that a much smaller area of skin contact suffices to maintain a pharmacologically effective concentration of the amine in the system. Such solvents are generally more lipophilic than hydrophilic in nature. Moreover, it has also been found that salts of skin-irritating amines with fatty acids having 8 to 20 carbon atoms cause little or no irritation or inflammation of the skin and that the amines are transported through the skin at high rates from dilutions of such salts with nonpolar nonvolatile solvents. Amines are transported only at much lower rates from dilutions of salts of the amines with more polar acids such as the maleates or tartrates. The present invention makes it possible to produce and maintain with little or no irritation a therapeutically and systemically effective concentration of a physiologically active amine in a human by transdermal administration thereof using an area of application of practical size.

Although it previously has been proposed in Abramson U.S. Patent 3,304,230 to provide solutions of salts of physiologically active amines with monocarboxylic fatty acids having from 4 to 18 carbon atoms dissolved in aerosol compositions which include various highly volatile solvents or propellants, such solutions are ineffective for the purpose of the present invention because of the virtually immediate loss of solvent after application to the skin.

Accordingly, the present invention comprises a method of administering a physiologically active non-skin-irritating amine systemically to a human which comprises providing a dilution of said amine in a nonpolar nonvolatile solvent, and maintaining said dilution in contact with the skin of the human. The invention also comprises a composition adapted to be maintained in contact with human skin to produce and maintain a therapeutically and systemically effective concentration of said amine in said human, said composition comprising a solution comprising said amine in a nonpolar nonvolatile solvent. The invention also comprises a method of administering a physiologically active amine, particularly a skin-irritating amine, systemically to a human which comprises providing a dilution of a salt of said amine with a fatty acid having 8 to 20 carbon atoms in a nonpolar nonvolatile solvent, maintaining said dilution in contact with the skin of the human. In addition, the invention comprises a method and composition in which said amine is an antihistamine and in which said solution includes an excess of as much as 200% of said acid over the stoichiometric amount required to form said salt. Compositions as employed in these latter methods are also aspects of the invention. Finally, the invention includes articles adapted to be maintained in contact with human skin to provide systemic administration of a physiologically active amine in said human, said articles comprising the aforesaid compositions absorbed in a solid porous water-insoluble polymeric matrix.

Any physiologically active amine may be used in the present invention. Particularly preferred are the antihistamines and adrenergic amines. Among suitable amines are diphenhydramine, bromodiphenhydramine, doxylamine, phenyltoloxamine, carbinoxamine, methapheniline, pyrilamine, tripeleminamine, methapyrilene, chlorothene, theryldamine, methafurylene, thonzylamine, pheniramine, chlorpheniramine, brompheniramine, dexbrompheniramine, pyrrobutamine, promethazine, pyrazthiazine, trimeprazine, methdilazine, isothipendil, ephedrine, epinephrine, norepinephrine, isoproterenol, phenylephrine, butaneftin, amphetamine, vonedrine, cyclizine, clorocyclizine, meclizine, pilocarpene, nicotine, scopolamine, chonidine, naphedapine, diphenylpyraline, phenindamine, dimethylpyrindene, and clemizole, and the like. Those amines which do not irritate the skin when in contact with it may be employed in the form of the free base or in the form of a salt with a fatty acid, preferably an unsaturated fatty acid, having 8-20 carbon atoms. The free base form is preferred because it generally displays a higher flux through the skin than the salt form. Among such non-irritating amines is diphenhydramine. Amines which do irritate the skin when in contact with it, such as chlorpheniramine, may be employed in the form of a salt with a fatty acid, preferably an unsaturated fatty acid, having 8-20 carbon atoms.

Whether or not an amine is irritating can readily be determined by a conventional patch test involving maintaining the amine in contact with the skin for 24 hours, then observing the skin. If no irritation such as permanent injury, edema, pain, itching or blistering appears (although mild erythema or reddening may occur), the amine is non-irritating for the purpose of the present invention.

The solvents which can be used in the present invention are organic nonpolar nonvolatile solvents, particularly those having dielectric constants less than 4 and boiling points above 150°C. More volatile

solvents are undesirable because of their tendency to evaporate while in contact with the skin. In the absence of solvent the rate of transport of the drug through the skin is so low, in many cases, as to be impractical. The rate of transport or flux of the drug through the skin must be sufficiently high so that a pharmaceutically effective systemic concentration can be provided using a skin contact area of reasonable size. In general, the maximum area of skin contact which is practical for a single application is no more than 20 in², and preferably less than 6 in², although in some cases two or more applications can be employed simultaneously on separate skin areas. Since it is well known that the therapeutically effective systemic dose varies depending upon the specific bioactivity and pharmacokinetics of the particular amine being used and the weight of the patient, the minimum flux or transport rate required can readily be determined by simple arithmetic for an applicator of given area.

The rate of transport or flux of an amine through the skin can readily be determined *in vitro* by placing the amine or amine salt composition, with the amine suitably labeled, for example with tritium to a final specific activity of 300 disintegrations per minute per microgram, in contact with a specimen of human epidermis, e.g. human breast epidermis, with intact stratum corneum, mounted in a conventional diffusion cell providing an exposed skin surface area of 0.33 cm² each. The receptor chamber of each cell is swept with a stream of 0.1 M phosphate buffered (pH 7.4) isotonic saline in direct contact with the rear surface of the epidermal sample, the flow rate being maintained at 3 mL per hour. Samples of the saline are collected at two hour intervals and assayed by a liquid scintillation counter, applying the appropriate quench correction procedure. Steady state transport or flux of the drug through the epidermis is generally observed in less than two hours.

In addition to the foregoing characteristics of the solvent, it must itself be non-irritating to the skin and chemically inert to the amine or salt. Among suitable solvents are hydrocarbons such as mineral oil, alcohols such as benzyl alcohol, dodecyl alcohol, esters such as isopropyl myristate, isopropyl oleate, methyl stearate, tributyl citrate, ethyl laurate, diethyl maleate and similar solvents which have seven or more carbon atoms in the molecule.

The relative proportions of amine or salt and solvent present may be varied over a wide range. The minimum amount of solvent needed is the amount required to dissolve the amine or salt if the two are not miscible liquids. In general, it is found that the flux of the amine through the skin at first increases as the proportion of solvent increases, reaching a maximum at a relative proportion or concentration which differs depending upon the specific amine or salt and specific solvent present, and then decreases. Moreover, as the relative amount of solvent increases further, a larger volume of the dilution and a larger area of contact with the skin is required to maintain the desired systemic concentration of amine for the desired time period. Within these broad limits the optimal ratio or proportion of solvent to amine or amine salt can readily be determined by simple experimentation in the case of any particular combination of solvent with amine or salt. In general, satisfactory results are obtained with compositions containing 10 to 90% by weight of solvent based on the total weight of solvent and amine, whether the amine is in the form of free base or salt, with best results often obtained at 40 to 60% solvent by weight.

The fatty acids which are effective in the amine salts of the preferred embodiment of the present invention include octenoic, undecylenic, lauric, linoleic, oleic, myristic, stearic, isostearic, and the like. The amine salt may be employed in pure form, in which the amine and the acid component are present in stoichiometric proportions. Although an excess of acid tends to decrease the rate of transport of the amine through the skin, it may be desirable to use an excess of acid because such excess acid reduces the tendency toward skin irritation. In general, an excess above about 200% molar percent of acid offers no advantage. A 100% molar excess acid composition in the case of chlorpheniramine provides a reasonable balance between non-irritation and high transport rate of the amine through the skin.

For effective systemic administration of the amines, the dilution or solution must be maintained in contact with the skin for a prolonged period of time. This can be accomplished, for example, by thickening the solution to the point where it does not readily flow and approaches a solid in properties, either by appropriate selection of solvent or by adding appropriate thickeners or gelling agents to the solution. It can also be accomplished by dispersing into the organic solution an aqueous medium to form a very viscous or gel-like water-in-oil emulsion or slurry. In either of the foregoing cases the substantially non-flowing solution can simply be applied to or coated on the skin; preferably some mechanical protection in the form of a cover or bandage is provided to prevent it from being wiped off. Another method for maintaining contact between the solution and the skin is to compound the solution with a suitable inert adhesive to produce a semisolid adhesive layer combining in one component the required payload of amine or amine salt, the nonpolar diluent, and dermal adhesive properties. Such an adhesive layer can usefully be backed with a nonpermeable covering such as foil or plastic film to confine the drug and avoid adhesion to other surfaces. The organic solution can also be maintained in place by imbibing or absorbing it in a suitable solid carrier such as an absorbent pad of fibrous material or a porous water-insoluble polymeric matrix, the latter being preferred. It is particularly advantageous to incorporate the drug solution in a gelled cellulose triacetate matrix, as described, for example, in Nichols U.S. Patent 3,846,404, incorporated herein by reference. In general, suitable carriers are porous, preferably microporous, water-insoluble materials throughout which the amine solution can be distributed or dispersed so that a supply of the amine is maintained in contact with the skin. In a preferred embodiment the carrier is provided with means for maintaining it in contact with the skin, such as a layer of adhesive. The adhesive may extend only along part or all of the periphery of the face of the carrier, or it may, if it is sufficiently permeable, cover the skin contacting face of the carrier. In the simplest case, a separate strip of adhesive tape may be employed to

maintain the carrier in place. Among suitable carriers are absorbent paper, fibrous batts such as cotton batting, and various porous or microporous polymeric gel compositions such as partially cross-linked polyvinyl alcohol, polyvinyl pyrrolidone, or polyacrylamide; and porous or microporous gels of cellulose esters or ethers including cellulose acetate, cellulose butyrate, cellulose nitrate, and the like. Particularly preferred is microporous cellulose triacetate gel, as pointed out above.

Overall rate of transport of the amine through the skin, hence the systemic concentration level of the amine, can be adjusted by varying the area of the skin with which the solution is in contact, as pointed out above, or by varying the type and amount of fatty acid and/or solvent present, while the length of time during which a desired level of concentration is maintained can be adjusted by varying the amount of amine present.

The following specific examples will serve to illustrate the invention without acting as a limitation upon its scope.

Examples

Chlorpheniramine, an antihistaminic amine widely used in the form of its maleate salt, was tested for skin irritancy by absorbing the pure amine (chlorpheniramine base) in a porous cellulose triacetate film (0.20 inch thick) prepared as described in U.S. Patent 3,848,404 (MA-92 POROPLASTIC film). Patches of the saturated film 2 cm² in area were placed by test subjects on their own forearm skin and held in place by clear, nonocclusive adhesive (Tegaderm), allowing constant observation of the skin under the patch. After 17 hours, severe irritation including blistering was observed in all subjects.

The pure chlorpheniramine was also converted to a salt of a fatty acid by stirring the two together in stoichiometric (equimolar) proportions, and the irritancy of the resulting salt was determined by the foregoing procedure.

Additional specimens of salts were prepared containing an excess of fatty acid above the stoichiometric amount and tested as described above.

In each case the effect on the skin was rated by visual observation on a scale from 1 (no visible change) to 7 (severe irritation with marked reddening, edema and blistering). The results were as follows, the molar ratio of amine to fatty acid for each salt being given in parentheses:

TABLE I

<u>Formulation</u>	<u>Number of Skin Tests</u>	<u>Irritation Rating (1 - 7)</u>	
1. FREE BASE			5
a. Chlorpheniramine Base	2	7.0	10
b. Chlorpheniramine Base, 23.5% solution in isopropyl oleate (IPO)	2	6.5	
2. SATURATED FATTY ACID SALTS			15
a. Chlorpheniramine Stearate (1:2M)	4	4.0	
b. Chlorpheniramine Myristate (1:2M)	2	3.0	20
c. Chlorpheniramine Isostearate (1:2M)	1	3.5	
3. UNSATURATED FATTY ACID SALTS			25
a. Chlorpheniramine Oleate (1:3M)	2	1.0	
b. Chlorpheniramine Oleate (1.:2M)	21	2.3	30
c. Chlorpheniramine Oleate (1:1M)	26	3.5	
d. Chlorpheniramine Undecylenate (1.3M)	2	1.0	35
e. Chlorpheniramine Undecylenate (1.2M)	2	2.0	
f. Chlorpheniramine Undecylenate (1.:2M) in 70% IPO	14	1.4	40
g. Chlorpheniramine Octenoate (1.2M)	2	1.5	
h. Chlorpheniramine Linoleate (1:1M)	1	3.0	45
4. CARBOXYLIC ACID SALTS			50
a. Chlorpheniramine Maleate (1:1M)	9	1.0	
b. Chlorpheniramine Salicylate (1:1M)	2	1.0	55

Chlorpheniramine labelled with tritium was prepared by first synthesizing an unsaturated precursor, 1-(p-chlorophenyl)-1-(2-pyridyl)-3-dimethylamino propene by the procedure of Adamson et al., J.Chem.Soc., 85

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1957. The compound was tritiated by reaction with tritium over Raney nickel catalyst as described by Adkins et al., Organic Chemistry, Vol. I, Chapter 9 (New York, 1943). The labelled chlorpheniramine thus produced was purified by thin layer chromatography and high pressure liquid chromatography. Chlorpheniramine labelled to a final specific activity of 3 disintegrations per minute per microgram was then used to prepare salts as listed above.

5 The foregoing fatty acid salts all displayed a rate of transport or flux through human skin when measured as described above in a diffusion cell which was substantially less than that of the free amine ($40 \mu\text{g}/\text{cm}^2/\text{hr}$), ranging from about $10\text{-}20 \mu\text{g}/\text{cm}^2/\text{hr}$; the maleate and salicylate salts displayed extremely low rates, less than $6 \mu\text{g}/\text{cm}^2/\text{hr}$. However, when diluted with nonpolar nonvolatile solvents in amounts ranging from 25-90%
10 by weight based on the total weight of solvent and amine or amine salt, the flux rate was increased, as shown by the following table:

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TABLE II

<u>Chlorpheniramine</u>		<u>Undecylenic Acid</u>		<u>Nonpolar Solvent</u>	<u>Base:Acid</u>		<u>molar ratio</u>	<u>Flux</u> <u>µg/cm²/hr</u>
<u>wt%</u>	<u>mole%</u>	<u>wt%</u>	<u>mole%</u>	<u>compound</u>	<u>wt%</u>	<u>mole%</u>		
2.1	2.5	2.9	4.9	Isopropyl Oleate	95.0	92.6	1:2	17.4
6.5	7.1	8.9	14.4	"	84.6	78.5	1:2	40.7
12.7	11.6	17.1	23.4	"	70.2	65.0	1:2	43.5
14.0	14.3	18.8	28.5	"	67.0	57.2	1:2	27.4
27.3	24.2	36.9	48.9	"	35.7	26.9	1:2	12.9
42.3	33.0	57.7	67.0	None	---	---	1:2	11.1
31.2	26.6	42.7	54.5	Isopropyl Myristate	26.1	18.8	1:2	17.8
20.4	19.3	28.0	39.3	"	51.7	41.4	1:2	39.6
8.5	9.3	11.7	18.5	"	79.7	72.2	1:2	53.6
100.0	100.0	---	---	None	---	---	1:0	39.5

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As can be seen from these results, the amount of solvent producing optimum flux rate varies depending upon the identity of the specific solvent. In the case of isopropyl oleate and isopropyl myristate, the optimum

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flux rate exceeded that of the pure or free amine as well as that of the pure amine salt.

Similar results are obtained in the case of dexchlorpheniramine, brompheniramine, and dexbrompheniramine salts.

5 Example 2

Diphenhydramine was found by patch tests as described in Example 1 to have little or no skin irritancy. A dilution of pure diphenhydramine with 29.8% by weight of mineral oil was prepared and the rate of transport of the amine through human skin was determined as described in Example 1 to be 76.6 $\mu\text{g}/\text{cm}^2/\text{hr}$ as compared to 4.0 $\mu\text{g}/\text{cm}^2/\text{hr}$ for the pure amine without solvent.

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Example 3

A salt of diphenhydramine was prepared by stirring it with an equimolar quantity of linoleic acid and was found to be non-irritating by the patch test. Samples of the salt were diluted with varying amounts of isopropyl myristate and the flux was measured as described in Example 1, with the following results:

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TABLE III

20	<u>Diphenhydramine</u>		<u>Linoleic Acid</u>		<u>Isopropyl Myristate</u>		<u>Base:Acid</u>	<u>Flux</u>
	<u>wt%</u>	<u>mole%</u>	<u>wt%</u>	<u>mole%</u>	<u>wt%</u>	<u>mole%</u>	<u>molar ratio</u>	<u>$\mu\text{g}/\text{cm}^2/\text{hr}$</u>
	12.0	12.7	13.2	12.7	74.8	74.6	1:1	21.0
	23.7	25.0	26.0	25.0	50.3	50.0	1:1	61.8
25	35.5	37.3	39.0	37.3	25.5	25.4	1:1	29.2

30 The flux determined for the salt in the absence of solvent was 60 $\mu\text{g}/\text{cm}^2/\text{hr}$.

Example 4

Nicotine was found by patch test to be irritating to the skin. A salt was prepared by stirring the nicotine with the stoichiometric amount of isostearic acid (a 1:2 molar proportion) and was found to be non-irritating by patch test. Dilutions of the salt with varying amounts of isopropyl myristate solvent were also prepared, and the flux was measured as described in Example 1 with the following results:

40	<u>Nicotine</u>		<u>Isostearic Acid</u>		<u>IPM</u>		<u>FLUX</u>
	<u>wt%</u>	<u>mole%</u>	<u>wt%</u>	<u>mole%</u>	<u>wt%</u>	<u>mole%</u>	<u>$\mu\text{g}/\text{cm}^2/\text{hr}$</u>
	22.2	33.3	77.8	66.7	0.0	0.0	40.3
	16.6	25.6	58.4	51.3	25.0	23.1	100.3
45	11.1	17.5	38.9	35.1	50.0	47.4	98.8
	5.6	9.0	19.4	18.0	75.0	73.0	57.5

50 In general and in summary, the invention provides the use of a physiologically active non-irritating amine, e.g., an antihistamine, in preparing a medicament for administration systemically to a human by providing a dilution comprising said amine dissolved in an effective amount of a nonpolar nonvolatile solvent, or by providing a dilution of a salt of said amine with a fatty acid having 8 to 20 carbon atoms dissolved in an effective amount of a nonpolar nonvolatile solvent, and in either case maintaining said dilution in a form adapted to contact the skin of said human.

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Also included in the invention is the use of a nonpolar nonvolatile solvent in diluting a physiologically active amine or salt thereof in preparation for transdermal or percutaneous delivery.

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Claims

1. A composition adapted to be maintained in contact with human skin to provide systemic administration of a physiologically active non-irritating amine in said human, said composition comprising

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a dilution comprising said amine dissolved in an effective amount of a nonpolar nonvolatile solvent.

2. A composition adapted to be maintained in contact with human skin to provide systemic administration of a physiologically active amine in said human, said composition comprising a dilution comprising a salt of said amine with a fatty acid having 8 to 20 carbon atoms dissolved in an effective amount of a nonpolar nonvolatile solvent.

3. A composition as claimed in claim 1 or claim 2 in which said solvent has a dielectric constant less than 4 and a boiling point above 150°C.

4. A composition as claimed in any one of claims 1 to 3 in which said amine is an antihistamine.

5. An article adapted to be maintained in contact with human skin to provide systemic administration of a physiologically active amine in said human, said article comprising a composition as claimed in any one of claims 1 to 4 absorbed in a solid porous water-insoluble carrier.

6. An article as claimed in claim 5 in which said carrier comprises a polymeric matrix.

7. An article as claimed in claim 6 in which said polymeric matrix comprises cellulose triacetate.

8. The use of a physiologically active non-irritating amine, e.g., an antihistamine, in preparing a medicament for administration systemically to a human by providing a dilution comprising said amine dissolved in an effective amount of a nonpolar nonvolatile solvent, or by providing a dilution of a salt of said amine with a fatty acid having 8 to 20 carbon atoms dissolved in an effective amount of a nonpolar nonvolatile solvent, and in either case maintaining said dilution in a form adapted to contact the skin of said human.

9. The use claimed in claim 8 in which said dilution is absorbed into a solid porous water-insoluble carrier designed to contact the skin of said human

10. The use claimed in claim 9 in which said carrier comprises a polymeric matrix.

11. The use claimed in claim 10 in which said polymeric matrix comprises cellulose triacetate.

12. The use claimed in any one of claims 8 to 11 in which said dilution includes an excess of said acid above the stoichiometric amount required to form said salt.

13. The use claimed in any one of claims 8 to 12 in which said solvent has a dielectric constant less than 4 and a boiling point above 150°C.

14. The use of a nonpolar nonvolatile solvent in diluting a physiologically active amine or salt thereof in preparation for transdermal or percutaneous delivery.