

No. 09-045866- -00003-0000

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Act. 400 OPOSIOBSERVTER Folios: 36

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

**SOLICITUD
PUBLICADA**

Número del expediente: 09 045.866
Solicitante: WYETH

Apoderado: ALVARO CORREA ORDONEZ
Título de la nueva creación o denominación del signo: REVESTIMIENTOS DE AZÚCAR Y MÉTODOS PARA LOS MISMOS.
Gaceta: 608

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: PROCAPS S.A. Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Teléfono: 371 99 00 Fax: 373 08 18 E-mail:	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>890.106.527-5</u>
REPRESENTANTE O APODERADO	Nombre: CIELO ANGELA PEÑA RODRIGUEZ Dirección: CARRERA 13 No. 119-95 Teléfono: (571)213 12 13 Fax: (571)612 19 79 E-mail: negocios@optimum-co.com	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>51.940.252</u> TP <u>82701</u>

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

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

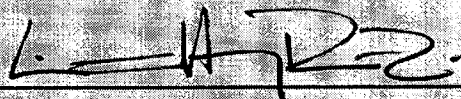
⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZFIRMA: 

C.C. 51.940.252

TP. 82701



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 09 045866

Asunto : Oposición a la solicitud de patente de Invención titulada
"REVESTIMIENTOS DE AZÚCAR Y MÉTODOS PARA
LOS MISMOS."

Solicitante : WYETH

Opositora : PROCAPS S.A. ✓

Publicada en la Gaceta de la Propiedad Industrial

N° 608 del 30 de septiembre de 2009

Yo, *CIELO ANGELA PEÑA RODRIGUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **82701** del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **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 "REVESTIMIENTOS DE AZÚCAR Y MÉTODOS PARA LOS MISMOS", cuyo titular es **WYETH**, 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 medroxiprogesterona. 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 6 de mayo de 2009 reivindicando prioridad bajo la solicitud US20060864718P del 2006-11-07; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 608 del 30 de septiembre de 2009, cuya publicación internacional corresponde a la WO2008058074 del 2008-02-15.

2.2. La solicitud colombiana 09 045866 objeto de la presente oposición, se refiere a composiciones que contienen azúcar adecuadas para utilizarse en preparaciones sólidas de revestimiento, tales como tabletas, píldoras, gránulos y granos; se proporcionan métodos para utilizar tales revestimientos, como formas de dosis sólida revestidas con las composiciones, en algunas modalidades, los métodos proporcionan tabletas revestidas con azúcar que comprenden estrógenos conjugados y una progestina, por ejemplo, acetato de medroxiprogesterona. Según

esta solicitud, se revela una forma de dosificación sólida que comprende un material de núcleo y al menos un revestimiento colocado en el mismo, en donde el revestimiento comprende: de aproximadamente 30% en peso a aproximadamente 95% en peso de al menos un azúcar; de aproximadamente 0.3% en peso a aproximadamente 0.8% en peso de al menos un diluyente/aglutinante; de aproximadamente 0.28% en peso a aproximadamente 0.4% en peso de al menos un agente tensoactivo; de aproximadamente 4% en peso a aproximadamente 6% en peso de al menos un aglutinante; opcionalmente, al menos un plastificante en una cantidad de hasta aproximadamente 5% en peso; opcionalmente, un resbalante, en una cantidad de hasta aproximadamente 3% en peso; y opcionalmente, un agente terapéutico en una cantidad de hasta aproximadamente 10% en peso.

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

- D1: EP0868911 publicada el 7 de octubre de 1998.
- D2: EP0803250 publicada el 29 de octubre de 1997.

2.4. Ahora bien, el documento D1 revela una unidad de dosificación sólida de rapamicina que comprende un núcleo y una cubierta de azúcar. Particularmente,

en la página 4, líneas 20 a 27 así como en el ejemplo 1 de dicho documento D1, se revela una forma de dosificación sólida que comprende un material principal y al menos una cubierta. Se define en dicha anterioridad que dicha capa comprende a) 35-99 % de azúcar, b) el 0.2-1 % de un diluyente (povidona), c) un surfactante (aproximadamente 0.008-9 %), d) celulosa microcristalina (aproximadamente 0.1-3 %), y agua (aproximadamente el 30 %). Por su parte, el documento D2, revela una pastilla comprimida que comprende un núcleo y una capa de azúcar, donde dicha capa de azúcar contiene una dosis de un esteroide hormonal y una tarifa de liberación de esteroide que controla la cantidad de celulosa microcristalina. Particularmente, en la página 3, líneas 8 a 16 se refiere a una composición que comprende una cubierta de azúcar que contiene un esteroide hormonal tal como acetato de medroxiprogesterona. Así las cosas, como lo evidencia dicho documento D1, en combinación con la materia revelada en el documento D2, cualquier persona versada en la materia puede llegar de manera obvia y evidente a deducir una composiciones que contienen azúcar adecuadas para utilizarse en preparaciones sólidas de revestimiento, tales como tabletas, píldoras, gránulos y granos; así como métodos para utilizar tales revestimientos, como formas de dosis sólida revestidas con las composiciones, en algunas modalidades, los métodos proporcionan tabletas revestidas con azúcar que comprenden estrógenos conjugados y una progestina, por ejemplo, acetato de medroxiprogesterona. Por lo tanto, la presente solicitud a los ojos de dichas anterioridades D1 y D2, carece evidentemente de ALTURA INVENTIVA.

2.5. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 045866 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.6.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”* A la fecha de prioridad, 7 de noviembre de 2006, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a composiciones que contienen azúcar adecuadas para utilizarse en preparaciones sólidas de revestimiento, sobre el cual busca protección en el capítulo reivindicatorio.

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

2.8. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada **“REVESTIMIENTOS DE AZÚCAR Y MÉTODOS PARA LOS MISMOS”**, cuyo titular es **WYETH**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 608 del 30 de septiembre de 2009.

3. PRUEBAS

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

- D1: EP0868911 publicada el 7 de octubre de 1998.
- D2: EP0803250 publicada el 29 de octubre de 1997.

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: EP0868911 publicada el 7 de octubre de 1998.
- D2: EP0803250 publicada el 29 de octubre de 1997.

6. NOTIFICACIONES

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

Señor Superintendente,



CIELO ANGELA PEÑA RODRIGUEZ
C.C. 51'940.252 de Bogotá
T.P.A. 82701 del C.S. de la J.



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 09 045.866, titulada "**REVESTIMIENTOS DE AZÚCAR Y MÉTODOS PARA LOS MISMOS**", cuyo titular es **WYETH**, publicada en la gaceta No. 608 del 30 de septiembre de 2009.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 3 días del mes de Diciembre de 2009.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

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



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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

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

PROCAPS S.A.-----

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

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A.-----

C E R T I F I C A

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

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

C E R T I F I C A

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

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT N°: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.



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

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

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, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a) b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

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

farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,229,071,000	*****1,229,071	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

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

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



***** Pag. 3
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

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 socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

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

ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

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

PROCAPS S.A.-----

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

PROCAPS S.A.-----

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

CLASE: JUNTA DIRECTIVA

Principales

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

Suplentes

1. Minski Zirberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A



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C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

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

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

C E R T I F I C A

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

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

C E R T I F I C A

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

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

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS 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
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

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

Revisor Fiscal Ppal.
Vargas Pertuz Ana Isabel

CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 151 del 31 de Marzo de 2009 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 30 de Julio de 2009 bajo el No. 151,129 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre
Suplente del Revisor Fiscal.
Duarte Diaz David

Identificación

CC.*****73,115,965

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----

y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ----

obrando como Presidente y Representante Legal de la sociedad C.I.

NATURMEGA S.A., que obrando en su condicion de Presidente y -----

Representante Legagl de la sociedad PROCAPS S.A., el presidente ----

debidamente facultado por los Estatutos Sociales y por el Maximo

Organo Social, otorga los siguientes poderes: Otorgar poder -----

general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----

MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----

CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con

las facultades que se transcriben a continuacion: a.- Para que ----

representen a la sociedad PROCAPS S.A, ante todo tipo de -----

autoridades administrativas y jurisdiccionales, en asuntos de -----

naturaleza civil, laboral, comercial, penal, aduanera, cambiaria,

tributaria, policiva, administrativa y fiscal. b.- Contestar y ----

presentar demandas, requerimientos, recursos, pedir y aportar ----

pruebas, recibir, notificarse, ejercer la accion de tutela, -----

tramitar incidente de desacato, comparecer en los procesos que ----

cursen contra la sociedad, allanarse en nombre de la sociedad en

los asuntos que sean necesarios, transigir, desistir, sustituir,

renunciar y reasumir el poder. c.- La facultad expresa de -----

conciliar, por tanto pueden llegar a acuerdos conciliatorios, ----

transaccionales, judiciales o extrajudiciales o extrajudiciales,

cualquiera que sea su cuantia, para lo cual las apoderadas deben

aportar la autorizacion simple y escrita del Representante legal

de la sociedad. d.- Podran presentar solicitudes de devolucion y/o

compensacion de impuestos, ventas y rentas, recibir los pagos por

las devoluciones y adelantar todo tramite o proceso administrativo

ante la DIAN, de tal forma que en ningun momento quede sin -----

representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ----

confiere poder especial amplio y suficiente a las personas que se

determinan seguidamente, que conforman el grupo A y B, para, para



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CAMARA DE COMERCIO
DE BARRANQUILLA
12*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

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

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaría 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008 bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condición de Presidente y Representante Legal de la Sociedad PROCAPS S.A., confiere por medio de este instrumento ----- publico Poder especial Amplio y Suficiente a la doctora MILENA -----

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S.A.-----

NIT: 890.106.527-5.

ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y representacion de PROCAPS S.A., suscriba declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad en el giro normal de sus negocios y operaciones sociales, por tanto queda facultada para firmar, como tambien los demas documentos relacionados con ellas, notificarse, aportar y solicitar las pruebas que sean necesarias.-----

C E R T I F I C A

Que 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: 27 de Marzo de 2009.

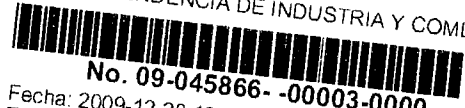
La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

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

m. fajon

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-045866-00003-0000

Fecha: 2009-12-28 12:36:53 Dep. 2020 DIR.NUEVASCR
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 Act. 400 OPOSIOBSERVTER Folios: 36

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 94.421
 FECHA : DICIEMBRE 15 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	RECIBO DE CAJA			56597	31/07/2009	540,000.00

***** CONCEPTO *****

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

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
07.10.1998 Bulletin 1998/41

(51) Int Cl.⁶: **A61K 9/28, A61K 31/435**

(21) Application number: **98301716.1**

(22) Date of filing: **09.03.1998**

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC
NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **14.03.1997 US 815015**

(71) Applicant: **AMERICAN HOME PRODUCTS**
CORPORATION
Madison, New Jersey 07940-0874 (US)

(72) Inventor: **Nagi, Arwinder S.**
Swanton, Vermont 05488 (US)

(74) Representative: **Wileman, David Francis, Dr. et al**
c/o Wyeth Laboratories
Huntercombe Lane South
Taplow Maidenhead Berkshire SL6 OPH (GB)

(54) **Rapamycin formulations for oral administration**

(57) This invention provides rapamycin solid dosage unit which comprises a core and a sugar overcoat,

said sugar overcoat comprising rapamycin, one or more surface modifying agents, one or more sugars, and optionally one or more binders.

Description

This invention relates to formulations containing rapamycin or pharmaceutically acceptable salts of rapamycin, which are useful in oral administrations for inducing immunosuppression and for treating transplantation rejection, host vs. graft disease, autoimmune diseases, diseases of inflammation, solid tumors, fungal infections, adult T-cell leukemia/lymphomas and hyperproliferative vascular disorders.

Background of the Invention

Rapamycin is a macrolide antibiotic produced by *Streptomyces hygroscopicus* which was discovered first for its properties as an antifungal agent. It adversely affects the growth of fungi such as *Candida albicans* and *Microsporum gypseum*. Rapamycin, its preparation and its antibiotic activity were described in U.S. Patent No. 3,929,992, issued December 30, 1975 to Surendra Sehgal et al. In 1977 Martel, R. R. et al. reported on immunosuppressive properties of rapamycin against experimental allergic encephalitis and adjuvant arthritis in the Canadian Journal of Physiological Pharmacology, 55, 48-51 (1977). In 1989, Calne, R. Y. et al. in Lancet, 1989, no. 2, p. 227 and Morris, R. E. and Meiser, B. M. in Medicinal Science Research, 1989, No. 17, P. 609-10, separately reported on the effectiveness of rapamycin in inhibiting rejection *in vivo* in allograft transplantation. Numerous articles have followed describing the immunosuppressive and rejection inhibiting properties of rapamycin, and clinical investigations have begun for the use of rapamycin in inhibiting rejection in transplantation in man.

Rapamycin alone (U.S. Patent 4,885,171) or in combination with picibanil (U.S. Patent 4,401,653) has been shown to have antitumor activity. R. Martel et al. [Can. J. Physiol. Pharmacol. 55, 48 (1977)] disclosed that rapamycin is effective in the experimental allergic encephalomyelitis model, a model for multiple sclerosis; in the adjuvant arthritis model, a model for rheumatoid arthritis; and effectively inhibited the formation of IgE-like antibodies.

The immunosuppressive effects of rapamycin have been disclosed in FASEB 3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [FASEB 3, 3411 (1989); FASEB 3, 5256 (1989); R. Y. Calne et al., and Lancet 1183 (1978)].

Rapamycin has been shown to inhibit transplantation rejection in mammals [U.S. Patent 5,100,899]. Rapamycin, its derivatives and prodrugs have also been shown to be useful in treating pulmonary inflammation [U.S. Patent 5,080,899], systemic lupus erythematosus [U.S. Patent 5,078,899], immunoinflammatory skin disorders, such as psoriasis [U.S. Patent 5,286,730], immunoinflammatory bowel disorders [U.S. Patent 5,286,731], ocular inflammation [U.S. Patent 5,387,589], hyperproliferative vascular disorders, such as restenosis [U.S. Patents 5,512,781 and 5,288,711], carcinomas [U.S. Patent 5,206,018 and 4,885,171], and cardiac inflammatory disease [U.S. Patent 5,496,832]; and in preventing the onset of insulin dependent diabetes mellitus [U.S. Patent 5,321,009]. Additionally, rapamycin has been shown to be useful in treating adult T-cell leukemia/lymphoma [European Patent Application 525,960 A1], and in treating ocular inflammation [U.S. Patent 5,387,589].

Because of its poor oil and water solubility, only a few formulations of rapamycin have proven satisfactory. U.S. Patents 5,516,770 and 5,530,006 disclose intravenous rapamycin formulations, and U.S. Patents 5,536,729 and 5,559,121 disclose liquid oral rapamycin formulations.

Mono- and diacylated derivatives of rapamycin (esterified at the 28 and 43 positions) have been shown to be useful as antifungal agents (U.S. Patent 4,316,885) and used to make water soluble prodrugs of rapamycin (U.S. Patent 4,650,803). Recently, the numbering convention for rapamycin has been changed; therefore according to Chemical Abstracts nomenclature, the esters described above would be at the 31- and 42-positions. U.S. Patent 5,118,678 discloses carbamates of rapamycin that are useful as immunosuppressive, anti-inflammatory, antifungal, and antitumor agents. U. S. Patent 5,100,883 discloses fluorinated esters of rapamycin. U. S. Patent 5,118,677 discloses amide esters of rapamycin. U. S. Patent 5,130,307 discloses aminoesters of rapamycin. U. S. Patent 5,117,203 discloses sulfonates and sulfamates of rapamycin. U. S. Patent 5,194,447 discloses sulfonylcarbamates of rapamycin.

The primary immunosuppressive agent presently used for inhibiting rejection in the allograft transplantation of organs in man is SANDIMMUNE (cyclosporine). Cyclosporine is a cyclic polypeptide consisting of 11 amino acids. The intravenous injectable formulation of SANDIMMUNE (IV) is a sterile ampoule containing, per ml, 50 mg of cyclosporine, 650 mg of Cremophor® EL and alcohol Ph. Helv. (32.9% by volume) (under nitrogen). For administration this mixture is diluted further with 0.9 % Sodium Chloride Injection or 5% Dextrose Injection before use. (Physicians' Desk Reference, 45th ed., 1991, pp. 1962-64, Medical Economics Company, Inc.) The macrolide molecule designated FK506, which has certain structural similarities to rapamycin, is also currently undergoing clinical investigation for inhibiting rejection in allograft organ transplantation in man. FK506 is isolated from *Streptomyces tsukubaensis* and is described in U.S. Patent No. 4,894,366 to Okuhara et al., issued January 16, 1990 R. Venkataramanan et al., in Transplantation Proceedings, 22, No. 1, Suppl., 1 pp 52-56 (February 1990), report that the intravenous injectable formulation of FK506 is provided as a 10 mg/ml solution of FK506 in polyoxyethylated castor oil (HCO-60, a surfactant) and alcohol. The

EP 0 868 911 A2

intravenous preparation must be diluted with saline or dextrose and administered as an infusion for 1 to 2 hours.

The Physicians' Desk Reference (45th ed., 1991, p. 2119, Medical Economics Company, Inc.) lists SANDIMMUNE (cyclosporine) as available in 25 mg and 100 mg strength capsules and as an oral solution in 50 ml bottles. The 25 mg capsules contain 25 mg cyclosporine, USP, and alcohol, USP dehydrated, at a maximum of 12.7% by volume. The 100 mg capsules contain cyclosporine, USP, 100 mg and alcohol, USP dehydrated, at a maximum 12.7% by volume. Inactive ingredients in the oral capsules are corn oil, gelatin, glycerol, Labrafil M 2125 CS (polyoxyethylated glycolised glycerides), red iron oxide, sorbitol, titanium dioxide, and other ingredients. The oral solution is available in 50 mg bottles containing cyclosporine, USP, 100 mg and Ph. Helv. alcohol at 12.5% by volume dissolved in olive oil, Ph. Helv./Labrafil M 1944 CS (polyoxyethylated oleic glycerides) vehicle which must be diluted further with milk, chocolate milk or orange juice before oral administration.

IMURAN (azathioprine, available from Burroughs Wellcome Co., Research Triangle Park, N.C.) is another orally administered immunosuppressive agent prescribed alone or in conjunction with other immunosuppressive agents. The Physicians' Desk Reference (45th ed., 1991, pp. 785-787, Medical Economics Company, Inc.) lists azathioprine as 6-[1-methyl-4-nitroimidazol-5-yl]thio]purine, which is provided for oral administration in scored tablets containing 50 mg azathioprine and the inactive ingredients lactose, magnesium stearate, potato starch, povidone, and stearic acid.

Description of the Invention

Methods of drug delivery are designed to deliver an acceptable dosage of the medication to the patient. In the case of oral formulations, it is highly desirable to provide a dosage form which meets this criteria and which can be effectively administered, preferably self-administered, in either clinical or non-clinical situations.

The present invention concerns formulations useful in the oral administration of rapamycin. Rapamycin has been shown to possess immunosuppressive, antirejection, antifungal and antiinflammatory activity in vivo and to inhibit thymocyte proliferation in vitro. Therefore, these formulations are useful in the treatment or inhibition of transplantation rejection such as kidney, heart, liver, lung, bone marrow, pancreas (islet cells), cornea, small bowel, and skin allografts, and heart valve xenografts; in the treatment or inhibition of graft vs. host disease; in the treatment or inhibition of autoimmune diseases such as lupus, rheumatoid arthritis, diabetes mellitus, myasthenia gravis, and multiple sclerosis; and diseases of inflammation such as psoriasis, dermatitis, eczema, seborrhea, inflammatory bowel disease, pulmonary inflammation (including asthma, chronic obstructive pulmonary disease, emphysema, acute respiratory distress syndrome, bronchitis, and the like), and eye uveitis.

Rapamycin has also been shown to have antitumor, antifungal, and antiproliferative activities. The formulations of this invention therefore also useful in treating solid tumors, including sarcomas and carcinomas, such as astrocytomas, prostate cancer, breast cancer, small cell lung cancer, and ovarian cancer; adult T-cell leukemia/lymphoma; fungal infections; and hyperproliferative vascular diseases such as restenosis and atherosclerosis.

The present invention, also provides formulations for use in inducing immunosuppression in a mammal in such need.

In general, the formulations of this invention provides an oral tablet dosage form of rapamycin comprising a core which is overcoated with rapamycin, and a sugar coat containing one or more surface modifying agents and one or more sugars. It is preferred that the sugar coat also contain one or more binders. It is preferred that such dosage tablets contain 0.05 - 20 mg rapamycin, with it being more preferred that such tablet will contain 0.5 - 10 mg rapamycin.

In preparing rapamycin oral dosage tablets in accordance with this invention, a number of surface modifying agents are suitable to form a dispersion with rapamycin which is used in the overcoat. These can be selected from known pharmaceutical excipients including various polymers, low molecular weight oligomers, natural products and other surface modifying agents. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, Pluronic F68, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. It is more preferred that Pluronic F68 (available from BASF Corp.) is used as the surface modifying agent.

The sugar used in the production of the sugar overcoat described in this invention is a sugar product, such as sucrose, derived from beet or cane sources or starch, saccharide, or polysaccharide converted sources, which are considered suitable for preparing the sugar overcoat. When used in preparing the solid dosage form of this invention, it is preferred that the sugar is sucrose.

When binders are used in preparing the rapamycin oral dosage tablets, these can include gum acacia, cholesterol, tragacanth, stearic acid, gelatin, casein, lecithin (phosphatides), carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, microcrystalline cellulose, noncrystalline cellulose, polyvinylpyrrolidone (povidone, PVP), cetostearyl alcohol, cetyl alcohol, cetyl esters wax, dextrates, dextrin, lactose, dextrose, glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, polyoxyethylene alkyl ethers, polyethylene glycols, polyoxyethylene castor oil derivatives, polyoxyeth-

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ylene stearates, and polyvinyl alcohol.

The dosage tablets described herein provide rapamycin contained in a sugar overcoat that has been overcoated onto a core. The core can either be pharmaceutically inert or can contain a pharmaceutically active agent. As used in describing this invention the term "sugar overcoat" refers to the rapamycin, one or more surface modifying agents, and one or more sugars, which coat the core. If one or more binders are included in the formulation, they are also considered part of the sugar overcoat.

The following provides a preferred formulation for the sugar overcoat of a solid dosage tablet containing 0.05 - 20 mg rapamycin.

- a) rapamycin in an amount from about 0.05 - 20 mg
- b) Pluronic F-68 in an amount from about 0.008 - 10 mg
- c) sucrose in a range from about 40 - 99% weight of the sugar overcoat

In the formulations described in this invention, the quantities of the ingredients specified as percentages will vary according to the weight of the sugar overcoat. The sugar overcoat described in this invention will typically weigh about 50 - 200 mg. Therefore in the above formulation, the quantity of sucrose would be about 20 mg (about 40% weight of the sugar overcoat) for a 50 mg sugar overcoat containing 20 mg rapamycin and 10 mg Pluronic F68. Similarly, the percent weight of sucrose in the sugar overcoat can comprise greater than 99% (e.g. 99.97%) of the sugar overcoat when a 200 mg sugar overcoat contains 0.05 mg rapamycin and 0.008 mg Pluronic F68.

The following provides a more preferred formulation for the sugar overcoat of a solid dosage tablet containing 0.05 - 20 mg rapamycin, in which the sugar overcoat contains povidone and microcrystalline cellulose.

- a) rapamycin in an amount from about 0.05 - 20 mg
- b) Pluronic F68 in an amount from about 0.008 - 10 mg
- b) sucrose in a range from about 35-99% weight of the final overcoat
- c) povidone in a range from about 0.2 - 1.0 % weight of the final overcoat
- d) microcrystalline cellulose in a range from about 0.1 - 3.0 % weight of the final overcoat

A rapamycin containing oral dosage tablet containing the above constituents can be prepared according to the following procedure. Briefly, a dispersion of rapamycin in a surface modifier, such as Pluronic F68, is prepared according to U.S. Patent 5,145,684, which is hereby incorporated by reference. The dispersion will typically have an effective average particle size of less than about 400 nm. A ratio of between 6:1 to 2:1 rapamycin:Pluronic F68 is typically desired, with 2:1 being preferred. When a 2:1 ratio is used, a dispersion typically containing 150 mg/ml is prepared, and used to prepare 0.05 - 20 mg rapamycin oral solid dosage tablets. For the higher strength tablets (i.e., 15 - 20 mg rapamycin) it may be desirable to increase the concentration of the dispersion, such as up to about 300 mg/ml. Sucrose is added to the rapamycin / Pluronic F68 dispersion, and mixed until it is dissolved. Povidone is added and mixed until well wetted. The mixture is mixed vigorously to dissolve. Microcrystalline cellulose is added and mixed well until wetted. Water is added (about 2 - 55 mg), mixed well and the mixture is spray coated onto a pharmaceutically inert core in small portions, and air dried in between portions, until the desired tablet strength is formed. During the manufacturing process, the majority of the water is removed, such that approximately less than 5% water remains in each tablet. Typically less than 2% residual water is present in each tablet. The rapamycin containing oral dosage tablets can be optionally coated with a color coat followed by a polish coat if desirable. The color coat typically contains a sugar such as sucrose, and a pigment such as titanium dioxide, and the polish coat contains carnuba wax, which can be applied as a dispersion in a solvent, such as mineral spirits.

When the core is a pharmaceutically inert core, it is typically a placebo core which may contain lactose, microcrystalline cellulose, PEG-6000, and other binders and fillers. The core, can be sealed with shellac to prevent disintegration from occurring during the overcoating process. A sucrose coat may also be placed on top of the shellac coat prior to the overcoating process.

The sugar overcoating described in this invention can be prepared to typically weigh about 50 - 200 mg. Using the process described herein, a 100 mg sugar overcoat containing 0.05 - 20 mg rapamycin would be made from the following ingredients according to the procedure described above:

- a) rapamycin in an amount from about 0.05 - 20 mg
- b) Pluronic F68 in an amount from about 0.008 - 10 mg
- b) sucrose in an amount from about 35 - 99 mg
- c) povidone in an the amount from about 0.2 - 1.0 mg
- d) microcrystalline cellulose in an amount from about 0.1 - 3.0 mg
- e) water in an amount from 2 - 55 mg (mostly removed during processing)

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It is contemplated that when the formulations of this invention are used as an immunosuppressive or antiinflammatory agent, they can be administered in conjunction with one or more other immunoregulatory agents. Such other antirejection chemotherapeutic agents include, but are not limited to azathioprine, corticosteroids, such as prednisone and methylprednisolone, cyclophosphamide, cyclosporin A, FK-506, OKT-3, and ATG. By combining one or more of the formulations of the present invention with such other drugs or agents for inducing immunosuppression or treating inflammatory conditions, lesser amounts of each of the agents may be required to achieve the desired effect. The basis for such combination therapy was established by Stepkowski whose results showed that the use of a combination of rapamycin and cyclosporin A at subtherapeutic doses significantly prolonged heart allograft survival time. [Transplantation Proc. 23:507 (1991)].

The dosage requirements may vary the severity of the symptoms presented and the particular subject being treated. Projected daily oral dosages of rapamycin would be 0.05 - 25 mg, with preferred projected daily doses being 0.5 - 10 mg when rapamycin is used in combination therapy, and 1 - 25 mg when rapamycin is used as monotherapy. More preferred projected daily doses are 2 - 5 mg when rapamycin is used in combination therapy, and 5 - 15 mg when rapamycin is used as monotherapy.

Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages will be determined by the administering physician based on experience with the individual subject treated. In general, the formulations of this invention are most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects.

The oral dosage tablet formulation of this invention can also be used to make oral dosage tablets containing derivatives of rapamycin, including, but not limited to rapamycin esters, carbamates, sulfates, ethers, oximes, carbonates, the like which are all well described in the patent literature.

The following provide the preparation and evaluation of representative examples of rapamycin solid dosage tablets.

EXAMPLE 1

The following shows the preparation and evaluation of a 1 mg rapamycin oral dosage tablet containing a 100 mg sugar overcoat.

Formula:	
Ingredients*	Amount
Rapamycin	1 mg
Pluronic F68	0.5 mg
Sucrose	98.940 mg
Povidone	0.510 mg
Microcrystalline cellulose	1.020 mg
Water	49.653 mg

*A 2% overage is included in these quantities to account for manufacturing losses.

Manufacturing Directions:

1. A dispersion of less than about 400 nm particle size of rapamycin and pluronic F68 was prepared according to U.S. Patent 5,145,684 using a 2:1 ratio of rapamycin:Pluronic F68. A dispersion concentration of 150 mg rapamycin/ml was used.
2. Sucrose was added and mixed until the sucrose dissolved.
3. Povidone was added and mixed until well wetted. Mixing was continued vigorously until the povidone dissolved.
4. Microcrystalline cellulose was added, and mixed well until wetted.
5. Water was added and mixed well.
6. The resulting solution was spray coated onto a pharmaceutically inert core portionwise and air dried in between portions.

Evaluation

Six Cynomolgus monkeys, listed below as A-F, were administered the above formulation at a dose of 3 mg rapamycin per monkey and the following serum concentrations of rapamycin were determined at the indicated time after dosing.

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Rapamycin Concentration (nanogram/ml) / Monkey Number						
Time	A	B	C	C	E	F
0 hr.	0.00	0.00	0.00	0.00	0.00	0.00
0.25 hr.	0.00	0.27	0.00	0.26	0.00	0.00
0.5 hr.	0.31	0.28	0.00	0.00	0.54	0.00
1.0 hr.	0.41	3.39	4.08	3.43	1.68	0.39
2 hr.	1.31	5.26	11.51	9.86	3.31	2.96
4 hr.	9.04	4.08	20.23	31.37	3.12	2.36
8 hr.	11.24	8.40	26.57	40.01	16.58	8.90
12 hr.	11.20	7.83	22.95	42.64	11.33	8.27
16 hr.	9.74	6.59	19.50	30.58	10.10	8.15
24 hr.	7.92	5.62	14.37	18.34	6.48	7.19

The results obtained demonstrate that serum concentrations of rapamycin were observed following the administration of a representative oral dosage tablet of this invention.

EXAMPLE 2

A 0.5 mg rapamycin oral dosage tablet containing a 100 mg sugar overcoat was prepared according the procedure described in Example 1. The dispersion contained a 2:1 ratio of rapamycin:Pluronic F68, and was used at a concentration of 150 mg rapamycin/ml. The following lists the quantities of ingredients used.

Formula:	
Ingredients*	Amount
Rapamycin	0.5 mg
Pluronic F68	0.25 mg
Sucrose	99.705 mg
Povidone	0.510 mg
Microcrystalline cellulose	1.020 mg
Water	52.288 mg

*A 2% overage is included in these quantities to account for manufacturing losses.

EXAMPLE 3

A 3.0 mg rapamycin oral dosage tablet containing a 100 mg sugar overcoat was prepared according the procedure described in Example 1. The dispersion contained a 2:1 ratio of rapamycin:Pluronic F68, and was used at a concentration of 150 mg rapamycin/ml. The following lists the quantities of ingredients used.

Formula:	
Ingredients*	Amount
Rapamycin	3.0 mg
Pluronic F68	1.5 mg
Sucrose	95.880 mg

*A 2% overage is included in these quantities to account for manufacturing losses.

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(continued)

Formula:	
Ingredients*	Amount
Povidone	0.510 mg
Microcrystalline cellulose	1.020 mg
Water	39.113 mg

*A 2% overage is included in these quantities to account for manufacturing losses.

EXAMPLE 4

A 5.0 mg rapamycin oral dosage tablet containing a 100 mg sugar overcoat was prepared according the procedure described in Example 1. The dispersion contained a 2:1 ratio of rapamycin:Pluronic F68, and was used at a concentration of 150 mg rapamycin/ml. The following lists the quantities of ingredients used.

Formula:	
Ingredients*	Amount
Rapamycin	5.0 mg
Pluronic F68	2.5 mg
Sucrose	92.820 mg
Povidone	0.510 mg
Microcrystalline cellulose	1.020 mg
Water	28.573 mg

*A 2% overage is included in these quantities to account for manufacturing losses.

EXAMPLE 5

A 7.5 mg rapamycin oral dosage tablet containing a 100 mg sugar overcoat was prepared according the procedure described in Example 1. The dispersion contained a 2:1 ratio of rapamycin:Pluronic F68, and was used at a concentration of 150 mg rapamycin/ml. The following lists the quantities of ingredients used.

Formula:	
Ingredients*	Amount
Rapamycin	7.5 mg
Pluronic F68	3.75 mg
Sucrose	88.995 mg
Povidone	0.510 mg
Microcrystalline cellulose	1.020 mg
Water	15.398 mg

*A 2% overage is added to these quantities to account for manufacturing losses.

EXAMPLE 6

A 10 mg rapamycin oral dosage tablet containing a 100 mg sugar overcoat was prepared according the procedure described in Example 1. The dispersion contained a 2:1 ratio of rapamycin:Pluronic F68, and was used at a concentration of 150 mg rapamycin/ml. The following lists the quantities of ingredients used.

Formula:	
Ingredients*	Amount
Rapamycin	10 mg
Pluronic F68	5 mg

*A 2% overage is included in these quantities to account for manufacturing losses.

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(continued)

Formula:	
Ingredients*	Amount
Sucrose	85.170 mg
Povidone	0.510 mg
Microcrystalline cellulose	1.020 mg
Water	2.223 mg

*A 2% overage is included in these quantities to account for manufacturing losses.

Claims

1. A rapamycin solid dosage unit which comprises a core and a sugar overcoat, said sugar overcoat comprising:
 - (a) rapamycin,
 - (b) one or more surface modifying agents, and
 - (c) one or more sugars.
2. A rapamycin solid dosage unit which comprises a core and a sugar overcoat, said sugar overcoat comprising:
 - (a) rapamycin in an amount from about 0.05 - 20 mg,
 - (b) Pluronic F68 in an amount from about 0.008 - 10 mg, and
 - (c) sucrose in an amount comprising up to about 99% weight of the sugar overcoat.
3. A dosage unit according to Claim 2, wherein the sucrose is in a range from about 40 - 99% weight of the sugar overcoat.
4. A dosage unit according to any one of Claims 1 to 3, which further comprises one or more binders.
5. A dosage unit as Claimed in any one of Claims 1 to 4 in which the surface modifying agent is Pluronic F68
6. A rapamycin solid dosage unit as Claimed in Claim 1 which comprises a core and a sugar overcoat; said sugar overcoat comprising
 - (a) rapamycin in an amount from about 0.05 - 20 mg,
 - (b) Pluronic F68 in an amount from about 0.008 - 10 mg,
 - (c) povidone in a range from about 0.2 - 1.0 % weight of said sugar overcoat,
 - (d) microcrystalline cellulose in a range from about 0.1 - 3 % weight of said sugar overcoat, and
 - (e) sucrose in a range from about 35 - 99% weight of said sugar overcoat
7. A dosage unit according to Claim 6, wherein the povidone is contained as about 0.5% weight of said sugar overcoat.
8. A dosage unit according to Claim 6 or Claim 7, wherein the microcrystalline cellulose as about 1% weight of said sugar overcoat.
9. A dosage unit according to any one of Claims 5 to 8 wherein the Pluronic F68 is contained in an amount from about 0.25 - 10 mg.
10. A dosage unit according to Claim 6, wherein
 - (a) rapamycin is contained in an amount of about 1 mg,
 - (b) Pluronic F68 is contained in an amount of about 0.5 mg,
 - (c) povidone is contained as about 0.5% weight of said sugar overcoat,
 - (d) microcrystalline cellulose is contained as about 1% weight of said sugar overcoat, and
 - (e) sucrose is contained in a range from about 95-99% weight of said sugar overcoat

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11. A dosage unit according to Claim 6, wherein

- (a) rapamycin is contained in an amount of about 0.5 mg,
- (b) Pluronic F68 is contained in an amount of about 0.25 mg,
- (c) povidone is contained as about 0.5% weight of said sugar overcoat,
- (d) microcrystalline cellulose is contained as about 1% weight of said sugar overcoat, and
- (e) sucrose is contained in a range from about 96-99% weight of said sugar overcoat

12. The dosage unit according to Claim 6, wherein

- (a) rapamycin is contained in an amount of about 3 mg,
- (b) Pluronic F68 is contained in an amount of about 1.5 mg,
- (c) povidone is contained as about 0.5% weight of said sugar overcoat,
- (d) microcrystalline cellulose is contained as about 1 % weight of said sugar overcoat, and
- (e) sucrose is contained in a range from about 90-96% weight of said sugar overcoat

13. The dosage unit according to Claim 6, wherein

- (a) rapamycin is contained in an amount of about 5 mg,
- (b) Pluronic F68 is contained in an amount of about 2.5 mg,
- (c) povidone is contained as about 0.5% weight of said sugar overcoat,
- (d) microcrystalline cellulose is contained as about 1% weight of said sugar overcoat, and
- (e) sucrose is contained in a range from about 80-96% weight of said sugar overcoat

14. A dosage unit according to Claim 6, wherein

- (a) rapamycin is contained in an amount of about 7.5 mg,
- (b) Pluronic F68 is contained in an amount of about 3.75 mg,
- (c) povidone is contained as about 0.5% weight of said sugar overcoat,
- (d) microcrystalline cellulose is contained as about 1% weight of said sugar overcoat, and
- (e) sucrose is contained in a range from about 75-90% weight of said sugar overcoat

15. A dosage unit according to Claim 6, wherein

- (a) rapamycin is contained in an amount of about 10 mg,
- (b) Pluronic F68 is contained in an amount of about 5 mg,
- (c) povidone is contained as about 0.5% weight of said sugar overcoat,
- (d) microcrystalline cellulose is contained as about 1% weight of said sugar overcoat, and
- (e) sucrose is contained in a range from about 65-90% weight of said sugar overcoat

16. A process for preparing a rapamycin oral dosage tablet which comprises preparing a sugar overcoat by employing to the following steps,

- (a) preparing a rapamycin dispersion in one or more surface modifying agents,
- (b) adding one or more sugars to the dispersion and stirring until dissolved,
- (c) adding water to the mixture, and stirring until dissolved, and

spraying the overcoat onto a core and drying until the desired quantity of rapamycin has been sprayed onto the core.

17. A process according to Claim 16 which further comprises adding one or more binders to the dispersion either before or after the sugar has been added to the dispersion.

18. A process according to Claim 16 or Claim 17 wherein the surface modifying agent is Pluronic F68.

19. A process according to Claim 18, wherein the ratio of rapamycin to Pluronic F68 is between about 2:1 and about 6:1 by weight.

20. A process according to Claim 19, wherein the ratio of rapamycin to Pluronic F68 is about 2:1 by weight.

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21. A process according to any one of Claims 16 to 20 wherein the sugar is sucrose.

22. A process according to Claim 21, wherein the quantity of sucrose is about 35 - 99% weight of the dried overcoat.

5 **23.** A process according to any one of Claims 17 to 22 wherein the binders are povidone and microcrystalline cellulose.

24. A process according to Claim 23, wherein the quantity of povidone is about 0.2 - 1% weight of the dried overcoat.

10 **25.** A process according to Claim 23, wherein the quantity of microcrystalline cellulose is about 0.1 - 3% of the dried overcoat.

26. A rapamycin oral dosage tablet obtainable by a process as claimed in any one of Claims 16 to 25.

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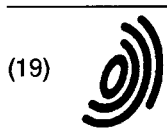
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ANEXO 2



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(54) **Controlled release of steroids from sugar coatings**

(57) A compressed medicinal tablet comprising a tablet core and a sugar coating, said sugar coating containing a dose of a hormonal steroid and a steroid release rate controlling amount of microcrystalline cellulose.

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Description

BACKGROUND OF THE INVENTION

5 In the past three decades, substantial effort has gone into the identification of methods for controlling the rate of release of drug from pharmaceutical tablets. Excipients have been incorporated into tablet cores to control dissolution, and hence absorption, of drugs. Tablets and spheroids have been coated with polymers to provide slow, diffusion - controlled release or site-specific release of drugs.

10 Tablets and encapsulated spheroid dosage forms have also been prepared containing multiple drugs, either in admixture or as separate tablet layers or spheroids. The drugs are provided to perform multiple functions or to provide synergism. Such tablets are especially useful in those circumstances where conventional therapy dictates the use of more than one drug possessing different but compatible activities. For example, diuretic agents are frequently administered with antihypertensive agents, and progestational agents in conjunction with estrogens.

Brief Description of the Invention

15 In accordance with this invention, there is provided a pharmaceutical tablet comprising an internal compressed core and an external sugar coating, wherein said compressed core optionally contains no pharmacologically-active agent or one or more non-steroidal, pharmacologically-active agents that are conventionally administered in conjunction with a hormonal steroid, the improvement which comprises the incorporation of a hormonal steroid and a hormonal steroid release rate controlling amount of micro-crystalline cellulose in said sugar coating. The compressed tablet core may be devoid of any medicament or it may contain a pharmaceutical agent other than a steroid, that is compatible with the steroid and any other therapeutic agent in the sugar coating. Thus, the sugar coated tablets of this invention may contain one or more pharmacologically-active agents, where the improvement in prior sugar coated tablets comprises the incorporation of a hormonal steroid release rate controlling amount of microcrystalline cellulose in conjunction with a hormonal steroid in said sugar coating. The sugar-coated tablet may be finished with color coatings and polished as is common in coated tablets.

20 The contents of the tablet core are quite independent from the sugar coating in the sense that the sugar coating and the hormonal steroid contained in it are dissolved before disintegration of the compressed tablet core and dissolution of any drug component present in the core. The excipient components employed in formulation of the core tablet may include pharmaceutically-acceptable water-soluble and/or insoluble substances such as lactose, calcium phosphate, starch, calcium carbonate, dextrose, sorbitol, mannitol, microcrystalline cellulose, sucrose, polyvinylpyrrolidone, methylcellulose, carboxymethylcellulose, alginates, hydroxypropylcellulose, hydroxypropylmethyl-cellulose, ethylcellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, stearic acid, polyethylene glycol, sodium lauryl sulfate, fumed silica, talc and the like.

25 The sugar coat containing the hormonal steroid also contains a steroid release rate-controlling amount of microcrystalline cellulose and, in certain circumstances, polyvinylpyrrolidone to aid in application of the sugar coat.

30 The tablet core is produced by compression of an admixture, which has preferably, been granulated, of the pharmaceutically-acceptable excipients, and, if desired, a therapeutic agent compatible with the steroid to be incorporated with the release rate controlling amount of microcrystalline cellulose in the sugar coating. The tablet core may have an unplasticized or plasticized seal coat designed to modify the drug release characteristics of any drug(s) contained within the core, or to protect them against moisture and/or oxygen. The non-medicated cores are those conventionally employed as placebo tablets in pharmacological studies.

Detailed Description of the Invention

35 This invention provides an improved compressed tablet in which, in addition to a conventional internal tablet core optionally containing no drug or one or more drugs that are pharmacologically compatible with a steroid in the external sugar coating, a sugar coating is present which comprises a hormonal steroid in an amount of about 0.1 to about 20 percent by weight of the sugar coating; microcrystalline cellulose in an amount from about 0.1 to about 3 percent by weight of the sugar coating; polyvinylpyrrolidone in from about 0 to about 5 percent by weight of the sugar coating; and sugar. On a unit dose basis, the tablet contains about 0.01 to about 50 milligrams, preferably about 0.015 to about 40 milligrams and more preferably about 0.02 to 30 milligrams, of total hormonal steroid load in the loaded sugar coating layer. If desired, an undercoat of inert filled sugar may be applied over a seal coat prior to the steroid loaded sugar coat layer. The inert filler-containing sub-layer sugar coating may be made up with sucrose containing about 7.5 to about 15 percent microcrystalline cellulose. The outer sugar coating may contain a coloring agent such as titanium dioxide or a primary, secondary or grayed tint as is customary in the tableting art. If desired, the coloring agent may be applied as a separate coating layer over the outer sugar layer. A final polish may be used to further finish and complete the tablet.

40 The sugar used in production of the sugar coatings referred to throughout this specification is a sugar product, such

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as sucrose, derived from beet or cane sources or starch, saccharide or polysaccharide converted sources, which are considered suitable for tablet coating purposes. The currently preferred sugar is sucrose.

It has been discovered that the release of a hormonal steroid from the sugar coating can be controlled by limiting the quantity of microcrystalline cellulose to from about 0.1 to about 3 percent by weight of the sugar coating. This use of a small quantity of microcrystalline cellulose in the sugar coat is unlike the use of this excipient as a compression aid or to assist disintegration of a tablet core. In the latter case, the concentration of microcrystalline cellulose may rise to as high as 15 to 30 percent of weight.

Examples of hormonal steroids suitable for incorporation into the sugar coating formulations of this invention include, for instance, one or more of the following steroids; medroxyprogesterone acetate, levonorgestrel, gestodene, medrogestone, estradiol, estriol, ethinylestradiol, mestranol, estrone, dienestrol, hexestrol, diethylstilbestrol, progesterone, desogestrel, norgestimate, hydroxyprogesterone, norethindrone, norethindone acetate, norgestrel, megestrol acetate, methyltestosterone, ethylestrenol, methandienone, oxandrolone, trimegestone, dienogest, and the like. Additionally, the tissue selective progesterones and/or progesterone antagonists which may or may not have the typical steroidal functionality may be formulated into this technology. These include, but are not limited to: RU-486, onapristone, ZK-137316, ORG-31730, and HRP-2000. Where desired, estrogenic steroids and progestogenic steroids may be used in combination in the sugar coatings.

To illustrate in vitro dissolution rate control of steroid in the absence and presence of microcrystalline cellulose, the following illustrative examples are presented, without limitation:

EXAMPLE 1

A sugar coating consisting of the following solids was applied over a tablet core using either a non-perforated or perforated coating pan:

Sucrose, NF	87%
Polyvinylpyrrolidone	3%
Medroxyprogesterone Acetate, USP	10%

The rate of dissolution of the steroid was determined in accordance with 711 of USP XX, p.959 (1980), employing Apparatus 2, operating at 50 rpm by dissolving in 0.54% sodium lauryl sulfate in water at 37°C in six repeated trials (Method A). CV represents the coefficient of variation between these trials expressed as a percentage.

Time (min.)	Percent Steroid Released (CV%)
5	93 (5.2)
10	94 (5.3)
30	95 (5.3)
60	95 (5.4)
120	95 (5.4)

EXAMPLE 2

Tablets coated in the same manner with the same sugar coating as above were dissolved in 0.13% sodium lauryl sulfate in 0.1N HCl at 37°C using USP Apparatus 1 at 100 rpm, in six trials (method B). The results of this study were:

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Time (min.)	Percent Steroid Released (CV%)
5	83 (6.0)
10	85 (5.8)
30	85 (6.2)
60	85 (6.1)
120	85 (6.2)

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EXAMPLE 3

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Additional tablets coated in the same manner with the same sugar composition were subjected to a flow-through dissolution test procedure in 0.12% sodium lauryl sulfate in 0.1N HCl at 37°C using a SOTAX Dissotest Apparatus at 5.7 mL/min. flow rate (Method C). The results of three separate runs were as follows:

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Time (min.)	Percent Steroid Released (CV%)
30	90.9 (2.9)
60	94.2 (3.0)
90	95.3 (2.9)
120	96.0 (3.0)
210	97.4 (3.0)
300	98.9 (3.6)

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From these in vitro studies it is clear that medroxyprogesterone acetate, used here as a typical hormonal steroid, is released from the sugar coating extremely rapidly.

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EXAMPLE 4

For comparison purposes, and to illustrate the unexpected properties of the sugar coatings of this invention, a sugar coating consisting of the following solids was applied over a tablet core:

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Sucrose, NF	86.5%
Microcrystalline Cellulose	0.5%
PVP	3.0%
Medroxyprogesterone Acetate, USP	10.0%

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Employing the microcrystalline cellulose - containing sugar coated tablets and following Method A, the following in vitro dissolution data were obtained from three runs:

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Time (min.)	Percent Steroid Released (CV%)
5	19.5 (49.5)
10	29.9 (32.8)
30	50.0 (23.0)
60	61.6 (19.5)
120	74.2 (19.2)

EXAMPLE 5

With additional microcrystalline cellulose - containing sugar coated tablets prepared in the same manner as above, following Method B in six runs, the following data were obtained:

Time (min.)	Percent Steroid Released (CV%)
5	2.3 (34.4)
10	8.2 (27.0)
30	17.9 (16.1)
60	26.5 (13.6)
120	32.7 (16.6)

EXAMPLE 6

And, following method C, with the tablets containing microcrystalline cellulose in the sugar coating, in three runs, the following data were obtained:

Time (min.)	Percent Steroid Released (CV%)
30	2.8 (34.4)
60	4.1 (24.8)
90	5.1 (22.3)
120	6.4 (22.3)
210	11.0 (19.4)
300	14.3 (11.0)

From these data it is apparent that a small amount of microcrystalline cellulose in the sugar coating (in this case 0.5% by weight of the sugar coating solids) has markedly retarded the release rate of hormonal steroid.

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EXAMPLE 7

Sugar coated tablets were prepared in which the sugar coat contained 0.0%, 0.5% or 2% microcrystalline cellulose in combination with 3.0% polyvinyl pyrrolidone, 10.0% medroxyprogesterone acetate and sucrose. These tablets were fed to four beagle dogs under fasting conditions and the blood plasma levels of steroid were determined at 0, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, and 24 hours. The resulting data were plotted, the area under the curve (AUC) calculated for a twenty four hour period and the time at which the maximum plasma concentration occurred was determined to be as follows:

Microcrystalline Cellulose %	AUC(0-24 Hrs) ngxhr/mL	tmax (Hr)	Cmax (ng/mL)
0.0	345	0.6	37.8
0.5	294	1.0	36.9
2.0	294	1.1	24.6

From these *in vivo* dog data, it is obvious that a marked change in bioavailability of a hormonal steroid occurs as the concentration of microcrystalline cellulose in the sugar coating increases from 0.0 to one containing 0.5 to 2.0% microcrystalline cellulose. Thus, the rate of release of hormonal steroid incorporated in a sugar coating may be controlled by incorporation of very small amounts of microcrystalline cellulose into sugar coating.

EXAMPLE 8

Sugar coated tablets were prepared in which the sugar coat contained 0.25%, 0.5% or 0.8% microcrystalline cellulose in combination with 0.5% polyvinyl pyrrolidone, 5.0% medroxyprogesterone acetate and sucrose. These tablets were subjected to an *in vitro* dissolution test employing the USP Disintegration Apparatus (USP XX, 201, p958) (1980) with a 0.54% sodium lauryl sulfate dissolution medium at 37°C. The following test data were obtained:

Percentage Medroxyprogesterone Acetate Dissolved (CV%)			
Time (Minutes)	0.25% Microcrystalline Cellulose	0.5% Microcrystalline Cellulose	0.8% Microcrystalline Cellulose
15	97.8 (5.2)	72.6 (9.5)	32.4 (15.2)
30	98.8 (5.3)	89.9 (6.3)	62.8 (8.2)
45	99.3 (5.2)	95.2 (5.6)	76.6 (6.9)
60	99.1 (5.2)	98.3 (5.7)	84.8 (6.6)
90	99.9 (5.3)	100.9 (6.0)	94.4 (6.9)
120	100.3 (5.6)	102.4 (5.3)	98.0 (7.1)

These dosage forms were also evaluated in a human bioavailability study. The dosage forms were administered in a cross-over design to twelve healthy female subjects. Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4.5, 6, 8, and 12 hours and the plasma assayed for medroxyprogesterone acetate. The following data were obtained:

Microcrystalline Cellulose	AUC (0-12 h)	tmax (hr)	Cmax (ng/mL)
0.25%	26.0 ± 14.3*	2.9 ± 1.3	4.24 ± 3.0
0.5%	25.8 ± 10.5	3.2 ± 1.2	3.88 ± 1.87
0.8%	13.2 ± 4.0	3.9 ± 1.6	1.99 ± 0.73

*Mean values ± 1 Standard Deviation

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From the in vitro dissolution and in vivo human bioavailability data, it is clear that the drug release characteristics and bioavailability of the hormonal steroid, are controlled by the concentration of microcrystalline cellulose in the sugar coating.

EXAMPLE 9

A sugar coating containing 5 mg of medrogestone in a matrix of sucrose with 0.4% microcrystalline cellulose and 0.5% polyvinyl pyrrolidone was applied to a sealed and sugar-coated tablet core. The in vitro dissolution profile of this dosage form was compared to that of a rapidly-disintegrating compressed tablet containing 5 mg of medrogestone using the dissolution test described in 711 of USP XX, p. 959 (1980) employing Apparatus 2 operating at 50 r.p.m., with 900 mL of 0.54% sodium lauryl sulfate at 37°C. The following data were obtained:

Mean Percentage Medrogestone Released (CV%)		
Time (Minutes)	Conventional Rapidly Disintegrating Tablet	Sugar Coated Tablet Containing Medrogestone in Sugar Coat
15	95 (2.0)	6 (11.2)
30	95 (2.9)	11 (6.9)
45	97 (1.6)	15 (6.4)
60	97 (1.9)	18 (6.6)
120	98 (1.9)	25 (6.2)

The dramatic effect of reduced dissolution of medrogestone when the hormone is incorporated in a sugar coat containing 0.4% microcrystalline cellulose is clearly demonstrated.

One preferred embodiment of this invention is a compressed tablet in which the tablet core contains a unit dose of an estrogenic compound or a mixture thereof in an amount of from about 0.1 to about 5.0 milligrams, or more preferably from about 0.3 to about 2.5 milligrams, in combination with standard excipient compression aids and fillers. Most desirably, the conjugated estrogens found in the tablet core comprise the naturally occurring conjugated estrogen product known as Premarin®. Over a sugar coat on the compressed tablet is applied an additional sugar coat containing about 1 to about 50 milligrams and preferably about 1.5 to about 30 milligrams, of medroxyprogesterone acetate, a color coat, and finally, a polish coat. In other applications, it is preferable to employ a non-medicated core with a sugar coating containing a steroid such as trimegestone and more preferably, a sugar coating containing a mixture of steroids such as trimegestone and a conjugated estrogen.

Claims

1. A pharmaceutical tablet comprising an internal compressed core and an external sugar coating, wherein said compressed core contains either
 - i) no pharmacologically-active agent
 - or ii) one or more non-steroidal, pharmacologically-active agents that are conventionally administered in conjunction with a hormonal steroid, characterised in that the sugar coating comprises a hormonal steroid and a hormonal steroid release rate controlling amount of microcrystalline cellulose.
2. A pharmaceutical tablet comprising a non-medicated, compressed core and a sugar coating characterised in that the sugar coating comprises a hormonal steroid and a hormonal steroid release rate controlling amount of microcrystalline cellulose.
3. A pharmaceutical tablet as claimed in Claim 1 or Claim 2, wherein the sugar present in the coating is sucrose.
4. A pharmaceutical tablet as claimed in any one of Claims 1 to 3 wherein the hormonal steroid present in the sugar

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coating is medroxyprogesterone acetate, levonorgestrel, gestodene, medrogestone, estradiol, estriol, ethinylestradiol, mestranol, estrone, dienestrol, hexestrol, diethylstilbestrol, progesterone, desogestrel, norgestimate, hydroxyprogesterone, norethindrone, norethindrone acetate, norgestrel, megestrol acetate, methyltestosterone, ethylestrenol, methandienone, oxandrolone, trimegestone or dienogest .

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5. A pharmaceutical tablet as claimed in any one of Claims 1 to 4 wherein the hormonal steroid present in the sugar coating is RU-486, onapristone, ZK-137316, ORG-31730 or HRP-2000.

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6. A pharmaceutical tablet as claimed in any one of Claims 1 to 5 wherein the sugar coating comprises from about 0.1% to about 3% microcrystalline cellulose, by weight.

7. A pharmaceutical tablet as claimed in any one of Claims 1 to 6 wherein the sugar coating comprises from about 0 to about 5% polyvinylpyrrolidone, by weight.

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8. A pharmaceutical tablet as claimed in any one of Claims 1 to 7 wherein the sugar coating comprises from about 0.1 to about 20% hormonal steroid, by weight.

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9. A pharmaceutical tablet as claimed in any one of Claims 1 to 8 wherein the sugar coat contains an estrogenic steroid and a progestogenic steroid.

10. A method for the preparation of a pharmaceutical tablet as claimed in any one of Claims 1 to 9 comprising applying a sugar coating comprising a hormonal steroid and a hormonal steroid release rate controlling amount of microcrystalline cellulose to a core containing either

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- i) no pharmacologically-active agent
- or ii) one or more non-steroidal, pharmacologically-active agents that are conventionally administered in conjunction with a hormonal steroid.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 8424

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
P,X	EP 0 722 720 A (AMERICAN HOME PROD) 24 July 1996 * see the whole document*	1,3,4,6-8,10	A61K9/20
Y	* " *	2,5	
Y	--- WO 94 09762 A (MERCK & CO INC ;DEMPSKI ROBERT E (US); OLIVERO ROBERT C (US); SCHO) 11 May 1994 * see claim 1, page 4 lines 5-19, and page 8 lines 26-34 *	2,5	
A	--- EP 0 009 410 A (LILLY CO ELI) 2 April 1980 * see claim 1 * -----	1,2,5	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61K
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 18 June 1997	Examiner Isert, B
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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2020
Bogotá, D.C.,

Doctor:
Álvaro Correa Ordóñez
Apoderado

Oficio N°: 08876

ASUNTO:	Radicación PCT N°	09-45866
	Trámite	011
	Evento	378
	Actuación	440
	Folios	008

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Cielo Ángela Peña Rodríguez, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPÉDES DE VERGEL
Directora de Nuevas Creaciones (C).

El anterior oficio fue notificado por fijación en lista de fecha, 16 JUL. 2010.

202021

2020
Bogotá, D.C.,

Doctor:
Álvaro Correa Ordóñez
Apoderado

Oficio N°: № 08875

ASUNTO:	Radicación PCT N°	09-45866
	Trámite	011
	Evento	378
	Actuación	440
	Folios	007

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor Tito Noe Parra Murillo, en su calidad de apoderado de Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

El anterior oficio fue notificado por fijación en lista de fecha, 16 JUL. 2010.

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