



No. 09-070672- -00003-0000

Fecha: 2011-01-18 11:52:26 Dep. 2020 DIR NUEVASCR
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Act. 400 OPOSIOBSERVTER Folios: 85

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: 09-70672

Solicitante: WYETH

Apoderado: ALVARO CORREA ORDONEZ

Título de la nueva creación o denominación del signo: COMPOSICIONES CON FORMA

DE DOSIFICACION SIMPLE PARA LIBERAR MULTIPLES FARMACOS A DIFERENTES VELOCIDADES DE LIBERACIÓN

Gaceta: 621

③

OPOSICION PRESENTADA POR:

SOLICITANTE

Nombre: LABORATORIOS SYNTHESIS S.A.S.

Dirección: CARRERA 44 N° 20C-73

Nacionalidad o Domicilio: COLOMBIA

Lugar de Constitución: BOGOTÁ

Teléfono: 3 69 22 22 Fax:

E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Número: 860,000,760-1

REPRESENTANTE
O APODERADO

Nombre: ELIANA ISaura MORENO

BOHORQUEZ

Dirección: CARRERA 13 No. 119-95

Teléfono: (571)213 12 13 Fax: (571)612 19 79

E-mail: negocios@optimum-co.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número: 51'975.664 TP 83823

④

FUNDAMENTOS DE LA OPOSICION

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 _____

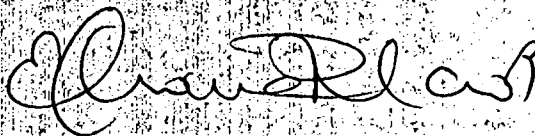
⑥ ANEXOS

- ☒ 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: ELIANA ISAURA MORENO BOHÓRQUEZ

FIRMA:



C.C. 51.975.664

TP. 83823

Señor Jefe,

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 09 70672

Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIONES CON FORMA DE DOSIFICACION
SIMPLE PARA LIBERAR MULTIPLES FARMACOS A
DIFERENTES VELOCIDADES DE LIBERACION"

Solicitante : WYETH

Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 621 del 20 de octubre de 2010

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *83823* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** 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 "COMPOSICIONES CON FORMA DE DOSIFICACION SIMPLE PARA LIBERAR MULTIPLES FARMACOS A DIFERENTES VELOCIDADES DE

LIBERACION", 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 ESTROGENOS. 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 08 de julio de 2009 reivindicando prioridad bajo la solicitud US20070884801 del 2007-01-12; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 621 del 20 de octubre de 2010, cuya publicación internacional corresponde a la WO2008089087 del 2008-07-24.

2.2. La solicitud colombiana 09 70672 objeto de la presente oposición se refiere a composiciones de tableta en tableta que comprenden uno o más estrógenos en una



primera capa y un agente terapéutico en una segunda capa y con procesos para su producción, en donde la composición de tableta en tableta, es caracterizada porque comprende: a) una tableta central que comprende: uno o más estrógenos; un componente rellenedor/ diluyente central; un componente rellenedor/aglomerante central; un componente polimérico de formación de gel hidrofílico central; y opcionalmente, un componente lubricante central; y b) una capa de tableta exterior comprimida que comprende uno o más agentes terapéuticos seleccionados del grupo que consiste de modulador del receptor de estrógeno selectivos y agentes progestacionales; un componente rellenedor/diluyente de la capa exterior; un componente rellenedor/aglomerante de la capa; un componente de polímero de formación de gel hidrofílico de la capa exterior; opcionalmente, un componente antioxidante; y opcionalmente, un componente lubricante de la capa exterior.

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

- D1: WO2005120466 publicada el 22 de diciembre de 2005.
- D2: EP0308637 publicada el 29 de marzo de 1989.

2.4. Ahora bien, el documento D1, se refiere a composiciones particularmente útiles como revestimientos para formas de dosis en sólidos de agentes terapéuticos, que se encuentran como formas de dosis en sólidos que comprenden dichos revestimientos, procedimientos para la preparación de dichas formas de dosis en



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

sólidos, y los productos de esos procedimientos; las composiciones para revestimiento generalmente proveen una excelente fuerza y resistencia a la fragmentación, incluso cuando se aplica a núcleos de tabletas flexibles que se pueden hinchar tales como núcleos tipo hidrogel; Dicho documento D1 describe una tableta comprimida que comprende los estrógenos conjugados en el núcleo, recubierta con una capa externa que comprende un agente terapéutico como acetato de medroxiprogesterona; el mismo documento D1 se refiere a la utilización de capas y/o revestimientos en tabletas, o similares para obtener diferentes beneficios, y revela particularmente que los revestimientos de película también han sido utilizados para modificar la liberación de los constituyentes de núcleo de tableta como, por ejemplo, vía revestimientos entéricos en los cuales el polímero empleado en el revestimiento es esencialmente impermeable al PH gástrico pero es soluble en el PH incrementado de los intestinos, mas adelante el documento D1 menciona ventajas del revestimiento de película como la formulación de revestimientos de liberación extendida que ayudan a eliminar la necesidad de regímenes de dosis múltiples de un agente terapéutico particular. El documento D1 se refiere también al perfil de liberación del agente terapéutico anotando que se puede modificar mediante diferentes métodos conocidos como la inclusión de sustancias solubles al agua dentro de las membranas, o revestimientos, sustancias que se disuelven por los fluidos gastrointestinales, creando poros dentro de la película que permiten que los fluidos gastrointestinales pasen a través de la membrana y disuelvan el agente terapéutico dentro del núcleo de la tableta, etc. Finalmente el documento D1 menciona que la velocidad de difusión se puede controlar de varias formas, como por ejemplo mediante el grosor y composición de la membrana para difusión.



2.5. El documento D2 por su parte revela una cápsula, compuesta por dos capsulas individuales, las cuales pueden tener características diferentes, considerando las necesidades de los ingredientes activos o las necesidades relativas a las afecciones que se desee tratar; ingredientes activos, lubricantes y similares, en cada capsula. Dicho documento D2 describe características de diferenciación de capsulas y fases, considerando si es necesario una capa para evitar que los componentes se mezclen de forma indeseada, y particularmente el documento D2 menciona el uso de diferentes compuestos adyuvantes, excipientes, o similares conocidos como rellenos, estabilizadores de PH, formadores de gel, diluyentes, etc.

2.6. Tomando los documentos D1 y D2 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir del documento D1 en combinación con D2, concebir composiciones de tableta en tableta que comprenden uno o más estrógenos en una primera capa y un agente terapéutico en una segunda capa y a procesos para su producción, en donde la composición de tableta en tableta, es caracterizada porque comprende: a) una tableta central que comprende: uno o más estrógenos; un componente relleno/diluyente central; un componente relleno/aglomerante central. Un componente polimérico de formación de gel hidrofílico central; y opcionalmente, un componente lubricante central; y b) una capa de tableta exterior comprimida que comprende uno o más agentes terapéuticos seleccionados del grupo que consiste de modulador del receptor de estrógeno selectivos y agentes progestacionales; un componente relleno/diluyente de la capa exterior; un componente relleno/aglomerante de la capa; un componente de polímero de formación de gel hidrofílico de la capa exterior; opcionalmente, un componente antioxidante; y opcionalmente, un



componente lubricante de la capa exterior. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 70672 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.

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

2.8.1. 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, 12 de enero de 2007, a partir del documento D1, en combinación con D2 un experto en la materia puede llegar de manera evidente a composiciones de tableta en tableta que comprenden uno o más estrógenos en una primera capa y un agente terapéutico en una segunda capa, en donde la composición de tableta en tableta, es caracterizada porque comprende: a) una tableta central que comprende: uno o más estrógenos u otros activos; un componente rellenedor/diluyente central, un componente rellenedor/aglomerante central, y/o similares. Un componente polimérico de formación de gel hidrofílico central; y opcionalmente, un componente lubricante central; y b) una capa de tableta exterior comprimida que comprende uno o más agentes terapéuticos seleccionados del grupo que consiste de moduladores del receptor de estrógeno selectivos y agentes progestacionales; un componente rellenedor/diluyente de la

capa exterior; un componente rellenedor/aglomerante de la capa; un componente de polímero de formación de gel hidrofílico de la capa exterior, o componentes similares, opcionalmente un componente antioxidante; y opcionalmente, un componente lubricante de la capa exterior; sobre lo cual busca protección en el capítulo reivindicatorio.

2.9. 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.

2.10. 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 **“COMPOSICIONES CON FORMA DE DOSIFICACION SIMPLE PARA LIBERAR MULTIPLES FARMACOS A DIFERENTES VELOCIDADES DE LIBERACION”**, cuyos titulares son WYETH, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 621 del 20 de octubre de 2010.

3. PRUEBAS

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

D1: WO2005120466 publicada el 22 de diciembre de 2005.

D2: EP0308637 publicada el 29 de marzo de 1989.

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 **LABORATORIOS
SYNTHESIS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

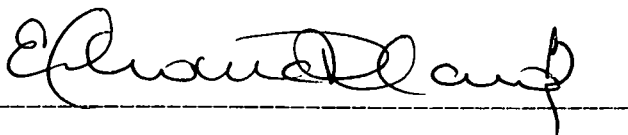
D1: WO2005120466 publicada el 22 de diciembre de 2005.

D2: EP0308637 publicada el 29 de marzo de 1989.

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,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

Industria y Comercio

SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 004762

Bogotá D.C., 18 de 2011 - 11:28:31

RECIBIDO DE : LABORATORIOS SYNTHESIS LTDA & CIA S.C.A.

NI 860.000.760

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	396966916	17/01/2011	1.216.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-070672- -00003-0000

Fecha: 2011-01-18 11:52:26 Dep. 2020 DIR. NUEVAS CR
 Tra. 11 PATENTE IYII Eve: 378 FASE NACIONAL I
 Act. 400 OPOSIOBSERVTER Folios: 85

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Gerente de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Bogotá (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **09 070.672**, titulada "**COMPOSICIONES CON FORMA DE DOSIFICACIÓN SIMPLE PARA LIBERAR MÚLTIPLES FÁRMACOS A DIFERENTES VELOCIDADES DE LIBERACIÓN**", cuyo titular es WYETH, publicada en la gaceta No. 621 del 20 de Octubre de 2010.

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 fuere 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 Bogotá (Colombia) a los ____ días del mes de ____ de 2011.

LABORATORIOS SYNTHESIS S.A.S.

Cédula de Extranjería: No. 319788.

NIT: 860.090.760-1

Gerente

Acepto:

ELIANA ISAURA MORENO BOHÓRQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



200



DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Circulo de Bogotá,

ALBERTO PALACIO
quien exhibió la C. E. B/19/88

Expedida en BOGOTÁ y
declaró que la firma y huella que
aparecen en el presente documento
son suyas y que el contenido del mismo
es cierto.

BOGOTÁ, D.C. 17 ENE 2011

[Signature]
FIRMA

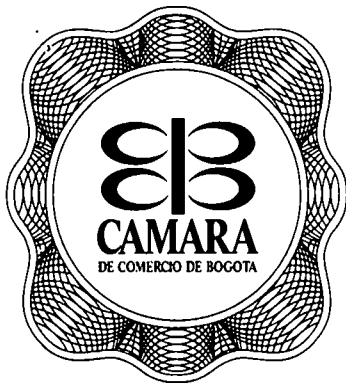


HUELLA DEL INDICE DERECHO

[Signature]
EL NOTARIO

18 NOTARIA DIECIOCHO DEL 18
CIRCULO DE BOGOTÁ D.C.
LA HUELLA SE AUTENTICA POR
SOLICITUD DEL INTERESADO





01



* 9 9 9 1 8 7 0 7 *

24

CAMARA DE COMERCIO DE BOGOTA

SEDE CENTRO

14 DE ENERO DE 2011

HORA 10:58:20

R030239466

PAGINA: 1 de 5

* * * * *

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL

CERTIFICA:

NOMBRE : LABORATORIOS SYNTHESIS S A S

N.I.T. : 860000760-1

DOMICILIO : BOGOTA D.C.

CERTIFICA:

MATRICULA NO: 00008059 DEL 23 DE MARZO DE 1972

CERTIFICA:

DIRECCION DE NOTIFICACION JUDICIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL DE NOTIFICACION JUDICIAL : synthe@synthesis.com.co

DIRECCION COMERCIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL COMERCIAL : synthe@synthesis.com.co

CERTIFICA:

CONSTITUCION: ESCRITURA PUBLICA NO.2078, NOTARIA 8 BOGOTA, DEL 27 DE JULIO DE 1.950, INSCRITA EL 10 DE AGOSTO DE 1.950, BAJO EL NO. 21.766 DEL LIBRO RESPECTIVO ACLARADA POR ESCRITURA NO. 3608 DEL 8 DE OCTUBRE DE 1.956 NOTARIA 8 DE BOGOTA INSCRITA EN ESTA CAMARA DE COMERCIO EL 19 DE OCTUBRE DE 1.956 BAJO EL NO. 35.547 DEL LIBRO RESPECTIVO, SE CONSTITUYO LA SOCIEDAD DENOMINADA: "LABORATORIOS BALBAG".

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 3997 OTORGADA EN LA NOTARIA 8 DE BOGOTA EL 24 DE NOVIEMBRE DE 1.952, INSCRITA EN ESTA CAMARA DE COMERCIO EL 1 DE DICIEMBRE DE 1.952, BAJO EL NUMERO 26.158 DEL LIBRO RESPECTIVO, LA SOCIEDAD CAMBIO SU NOMBRE DE: "LABORATORIOS BALBAG" POR EL DE "LABORATORIO SYNTHESIS", E INTRODUJO OTRAS REFORMAS.

CERTIFICA :

QUE POR ESCRITURA PUBLICA NUMERO 6491 OTORGADA EN LA NOTARIA 1. DE BOGOTA EL 24 DE DICIEMBRE DE 1.981, INSCRITA EN ESTA CAMARA DE COMERCIO EL 12 DE MARZO DE 1.982, BAJO EL NUMERO 113.297 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE "LABORATORIOS SYNTHESIS BALAVOINE Y CIA. S.C.A" POR EL DE "LABORATORIOS SYNTHESIS LTDA. Y CIA. S.C.A" E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 8580 OTORGADA EN LA NOTARIA 3 DE BOGOTA EL 4 DE DICIEMBRE DE 1.973, INSCRITA EN ESTA CAMARA DE COMERCIO EL 7 DE ENERO DE 1.974, BAJO EL NUMERO 14.478 DEL LIBRO IX, LA SOCIEDAD SE TRASFORMO DE LIMITADA EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE LABORATORIOS SYNTHESIS BALAVOINE Y CIA. S.C.A.

CERTIFICA:

QUE POR ACTA NO. 117 DE LA ASAMBLEA DE ACCIONISTAS, DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NÚMERO 1390261 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES A SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE: LABORATORIOS SYNTHESIS S.A.S.

CERTIFICA:

QUE POR E.P. NO.5.435 DEL 17 DE SEPTIEMBRE DE 1.996, NOTARIA PRIMERA DE SANTAFE DE BOGOTA, INSCRITA EL 30 DE SEPTIEMBRE DE 1.996, BAJO EL NO.556.909 DEL LIBRO IX, ADICIONADA POR LOS REGISTROS 557 146 DEL 1 DE OCTUBRE DE 1.996, Y 557.301 DEL 2 DE OCTUBRE DE 1996 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA COMUNICO QUE SE FUSIONO, ABSORBIENDO A LA SOCIEDAD "SYNTHESIS VETERINARIA LTDA Y CIA S C A"

CERTIFICA:

QUE POR E.P. NO.1024 DEL 28 DE FEBRERO DE 1997, DE LA NOTARIA 1. DE SANTAFE DE BOGOTA, INSCRITA EL 31 DE MARZO DE 1997, BAJO EL NUMERO 579245 DEL LIBRO IX, CELEBRO ACUERDO DE FUSIÓN CON LA SOCIEDAD PRODUCTOS DIETÉTICAS DIETESYN S.A, DONDE LA SOCIEDAD DE LA REFERENCIA FUE LA ABSORBENTE.

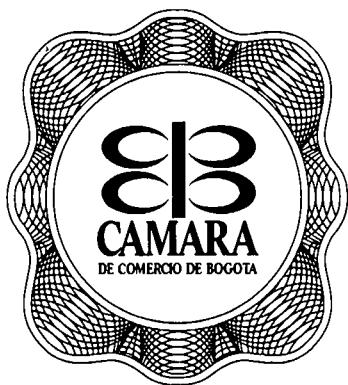
CERTIFICA:

QUE POR ACTA NO. 120 DE LA ASAMBLEA DE ACCIONISTAS DEL 29 DE JULIO DE 2010, INSCRITA EL 19 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01429837 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA (ABSORBENTE) ABSORBE MEDIANTE FUSIÓN A LAS SOCIEDADES INMUNOSYN SAS Y GYNOPHARM SAS LAS CUALES SE DISUELVEN SIN LIQUIDARSE.

CERTIFICA:

REFORMAS:

ESCRITURAS NO.	FECHA	NOTARIA	INSCRIPCION
4471	18-XII-1.956	8 BTA.	22-XII-1.956 NO. 36.077
3322	31-XII-1.958	8 BTA.	12-I-1.959 NO. 42.034
2322	22-IX-1.961	8 BTA.	29-IX-1.961 NO. 51.161
290	2-II-1.967	6 BTA.	24-II-1.967 NO. 71.304
8545	16-XII-1.967	6 BTA.	26-I-1.968 NO. 75.041
4679	20-XII-1.967	8 BTA.	26-I-1.968 NO. 75.042
3010	14-V-1.968	6 BTA.	30-V-1.968 NO. 76.244
2931	4-V-1.970	6 BTA.	18-V-1.970 NO. 84.983
5656	13-VII-1.970	6 BTA.	13-VIII-1.970 NO. 86.126
3487	15-VII-1.971	3 BTA.	29-VII-1.971 NO. 90.980
4638	10-VII-1.984	11 BTA.	27-VIII-1.984 NO.157.001
1443	14-III-1.985	11 BTA.	26- III-1.985 NO.167.627
724	11- II-1.985	1 BTA.	21- II-1.985 NO.165.940
4836	11-VIII-1986	1 BTA.	23- IX -1.986 NO.197.784
5659	15- IX -1986	1 BTA.	23- IX -1.986 NO.197.784
6326	16- X -1987	1 BTA.	23- X -1.987 NO.221.604
5164	21-VIII-1990	1 BTA.	3- IX -1.990 NO.303.579
9244	23-XII- 1991	1 STAFE.BTA.	8-I -1.992 NO.351.255
8145	15- X - 1992	1 STAFE.BTA.	16- X-1.992 NO.382.488
1374	26- III-1993	1 STAFE.BTA.	19- III-1993 NO.399972
3120	01-VI-1.995	1A.STAFE BTA	23-VI- 1.995 NO.498.060
5435	17-IX-1.996	1A.STAFE BTA	30-IX- 1.996 NO.556.909
5435	17-IX-1.996	1A.STAFE BTA	01- X- 1.996 NO.557.146
5435	17-IX-1.996	1A.STAFE BTA	02- X- 1.996 NO.557.301
5942	7-X -1.996	1A.STAFE BTA	11- X- 1.996 NO.558.222
6305	24-X--1.996	1A.STAFE BTA	07-XI--1.996 NO.561.207
6929	25-XI-1.996	1A.STAFE BTA	12-XII-1.996 NO.565.961
787	19-II-1.997	1A.STAFE BTA	25-II -1.997 NO.575.141



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28-II-1.997 1A.STAFE BTA 31-III-1.997 NO.579.245

CERTIFICA:

REFORMAS:

E.P. NO.	FECHA	NOTARIA	CIUDAD	FECHA	NO. INSC.
0007110	1997/10/28	0001	BOGOTA D.C.	1997/11/06	00609204
0001896	1998/03/16	0001	BOGOTA D.C.	1998/04/01	00628368
0002924	1998/04/21	0001	BOGOTA D.C.	1998/05/18	00634309
0002377	2000/06/14	0001	BOGOTA D.C.	2000/06/20	00733626
0000SIN	2004/06/22	0000	BOGOTA D.C.	2004/06/28	00940785
117	2010/04/30	0000	BOGOTA D.C.	2010/06/10	01390261
120	2010/08/18	0000	BOGOTA D.C.	2010/08/26	01409241
120	2010/08/30	0000	BOGOTA D.C.	2010/09/13	01413659
120	2010/07/29	0000	BOGOTA D.C.	2010/11/19	01429837

CERTIFICA:

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 27 DE JULIO DE 2040

CERTIFICA:

OBJETO SOCIAL: EL OBJETO DE LA SOCIEDAD ES EL EJERCICIO DE TODAS LAS ACTIVIDADES COMERCIALES PARA: 1) LA IMPORTACIÓN, EXPORTACIÓN, FABRICACIÓN, COMERCIALIZACIÓN, DISTRIBUCIÓN Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, VETERINARIOS E IMPLEMENTOS MÉDICOS. 2) CUALQUIER OTRA ACTIVIDAD LÍCITA DE COMERCIO RELACIONADA CON SU OBJETO SOCIAL PRINCIPAL Y TODO LO QUE SE RELACIONA CON LA IMPORTACIÓN DE LOS BIENES Y EQUIPOS NECESARIOS PARA EL DESARROLLO DE SU OBJETO SOCIAL. 3) TENER LA REPRESENTACIÓN EN COLOMBIA DE EMPRESAS O SOCIEDADES ESTABLECIDAS FUERA DEL TERRITORIO COLOMBIANO, CUYO OBJETO SEA SIMILAR O COMPLEMENTARIO. EN DESARROLLO DE SU OBJETO SOCIAL PRINCIPAL, LA SOCIEDAD PODRÁ ADELANTE Y CELEBRAR LOS SIGUIENTES ACTOS Y CONTRATOS: A) EXPORTAR E IMPORTAR, AGENCIAR, DISTRIBUIR, COMERCIALIZAR, COMPRAR O VENDER A COMISIÓN O CONSIGNACIÓN O DE CUALQUIER OTRA FORMA O MODALIDAD, TODA CLASE DE EQUIPOS, APARATOS, BIENES AL POR MAYOR O AL DETAL, Y SERVICIOS RELACIONADOS CON SU ACTIVIDAD. B) GRAVAR EN CUALQUIER FORMA LOS BIENES DE SU PROPIEDAD MUEBLES O INMUEBLES, DAR EN PRENDA LOS PRIMEROS O HIPOTECAR LOS SEGUNDOS PARA GARANTIZAR OBLIGACIONES DE LA SOCIEDAD. C) CONSTITUIR APODERADOS QUE LE REPRESENTEN, ASOCIARSE CON OTRAS COMPAÑÍAS DE LA MISMA O PARECIDA NATURALEZA Y EN GENERAL REALIZAR TODA CLASE DE OPERACIONES COMERCIALES O CIVILES Y EJECUTAR O CELEBRAR TODA CLASE DE CONTRATOS O ACTOS DEL MISMO ORDEN, YA SEAN INDUSTRIALES, COMERCIALES O FINANCIEROS ENCAMINADOS A ALCANZAR LOS FINES QUE SE PROPONEN. D) ADQUIRIR, ENAJENAR, ADMINISTRAR, RECIBIR O DAR EN ARRENDATARIO O A CUALQUIER TÍTULO, TODA CLASE DE BIENES MUEBLES E INMUEBLES. E) INTERVENIR ANTE TERCEROS O ANTE LOS ACCIONISTAS MISMOS COMO ACREEDORA O COMO DEUDORA EN TODA CLASE DE OPERACIONES DE CRÉDITO, DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER

CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRESTAMOS. OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR Y NEGOCIAR EN GENERAL TÍTULOS VALORES RECIBIRLOS EN PAGO; G) CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCTENTES AL BUEN LOGRO DE LOS FINES SOCIALES.

CERTIFICA:

CAPITAL:

** CAPITAL AUTORIZADO **

VALOR : \$20,000,000,000.00
NO. DE ACCIONES : 20,000,000.00
VALOR NOMINAL : \$1,000.00

** CAPITAL SUSCRITO **

VALOR : \$17,207,141,000.00
NO. DE ACCIONES : 17,207,141.00
VALOR NOMINAL : \$1,000.00

** CAPITAL PAGADO **

VALOR : \$17,207,141,000.00
NO. DE ACCIONES : 17,207,141.00
VALOR NOMINAL : \$1,000.00

CERTIFICA:

REPRESENTACION LEGAL: GERENCIA LA CUAL SERÁ ASUMIDA POR UN GERENTE Y UN SUBGERENTE QUIENES TENDRÁN REPRESENTACIÓN LEGAL DE LA SOCIEDAD.

CERTIFICA:

** NOMBRAMIENTOS **

QUE POR ACTA NO. 127 DE ASAMBLEA DE ACCIONISTAS DEL 12 DE NOVIEMBRE DE 2010, INSCRITA EL 23 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01430759 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

GERENTE

PALACIOS LUIS ALBERTO

C.E. 000000000319788

QUE POR ACTA NO. 117 DE ASAMBLEA DE ACCIONISTAS DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NUMERO 01390261 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

SUBGERENTE

MUÑOZ MARTINEZ ORLANDO

C.C. 000000008317044

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A SU CARGO LA ADMINISTRACIÓN INMEDIATA DE LA SOCIEDAD, ASÍ COMO LA REPRESENTACIÓN LEGAL DE LA MISMA Y EN TAL VIRTUD LE ESTÁN ASIGNADAS LAS SIGUIENTES FUNCIONES Y ATRIBUCIONES: A) LLEVAR LA REPRESENTACIÓN DE LA ENTIDAD, TANTO JUDICIAL COMO EXTRAJUDICIALMENTE. B) EJECUTAR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. C) CONSTITUIR, PARA CASOS ESPECIALES, APODERADOS JUDICIALES O EXTRAJUDICIALES. D) CELEBRAR LOS ACTOS, OPERACIONES Y CONTRATOS CONDUCTENTES AL BUEN LOGRO DEL OBJETO DE LA SOCIEDAD. E) CUIDAR DE LA RECAUDACIÓN E INVERSIÓN DE LOS FONDOS DE LA SOCIEDAD. F) PRESENTAR A LA REUNIÓN ORDINARIA ANUAL DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL INVENTARIO Y LOS ESTADOS FINANCIEROS DE PROPÓSITO GENERAL DE FIN DE EJERCICIO, JUNTO CON UN INFORME ESCRITO RELACIONADO CON LA SITUACIÓN Y LA MARCHA DE LA ENTIDAD. G) CREAR LOS EMPLEADOS NECESARIOS PARA LA



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DEBIDA MARCHA DE LA SOCIEDAD, SEÑALAR SUS FUNCIONES Y ASIGNACIONES Y HACER LOS NOMBRAMIENTOS CORRESPONDIENTES. H) CONVOCAR A LA ASAMBLEA GENERAL CUANDO PROCEDA HACERLO CONFORME A LA LEY O A ESTOS ESTATUTOS. I) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO ASÍ LO SOLICITE, ESTADOS FINANCIEROS MENSUALES DE PRUEBA E INFORMES. J) EJERCER LAS FUNCIONES QUE LE DELEGUE LA ASAMBLEA GENERAL DE ACCIONISTAS. K) CUMPLIR Y HACER QUE SE CUMPLAN EN OPORTUNIDAD Y DEBIDAMENTE TODAS LAS EXIGENCIAS DE LAS LEYES EN RELACIÓN CON EL FUNCIONAMIENTO Y LAS ACTIVIDADES DE LA INSTITUCIÓN. L) LAS DEMÁS QUE LE CORRESPONDAN CONFORME A LA LEY Y A ESTOS ESTATUTOS. EL GERENTE DE LA SOCIEDAD DEBERÁ CONTAR CON AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO PRETENDA SUSCRIBIR EN NOMBRE DE LA SOCIEDAD (I) ACTOS O CONTRATOS PARA ADQUIRIR, ENAJENAR, RECIBIR O DAR EN ARRENDAMIENTO O A CUALQUIER OTRO TÍTULO, TODA CLASE DE BIENES INMUEBLES DE LA SOCIEDAD O BIENES MUEBLES DIFERENTES A LOS PRODUCTOS COMERCIALIZADOS ORDINARIAMENTE POR LA SOCIEDAD, ASÍ COMO (II) ACTOS O CONTRATOS, INDEPENDIENTE DE SU OBJETO, QUE SUPERE EN CUANTÍA EL EQUIVALENTE A 300 SMLMV (TRESCIENTOS SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES).

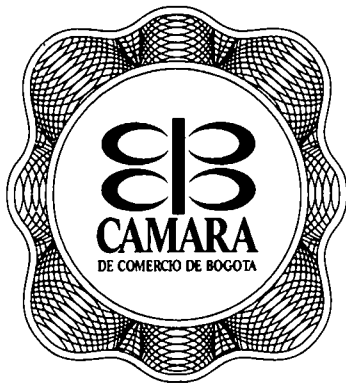
CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 654 DE LA NOTARIA 01 DE BOGOTA D.C., DEL 20 DE FEBRERO DE 2009, INSCRITA EL 02 DE MARZO DE 2009 BAJO EL NO. 15209 DEL LIBRO V, COMPARECIO ORLANDO MUÑOZ MARTINEZ IDENTIFICADO CON CÉDULA DE CIUDADANIA NO. 8.317.044 EN SU CALIDAD DE DELEGADO GENERAL SUPLENTE DEL SOCIO GESTOR LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL SEÑOR ANDRES FERNANDO MOLLAJOLI CENTURION, IDENTIFICADO CON CÉDULA DE EXTRANJERÍA NO. 351.283 QUE EN NOMBRE DE LA SOCIEDAD QUE REPRESENTO, ACTUÉ CON LAS MÁS AMPLIAS FACULTADES EN LA REPÚBLICA DE COLOMBIA, EN LOS SIGUIENTES ASUNTOS 1. PARTICIPAR EN CALIDAD DE SOCIO, ACCIONISTA O EMPRESARIO EN PERSONAS JURÍDICAS COLOMBIANAS, CONSTITUIDAS O POR CONSTITUIRSE, EN EL PORCENTAJE QUE LA APODERADA AQUÍ NOMBRADA ESTIME CONVENIENTE A NUESTROS INTERESES, CON FACULTAD PARA ENTREGAR LAS SUMAS CORRESPONDIENTES AL PAGO DEL MISMO; 2. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS; 3. REPRESENTAR A LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., EN LAS REUNIONES ASAMBLEA GENERAL O JUNTAS EN LAS CUALES TENGA INTERÉS; 4. EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRÉSTAMOS DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS, OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR, Y NEGOCIAR EN GENERAL TÍTULOS VALORES Y RECIBIRLOS EN PAGO; 5. CELEBRAR ASÍ MISMO OPERACIONES RELACIONADAS CON LA PROTECCIÓN DE SUS BIENES, NEGOCIOS Y PERSONAS A SU SERVICIO; 6. CELEBRAR CONTRATOS DE CUENTAS EN

PARTICIPACIÓN, SEA COMO PARTICÍPE ACTIVA O COMO PARTICÍPE INACTIVA; 7. TRANSIGIR, DESISTIR Y APELAR DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES; 8. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. 9. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEA CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES; 10. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. 11. NOTIFICARSE VÁLIDAMENTE DE AQUELLOS ACTOS DEL ORDEN ADMINISTRATIVO O JUDICIAL QUE SE FORMULEN CONTRA LA SOCIEDAD, ASÍ CÓMO ABSOLVER INTERROGATORIOS CON CAPACIDAD PARA CONFESAR; 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SYNTHESIS LTDA & CIA S.C.A. 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SÍNTESIS LTDA. & CIA S.C.A., RECAUDAR O RECIBIR POR SUS FRUTOS Y CELEBRAR TODA CLASE DE CONTRATOS RELACIONADOS CON LA ADMINISTRACIÓN. 13. ENAJENAR, ADQUIRIR, PERMUTAR, GRAVAR, ARRENDAR BIENES MUEBLES, PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTIIESIS LTDA & CIA S.C.A, SIN LÍMITE DE CUANTIA. 14. ENAJENAR, PERMUTAR, ADQUIRIR, GRAVAR, ARRENDAR BIENES MUEBLES E INMUEBLES PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL SALARIO MÍNIMO LEGAL MENSUAL MAS ALTO EN LA FECHA DE CELEBRACIÓN Y TENGA RELACIÓN DIRECTA CON EL DESARROLLO SOCIAL, ASÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DE LA SOCIEDAD GESTORA. 15. TOMAR DINERO EN MUTUO, CON FACULTAD PARA ESTIPULAR TODO TIPO DE INTERESES, PLAZOS Y DEMÁS CONDICIONES Y CELEBRAR CONTRATOS DE CUENTA CORRIENTE; 16. GIRAR, ORDENAR GIRAR, ENDOSAR, PROTESTAR, OTORGAR, ACEPTAR ORDENAR AVALÚOS Y HACER TODA CLASE DE NEGOCIOS RELACIONADOS CON TÍTULOS VALORES CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL SALARIO MÍNIMO LEGAL MENSUAL MÁS ALTO EN LA FECHA DE SU CELEBRACIÓN, SÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DEL REPRESENTANTE LEGAL DE LA SOCIEDAD GESTORA. 17. PRESENTAR DECLARACIÓN DE RENTA, PATRIMONIO, IMPUESTOS A LAS VENTAS EN ADMINISTRACIÓN DE IMPUESTOS NACIONES Y MUNICIPALES E INTERPONER LOS RECURSOS Y DECLARACIONES PERTINENTES CONTRA ACTOS DE DICHA ADMINISTRACIÓN CON FACULTAD PARA DEFENDER LOS INTERESES DE LA SOCIEDAD EN ÉSTA MATERIA. 18. DESIGNAR APODERADO ESPECIAL PARA CADA PROCESO JUDICIAL O ADMINISTRATIVO. 19. PRÉSENTAR RECURSOS POR VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR 20. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES 21. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES 22. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA REPÚBLICA DE COLOMBIA

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 3511 DE LA NOTARIA 18 DE BOGOTA D.C., DEL 8 DE SEPTIEMBRE DE 2010, INSCRITA EL 1 DE OCTUBRE DE 2010 BAJO EL NO. 00018604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE



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BOGOTA, EN SU CALIDAD DE GERENTE DE LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL A OLGA VICTORIA PRIETO ZAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.308 DE BOGOTA PARA QUE EN NOMBRE DE LA SOCIEDAD LABORATORIOS SYNTHESIS S.A.S., PROMUEVA Y DEFienda LOS INTERESES DE LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE, EN TODA ESPECIE DE GESTIONES Y ACTUACIONES ANTE LAS AUTORIDADES ADMINISTRATIVAS O JURISDICCIONALES Y EN ESPECIAL PARA: A. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS. B. TRANSIGIR, DESISTIR Y APELAR A DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C. ADELANSTAR CUALQUIER TIPO DE TRÁMITE ANTE EL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES. D. RECIBIR NOTIFICACIÓN DE TODAS LAS PROVIDENCIAS QUE SE EXPIDAN DENTRO DE LOS DIFERENTES TRÁMITES E INTERPONER LOS RECURSOS PROPIOS DE LA VÍA GUBERNATIVA. E. REPRESENTAR Y VIGILAR ANTE LOS FUNCIONARIOS, OFICINAS Y DEPENDENCIAS DEL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES, TODAS LAS SOLICITUDES QUE CONTENGAN TRÁMITES A NOMBRE DE LABORATORIOS SYNTHESIS S.A.S. F. SOLICITAR, OBTENER, REVISAR Y MODIFICAR REGISTROS SANITARIOS. G. OBTENER ANTE LAS OFICINAS Y AUTORIDADES NACIONALES QUE CORRESPONDAN Y EN ESPECIAL DE LA DIVISIÓN DE PROPIEDAD INDUSTRIAL DE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, REGISTROS DE MARCAS, RENOVACIÓN DE REGISTROS MARCARIOS, ANOTACIÓN DE TRASPASOS Y CAMBIO DE NOMBRE, PRESENTACIÓN Y TRÁMITE DE OPOSICIONES, PRESENTACIÓN Y TRÁMITE DE RECURSOS POR LA VÍA GUBERNATIVA Y DEMÁS DILIGENCIAS RELACIONADAS, A CUYO EFECTO LA FACULTA PARA DAR ANTE DICHAS AUTORIDADES, PARA ELEVAR SOLICITUDES, FORMULAR DESCRIPCIONES, APELACIONES Y RECLAMOS, SOLICITAR TESTIMONIO, RECIBIR, DESISTIR, SUSTITUIR, CANCELAR, TRANSIGIR, RENUNCIAR, ACEPTAR NOTIFICACIONES Y NOMBRAR APODERADOS JUDICIALES Y EXTRAJUDICIALES. H. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. I. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES. J. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. K. PRESENTAR RECURSOS POR LA VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR. L. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES. M. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES.

N. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA
REPÚBLICA DE COLOMBIA.

CERTIFICA:

** REVISOR FISCAL **

QUE POR DOCUMENTO PRIVADO DE REVISOR FISCAL DEL 28 DE JUNIO DE 2010,
INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397034 DEL LIBRO IX,
FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PRINCIPAL	
AGUILLON ROJAS SANDRA MILENA	C.C. 000000047436442

REVISOR FISCAL SUPLENTE	
PRADA SANCHEZ NUBIA MARCELA	C.C. 000001032358923

QUE POR ACTA NO. 119 DE ASAMBLEA DE ACCIONISTAS DEL 22 DE JUNIO DE
2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397026 DEL LIBRO
IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PERSONA JURIDICA	
DELOITTE & TOUCHE LTDA	N.I.T. 000008600058134

CERTIFICA:

PERMISO DE FUNCIONAMIENTO:QUE POR RESOLUCION NO.05952 DEL 11 DE -
JUNIO DE 1.985, INSCRITA EN ESTA CAMARA DE COMERCIO EL 8 DE JULIO
DE 1.985 BAJO EL NO. 172.879 DEL LIBRO IX, LA SUPERINTENDENCIA -
DE SOCIEDADES CONCEDIO PERMISO DEFINITIVO DE FUNCIONAMIENTO A LA
SOCIEDAD.

CERTIFICA:

QUE POR RESOLUCION NO.09006 DEL 19 DE DICIEMBRE DE 1.986 SUPERIN-
TENDENCIA DE SOCIEDADES INSCRITA EL 16 DE ENERO DE 1.987 BAJO EL
NO.204.133 DEL LIBRO IX, SE AUTORIZO A LA SOCIEDAD PARA COLOCAR
SETENTA Y CUATRO MIL (\$74.000) ACCIONES DE LAS QUE TIENE EN RE-
SERVA, A SU VALOR NOMINAL DE CIENTOS PESOS (\$100.00) M/CTE., CADA
UNA.

CERTIFICA:

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS:

NOMBRE : CARDIOPHARM

MATRICULA NO : 00537358 DE 3 DE MARZO DE 1993

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

NOMBRE : GENERICS

MATRICULA NO : 00664623 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

NOMBRE : MASCOTT

MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

NOMBRE : ONCOPHARM

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

NOMBRE : GASTROPHARM

MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010



CAMARA DE COMERCIO DE BOGOTA

SEDE CENTRO

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ULTIMO AÑO RENOVADO : 2010

NOMBRE : GYNECOPHARM

NOMBRE : GYNECOPHARM

MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

NOMBRE : ENTEROPHARM

MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

NOMBRE : EQUIPHARMA

MATRICULA NO : 00556630 DE 21-DE JULIO DE 1993

RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010

CERTIFICA:

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

* * * EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE
* * * FUNCIONAMIENTO EN NINGUN CASO

SEÑOR EMPRESARIO, SI SU EMPRESA TIENE ACTIVOS INFERIORES A 30.000 SMLMV Y UNA PLANTA DE PERSONAL DE MENOS DE 200 TRABAJADORES, USTED TIENE DERECHO A RECIBIR UN DESCUENTO EN EL PAGO DE LOS PARAFISCALES DE 75% EN EL PRIMER AÑO DE CONSTITUCION DE SU EMPRESA, DE 50% EN EL SEGUNDO AÑO Y DE 25% EN EL TERCER AÑO. LEY 590 DE 2000 Y DECRETO 525 DE 2009.

RECUERDE INGRESAR A www.supersociedades.gov.co PARA VERIFICAR SI SU EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

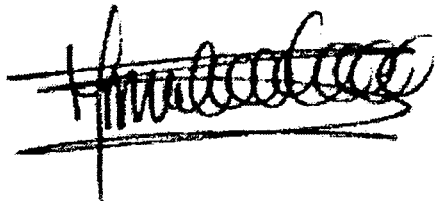
EL SECRETARIO DE LA CAMARA DE COMERCIO,

$\mu \in \Lambda_{\mathbb{R}}^{n-1}$

$\mathbf{A} = \begin{pmatrix} 1 & 2 & 3 \\ 2 & 3 & 4 \\ 3 & 4 & 5 \end{pmatrix}$

VALOR : \$ 3,700

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES

A handwritten signature in dark ink, appearing to be "H. M. L. C.", is written over two horizontal lines.

Anexo 1

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- (71) Applicant (for all designated States except US): **WYETH**
[US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **CLARK, John, C.** [US/US]; 375 Route 22B, Peru, NY 12972 (US). **MICHELUCCI, John, J.** [US/US]; 16 Sandra Avenue, Plattsburgh, NY 12901 (US). **SHERMAN, Deborah, M.** [US/US]; 5 Belmont Avenue, Plattsburgh, NY 12901 (US).
- (74) Agent: **BUCK, Margaret, M.**; Cozen O'Connor, 1900 Market Street, Philadelphia, PA 19103 (US).
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- Published:
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUGAR COATINGS AND METHODS THEREFOR

(57) Abstract: Compositions particularly useful as coatings for solid dosage forms of therapeutic agents are provided, as are solid dosage forms comprising such coatings, processes for preparing such solid dosage forms, and the products of those processes. The coating compositions generally provide excellent strength and resistance to cracking, even when applied to flexible/swellable tablet cores such as hydrogel-type cores. The compositions also exhibit excellent odor-blocking characteristics.

WO 2005/120466 A2

SUGAR COATINGS AND METHODS THEREFOR

FIELD OF THE INVENTION

The invention is directed generally to the field of pharmaceutical formulations.
5 More specifically, the invention relates to sugar-containing compositions suitable for use in coating solid preparations such as tablets, pills, granules and grains. Methods of using such coatings are provided, as are solid dosage forms coated with the compositions.

BACKGROUND OF THE INVENTION

10 Solid pharmaceutical dosage forms, most notably tablets, have been coated using a wide variety of materials and processes. The reasons for this include the aesthetic as well as the practical. For example, tablet coatings can mask an unpleasant taste or odor, can increase ease of ingestion by the patient and can serve to improve the ultimate appearance of the dosage form. Similarly, coatings can
15 protect a product from the effects of air, moisture and light, can improve product identification and can facilitate handling in packaging and filling lines during manufacture.

Typically, pharmaceutical dosage forms can be sugar coated or film coated. Conventional sugar coating compositions have been prepared as aqueous solutions
20 of sugar (syrops), most commonly sucrose, and it is said that tablets with excellent hermetic properties and smooth surface are obtained by the formation of tight, block-form structures of sugar crystals. Additional agents that may be included in sugar-coated tablets include talc (used as a sugar coating dispersion agent), precipitated calcium carbonate (used as a sugar coating suspension agent), gelatin, gum arabic
25 and pullulan (used as sugar coating binders), and carnauba wax (often applied as a sugar coating glossing agent).

Unfortunately, sugar-coating is a multi-step and tedious process, and is highly dependent on the use of skilled manpower. The typical sugar-coating process can be subdivided into six main steps: (1) sealing; (2) subcoating; (3) smoothing; (4)
30 color coating; (5) polishing; and (6) printing. In the hands of a skilled worker, sugar coated products are elegant in appearance, but certain problems beset the process and the ultimate product. For example, the sugar coating process requires that the tablets be kept constantly tumbling, thus presenting difficulties such as fragmenting

of those units not strong enough to withstand the stress encountered. Also, color nonuniformity, rough or overly soft coatings and/or marbling may present additional problems to be addressed.

In an attempt to overcome some of these difficulties, film coating was introduced to the pharmaceutical industry in the 1950's. Film coating involves the deposition of a thin, uniform, typically polymeric membrane to the substrate, usually by a spray technique. Advantages of the film coating process include minimal weight increase of the ultimate dosage form, reduction in processing times, and improved resistance to chipping.

Film coatings also have been utilized to modify the release of the constituents of the core tablet as, for example, via enteric coatings in which the polymer employed in the coating is essentially impervious to gastric pH but is soluble in the increased pH of the intestines. A further application of film coating lies in the formulation of extended-release coatings that help eliminate the need for multiple dose regimens of a particular therapeutic agent. Various types of extended release approaches are known. One such approach is a diffusion coating, which involves depositing a coating (usually from an organic solvent) on a soluble substrate core with a porous membrane that is water-permeable but water-insoluble. The release profile of the therapeutic agent can be modified by the inclusion of water-soluble substances within the membrane. These substances are dissolved by the gastrointestinal fluids, thereby creating pores within the film. These pores allow the gastrointestinal fluids to pass through the membrane and dissolve the therapeutic agent within the tablet core. The diffusion rate can be controlled by the thickness and composition of the diffusion membrane. For this system to function properly, the constituents of the diffusion coating formulation should exhibit good mechanical strength and flexibility. Unfortunately, however, such coating formulations, when deposited on the substrate, frequently lack the requisite mechanical strength and flexibility, thereby leading to rupture of the deposited film during dissolution in the gastrointestinal tract. This, in turn, permits the sudden release of the entire contents of the substrate containing the therapeutic agent in a phenomenon referred to as "dose dumping". Such a situation is clearly undesirable for extended-release dosage forms given the higher amount of therapeutic agent found therein as compared to conventional formulations.

Additionally, notwithstanding the advantages that film-coating provides, certain difficulties attend the film coating process, including the tendency to laminate if the tablets being coated are not of sufficient strength, the inability to hide defects in the tablet core, mottling and the like. Ironically, the use of organic solvents in film coating, which permits a number of process advantages, also presents some of the major disadvantages. Due to their volatility, the use of organic solvents in the film coating process can lead to flammability hazards as well as concerns over environmental effects and potential toxicity to the operators. Organic solvents also add to the cost of the overall process, due to the costs of the solvents *per se* or costs encountered in reducing any potential hazards thereof.

Moreover, film-coating may not be suitable for tablets that contain a particularly hygroscopic core that is apt to swell either during processing or storage. For example, film-coated tablets with hydrogel cores, which contain relatively high percentages of water-soluble cellulosic materials in the tablet cores, have a tendency to crack. Tablets with cracked coatings are unacceptable, from both an aesthetic and functional standpoint; the elegant appearance, ease of ingestion, and odor-masking properties are diminished, and the active ingredient in the tablet cores may become exposed to environmental conditions detrimental to product stability.

The present invention addresses one or more of these problems by providing coatings that exhibit good mechanical strength and flexibility when applied to a substrate, thereby reducing the possibility of cracking. The coating formulation of the present invention also utilizes an aqueous solvent system thereby eliminating or at least minimizing the use of organic solvents in the film coating process delineated above. At the same time, the compositions generally can be applied using traditional film-coating equipment, and thus may be utilized in simpler and less labor-intensive methods than are necessary to produce the sugar-coated tablets of the prior art.

SUMMARY OF THE INVENTION

In one embodiment, the invention is directed to compositions comprising water and a solids component that comprises: from about 30 weight percent (%) to about 60 weight % of at least one sugar; from about 5 weight % to about 10 weight % of at least one binder; from about 3 weight % to about 10 weight % of at least one hydroxyalkyl cellulose; from about 15 weight % to about 50 weight % of at least one water soluble polymer; optionally, a therapeutic agent in an amount of up to about 3

weight %; optionally, a second polymer that is water soluble or water dispersible, in an amount of up to about 20 weight %; and optionally, at least one plasticizer in an amount of up to about 8 weight %.

The invention also is directed to solid dosage forms comprising a core material and one or more coatings disposed thereon, wherein the coating comprises:
5 from about 30 weight % to about 60 weight % of at least one sugar; from about 5 weight % to about 10 weight % of at least one binder; from about 3 weight % to about 10 weight % of at least one hydroxyalkyl cellulose; from about 15 weight % to about 50 weight % of at least one water soluble polymer; optionally, a therapeutic agent in
10 an amount of up to about 3 weight %; optionally, a second polymer that is water soluble or water dispersible, in an amount of up to about 20 weight %; and optionally, at least one plasticizer in an amount of up to about 8 weight %.

In some further embodiments, the coating can include one or more therapeutic agents. In some such embodiments, the coating further includes one or
15 more polymers that provide control of the release of the therapeutic agent from the coating.

In another embodiment, the invention is directed to processes comprising: providing a tablet core; spraying or otherwise applying to said tablet core a sugar coating composition comprising water and a solids component that comprises: from
20 about 30 weight % to about 60 weight % of at least one sugar; from about 5 weight % to about 10 weight % of at least one binder; from about 3 weight % to about 10 weight % of at least one hydroxyalkyl cellulose; from about 15 weight % to about 50 weight % of at least one water soluble polymer; optionally, a therapeutic agent in an amount of up to about 3 weight %; optionally, a second polymer that is water soluble
25 or water dispersible, in an amount of up to about 20 weight %; and optionally, at least one plasticizer in an amount of up to about 8 weight %; resulting in a coated tablet core.

In further embodiments, the invention is directed to the products of the foregoing processes.

30 DESCRIPTION OF THE DRAWINGS

Figure 1 shows plasma MPA levels in six beagle dogs following oral administration of the tablet formulation described in Example 3.

DETAILED DESCRIPTION OF THE INVENTION

Concentrations, amounts, percentages, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus, should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also, to include each of the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited.

As an illustration, a concentration range of "about 1 weight % to about 10 weight %" should be interpreted to include not only the explicitly recited concentration of about 1 weight % to about 10 weight %, but also individual concentrations and the sub-ranges within the indicated range. Thus, included in this numerical range are individual concentrations such as 2 weight %, 5 weight %, and 8 weight %, and sub-ranges such as from 1 weight % to 3 weight %, from 5 weight % to 9 weight %, etc. The same principle applies to ranges reciting only one numerical value.

Similarly, an open ended range recited as "less than about 10 weight %" should be interpreted to include all of the values and ranges as elaborated above. Furthermore, it is understood that functional limitations may exist for limits not expressly recited by an open ended range, and that such limitations are included inherently as part of the disclosure of the present application, though not expressly recited. Such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

In one embodiment, the invention is directed to compositions suitable for use in coating a solid preparation, such as a tablet, pill, granule, or the like. The compositions comprise water, and a solids component, and also optionally may include a therapeutic agent. Up to about 50% by weight of water may be replaced by another solvent, such as an alcohol. Preferably, the composition is in the form of an aqueous suspension, obtained by combining from about 30 weight % to about 98 weight % water, and from about 2 weight % to about 70 weight % of the solids component. In certain embodiments, the composition comprises from about 75 weight % to about 85 weight % water and from about 15 weight % to about 25 weight % of the solids component. In one such embodiment, the composition comprises about 82 weight % water.

The solids component contains, *inter alia*, one or more sugars. As used herein, the term "sugar" refers to any type of simple carbohydrate, such as a mono or disaccharide, either naturally obtained, refined from a natural source, or artificially produced, and includes, without limitation, sucrose, dextrose, maltose, glucose, fructose, galactose, mannose, lactose, trehalose, lactulose, levulose, raffinose, ribose, and xylose. The term "sugar," as used herein, also includes various "sugar substitutes" widely known to those of ordinary skill in the art of preparing solid dosage forms, such as the polyhydric alcohols (sometimes referred to as "sugar alcohols" or hydrogenated saccharides), for example sorbitol, mannitol, xylitol, and erythritol, and the sugar derivatives of polyhydric alcohols, such as maltitol, lactitol, isomalt, and polyalditol. Accordingly, the recitation of the term "sugar" generically should be interpreted to include such specific compounds, as well as others not expressly recited. In certain embodiments, the solids component of compositions of the invention include at least one sugar that is a mono- or disaccharide, for example, sucrose, dextrose, maltose, glucose, fructose, galactose, mannose, lactose. In some such embodiment, the sugar is sucrose.

Unlike traditional sugar coatings, which are produced using syrups that contain upwards of 80 weight % sugars, on a dry weight basis, the compositions of the present invention contain a solids component that comprises from about 30 weight % to about 60 weight % of at least one sugar, for example, sucrose. In some embodiments, the solids component contains from about 35 weight % to about 55 weight % sugar. In still other embodiments, the solids component contains from about 35 to about 45 weight % sugar.

The solids component also contains a binder, such as microcrystalline cellulose or powdered cellulose, in an amount of from about 5 weight % to about 10 weight %. In some embodiments, the binder is present in an amount of from about 5.5 weight % to about 9 weight %, or in further embodiments, in an amount of from about 5.5 to about 7.5 weight %.

The solids component further contains from about 3 weight % to about 10 weight % of at least one hydroxyalkyl cellulose in which the alkyl group has from between one and ten carbon atoms. Representative hydroxyalkyl celluloses, without limitation, include hydroxyethyl cellulose (HEC) and hydroxypropyl cellulose (HPC). In some embodiments, the hydroxyalkyl cellulose is HPC. In some embodiments, the

solids component comprises from about 4 weight % to about 7 weight % hydroxyalkyl celluloses; and in further embodiments, from about 4 to about 5.5 weight % hydroxyalkyl celluloses.

In addition, the solids component preferably contains from about 15 weight %
5 to about 50 weight % of at least one water soluble polymer. Water soluble polymers suitable for use in coatings and as excipients in pharmaceutical dosage forms are widely known to those of skill in the art, and include, *inter alia*, Hypromellose (hydroxypropyl methylcellulose), acacia, sodium carboxymethylcellulose, dextrin, alginic acid, gelatin, guar gum, methylcellulose, sodium alginate, zein,
10 polyvinylpyrrolidone, vinylpyrrolidone-vinyl acetate copolymer, vinyl acetate-crotonic acid copolymer and ethyl acrylate-methacrylate acid copolymer. In some embodiments, the water soluble polymer is Hypromellose. In other embodiments, the polymer is sodium carboxymethylcellulose; and still other embodiments, methylcellulose. The specific amount of water soluble polymer to be used in the
15 solids component varies, depending upon the polymer selected. In some embodiments, the water soluble polymer is present in an amount from about 25 weight % to about 40 weight %, and further, in an amount from about 20 weight % to about 30 weight %.

The solids component of the compositions also contains at least one
20 plasticizer. Suitable plasticizers also are well known to those skilled in the art, and include, for example, propylene glycol, glycerin, trimethylolpropane, polyethylene glycol (PEG) polymers, dibutyl sebacate, acetylated monoglycerides, diethylphthalate, triacetin, glyceryltriacetate, acetyltriethyl citrate and triethyl citrate. In certain embodiments, a PEG polymer is used. Such polymers are available
25 commercially by grades of average molecular weight such as PEG 100 to PEG 4,000. In some such embodiments, PEG 400 is used. The plasticizer usually is present in the solid components in an amount of from about 0 weight % to about 8 weight %. In some embodiments, the plasticizer is present in an amount from about 5 weight % to about 7 weight %, or from about 2 weight % to about 4 weight %, or
30 from about 2.5 to about 3.5 weight %.

The solids component of the compositions also may contain a second polymer, which is water soluble, or which is water dispersible, i.e., capable of forming an aqueous dispersion. Suitable polymers that can be used as, for example, a

second polymer, without limitation, are polyvinyl acetates such as Kollicoat® SR30D (BASF Corp., Mt. Olive, NJ), ethylcelluloses such as Aquacoat® ECD (FMC Corp., Philadelphia, PA), polymethacrylates such as Eudragit® NE30D, NE40D, RS30D and RL30D (Degussa Corp., Parsippany, NJ) and Kollicoat® MAE30DP (BASF Corp.) and
5 polyvinyl alcohols such as Opadry® AMB (Colorcon, West Point, PA). In some embodiments, the second polymer may be a mixture of one or more suitable polymers, for example, a mixture of RS30D and RL30D; and thus, the solids component of the compositions would comprise at least two additional polymers. In some embodiments, the second polymer is a polymethacrylate. In some such
10 embodiments, the polymethacrylate contains neutral methacrylic acid esters. In some such embodiments, the polymethacrylate contains neutral methacrylic acid esters having trimethylammonioethyl methacrylate chloride in a molar ratio of quaternary ammonium groups to neutral ester groups of 1:20; or in further
15 embodiments, of 1:40. In some embodiments, the polymethacrylate contains neutral methacrylic acid esters without any functional groups. As used herein, the term "functional groups" refers to atoms or small groups of atoms (for example, two to four atoms) that exhibit a characteristic reactivity when treated with certain reagents; for example, and without limitation, the term includes, alkanes, alkenes, alkynes, alkyl halides, benzene, amines, ammonium, ethers, alcohols, aldehydes, ketones and
20 carboxylic acids. In some embodiments, the second polymer that is water soluble or water dispersible is in an amount from about 3 weight % to about 20 weight % based on the percentage of solids in the solids component of the composition.

The compositions also may include optional ingredients, such as other flavoring agents, artificial sweeteners, color pigments, lubricants, glidants,
25 surfactants. The selection of such alternative ingredients is within the skill of those in the art.

As noted previously, the compositions also may include one or more therapeutic agents. As used herein, the term "therapeutic agent" also refers to a substance which is capable of exerting a therapeutic biological effect *in vivo*. The
30 therapeutic agents may be neutral or positively or negatively charged. Examples of suitable pharmaceutical agents include, *inter alia*, diagnostic agents, pharmaceuticals, drugs, synthetic organic molecules, proteins, peptides, vitamins, and steroids. For example, the composition may include one or more hormonal

steroids, such as 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, 5 trimegestone, dionogest, and the like. Additionally, tissue selective progesterones and/or progesterone antagonists, which may or may not have the typical steroidal functionality, may be present in the composition. These include, but are not limited to: RU-486 (mifepristone), ZK 98 299 (onapristone), ZK-137316 (Schering AG, Berlin), ZK-230211 (Schering AG, Berlin), and HRP-2000 (17-acetoxy-[11 β -(4-N,N-dimethylaminophenyl)]-19-norpregna-4,9-diene-3,20-dione). Where desired, 10 estrogenic steroids and progestogenic steroids may be used in combination.

The composition of the present invention is particularly suitable for use in coating a core material to produce a solid dosage form. The term "core material" 15 refers to any tablet, caplet, particle, micronized particle, particulate, pellet, pill, core, powder, granule, granulate, small mass, seed, specks, spheres, crystals, beads, agglomerates, mixtures thereof and the like. Typically, the preferred core material will be in a form sufficiently stable physically and chemically to be effectively coated in a system that involves some movement of the tablet, as for example, in a perforated 20 coating pan.

In a preferred embodiment, the core material is present in the form of a tablet. As used herein, the term "tablet" refers to a solid pharmaceutical dosage form containing a therapeutic agent with or without suitable diluents and prepared by either compression or molding methods, such as are well known to those of ordinary 25 skill in the art. Suitable methods of forming tablets are described, for example, in Edward M Rudnick, et al., "Oral Solid Dosage Forms," in *Remington: The Science and Practice of Pharmacy*, 20th Ed., Chap. 45, Alfonso R. Gennaro, ed., Philadelphia College of Pharmacy and Science, Philadelphia, PA (2000), herein incorporated by reference in its entirety. In more preferred embodiments, the core material is a tablet 30 formed by compression methods.

Most frequently, the core material will comprise at least one therapeutic agent, as defined previously, and at least one pharmaceutically acceptable excipient. The term "pharmaceutically acceptable," as used herein, refers to materials that are

generally not toxic or injurious to a patient when used in the compositions of the present invention, including when the compositions are administered by the oral route. The term "patient," as used herein, refers to animals, including mammals, preferably humans. "Excipients," as that term is used herein, refers to ingredients that provide bulk, impart satisfactory processing and compression characteristics, help control the dissolution rate, and/or otherwise give additional desirable physical characteristics to the core material. Included within this term, for example, are diluents, binders, lubricants and disintegrants well known to those of ordinary skill in the art, as described, for example, in the *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association, Washington, D.C. and The Pharmaceutical Society of Great Britain, London, England (1986), herein incorporated by reference in its entirety. Suitable excipients may include, for example, cellulosic material, such as, Hypromellose, HPC, HEC, carboxymethylcellulose, microcrystalline cellulose, ethyl cellulose, methyl cellulose, and their derivatives and salts; other organic compounds, such as PEG, talc, lactose and other sugars (as described above), acacia, dextrin, alginic acid, ethylcellulose resin, gelatin, guar gum, methylcellulose, pregelatinized starch, sodium alginate, starch, zein, polyvinylpyrrolidone, vinylpyrrolidone-vinyl acetate copolymer, vinyl acetate-crotonic acid copolymer and ethyl acrylate-methacrylate acid copolymer; plasticizers, such as propylene glycol, glycerin, trimethylolpropane, PEG polymers, dibutyl sebacate, acetylated monoglycerides, diethylphthalate, triacetin, glyceryltriacetate, acetyltriethyl citrate and triethyl citrate; and lubricants, such as talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, magnesium lauryl sulfate, sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine, and Carbowax® 4000.

A wide variety of therapeutic agents may be utilized in the core material. Specific examples of therapeutic agents include, but are not limited to: acetazolamide, acetoexamide, acrivastine, alatrofloxacin, albuterol, alclofenac, aloxiprin, alprostadil, amodiaquine, amphotericin, amylobarbitol, aspirin, atorvastatin, atovaquone, baclofen, barbitol, benazepril, bezafibrate, bromfenac, bumetanide, butobarbitol, candesartan, capsaicin, captopril, cefazolin, celecoxib, cephadrine, cephalixin, cerivastatin, cetirizine, chlorambucil, chlorothiazide, chlorpropamide, chlorthalidone, cinoxacin, ciprofloxacin, clinofibrate, cloxacillin, cromoglicate,

- cromolyn, dantrolene, dichlorophen, diclofenac, dicioxacillin, dicumarol, diflunisal, dimenhydrinate, divalproex, docusate, dronabinol, enoximone, enalapril, enoxacin, enrofloxacin, epalrestat, eposartan, essential fatty acids, estramustine, ethacrynic acid, ethotoin, etodolac, etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole,
- 5 flurbiprofen, fluvastatin, fosinopril, fosphenytoin, fumagillin, furosemide, gabapentin, gemfibrozil, glliclazide, glipizide, glybenclamide, glyburide, glimepiride, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, lisinopril, lomefloxacin, losartan, lovastatin, meclofenamic acid, mefenamic acid, mesalamine, methotrexate, metolazone,
- 10 montelukast, nalidixic acid, naproxen, natamycin, nimesulide, nitrofurantoin, non-essential fatty acids, norfloxacin, nystatin, ofloxacin, oxacillin, oxaprozin, oxyphenbutazone, penicillins, pentobarbital, perfloxacin, phenobarbital, phenytoin, pioglitazone, piroxicam, pramipexol, pranlukast, pravastatin, probenecid, probucol, propofol, propylthiouracil, quinapril, rabeprazole, repaglinide, rifampin, rifapentine,
- 15 sparfloxacin, sulfabenzamide, sulfacetamide, sulfadiazine, sulfadoxine, sulfamerazine, sulfamethoxazole, sulfafurazole, sulfapyridine, sulfasalazine, sulindac, sulphasalazine, sulthiame, telmisartan, teniposide, terbutaline, tetrahydrocannabinol, tirofiban, tolazamide, tolbutamide, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, undecenoic acid, ursodeoxycholic acid, valproic acid, valsartan, vancomycin, verteporfin, vigabatrin, vitamin K-S (II) and zafirlukast.
- 20 Additional therapeutic agents include abacavir, acebutolol, acrivastine, alatrofloxacin, albuterol, albendazole, alfentanil, alprazolam, alprenolol, amantadine, amiloride, aminoglutethimide, amiodarone, amitriptyline, amlodipine, amodiaquine, amoxapine, amphetamine, amphotericin, amprenavir, amrinone, amsacrine, apomorphine,
- 25 astemizole, atenolol, atropine, azathioprine, azelastine, azithromycin, baclofen, benethamine, benidipine, benzhexol, benznidazole, benztropine, biperiden, bisacodyl, bisanthrene, bromazepam, bromocriptine, bromperidol, brompheniramine, brotizolam, bupropion, butenafine, butoconazole, cambendazole, camptothecin, carbinoxamine, cephradine, cephalixin, cetirizine, cinnarizine, chlorambucil,
- 30 chlorpheniramine, chlorproguanil, chlordiazepoxide, chlorpromazine, chlorprothixene, chloroquine, cimetidine, ciprofloxacin, cisapride, citalopram, clarithromycin, clemastine, clemizole, clenbuterol, clofazimine, clomiphene, clonazepam, clopidogrel, clozapine, clotiazepam, clotrimazole, codeine, cyclizine, cyproheptadine,

- dacarbazine, darodipine, decoquinat, delavirdine, demeclo-cycline,
dexamphetamine, dexchlorpheniramine, dexfenfluramine, diamorphine, diazepam,
diethylpropion, dihydrocodeine, dihydroergotamine, diltiazem, dimenhydrinate,
diphenhydramine, diphenoxylate, diphenyl-imidazole, diphenylpyraline, dipyridamole,
5 dirithromycin, disopyramide, dolasetron, domperidone, donepezil, doxazosin,
doxycycline, droperidol, econazole, efavirenz, ellipticine, enalapril, enoxacin,
enrofloxacin, eperisone, ephedrine, ergotamine, erythromycin, ethambutol,
ethionamide, ethopropazine, etoperidone, famotidine, felodipine, fenbendazole,
fenfluramine, fenoldopam, fentanyl, fexofenadine, flecainide, flucytosine, flunarizine,
10 flunitrazepam, fluopromazine, fluoxetine, fluphenthixol, fluphenthixol decanoate,
fluphenazine, fluphenazine decanoate, flurazepam, flurithromycin, frovatriptan,
gabapentin, granisetron, grepafloxacin, guanabenz, halofantrine, haloperidol,
hyoscyamine, imipenem, indinavir, irinotecan, isoxazole, isradipine, itraconazole,
ketoconazole, ketotifen, labetalol, lamivudine, lansoprazole, leflunomide,
15 levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine, lorazepam,
lormetazepam, lysuride, mepacrine, maprotiline, mazindol, mebendazole, meclizine,
medazepam, mefloquine, meloxicam, meptazinol, mercaptopurine, mesalamine,
mesoridazine, metformin, methadone, methaqualone, methylphenidate,
methylphenobarbital, methysergide, metoclopramide, metoprolol, metronidazole,
20 mianserin, miconazole, midazolam, miglitol, minoxidil, mitomycins, mitoxantrone,
modafinil, molindone, montelukast, morphine, moxifloxacin, nadoiol, nalbuphine,
naratriptan, natamycin, nefazodone, nelfinavir, nevirapine, nicardipine, nicotine,
nifedipine, nimodipine, nimorazole, nisoldipine, nitrazepam, nitrofurazone, nizatidine,
norfloxacin, nortriptyline, nystatin, ofloxacin, olanzapine, omeprazole, ondansetron,
25 omidazole, oxamniquine, oxantel, oxatomide, oxazepam, oxendazole, oxiconazole,
oxprenolol, oxybutynin, oxyphencyclimine, paroxetine, pentazocine, pentoxifylline,
perchlorperazine, perfloxacin, perphenazine, phenbenzamine, pheniramine,
phenoxybenzamine, phentermine, physostigmine, pimozide, pindolol, pizotifen,
pramipexol, pranlukast, praziquantel, prazosin, procarbazine, prochlorperazine,
30 proguanil, propranolol, pseudoephedrine, pyrantel, pyrimethamine, quetiapine,
quinidine, quinine, raloxifene, ranitidine, remifentanyl, repaglinide, reserpine,
ricobendazole, rifabutin, rifampin, rifapentine, rimantadine, risperidone, ritonavir,
rizatriptan, ropinirole, rosiglitazone, roxatidine, roxithromycin, saibutamol, saquinavir,

selegiline, sertraline, sibutramine, sildenafil, sparfloxacin, spiramycins, stavudine, sufentanil, sulconazole, sulphasalazine, sulpiride, sumatriptan, tacrine, tamoxifen, tamsulosin, temazepam, terazosin, terbinafine, terbutaline, terconazole, terfenadine, tetramisole, thiabendazole, thioguanine, thioridazine, tiagabine, ticlopidine, timolol, 5 tinidazole, tioconazole, tirofiban, tizanidine, tolterodine, topotecan, toremifene, tramadol, trazodone, triamterene, triazolam, trifluoperazine, trimethoprim, trimipramine, tromethamine, tropicamide, trovafloxacin, vancomycin, venlafaxine, vigabatrin, vinblastine, vincristine, vinorelbine, vitamin K₅, vitamin K₆, vitamin K₇, zafirlukast, zolmitriptan, zolpidem and zopiclone. Of course, any of the foregoing 10 therapeutic agents may be included in the coating composition, as discussed previously, and any of the therapeutic agents discussed with regard to the coating composition alternatively may be included in the core material.

The core material may be designed for delivering therapeutic agents intended to be delivered over a sustained period of time. The following are representative of 15 such therapeutic agents: anti-inflammatory, antipyretic, anti-spasmodics or analgesics such as indomethacin, diclofenac, diclofenac sodium, codeine, ibuprofen, phenylbutazone, oxyphenbutazone, mepirizole, aspirin, ethenzamide, acetaminophen, aminopyrine, phenacetin, butylscopolamine bromide, morphine, etomidolone, pentazocine, fenoprofen calcium, naproxen, selecxip, valdecxip, and 20 tolamadol, anti-rheumatism drugs such as etodolac, anti-tuberculoses drugs such as isoniazide and ethambutol hydrochloride, cardiovascular drugs such as isosorbide dinitrate, nitroglycerin, nifedipine, barnidipine hydrochloride, nicardipine hydrochloride, dipyridamole, amrinone, indenolol hydrochloride, hydralazine hydrochloride, methyl dopa, furosemide, spironolactone, guanethidine nitrate, 25 reserpine, amosulalol hydrochloride, lisinopril, metoprolol, pilocarpine, and talcetin, antipsychotic drugs such as chlorpromazine hydrochloride, amitriptyline hydrochloride, nemonapride, haloperidol, moperone hydrochloride, perphenazine, diazepam, lorazepam, chlorodiazepoxide, adinazolam, alprazolam, methylphenidate, myrnasipran, peroxetin, risperidone, and sodium valproate, anti-emetics such as 30 metoclopramide, lamocetron hydrochloride, granisetron hydrochloride, ondansetron hydrochloride, and azacetron hydrochloride, antihistamines such as chlorpheniramine maleate and diphenhydramine hydrochloride, vitamins such as thiamine nitrate, tocopherol acetate, cycothiamine, pyridoxal phosphate,

cobarnamide, ascorbic acid, and nicotinamide, anti-gout drugs such as allopurinol, colchicine, and probenecide, anti-Parkinson's disease drugs such as levodopa and selegiline, sedatives and hypnotics such as amobarbital, bromuralyl urea, midazolam, and chloral hydrate, antineoplastics such as fluorouracil, carmofur, acralvidine

5 hydrochloride, cyclophosphamide, and thiodepa, anti-allergy drugs such as pseudoephedrine and terfenadine, decongestants such as phenylpropanolamine and ephedrine, diabetes mellitus drugs such as acetohexamide, insulin, tolbutamide, desmopressin, and glipizide, diuretics such as hydrochlorothiazide, polythiazide, and triamterene, bronchodilators such as aminophylline, formoterol fumarate, and

10 theophylline, antitussives such as codeine phosphate, noscapine, dimorfan phosphate, and dextromethorphan, anti-arrhythmics such as quinidine nitrate, digitoxin, propafenone hydrochloride, and procainamide, topical anesthetics such as ethyl aminobenzoate, lidocaine, and dibucaine hydrochloride, anti-convulsants such as phenytoin, ethosuximide, and primidone, synthetic glucocorticoids such as

15 hydrocortisone, prednisolone, triamcinolone, and betamethasone, antiulceratives such as famotidine, ranitidine hydrochloride, cimetidine, sucralfate, sulpiride, teprenone, plaunotol, 5-aminosalicylic acid, sulfasalazine, omeprazole, and lansoprazol, central nervous system drugs such as indeloxazine, idebenone, thiapride hydrochloride, bifemelane hydrocide, and calcium homopantothenate,

20 antihyperlipoproteinemics such as pravastatin sodium, simvastatin, lovastatin, and atorvastatin, antibiotics such as ampicillin hydrochloride, phthalylsulfacetamide, cefotetan, and josamycin, BPH therapeutic agents such as tamsulosin hydrochloride, doxazosin mesylate, and terazosin hydrochloride, drugs affecting uterine motility such as branylcast, zafylcast, albuterol, ambroxol, budesonide, and reproterol,

25 peripheral circulation improvers of prostaglandin I derivatives such as beraprost sodium, anticoagulants, hypotensives, agents for treatment of cardiac insufficiency, agents used to treat the various complications of diabetes, peptic ulcer therapeutic agents, skin ulcer therapeutic agents, agents used to treat hyperlipemia, tocolytics, etc. The therapeutic agent can be used in its free form or as a pharmaceutically

30 acceptable salt. Moreover, one or a combination of two or more therapeutic agents may be present in the core material.

In some embodiments, the therapeutic agent in the core material includes conjugated estrogens. "Conjugated estrogens" (CE) as used herein includes both

5 natural and synthetic conjugated estrogens, such as the compounds described in the United States Pharmacopeia (USP 23), as well as other estrogens so considered by those skilled in the art. Further, "conjugated estrogens" refers to esters of such compounds, such as the sulfate esters, salts of such compounds, such as sodium salts, and esters of the salts of such compounds, such as sodium salts of a sulfate ester, as well as other derivatives known in the art. Some specific examples include: 17-alpha and beta-dihydroequilin, equilenin, 17-alpha and beta-dihydroequilenin, estrone, 17-beta-estradiol, and their sodium sulfate esters.

10 Although CE are typically a mixture of estrogenic components, such as estrone and equilin, the core material may be formulated to either utilize such a mixture, or to include only selected or individual estrogenic components. These CE may be of synthetic or natural origin. Examples of synthetically produced estrogens include, *inter alia*, sodium estrone sulfate, sodium equilin sulfate, sodium 17 α -dihydroequilin sulfate, sodium 17 β -dihydroequilin sulfate, sodium 17 α -estradiol sulfate, sodium 17 β -estradiol sulfate, sodium equilenin sulfate, sodium 17 α -dihydroequilenin sulfate, sodium 17 β -dihydroequilenin sulfate, estropipate and ethinyl estradiol. The alkali metal salts of 8,9-dehydroestrone and the alkali metal salts of 8,9-dehydroestrone sulfate ester, as described in U.S. Patent No. 5,210,081, which is herein incorporated by reference, also may be used. Naturally occurring CE are 20 usually obtained from pregnant mare urine and then are processed and may be stabilized. Examples of such processes are set forth in U.S. Pat. Nos. 2,565,115 and 2,720,483, each of which are herein incorporated by reference.

Many CE products are commercially available. Preferred among these is the naturally occurring CE product known as Premarin® (Wyeth, Madison, NJ). Another 25 commercially available CE product prepared from synthetic estrogens is Cenestin® (Duramed Pharmaceuticals, Inc., Cincinnati, Ohio). The specific CE dose included in the core material may be any dosage required to achieve a specific therapeutic effect, and may vary depending on the specific treatment indicated, and on the specific CE included in the tablet. However, in general, dosages of CE included in 30 the tablet can range from about 0.1 mg CE/dosage form to about 5.0 mg CE/dosage form, with dosages of from about 0.3 mg CE/dosage form to about 2 mg CE/dosage form preferred. In some embodiments, the dosage of CE is from about 0.3 mg CE/dosage form, about 0.45 mg CE/dosage form, about 0.625 mg CE/dosage form,

about 0.9 mg CE/dosage form, or about 1.25 mg CE/dosage form. Viewed alternatively, based on the total weight of the solid dosage form, on a dry weight basis, the amount of CE/dosage form may range from about 0.05 weight % to about 1.0 weight %, with amounts of from 0.1 weight % to about 0.3 weight % preferred.

5 Thus, in addition to the coating compositions described previously, the present invention also is directed to solid dosage forms comprising a core material and one or more coating disposed thereon, as each element has been described heretofore. In certain embodiments, the dosage form is a coated tablet. In some
10 embodiments, the solid dosage forms comprise from about 30 weight % to about 70 weight % of the core material, and from about 30 weight % to about 70 weight % of the coating, and in still further embodiments, from about 40 weight % to about 60 weight % of the core material and from about 40 weight % to about 60 weight % of the coating. The solid dosage forms also can optionally include one or more additional coats. For example, a further sugar coating as described herein, disposed
15 either on top of the coating previously described, or in between the core and coating. The solid dosage form also can include a color coat and/or a polish coat. In some embodiments, the color coat constitutes from about 0.5 weight % to about 10 weight % of the dosage form, and/or a polish coat that constitutes from about 0.1 weight % to about 5 weight % of the dosage form.

20 In some embodiments, the solid dosage form is in the form of a coated tablet, wherein the core material comprises at least one therapeutic agent and at least one pharmaceutically acceptable excipient. In some such embodiments, the excipient in the core material can include one or more cellulosic materials in a cumulative amount of from about 15 weight % to about 50 weight % of the solid dosage form; from about
25 18 weight % to about 40 weight % of the solid dosage form; or from about 40 weight % to about 45 weight % of the solid dosage form. In some such embodiments, the cellulosic material includes Hypromellose, microcrystalline cellulose, and sodium carboxymethylcellulose, and mixtures thereof.

30 In addition to the cellulosic material, in certain embodiments, the core material also includes a sugar excipient, such as lactose. A preferred form of lactose is lactose monohydrate, which is well known to those of skill in the art. In some embodiments, the dosage form of the invention is a coated tablet that comprises a tablet core containing from about 4 weight % to about 35 weight % lactose

monohydrate, and from about 20 weight % to about 40 weight % cellulosic material based on the total weight of the solid dosage form. In a further such embodiment, the cellulosic material is a mixture of microcrystalline cellulose and Hypromellose. A lubricant, such as, for example, magnesium stearate, also can be utilized in the tablet
5 core of such embodiments, typically, at an amount of up to about 1 weight % based on the total weight of the solid dosage form.

The formulations of the invention can be utilized with any of the aforementioned therapeutic agents, but is particularly suited for coated tablets that utilize conjugated estrogens, such as the conjugated estrogens desiccation with
10 lactose. In some embodiments, from about 3 weight % to about 15 weight % of the conjugated estrogens desiccation with lactose (about 4.3 weight % conjugated estrogens), based on the total weight of the solid dosage form, is included in the tablet core. In still further such embodiments, about 4 weight % to about 10 weight % of the conjugated estrogens desiccation with lactose (about 4.3 weight % conjugated
15 estrogens), is included in the tablet core. In certain embodiments, the conjugated estrogens are present in an amount from about 0.1 mg CE/dosage form to about 5.0 mg CE/dosage form, or from about 0.3 mg CE/dosage form to about 2 mg CE/dosage form. In some embodiments, the dosage of CE is from about 0.3 mg CE/dosage form, about 0.45 mg CE/dosage form, about 0.625 mg CE/dosage form,
20 about 0.9 mg CE/dosage form, or about 1.25 mg CE/dosage form. Viewed alternatively, in such embodiments, the amount of CE/dosage form, based on the total weight of the solid dosage form (on a dry weight basis), is present from about 0.05 weight % to about 1.0 weight %, or further, from 0.1 weight % to about 0.3 weight %. The tablet core then can be coated with the coating composition
25 described above, in an amount of from about 30 weight % to about 75 weight %, based on the total weight of the solid dosage form, to produce a coated tablet. An optional color coat and/or polish coat also may be applied, as described previously.

In certain embodiments, the solid dosage form comprises a core material and at least one coating, wherein the core material includes (based on the total weight of
30 the solid dosage form on a dry weight basis) from about 0.1 weight % to about 0.3 weight % conjugated estrogens; from about 4 weight % to about 35 weight % of at least one sugar, for example, lactose monohydrate; from about 5 weight % to about 10 weight % of at least one binder, for example, microcrystalline cellulose; from

about 10 weight % to about 35 weight % of at least one water soluble polymer, for example, hydroxypropyl methylcellulose; and from about 0 to about 1 weight % of at least one lubricant, for example, magnesium stearate. In some such embodiments, the coating includes at least one sugar, e.g., sucrose, in an amount from about 30 weight % to about 60 weight %, from about 35 weight % to about 55 weight %, or from about 35 weight % to about 45 weight %; at least one binder, e.g., microcrystalline cellulose, in an amount from about 5 weight % to about 10 weight %, from about 5.5 weight % to about 9 weight %, or from about 5.5 weight % to about 7.5 weight %; at least one hydroxyalkyl cellulose, e.g., hydroxypropyl cellulose, in an amount from about 3 weight % to about 10 weight %, from about 4 weight % to about 5.5 weight %; at least one water soluble polymer, e.g., hydroxypropyl methylcellulose, in an amount from about 15 weight % to about 50 weight %, from about 25 weight % to about 40 weight %, or from about 20 weight % to about 30 weight %; optionally, a therapeutic agent in an amount of up to about 3 weight %; optionally, a second polymer that is water soluble or water dispersible, for example such as polymethacrylate, in an amount of up to about 20 weight %, or in an amount from about 3 weight % to 20 weight %; and optionally, at least one plasticizer in an amount of up to about 8 weight %, from about 2 weight % to about 4 weight %, or from about 2.5 weight % to about 3.5 weight %. In some such embodiments, the solid dosage form further comprises a color coat, a polish coat, or both a color coat and a polish coat.

One of the primary advantages of the present invention is that a wide variety of tablet cores, prepared according to the various processes known in the art, can readily be coated with the coating composition of the present invention, utilizing the simple spray techniques more frequently associated with film-coating applications. Thus, in a further embodiment, the present invention is directed to processes that comprise providing a tablet core and applying, e.g., by spraying, onto the core a sugar coating composition, as previously described. The invention also is directed to the products of such process, e.g., a coated tablet core. It should be noted, however, that although utilizing such spray techniques provides certain advantages, it is by no means required that the composition be applied in this manner. Other methods for coating pharmaceutical dosage forms, such as, for example, use of a fluidized bed application process, are well known to those of ordinary skill in the art.

In some embodiments, the sugar coating compositions utilized in the processes of the invention include water and a solids component that comprises: from about 30 weight % to about 60 weight % of at least one sugar; from about 5 weight % to about 10 weight % of at least one binder; from about 3 weight % to about 10 weight % of at least one hydroxyalkyl cellulose; from about 15 weight % to about 50 weight % of at least one water soluble polymer; optionally, a therapeutic agent in an amount of up to about 3 weight %; optionally, a second polymer that is water soluble or water dispersible, in an amount of up to about 20 weight %; and optionally, at least one plasticizer in an amount of up to about 8 weight %. In some embodiments, the second polymer is present in an amount from about 3 weight % to about 20 weight %. In some embodiments, the solids component of the sugar coating composition comprises: from about 30 weight % to about 60 weight % sucrose; from about 5 weight % to about 10 weight % microcrystalline cellulose; from about 3 weight % to about 10 weight % hydroxypropyl cellulose; from about 15 weight % to about 50 weight % hydroxypropyl methylcellulose; optionally, up to about 3 weight % medroxyprogesterone acetate; optionally, up to about 20 weight % of a polymethacrylate; and optionally up to about 8 weight % polyethylene glycol. In further embodiments, the solids component of the sugar coating composition comprises: from about 35 weight % to about 55 weight % sucrose; from about 5.5 weight % to about 9 weight % microcrystalline cellulose; from about 4 weight % to about 7 weight % hydroxypropyl cellulose; from about 25 weight % to about 40 weight % hydroxypropyl methylcellulose; optionally, up to about 3 weight % medroxyprogesterone acetate; optionally, up to about 20 weight % of a polymethacrylate; and from about 2 weight % to about 4 weight % polyethylene glycol. In still further embodiments, the solids component of the sugar coating composition comprises: from about 35 weight % to about 45 weight % sucrose; from about 5.5 weight % to about 7.5 weight % microcrystalline cellulose; from about 4 weight % to about 5.5 weight % hydroxypropyl cellulose; from about 20 weight % to about 30 weight % hydroxypropyl methylcellulose; optionally, up to about 3 weight % medroxyprogesterone acetate; optionally, up to about 20 weight % of a polymethacrylate; and from about 2.5 weight % to about 3.5 weight % PEG 400. In some embodiments, the core material is as previously described.

In certain embodiments, the sugar coating composition is disposed directly onto the tablet core without a the need for intervening sealing layers, as are used typically in traditional sugar-coating methods. If desired, however, a sealing layer, such as shellac and other agents known to those in the art, may be applied to the
5 tablet core prior to application of the sugar coating composition. In some embodiments, the sugar coating composition contains a therapeutic agent, such as medroxyprogesterone acetate, as previously described, and is disposed directly onto the tablet core without a non-therapeutic agent containing sugar coat being first applied, or an intervening sealing layer.

10 In some embodiments, the sugar coating composition is applied in a ratio of sugar coating to tablet core of from 3:1 to about 1:3, or in a ratio from about 2:1 to about 1:2, or in a ratio of from about 1.25:1 to about 1:1.25; and thus, providing a coated tablet. In some embodiments, the sugar coating composition is sprayed at an
15 air flow rate of from about 500 cubic feet per minute to about 9000 cubic feet per minute; and further, at an air flow rate of from about 1000 cubic feet per minute to about 5000 cubic feet per minute. In some embodiments, the tablet core temperature is about 35°C to about 50°C, while the inlet air temperature is about 50°C to about 80°C. While the processes of the present invention further may include the steps of spraying a color coat and/or polish coat onto the sugar coat,
20 such steps are optional, and all of the coating steps may be carried out in a single coating pan. Also, the step of printing a logo, trademark, word, symbol or the like optionally may be included in the processes of the present invention. Printing may be performed by any of the methods well known to those skilled in the art.

Thus, the process of the present invention may comprise the steps of
25 providing tablet cores, placing the tablet cores into a coating pan, such as a perforated coating pan commonly utilized in film-coating applications such as a perforated pan with side-vents, then sequentially spraying the tablet cores with the sugar coating composition, the color coat, and the polish coat (if desired). Spray techniques for coating tablets are well known to those of skill in the art, and are
30 described, for example, in Stuart C. Porter, "Coating of Pharmaceutical Dosage Forms," *Remington: The Science and Practice of Pharmacy*, 20th Ed., Chap. 46, Alfonso R. Gennaro, ed., Philadelphia College of Pharmacy and Science, Philadelphia, PA (2000), herein incorporated by reference in its entirety.

The processes of the present invention are much simpler, less labor intensive, and less reliant upon operator expertise than the traditional sugar-coating techniques known in the prior art. Additionally, due to the unique combination of ingredients utilized in the sugar coating composition and the volume of sugar coating that is applied, the coated tablets produced by the processes of the present invention are remarkably hard, durable, and resistant to cracking, even when highly hygroscopic tablet cores are utilized. In some embodiments, a plurality of tablet cores coated with the sugar coating compositions of the present invention contain cracking in less than 6 percent of the coated tablet cores. In further such embodiments, the percentage of cracks is about 1 to about 5 percent; and in still further embodiments, less than 1 percent. Additionally, the coating provides an excellent barrier to prevent the release of odors from the tablet core, and to prevent atmospheric elements from reaching and degrading the therapeutic agent(s) in the tablet core. Thus, the coating compositions and processes described herein are particularly well suited for preparing solid dosage forms that utilize therapeutic agents or other materials having strong odors, such as, sulfur-containing compounds, in the core material.

Moreover, as discussed previously, the sugar coating composition itself can include one or more therapeutic agents, in addition to the therapeutic agent(s) that are present within the tablet core. Thus, therapeutic agents can be separated by their compartmentalization into either the core or the coating, to thereby minimize unwanted chemical interaction between the agents. Additionally, since the coating and tablet core can be designed to release their ingredients at different rates, the present invention may be utilized to provide, in a single dosage form, both a quick release and a sustained release formulation of the therapeutic agent(s). Also, it has been found unexpectedly that utilizing, in a sugar coating containing a therapeutic agent, a control release agent, which has been used traditionally for controlling drug diffusion from a therapeutic core, allows effective control of the therapeutic agent in the sugar coating itself. For example, in some embodiments, the second polymer of the sugar coating compositions of the invention functions as the aforementioned control release agent. In some embodiments, the second polymer, which is water soluble or water dispersible, includes one or more of a polyvinyl acetate, an ethylcellulose, a polymethacrylate or a polyvinyl alcohol, that will function to retard

the release of the active therapeutic agent from the coating. In some preferred embodiments, the second polymer, which is water soluble or water dispersible, is a polymethacrylate, such as Eudragit® NE30D. The features of the coating compositions of the present invention, as described above, are particularly useful when delivering certain therapeutic agents such as hormones, where, for example, a quick release of one hormone, located in the coating, may be followed by a slow, sustained release of a second hormone from the tablet core. Of course, this property of the solid dosage forms also may be utilized to provide both a quick release and a sustained release of a single therapeutic agent, where both the tablet core and the coating contain the same therapeutic agent.

EXAMPLES

The invention is further demonstrated in the following examples. The examples are for purposes of illustration and are not intended to limit the scope of the present invention.

EXAMPLE 1

PREPARATION OF 1.25 MG CONJUGATED ESTROGEN COATED TABLETS

Tablet Core	Amt/tablet (mg)
CE Desiccation with Lactose @ 42.9 mg/g	29.14
Lactose Monohydrate, NF (Spray Dried)	120.3
Microcrystalline Cellulose, NF	36.0
Hypromellose, USP, 2208, K100M (100,000 cps)	54.0
Magnesium Stearate, NF	0.600
Totals	240.0
Sugar Coat Filler Suspension (A)	
Hydroxypropyl Cellulose, NF	13.80
Hypromellose, USP, 2910, E5 (5 cps)	59.8
Hypromellose, USP, 2910, E15 (15 cps)	15.00
Microcrystalline Cellulose, NF	18.40
Polyethylene Glycol 400, NF	8.05
Sucrose, NF	115.0
Totals	230
Color Suspension (B)	
Opadry® II, Yellow, 40L12916	15.00

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Polish Solution (C)

Opaglos® 2, Clear, 98Z19173	10.00
Total Finished Tablet Weight	495

Tablet Core

1. Add the lactose monohydrate, NF, C.E. desiccation with lactose,
5 microcrystalline cellulose, NF, and the Hypromellose, USP, 2208 (K100M Premium, CR) to a high shear mixer. Blend all ingredients with plows only.
2. Granulate the blend with water, U.S.P., purified, mixing with plows and choppers.
3. Size the granulation using a cutting mill.
- 10 4. Dry the granulation in a fluid bed dryer.
5. Size the dried granulation using a cutting mill.
6. Transfer the granulation to a V Blender. Blend.
7. Add the magnesium stearate, NF to the V Blender in step #6. Blend.
8. Compress granulation to target tablet weight, hardness and thickness using
15 appropriately sized oval tooling on a rotary tablet press.

Similar formulations and manufacturing procedures have been developed and prepared for tablets containing CE at strengths of 0.3 mg, 0.45 mg, 0.625 mg and 0.9 mg.

20

Sugar Coat Filler Suspension (A)

1. Place the purified water in a suitable stainless steel container.
2. With mixing, add the hydroxypropyl cellulose, hydroxypropyl methylcellulose,
25 2910, E5, hydroxypropyl methylcellulose, 2910, E15, and the polyethylene glycol 400 to Step #1.
3. With mixing, add the sucrose to Step #2 and mix until all ingredients are dissolved.
4. With mixing, add the microcrystalline cellulose to Step #3.
5. Allow Step #4 to de-aerate, bring to theoretical weight with purified water with
30 mixing, and cool to room temperature prior to use, if necessary.
6. Continue mixing Step #5 until the filler application is complete.

44

Color Suspension (B)

1. Add the purified water to a suitable stainless steel container.
2. With mixing, add the Opadry® II Yellow (Colorcon, West Point, PA) to Step
- 5 #1. Continue stirring until the suspension is complete.
3. Bring Step #2 to theoretical weight with purified water, with mixing, if necessary.
4. Continue mixing Step #3 until the color application is complete.

10 Polish Solution (C)

1. Add the purified water to a suitable stainless steel container.
2. With mixing, add the Opaglos® 2 Clear (Colorcon, West Point, PA) to Step
- #1. Continue mixing until the solution is complete.

- 15 Prior to application, allow the solution to de-aerate and bring Step #2 to theoretical weight with purified water with mixing, if necessary. Mixing is not necessary during the application.

Tablet Coating

- 20 1. Load the compressed tablet cores in perforated coating pan(s).
2. Apply sufficient sugar coat filler suspension (A) to step #1 tablet cores to achieve desired coating weight gain above the average tablet core weight.
3. Apply sufficient color suspension (B) to step #2 filled tablets to achieve desired coating weight gain above the average filled tablet weight.
- 25 4. Apply sufficient polish solution (C) to step #3 colored tablets to achieve desired coating weight gain above the average colored tablet weight.

EXAMPLE 2

- 30 The tablet core composition utilized in Example 1 contains hydrogel (Hypromellose) type polymers, which are useful to modify/control the release of the active ingredient. This type of tablet core is flexible, and prone to swelling, however. A conventional sugar coat tends to be brittle and is prone to chipping, cracking and splitting due to processing conditions and/or if exposed to inappropriate mechanical

stress (*Pharmaceutical Coating Technology*, Cole E, Hogan J., Aulton M., 1995, page 62, section 3.5). This example shows the ability of the coating composition of the present invention to resist cracking.

As controls, tablets containing hydrogel polymers and 1.25 mg/tablet of water-soluble estrogens, similar to the tablet cores described in Example 1, were coated with a conventional sugar coat. When exaggerated physical abuse was applied to the coated tablets, the vast majority of the tablets developed cracks in the coating. When the same tablets were coated with a sugar coat composition of the present invention, similar to the sugar coating suspension utilized in Example 1, and achieving the same coating weight gain, no cracks were observed in the coating. These data are presented in Table 1. Also included are data on traditional tablet cores (non-swelling) coated with a conventional sugar coat. These data also show that some coat cracking can be observed even on these more stable tablet cores with a conventional sugar coat.

Table 1

NEW TABLET FORMULATION			
Coated Tablet Cracking with Exaggerated Physical Abuse			
Formulation	Number of Batches Tested	Total # of tablets tested	Average % Cracks
Hydrogel core and sugar coating composition of the present invention	7	7x100=700	0
Traditional core and conventional Sugar Coat	5	5x 100=500	14
Hydrogel core and conventional Sugar Coat	7	7x100=700	95

20

EXAMPLE 3

PREPARATION OF 0.45 MG CE/1.5 MG MPA COATED TABLETS WITH INTERVENING SUGAR COAT

In this example, 0.45 mg CE tablet cores were prepared and coated with a sugar coat suspension, in accordance with the formulation and manufacturing process of Example 1, except that the tablet core weight was 120 mg and the total solids filler sugar coat applied was 90 mg. An active filler suspension containing

medroxyprogesterone acetate (MPA) then was applied followed by the color and polish coats, as described below. Alternatively, the active filler suspension could be sprayed directly onto the tablet cores without an intervening coating step (e.g., a first sugar coating of the present invention such as Example 4, below).

5

0.45 mg/tablet CE/1.50 mg/tablet MPA Preparation

Ingredient	Input/ Dosage Unit	
	Input	Unit
Sugar Coated Core	210	mg
Active MPA Filler Suspension Coat (D)		
Medroxyprogesterone Acetate, USP	1.5	mg
Sucrose, NF	50.5	mg
Microcrystalline Cellulose, NF	8.31	mg
Hydroxypropyl Cellulose, NF	6.23	mg
Hypromellose, 2910, USP, E6 (6 cps)	27.1	mg
Hypromellose, 2910, USP, E15 (15 cps)	6.75	mg
Polyethylene Glycol 400, NF	3.63	mg
Purified Water, USP *	474	mg
Color Suspension (E)		
Hypromellose, 2910, USP, E3 (3 cps)	7.79	mg
Polyethylene Glycol 400, NF	0.780	mg
Titanium Dioxide, USP	2.86	mg
Ferric Oxide, NF, Yellow	0.571	mg
Purified Water, USP *	69.6	mg
Polish Suspension (F)		
Opaglos® 2, Clear, 97W19196	6.0	mg
Purified Water, USP *	114	mg
Total tablet weight	332	mg

* Removed during processing.

The tablet core and sugar coat filler suspension are prepared substantially as
10 set forth in Example 1.

47

Active MPA Filler Suspension (D)

1. Place the purified water in a suitable stainless steel container.
2. With mixing, add the MPA powder until uniformly dispersed.
3. With mixing, add the Hypromellose, 2910, E6, Hypromellose, 2910, E15,
5 hydroxypropyl cellulose, polyethylene glycol 400 and sucrose; mix until all
ingredients are dissolved.
4. Allow suspension to de-aerate.
5. With mixing, add the microcrystalline cellulose.
6. Bring the suspension to theoretical weight with purified water with mixing, and
10 continue mixing until the MPA filler application is complete.

Color Suspension (E)

1. Place a portion of purified water to a suitable stainless steel container.
2. With mixing, add the ferric oxide and titanium dioxide; blend until uniform.
- 15 3. Add the balance of the purified water to a suitable stainless steel container.
4. With mixing, add the Hypromellose, E3 and PEG 400 and stir until dissolved.
5. Add the Step #2 color mixture and continue stirring until the suspension is
complete.
6. Allow suspension to de-aerate and bring to theoretical weight with purified
20 water. Continue mixing until the color application is complete.

Polish Solution (F)

1. Add the purified water to a suitable stainless steel container.
2. With mixing, add the Opaglos® 2 Clear. Continue mixing until the solution is
25 complete. Allow the solution to de-aerate and bring to theoretical weight with
purified water with mixing, if necessary.

Tablet Coating

1. Load the compressed tablet cores into perforated coating pan(s).
- 30 2. Apply sufficient sugar coat filler suspension (A) to Step #1 tablet cores to
achieve an average filler solids weight of 90 mg ($\pm$ 5 mg) above the average
compressed core weight.

- 48
3. Apply sufficient active filler suspension (D) to Step #2 tablet cores to achieve an average filler solids weight of 104 mg ($\pm$ 5 mg) above the average inert filled tablet core weight.
 4. Apply sufficient color suspension (E) to Step #3 filled tablets to achieve an average color solids weight of 12 mg ($\pm$ 2 mg) above the average MPA filled tablet weight.
 5. Apply sufficient polish solution (F) to Step #4 colored tablets to achieve an average total polish solids weight of 6 mg ($\pm$ 1 mg) above the average colored tablet weight.

10

The utility of the 0.45mg/1.5mg CE/MPA tablet is further supported based on actual *in vivo* data from a pilot bioavailability study in dogs. Figure 1 shows plasma MPA levels in 6 beagle dogs following oral administration of the subject tablet formulation. This data confirms that this type of formulation is capable of providing reproducible blood levels and is a viable delivery system for this class of drug.

15

EXAMPLE 4

PREPARATION OF 0.45 MG CE/1.5 MG MPA COATED TABLETS – I MPA-CONTAINING COAT APPLIED DIRECTLY

20

In this example, 0.45 mg CE tablet cores were prepared and coated with an active filler coat suspension, in accordance manufacturing process of Example 3, except the active filler coat suspension was sprayed directly onto the tablet core. That is to say, the coated tablet contained one sugar coat, which contained the MPA, and no intervening active-free sugar coat or sealing layer were applied initially to the tablet core.

25

30

0.45 mg/tablet CE/1.50 mg/tablet MPA Preparation

Ingredient	Input/ Dosage Unit	
	Input	Unit
Tablet Core	120	mg
CE Desiccation with Lactose @ 42.9 mg/g	10.5	mg
Lactose Monohydrate, NF (Spray Dried)	58.2	mg
Microcrystalline Cellulose, NF, EP	18.0	mg
Hypromellose, USP, 2208, K100M (100,000 cps)	33.0	mg
Magnesium Stearate, NF, EP	0.300	mg
Active MPA Filler Suspension Overcoat (G)		
Medroxyprogesterone Acetate, USP	1.5	mg
Sucrose, NF	36.5	mg
Microcrystalline Cellulose, NF, EP	6.09	mg
Hydroxypropyl Cellulose, Klucel® EF Pharma, NF	4.57	mg
Hypromellose, 2910, USP, E6	19.8	mg
Hypromellose, 2910, USP, E15	4.95	mg
Polyethylene Glycol 400, NF	2.66	mg
Polyacrylate dispersion 30% (Eudragit® NE30D), EP	46.5*	mg
Purified Water, USP**	300	mg
Color Suspension (H)		
Hypromellose, 2910, USP, E6	3.40	mg
Polyethylene Glycol 400, NF	0.340	mg
Titanium Dioxide, USP	1.07	mg
Ferric Oxide, NF, Yellow	0.187	mg
Purified Water, USP**	30.7	mg
Polish Suspension (I)		
Opaglos® 2, Clear, 98Z19173	2.0	mg
Purified Water, USP**	38	mg
Total tablet weight	217	mg

*13.9 mg solids

** Removed during processing.

- 5 The tablet core was prepared substantially as set forth in Example 1.

Active MPA Filler Suspension (G)

1. Place the purified water in a suitable stainless steel container.

2. With mixing, add the MPA powder until uniformly dispersed.
3. With mixing, add the Hypromelloses, hydroxypropyl cellulose, polyethylene glycol 400 and sucrose; mix until all ingredients are uniformly dispersed.
4. With mixing, add the microcrystalline cellulose until uniformly dispersed. Cool
- 5 the suspension to room temperature.
5. With mixing add the polyacrylate dispersion 30% (Eudragit® NE 30 D) EP through a stainless steel screen. Mix until uniformly dispersed.
6. Bring the suspension of Step #5 to theoretical weight with purified water with mixing, if necessary.
- 10 7. Continue mixing until the MPA filler application is complete.

Color Suspension (H)

1. Add the purified water to a suitable stainless steel container.
2. With mixing, add the ferric oxide and titanium dioxide; blend until uniform.
- 15 3. Add the Hypromellose, 2910, USP, E6 and PEG 400; continue mixing until the suspension is complete.
4. Allow the suspension of Step #3 to de-aerate; and bring the suspension to theoretical weight with purified water with mixing, if necessary.
5. Continue mixing until the color application is complete.

20

Polish Solution (I)

1. Add the purified water to a suitable stainless steel container.
2. With mixing, add the Opaglos® 2 Clear. Continue mixing until the solution is complete.
- 25 3. Prior to application, allow the solution to de-aerate and bring to theoretical weight with purified water with mixing, if necessary.

Tablet Coating

1. Load the tablet cores into perforated coating pan(s).
- 30 2. Apply sufficient active filler suspension (G) to Step #1 tablet cores to achieve an average filler solids weight of 90 mg ($\pm$ 2 mg) above the average tablet core weight.

3. Cure the tablets at a tablet bed temperature of 45-50 °C for approximately 1 hour.
 4. Apply sufficient color suspension (H) to Step #3 MPA filled tablets to achieve an average color solids weight of 5 mg ($\pm$ 1 mg) above the average MPA filled tablet weight.
 5. Apply sufficient polish solution (I) to Step #4 colored tablets to achieve an average total polish solids weight of 2 mg ($\pm$ 1 mg) above the average colored tablet weight.
- 10 Similar formulations that have an active sugar fill coat containing MPA in an amount from about 0.5 to 10 mg can be prepared as described in any of the preceding Examples.

EXAMPLE 5

- 15 The following prophetic example describes the production of coated tablets of the present invention containing a blend of the synthetic conjugated estrogenic substances sodium estrone sulfate, sodium equilin sulfate, sodium 17 α -dihydroequilin sulfate, sodium 17 β -dihydroequilin sulfate, sodium 17 α -estradiol sulfate, sodium 17 β -estradiol sulfate, sodium equilenin sulfate, sodium 17 α -dihydroequilenin sulfate, sodium 17 β -dihydroequilenin sulfate. Utilizing procedures
- 20 widely known to those of ordinary skill in the art, the conjugated estrogenic substances are mixed with commonly used excipients and compressed to form tablet cores of various strengths containing, for example, 0.3 mg, 0.45mg, 0.625 mg, 0.9 mg, and 1.25 mg CE. The tablet cores then may be coated as described in any of
- 25 the preceding examples.

EXAMPLE 6

DISSOLUTION STUDY OF 0.45 mg/TABLET CE/1.50 mg/TABLET MPA PREPARATIONS

- 30 Since the active filler sugar coating and tablet core can be designed to release their ingredients at different rates, the present invention may be utilized to provide, in a single dosage form, both a quick release and a sustained release

formulation of the therapeutic agent(s). The release time from the coating can be affected by, for example, the total solids of active applied to the core, the thickness of the active filler sugar coat applied, and the presence of a release controlling agent. This Example measured the MPA dissolution profiles of three formulations of 0.45 mg/tablet CE/1.50 mg/tablet MPA. The preparations were prepared as described in the preceding examples. All three preparations had the MPA filler sugar coat applied directly onto the CE tablet cores. The MPA filler sugar coat of one formulation further contained a second polymer, as described above, viz. polymethacrylate (15% Eudragit® NE30D), and the total solids of MPA sugar coat applied was 90 mg such as that of Example 4. The MPA sugar coat of the other two formulations were similar in composition to the Active Sugar Filler Suspension (D) and (S) of Example 3 and 11, respectively, i.e., with one water soluble polymer, with the total solids of MPA sugar coat applied being 90 mg and 200 mg, respectively. All three formulations were polished.

Percent MPA Dissolved[#]

Time (min.)	1.5 mg MPA + 15% NE30D @ 90mg	1.5 mg MPA @ 200 mg	1.5 mg MPA @ 90 mg
15	2	10	12
30	4	27	42
45	7	44	67
60	10	60	83

[#] Dissolution was performed at 50 rpm, in 0.54% SLS, 0.02 M sodium acetate, pH 4.5 in standard vessels with sinkers; n=6.

The data confirms that a coating containing a second polymer, which traditionally has been used to delay release of therapeutic agents from a tablet core, can effectively delay the release of a therapeutic agent from the coating applied to a tablet core. The data also confirms that a greater amount of active filler sugar coat applied to the tablet core effectively can slow the release of the therapeutic agent compared to a lesser amount of active filler sugar coat similarly applied to the tablet core.

Examples 7-10 show the compositions of coated tablets of the invention containing 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg of conjugated estrogens, respectively. The tablet core and sugar coat filler suspension are prepared substantially as set forth in any of the preceding Examples.

5

EXAMPLE 7
COMPOSITION OF 0.3 CONJUGATED ESTROGEN COATED TABLET

Tablet Core	Amt/tablet (mg)
CE Desiccation with Lactose @ 4.29% CE	6.993
Lactose Monohydrate (Spray Dried)	61.7
Microcrystalline Cellulose	18.0
Hypromellose 2208, K100M (100,000 cps)	33.0
Magnesium Stearate	0.300
Totals	120 mg
Sugar Coat Filler Suspension (J)	
Sucrose	45.0
Microcrystalline Cellulose	7.20
Hydroxypropyl Cellulose	5.40
Hypromellose, 2910, E6 (6 cps)	23.4
Hypromellose, 2910, E15 (15 cps)	5.85
Polyethylene Glycol 400	3.15
Totals	90
Color Suspension (K)	
Opadry® Green	5.00
Polish Solution (L)	
Opaglos® 2, Clear	3.00
Total Finished Tablet Weight	218

10

EXAMPLE 8
COMPOSITION OF 0.45 MG CONJUGATED ESTROGEN COATED TABLETS

Tablet Core	Amt/tablet (mg)
CE Desiccation with Lactose @ 4.29% CE	10.4895
Lactose Monohydrate (Spray Dried)	58.2
Microcrystalline Cellulose	18.0
Hypromellose 2208, K100M (100,000 cps)	33.0
Magnesium Stearate	0.300
Totals	120 mg

Sugar Coat Filler Suspension (M)

Sucrose	45.0
Microcrystalline Cellulose	7.20
Hydroxypropyl Cellulose	5.40
Hypromellose, 2910, E6 (6 cps)	23.4
Hypromellose, 2910, E15 (15 cps)	5.85
Polyethylene Glycol 400	3.15
Totals	90

Color Suspension (N)

Opadry® Blue	5.00
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Polish Solution (O)

Opaglos® 2, Clear	3.00
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Total Finished Tablet Weight	218
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EXAMPLE 9**COMPOSITION OF 0.625 MG CONJUGATED ESTROGEN COATED TABLETS**

5

Tablet Core	Amt/tablet (mg)
CE Desiccation with Lactose @ 4.29% CE	14.5688
Lactose Monohydrate (Spray Dried)	54.1
Microcrystalline Cellulose	18.0
Hypromellose 2208, K100M (100,000 cps)	33.0
Magnesium Stearate	0.300
Totals	120 mg

Sugar Coat Filler Suspension (P)

Sucrose	45.0
Microcrystalline Cellulose	7.20
Hydroxypropyl Cellulose	5.40
Hypromellose, 2910, E6 (6 cps)	23.4
Hypromellose, 2910, E15 (15 cps)	5.85
Polyethylene Glycol 400	3.15
Totals	90

Color Suspension (Q)

Opadry® Maroon	5.00
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Polish Solution (R)

Opaglos® 2, Clear	3.00
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Total Finished Tablet Weight	218
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EXAMPLE 10
COMPOSITION OF 0.9 MG CONJUGATED ESTROGEN COATED TABLETS

Tablet Core	Amt/tablet (mg)
CE Desiccation with Lactose @ 4.29% CE	20.979
Lactose Monohydrate (Spray Dried)	78.0
Microcrystalline Cellulose	26.0
Hypromellose 2208, K100M (100,000 cps)	47.6
Magnesium Stearate	0.433
Totals	173 mg
Sugar Coat Filler Suspension (S)	
Sucrose	65.0
Microcrystalline Cellulose	10.4
Hydroxypropyl Cellulose	7.80
Hypromellose, 2910, E6 (6 cps)	33.8
Hypromellose, 2910, E15 (15 cps)	8.45
Polyethylene Glycol 400	4.55
Totals	130
Color Suspension (T)	
Opadry® White	7.00
Polish Solution (U)	
Opaglos® 2, Clear	3.00
Total Finished Tablet Weight	313

5

Example 11 shows the composition of a coated tablet of the invention containing 0.45 mg of conjugated estrogens, and 1.50 mg of MPA.

EXAMPLE 11
COMPOSITION OF 0.45 MG CE / 1.5 MG MPA COATED TABLETS – II
MPA-CONTAINING COAT APPLIED DIRECTLY

10

Tablet Core	Amt/tablet (mg)
CE Desiccation with Lactose @ 4.29% mg/g CE	10.49
Lactose Monohydrate, NF/EP (powder)	58.21
Microcrystalline Cellulose, NF/EP	18.0
Hypromellose, USP, 2208 (100,000 cps) (K100M Prem, CR)	33.0
Magnesium Stearate, NF/EP, Hyqual Vegetable Code	0.300
Totals	120 mg

Active MPA Filler Suspension Overcoat (S)

Medroxyprogesterone Acetate, USP/EP	1.500
Sucrose, NF	98.50
Microcrystalline Cellulose, NF/EP	16.00
Hydroxypropyl Cellulose, Klucel EF Pharma, NF	12.00
Hypromellose, 2910, USP/EP E6	52.00
Hypromellose, 2910, USP E15	13.00
Polyethylene Glycol 400, NF	7.000
Totals	200

Color Suspension (T)

Spectrablend Yellow	6.00
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Polish Solution (U)

Opaglos® 2, Clear	1.50
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Total Finished Tablet Weight	328
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The disclosures of each patent, patent application and publication, including books, cited or described in this document are incorporated herein by reference in their entirety. This application claims priority to U.S. Provisional Application Serial No. 60/577,668, filed on June 7, 2004, which is incorporated herein by reference in its entirety.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications also are intended to fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A composition comprising water and a solids component that comprises:
from about 30 weight % to about 60 weight % of at least one sugar;
from about 5 weight % to about 10 weight % of at least one binder;
5 from about 3 weight % to about 10 weight % of at least one
hydroxyalkyl cellulose;
from about 15 weight % to about 50 weight % of at least one water
soluble polymer;
optionally, a therapeutic agent in an amount of up to about 3 weight
10 %;
optionally, a second polymer that is water soluble or water dispersible,
in an amount of up to about 20 weight %; and
optionally, at least one plasticizer in an amount of up to about 8
weight %.
- 15 2. The composition of claim 1 that is in the form of an aqueous suspension.
3. The composition of claim 1 or claim 2 that comprises:
from about 75 weight % to about 85 weight % water; and
20 from about 15 weight % to about 25 weight % of the solids
component.
4. The composition of any one of claims 1 to 3, wherein the binder comprises
microcrystalline cellulose.
- 25 5. The composition of any one of claims 1 to 4, wherein the hydroxyalkyl
cellulose comprises hydroxyethyl cellulose or hydroxypropyl cellulose.
6. The composition of claim 5, wherein the hydroxyalkyl cellulose comprises
30 hydroxypropyl cellulose.
7. The composition of any one of claims 1 to 6, wherein the water soluble
polymer comprises hydroxypropyl methylcellulose, acacia, sodium

carboxymethylcellulose, dextrin, alginic acid, gelatin, guar gum, methylcellulose, sodium alginate, zein, polyvinylpyrrolidone, vinylpyrrolidone-vinyl acetate copolymer, vinyl acetate-crotonic acid copolymer, or ethyl acrylate-methacrylate acid copolymer.

5 8. The composition of claim 7, wherein the water soluble polymer comprises hydroxypropyl methylcellulose, sodium carboxymethylcellulose, or methylcellulose.

9. The composition of claim 8, wherein the water soluble polymer comprises hydroxypropyl methylcellulose.

10

10. The composition of any one of claims 1 to 9, wherein the plasticizer comprises propylene glycol, glycerin, trimethylolpropane, polyethylene glycol polymers, dibutyl sebacate, acetylated monoglycerides, diethylphthalate, triacetin, glyceryltriacetate, acetyltriethyl citrate, or triethyl citrate.

15

11. The composition of claim 10, wherein the plasticizer comprises polyethylene glycol.

20

12. The composition of any one of claims 1 to 11, wherein the sugar comprises sucrose, dextrose, maltose, glucose, fructose, galactose, mannose, lactose, trehalose, lactulose, levulose, raffinose, ribose, xylose, sorbitol, mannitol, xylitol, erythritol, maltitol, lactitol, isomalt, or polyalditol.

25

13. The composition of claim 12, wherein the sugar comprises sucrose.

30

14. The composition of any one of claims 1 to 13, wherein:
 the sugar comprises sucrose;
 the binder comprises microcrystalline cellulose;
 the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
 the water soluble polymer comprises hydroxypropyl methylcellulose;
 the therapeutic agent, when present, comprises medroxyprogesterone acetate;

the second polymer, when present, comprises a polyvinyl acetate, an ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and the plasticizer, when present, comprises polyethylene glycol.

- 5 15. The composition of any one of claims 1 to 13, wherein the solids component comprises:

from about 35 weight % to about 55 weight % of at least one sugar;
from about 5.5 weight % to about 9 weight % of at least one binder;
from about 4 weight % to about 7 weight % of at least one
10 hydroxyalkyl cellulose;
from about 25 weight % to about 40 weight % of at least one water
soluble polymer;
optionally, from about 0.001 weight % to about 3 weight % of a
therapeutic agent;
15 optionally, from about 3 weight % to about 20 weight % of a second
polymer that is water soluble or water dispersible; and
from about 2 weight % to about 4 weight % at least one plasticizer.

- 20 16. The composition of claim 15, wherein:

the sugar comprises sucrose;
the binder comprises microcrystalline cellulose;
the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
the water soluble polymer comprises hydroxypropyl methylcellulose;
the therapeutic agent, when present, comprises medroxyprogesterone
25 acetate;
the second polymer, when present, comprises a polyvinyl acetate, an
ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and
the plasticizer comprises polyethylene glycol.

- 30 17. The composition of any one of claims 1 to 13, wherein the solids component comprises:

from about 35 weight % to about 45 weight % of at least one sugar;
from about 5.5 weight % to about 7.5 weight % of at least one binder;

- from about 4 weight % to about 5.5 weight % of at least one
hydroxyalkyl cellulose;
from about 20 weight % to about 30 weight % of at least one water
soluble polymer;
5 optionally, from about 0.001 weight % to about 3 weight % of a
therapeutic agent;
optionally, from about 3 weight % to about 20 weight % of a second
polymer that is water soluble or water dispersible; and
from about 2.5 weight % to about 3.5 weight % of at least one
10 plasticizer.
18. The composition of claim 17, wherein:
the sugar comprises sucrose;
the binder comprises microcrystalline cellulose;
15 the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
the water soluble polymer comprises hydroxypropyl methylcellulose;
the therapeutic agent, when present, comprises medroxyprogesterone
acetate;
the second polymer, when present, comprises a polyvinyl acetate, an
20 ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and
the plasticizer comprises polyethylene glycol.
19. The composition of any one of claims 1 to 18, wherein the composition
comprises a therapeutic agent.
- 25 20. The composition of claim 19, wherein the therapeutic agent is
medroxyprogesterone acetate.
21. The composition of claim 20, wherein the medroxyprogesterone acetate is in
30 an amount from about 0.5 mg to about 10 mg.
22. The composition of any one of claims 1 to 21, wherein the composition
comprises a second polymer, which is water soluble or water dispersible.

23. The composition of claim 22, wherein the second polymer comprises a polyvinyl acetate, an ethylcellulose, a polymethacrylate, or a polyvinyl alcohol.
- 5 24. The composition of claim 22, wherein the second polymer comprises a polymethacrylate.
25. The composition of claim 24, wherein the polymethacrylate comprises neutral methacrylic acid esters.
- 10 26. The composition of claim 25, wherein the neutral methacrylic acid esters comprise trimethylammonioethyl methacrylate chloride in a molar ratio of quaternary ammonium groups to neutral ester groups of 1:20.
- 15 27. The composition of claim 25, wherein the neutral methacrylic acid esters comprise trimethylammonioethyl methacrylate chloride in a molar ratio of quaternary ammonium groups to neutral ester groups of 1:40.
28. The composition of claim 25, wherein the neutral methacrylic acid esters are
- 20 without any functional groups.
29. The composition of any one of claims 22 to 28, wherein the second polymer is in an amount from about 3 weight % to about 20 weight % of the solids component.
- 25 30. The composition of any one of claims 1 to 29 suitable for application by spraying.
31. A solid dosage form comprising a core material and at least one coating disposed thereon, wherein the coating comprises:
- 30 from about 30 weight % to about 60 weight % of at least one sugar;
from about 5 weight % to about 10 weight % of at least one binder;
from about 3 weight % to about 10 weight % of at least one
hydroxyalkyl cellulose;

- from about 15 weight % to about 50 weight % of at least one water soluble polymer;
optionally, a therapeutic agent in an amount of up to about 3 weight %;
5 optionally, a second polymer that is water soluble or water dispersible, in an amount of up to about 20 weight %; and
optionally, at least one plasticizer in an amount of up to about 8 weight %.
- 10 32. The solid dosage form of claim 31, wherein in the coating:
the sugar comprises sucrose;
the binder comprises microcrystalline cellulose;
the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
the water soluble polymer comprises hydroxypropyl methylcellulose;
15 the therapeutic agent, when present, comprises medroxyprogesterone acetate;
the second polymer, when present, comprises a polyvinyl acetate, an ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and
the plasticizer, when present, comprises polyethylene glycol.
- 20 33. The solid dosage form of claim 31, wherein the coating comprises:
from about 35 weight % to about 55 weight % of at least one sugar;
from about 5.5 weight % to about 9 weight % of at least one binder;
from about 4 weight % to about 7 weight % of at least one
25 hydroxyalkyl cellulose;
from about 25 weight % to about 40 weight % of at least one water soluble polymer;
optionally, from about 0.001 weight % to about 3 weight % of a therapeutic agent;
30 optionally, from about 3 weight % to about 20 weight % of a second polymer that is water soluble or water dispersible; and
from about 2 weight % to about 4 weight % of at least one plasticizer

34. The solid dosage form of claim 33, wherein in the coating:
- the sugar comprises sucrose;
 - the binder comprises microcrystalline cellulose;
 - the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
 - the water soluble polymer comprises hydroxypropyl methylcellulose;
 - the therapeutic agent, when present, comprises medroxyprogesterone acetate;
 - the second polymer, when present, comprises a polyvinyl acetate, an ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and
 - the plasticizer comprises polyethylene glycol.
35. The solid dosage form of claim 31, wherein the coating comprises:
- from about 35 weight % to about 45 weight % of at least one sugar;
 - from about 5.5 weight % to about 7.5 weight % of at least one binder;
 - from about 4 weight % to about 5.5 weight % of at least one hydroxyalkyl cellulose;
 - from about 20 weight % to about 30 weight % of at least one water soluble polymer;
 - optionally, from about 0.001 weight % to about 3 weight % of a therapeutic agent;
 - optionally, from about 3 weight % to about 20 weight % of a second polymer that is water soluble or water dispersible; and
 - from about 2.5 weight % to about 3.5 weight % of at least one plasticizer.
36. The solid dosage form of claim 35, wherein in the coating:
- the sugar comprises sucrose;
 - the binder comprises microcrystalline cellulose;
 - the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
 - the water soluble polymer comprises hydroxypropyl methylcellulose;
 - the therapeutic agent, when present, comprises medroxyprogesterone acetate;

the second polymer, when present, comprises a polyvinyl acetate, an ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and the plasticizer comprises polyethylene glycol.

- 5 37. The solid dosage form of any one of claims 31 to 36, wherein the therapeutic agent comprises medroxyprogesterone acetate.
38. The solid dosage form of any one of claims 31 to 37, wherein the second polymer of the coating comprises a polyvinyl acetate, an ethylcellulose, a
10 polymethacrylate, or a polyvinyl alcohol.
39. The solid dosage form of any one of claims 31 to 38, wherein the second polymer of the coating comprises a polymethacrylate.
- 15 40. The solid dosage form of claim 39, wherein the polymethacrylate comprises neutral methacrylic acid esters.
41. The solid dosage form of claim 40, wherein the neutral methacrylic acid esters comprise trimethylammonioethyl methacrylate chloride in a molar ratio of
20 quaternary ammonium groups to neutral ester groups of 1:20.
42. The solid dosage form of claim 40, wherein the neutral methacrylic acid esters comprise trimethylammonioethyl methacrylate chloride in a molar ratio of
25 quaternary ammonium groups to neutral ester groups of 1:40.
43. The solid dosage form of claim 40, wherein the neutral methacrylic acid esters are without any functional groups.
44. The solid dosage form of any one of claims 31 to 43, wherein the second
30 polymer of the coating is in an amount from about 3 weight % to about 20 weight %.
45. The solid dosage form of any one of claims 31 to 44, which is in the form of a coated tablet.

46. The solid dosage form of claim 45, further comprising a color coat, a polish coat, or both a color coat and a polish coat.
- 5 47. The solid dosage form of claim 45 or claim 46, wherein the coating is disposed directly upon the core material.
48. The solid dosage form of any one of claims 31 to 47, wherein:
the core material comprises from about 30 weight % to about 70
10 weight % of the dosage form; and
the coating comprises from about 30 weight % to about 70 weight %
of the dosage form.
49. The solid dosage form of any one of claims 31 to 47, wherein:
15 the core material comprises from about 40 weight % to about 60
weight % of the dosage form; and
the coating comprises from about 40 weight % to about 60 weight %
of the dosage form.
- 20 50. The solid dosage form of claim 48, further comprising:
from about 0.5 weight % to about 10 weight % of a color coat; and
from about 0.1 weight % to about 5 weight % of a polish coat.
51. The solid dosage form of claim 49, further comprising:
25 from about 0.5 weight % to about 10 weight % of a color coat; and
from about 0.1 weight % to about 5 weight % of a polish coat.
52. The solid dosage form of any one of claims 31 to 45, wherein the core
material comprises a therapeutic agent.
30
53. The solid dosage form of claim 52, wherein the core material further
comprises at least one pharmaceutically acceptable excipient.

54. The solid dosage form of claim 53, wherein the excipient of the core material comprises a cellulosic material, a sugar, or a mixture thereof.
55. The solid dosage form of claim 54, wherein the cellulosic material of the
5 excipient of the core material is present in an amount from about 15 weight % to about 50 weight % based on the total weight of the solid dosage form.
56. The solid dosage form of claim 54, wherein the cellulosic material of the
10 excipient of the core material is present in an amount from about 18 weight % to about 40 weight % based on the total weight of the solid dosage form.
57. The solid dosage form of claim 54, wherein the cellulosic material of the
15 excipient of the core material is present in an amount from about 40 weight % to about 45 weight % based on the total weight of the solid dosage form.
58. The solid dosage form of any one of claims 54 to 57, wherein the sugar of the excipient of the core material comprises lactose or lactose monohydrate.
59. The solid dosage form of any one of claims 55 to 58, wherein the
20 pharmaceutically acceptable excipient of the core material comprises a mixture of lactose monohydrate and one or more of hydroxypropyl methylcellulose, microcrystalline cellulose, or sodium carboxymethylcellulose.
60. The solid dosage form of claim 59, wherein the mixture of the excipient of the
25 core material comprises from about 4 weight % to about 35 weight % lactose monohydrate and from about 20 weight % to about 40 weight % cellulosic material based on the total weight of the solid dosage form.
61. The solid dosage form of any one of claims 52 to 60, wherein the therapeutic
30 agent of the core material is a conjugated estrogen or a combination of conjugated estrogens.

62. The solid dosage form of claim 61, wherein the conjugated estrogens are provided as a conjugated estrogens desiccation with lactose.
63. The solid dosage form of claim 62, wherein the conjugated estrogens are present in the conjugated estrogens desiccation with lactose at a concentration of about 4.3 weight %.
64. The solid dosage form of any one of claims 61 to 63, wherein the conjugated estrogens are present in an amount:
- from about 0.1 mg to about 5 mg; or
from about 0.3 mg to about 2 mg.
65. The solid dosage form of any one of claims 61 to 64, wherein the conjugated estrogens are present, based on the total weight of the solid dosage form, on a dry weight basis, in an amount:
- from about 0.05 weight % to about 1.0 weight %; or
from about 0.1 weight % to about 0.3 weight %.
66. The solid dosage form of claim 61, wherein based on the total weight of the solid dosage form, on a dry weight basis, the core material comprises:
- from about 0.1 weight % to about 0.3 weight % conjugated estrogens;
from about 4 weight % to about 35 weight % lactose monohydrate;
from about 5 weight % to about 10 weight % microcrystalline cellulose;
from about 10 weight % to about 35 weight % hydroxypropyl methyl cellulose; and
from about 0 to about 1 weight % of a lubricant.
67. The solid dosage form of claim 66, wherein the coating comprises by weight as a percentage of the solids in the coating:
- from about 35 weight % to about 55 weight % sucrose;
from about 5.5 weight % to about 9 weight % microcrystalline cellulose;

from about 4 weight % to about 7 weight % hydroxypropyl cellulose;
from about 25 weight % to about 40 weight % hydroxypropyl
methylcellulose;
optionally, from about 0.001 weight % to about 3 weight % of a
therapeutic agent;
optionally, from about 3 weight % to about 20 weight % of a second
polymer that is water soluble or water dispersible; and
from about 2 weight % to about 4 weight % polyethylene glycol.

68. A solid dosage form comprising a core material and at least one coating disposed thereon, wherein on a dry weight basis, based on the total weight of the solid dosage form:
- the core material comprises:
- from about 0.1 weight % to about 0.3 weight % conjugated estrogens;
 - from about 4 weight % to about 35 weight % of at least one sugar;
 - from about 5 weight % to about 10 weight % of at least one binder;
 - from about 10 weight % to about 35 weight % of at least one water soluble polymer; and
 - from about 0 to about 1 weight % of at least one lubricant; and
- the coating comprises:
- from about 30 weight % to about 60 weight % of at least one sugar;
 - from about 5 weight % to about 10 weight % of at least one binder;
 - from about 3 weight % to about 10 weight % of at least one hydroxyalkyl cellulose;
 - from about 15 weight % to about 50 weight % of at least one water soluble polymer;
 - optionally, a therapeutic agent in an amount of up to about 3 weight %;
 - optionally, a second polymer that is water soluble or water dispersible, in an amount of up to about 20 weight %; and
 - optionally, at least one plasticizer in an amount of up to about 8 weight %.

69. The solid dosage form of claim 68, wherein in the core material:
the sugar comprises lactose monohydrate;
the binder comprises microcrystalline cellulose; and
the water soluble polymer comprises hydroxypropyl
5 methylcellulose.
70. The solid dosage form of claim 68 or claim 69, wherein in the coating:
the sugar comprises sucrose;
the binder comprises microcrystalline cellulose;
10 the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
the water soluble polymer comprises hydroxypropyl methyl cellulose;
the therapeutic agent, when present, comprises medroxyprogesterone
acetate;
the second polymer, when present, comprises a polyvinyl acetate, an
15 ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and
the plasticizer, when present, comprises polyethylene glycol..
71. The solid dosage form of claim 68, wherein the coating comprises:
from about 35 weight % to about 55 weight % of at least one sugar;
20 from about 5.5 weight % to about 9 weight % of at least one binder;
from about 4 weight % to about 7 weight % of at least one
hydroxyalkyl cellulose;
from about 25 weight % to about 40 weight % of at least one water
soluble polymer;
25 optionally, from about 0.001 weight % to about 3 weight % of a
therapeutic agent;
optionally, from about 3 weight % to about 20 weight % of a second
polymer that is water soluble or water dispersible; and
from about 2 weight % to about 4 weight % of at least one plasticizer.
30
72. The solid dosage form of claim 71, wherein in the coating:
the sugar comprises sucrose;
the binder comprises microcrystalline cellulose;

the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
the water soluble polymer comprises hydroxypropyl methyl cellulose;
the therapeutic agent, when present, comprises medroxyprogesterone
acetate;

5 the second polymer, when present, comprises a polyvinyl acetate, an
ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and
the plasticizer comprises propylene glycol.

73. The solid dosage form of claim 68, wherein the coating comprises:
10 from about 35 weight % to about 45 weight % of at least one sugar;
from about 5.5 weight % to about 7.5 weight % of at least one binder;
from about 4 weight % to about 5.5 weight % of at least one
hydroxyalkyl cellulose;
15 from about 20 weight % to about 30 weight % of at least one water
soluble polymer;
optionally, from about 0.001 weight % to about 3 weight % of a
therapeutic agent;
optionally, from about 3 weight % to about 20 weight % of a second
polymer that is water soluble or water dispersible; and
20 from about 2.5 weight % to about 3.5 weight % of at least one
plasticizer.

74. The solid dosage form of claim 73, wherein in the coating:
the sugar comprises sucrose;
25 the binder comprises microcrystalline cellulose;
the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
the water soluble polymer comprises hydroxypropyl methyl cellulose;
the therapeutic agent, when present, comprises medroxyprogesterone
acetate;
30 the second polymer, when present, comprises a polyvinyl acetate, an
ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and
the plasticizer comprises propylene glycol.

75. The solid dosage form of any one of claims 31 to 74, wherein the coating does not contain a therapeutic agent.
76. The solid dosage form of any one of claims 31 to 75, wherein the coating
5 does not contain a second polymer.
77. The solid dosage form of any one of claims 31 to 74, wherein the coating does not contain a therapeutic agent or a second polymer.
- 10 78. The solid dosage form of any one of claims 31 to 75, wherein the second polymer is a polymethacrylate.
79. The solid dosage form of claim 68, which further comprises a color coat, a polish coat, or both a color coat and a polish coat.
- 15 80. A solid dosage form comprising:
a tablet core comprising:
about 30 mg conjugated estrogens desiccation with lactose containing
about 4.3 weight % conjugated estrogens;
20 about 120 mg lactose monohydrate;
about 36 mg microcrystalline cellulose;
about 54 mg hydroxypropyl methylcellulose; and
less than about 1 mg of a lubricant;
a coating comprising:
25 about 115 mg sucrose;
about 18 mg microcrystalline cellulose;
about 14 mg hydroxypropyl cellulose;
about 75 mg hydroxypropyl methylcellulose; and
about 8 mg polyethylene glycol 400;
30 a color coat comprising about 15 mg of a coloring agent; and
a polish coat comprising about 10 mg of a polishing agent.
81. A solid dosage form comprising:

- a tablet core comprising:
 - about 11 mg conjugated estrogens desiccation with lactose containing about 4.3 weight % conjugated estrogens;
 - about 58 mg lactose monohydrate;
 - 5 about 18 mg microcrystalline cellulose;
 - about 33 mg hydroxypropyl methylcellulose; and
 - less than about 1 mg of a lubricant;
 - a coating comprising:
 - about 1.5 mg medroxyprogesterone acetate;
 - 10 about 37 mg sucrose;
 - about 6 mg microcrystalline cellulose;
 - about 4.5 mg hydroxypropyl cellulose;
 - about 25 mg hydroxypropyl methylcellulose;
 - about 3 mg polyethylene glycol 400; and
 - 15 about 47 mg polymethacrylate;
 - a color coat comprising about 0.2 mg of a coloring agent; and
 - a polish coat comprising about 2 mg of a polishing agent.
82. A process comprising:
 - 20 providing a tablet core;
 - applying to the tablet core a sugar coating composition comprising water and a solids component as defined in any one of claims 1 to 30 to provide a coated tablet core.
- 25 83. The process of claim 82, wherein the solids component of the sugar coating comprises a second polymer that is water soluble or water dispersible.
84. The process of claim 83, wherein the second polymer of the solids component of the sugar coating comprises a polyvinyl acetate, an ethylcellulose, a
30 polymethacrylate, or a polyvinyl alcohol.
85. The process of claim 83, wherein the second polymer of the solids component of the sugar coating comprises a polymethacrylate.

86. The process of any one of claims 82 to 85, further comprising the step of applying a color coat, a polish coat, or both a color coat and a polish coat to the coated tablet core.
- 5
87. The process of any one of claims 82 to 86, wherein the tablet core comprises a therapeutic agent and one or more cellulosic materials, wherein the cellulosic materials comprise from about 30 weight % to about 50 weight % of the tablet core.
- 10
88. The process of claim 87, wherein the tablet core further comprises from about 10 weight % to about 65 weight % lactose monohydrate, based on the weight of the tablet core.
- 15
89. The process of claim 82, wherein the tablet core comprises, based on the weight of the tablet core:
- from about 5 weight % to about 15 weight % conjugated estrogens desiccation with lactose containing about 4.3 weight % conjugated estrogens;
 - from about 10 weight % to about 65 weight % of at least one sugar;
 - from about 10 weight % to about 20 weight % of at least one binder;
 - from about 15 weight % to about 70 weight % of at least one water soluble polymer; and
 - from about 0 to about 1 weight % of at least one lubricant.
- 20
- 25
90. The process of claim 89, wherein in the tablet core:
- the sugar comprises lactose monohydrate;
 - the binder comprises microcrystalline cellulose; and
 - the water soluble polymer comprises hydroxypropyl methyl cellulose.
- 30
91. The process of claim 89, wherein the solids component of the sugar coating composition comprises:
- from about 35 weight % to about 55 weight % of at least one sugar;
 - from about 5.5 weight % to about 9 weight % of at least one binder;

from about 4 weight % to about 7 weight % of at least one
hydroxyalkyl cellulose;
from about 25 weight % to about 40 weight % of at least one water
soluble polymer;
5 optionally, from about 0.001 weight % to about 3 weight % of a
therapeutic agent;
optionally, from about 3 weight % to about 20 weight % of a second
polymer that is water soluble or water dispersible; and
from about 2 weight % to about 4 weight % of at least one plasticizer.

10

92. The process of claim 91, wherein in the solids component of the sugar
coating:

the sugar comprise sucrose;
the binder comprises microcrystalline cellulose;
15 the hydroxyalkyl cellulose comprises hydroxypropyl cellulose;
the water soluble polymer comprises hydroxypropyl methylcellulose;
the therapeutic agent, when present, comprises medroxyprogesterone
acetate;
the second polymer, when present, comprises a polyvinyl acetate, an
20 ethylcellulose, a polymethacrylate, or a polyvinyl alcohol; and
the plasticizer comprises polyethylene glycol.

93. The process of any one of claims 89 to 92, further comprising the step of
applying a color coat, a polish coat, or both a color coat and a polish coat to the
25 coated tablet core.

94. The process of claim 86 or 93, wherein the tablet core is placed in a pan, then
sequentially sprayed with the sugar coating composition, a color coat and a polish
coat.

30

95. The process of claim 94, wherein said pan is a perforated pan.

96. The process of claim 95, wherein said perforated pan is side-vented.

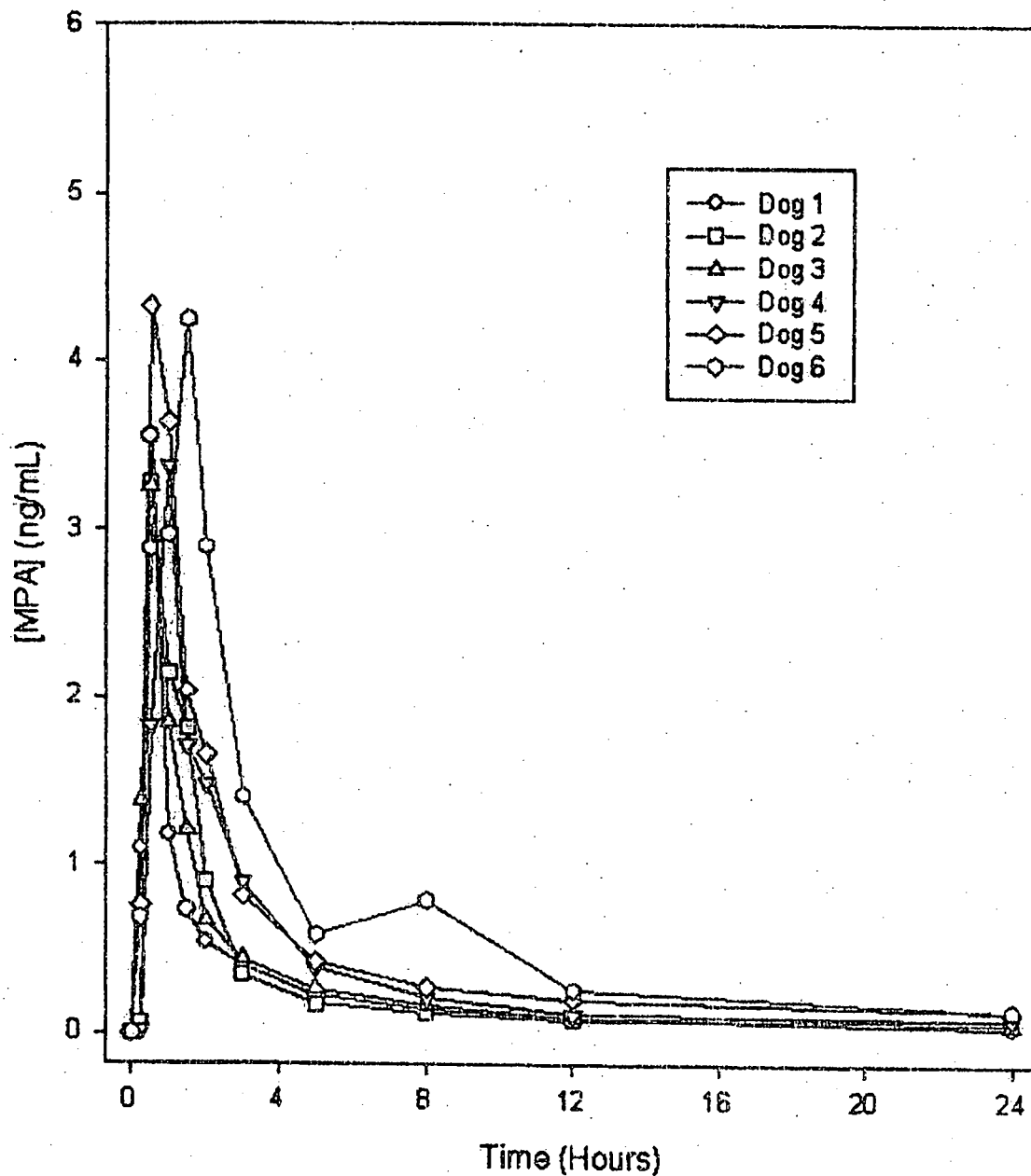
97. The process of any one of claims 94 to 96, wherein the sugar coating composition is sprayed at an air flow rate of from about 500 cubic feet per minute to about 9000 cubic feet per minute.
- 5
98. The process of any one of claims 94 to 96, wherein the sugar coating composition is sprayed at an air flow rate of from about 1000 cubic feet per minute to about 5000 cubic feet per minute.
- 10
99. The process of claim 97 or claim 98, wherein the tablet core is at a temperature of from about 35°C to about 50°C with an inlet air temperature of about 50°C to about 80°C.
- 15
100. The process of any one of claims 82 to 99, wherein the sugar coating composition comprises a therapeutic agent.
101. The process of claim 100, wherein the therapeutic agent of the sugar coating comprises medroxyprogesterone acetate.
- 20
102. The process of claim 82, wherein the tablet core further comprises a conjugated estrogen or a combination of conjugated estrogens.
103. The process of claim 101, wherein the tablet core further comprises a conjugated estrogen or a combination of conjugated estrogens.
- 25
104. A process consisting essentially of:
- placing a compressed tablet core, which comprises at least one therapeutic agent and at least one pharmaceutically acceptable excipient in a perforated film coating pan;
- 30
- spraying on the tablet core a sugar coating composition comprising water and a solids component comprising:
- from about 30 weight % to about 60 weight % of at least one sugar;
- from about 5 weight % to about 10 weight % of at least one binder;

- from about 3 weight % to about 10 weight % of at least one hydroxyalkyl cellulose;
from about 15 weight % to about 50 weight % of at least one water soluble polymer;
5 optionally, a therapeutic agent in an amount of up to about 3 weight %;
optionally, a second polymer that is water soluble or water dispersible, in an amount of up to about 20 weight %; and
optionally, at least one plasticizer in an amount of up to about 8
10 weight %;
spraying a color coat onto the sugar coating; and
spraying a polish coat onto the color coat,
wherein the spraying steps are all carried out in a single pan.
- 15 105. The process of claim 104, wherein the tablet core comprises :
from about 5 weight % to about 15 weight % conjugated estrogens desiccation with lactose containing about 4.3 weight % conjugated estrogens;
from about 10 weight % to about 65 weight % of at least one sugar;
20 from about 10 weight % to about 20 weight % of at least one binder;
from about 15 weight % to about 70 weight % at least one water soluble polymer; and
from about 0 to about 1 weight % of at least one lubricant.
- 25 106. The process of claim 105, wherein the sugar coating composition further comprises medroxyprogesterone acetate.
107. A coated tablet prepared by the process of any one of claims 104 to 106.
- 30 108. A coated tablet prepared by the process of any one of claims 82 to 103.
109. The coated tablet of claim 107 or 108, wherein a ratio of sugar coating to tablet core is from about 3:1 to about 1:3.

110. The coated tablet of claim 107 or 108, wherein a ratio of sugar coating to tablet core is from about 2:1 to about 1:2.
111. The coated tablet of claim 107 or 108, wherein a ratio of sugar coating to
5 tablet core is from about 1.25:1 to about 1:1.25.
112. A plurality of coated tablets as described in any one of claims 107 to 111, wherein a percentage of cracks in the sugar coating is less than 6 percent.
113. A plurality of coated tablets as described in any one of claims 107 to 111, wherein a percentage of cracks in said sugar coating is about 1 to about 5 percent.
- 10 114. A plurality of coated tablets as described in any one of claims 107 to 111, wherein a percentage of cracks in said sugar coating is less than 1 percent.

Figure 1

Plasma MPA Levels in Beagle Dogs Following Oral
Administration of 0.45/1.5 mg Premarin/MPA Tablet
L22891-199



Anexo 2

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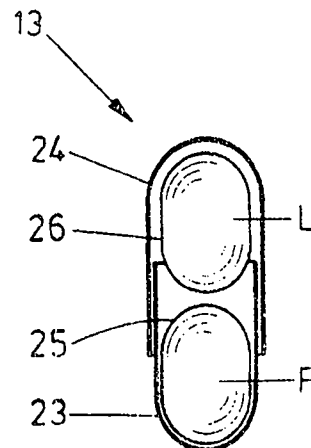
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Kapsel für pharmazeutisch wirksame Inhaltsstoffe einer Droge.

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Bei der Kapsel (13) für pharmazeutisch wirksame Inhaltsstoffe einer Droge sind die Inhaltsstoffe (L) lipophiler Phase und die Inhaltsstoffe (P) polarer Phase in je einem eigenen Aufnahmeteil (25; 26) der Kapsel (13) untergebracht. Wenigstens eine Wand der Aufnahmeteile (25; 26) ist so beschaffen, daß eine Vermischung der Inhaltsstoffe (L; P) beider Phasen vermieden wird.

Fig. 3



EP 0 308 637 A1

Kapsel für pharmazeutisch wirksame Inhaltsstoffe einer Droge

Bei der Herstellung pharmazeutischer Produkte auf der Basis pflanzlicher oder tierischer Drogen werden die pharmazeutisch wirksamen Inhaltsstoffe aus der betreffenden Droge extrahiert. Diese Extraktion ist notwendig, um die Droge auf bestimmte Mindestgehalte an bestimmten Inhaltsstoffen standardisieren zu können. Die Extraktion ist häufig auch deswegen erforderlich, um unwirksame oder unverträgliche Anteile der Droge in ihrem Ausgangszustand, wie beispielsweise radioaktive Nukleide, Pflanzenschutzmittelrückstände, wie Pestizide, Herbizide usw., entfernen zu können. Daneben oder darüber hinaus kann eine Extraktion auch deswegen erforderlich sein, um die pharmazeutisch wirksamen Inhaltsstoffe in einer Konzentration zu gewinnen, durch die die Einnahme der von den Standardmonographien vorgeschriebenen Drogenmenge überhaupt erst ermöglicht oder zumindest erleichtert wird.

Die Extraktionsbehandlung der Drogen erfolgt üblicherweise mit unterschiedlichen Lösungsmitteln. Die Wahl des Lösungsmittels hängt weitgehend von der Struktur der wirksamen Inhaltsstoffe ab. Bei Inhaltsstoffen polarer Phase wird die Extraktion mit Wasser und/oder mit Wasser-Äthylalkohol-Gemischen durchgeführt. Bei lipophilen Inhaltsstoffen erfolgt die Extraktion mit Pflanzenölen, mit Neutralölen oder mit Kohlendioxid im Hochdruckextraktionsverfahren (Destraktion).

Bei manchen Drogen sind pharmazeutisch wirksame Inhaltsstoffe sowohl polarer, wie auch lipophiler Phase vorhanden. Zur gemeinsamen Verabreichung dieser Inhaltsstoffe müssen sie in den durch die Standardmonographien vorgeschriebenen eng begrenzten Mengenverhältnissen miteinander gemischt werden. Das Mischen der Inhaltsstoffe, die entweder in wässriger Form oder in flüssiger Form in einem Wasser-Äthylalkohol-Gemisch vorliegen oder die nach dem Abdampfen der Lösungsmittel in getrockneter Form vorliegen, mit den Inhaltsstoffen lipophiler Phase in der Form einer Ölemulsion zum fertigen Arzneimittel ist allenfalls mit einem großen technischen Aufwand zu erreichen und manchmal sogar überhaupt nicht möglich. Um diese Schwierigkeiten zu überwinden ist es bekannt, die ölige Phase in Mikrokapseln einzuschließen und diese als eine Art festes Granulat mit den Trockenextrakten der polaren Phase zu mischen. Neben einem hohen technischen und finanziellen Aufwand treten analytische Probleme auf, im Fertigpräparat die einzelnen Bestandteile nachzuweisen und zu bestimmen.

Der in den Ansprüchen 1, 2 und 3 angegebenen Erfindung liegt die Aufgabe zugrunde, eine

Darreichungsform zu schaffen, die mit geringerem technischem und/oder finanziellem Aufwand verwirklicht werden kann und bei der im Fertigpräparat die pharmazeutisch wirksamen Inhaltsstoffe sowohl der lipophilen Phase, wie auch der polaren Phase miteinander vereinigt sind, ohne daß sie sich gegenseitig in unerwünschter Weise beeinflussen können.

Dadurch, daß nach Anspruch 1 eine Kapsel mit zwei Aufnahmeteilen verwendet wird, bei der die Wand wenigstens eines der beiden Aufnahmeteile die Inhaltsstoffe beider Phasen in keiner Richtung durchtreten läßt, oder dadurch, daß bei einer Kapsel nach Anspruch 2 die Wand jedes der beiden Aufnahmeteile den zugeordneten Inhaltsstoff nicht austreten läßt, oder dadurch, daß bei einer Kapsel nach Anspruch 3 die Trennwand für die Inhaltsstoffe beider Phasen undurchlässig ist, können diese Inhaltsstoffe sehr leicht gemeinsam verabreicht werden. Die getrennte Behandlung der Inhaltsstoffe beider Phasen beim Einbringen in eine dieser Kapseln erfordert keinen sehr hohen technischen und/oder finanziellen Aufwand. Dadurch lassen sich auch von solchen Drogen die Inhaltsstoffe unterschiedlicher Phase mit erträglichem Aufwand verarbeiten und verabreichen, die ihrer Natur nach nicht unmittelbar miteinander gemischt werden können.

Bei einer Ausgestaltung der Erfindung nach Anspruch 4 können die Inhaltsstoffe der einen Phase zunächst in einem eigenen Behältnis, beispielsweise in Form einer Weichgelatine-kapsel, untergebracht werden und dieses Behältnis dann in die Kapsel, beispielsweise in Form einer Hartgelatine-kapsel, eingebracht werden, in die entweder vorher oder nachher die Inhaltsstoffe der anderen Phase eingebracht wurden bzw. werden. Bei einer Ausgestaltung der Erfindung nach Anspruch 5 werden die Inhaltsstoffe beider Phasen je für sich in eine Abteilung einer Doppelkammerkapsel eingebracht, die durch den Steg, der beide Abteilungen miteinander verbindet, als Fertigpräparat trotzdem eine Einheit bildet. Bei einer Ausgestaltung der Erfindung nach Anspruch 6 können die Inhaltsstoffe beider Phasen auch bei voneinander unterschiedlicher Konsistenz zunächst je in ein eigenes Behältnis eingebracht werden und die beiden Behältnisse anschließend in die sie gemeinsam aufnehmende Kapsel, insbesondere in Form einer Hartgelatine-kapsel, eingebracht werden, die das Fertigpräparat bildet.

Im folgenden wird die Erfindung anhand mehrerer in der Zeichnung dargestellter Ausführungsbeispiele näher erläutert. Es zeigen:

Fig. 1 eine Ansicht eines ersten Ausführungsbeispiels der Kapsel;

Fig. 2 einen Längsschnitt eines zweiten Ausführungsbeispiels der Kapsel;

Fig. 3 einen Längsschnitt eines dritten Ausführungsbeispiels der Kapsel;

Fig. 4 einen Längsschnitt eines vierten Ausführungsbeispiels der Kapsel.

Die aus Fig. 1 ... 4 ersichtlichen Kapseln 11 ... 14 sind für die Aufnahme von pharmazeutisch wirksamen Inhaltsstoffen lipophiler Phase und polarer Phase einer Droge bestimmt. Zu ihrer Unterscheidung sind die lipophilen Inhaltsstoffe mit "L" und die polaren Inhaltsstoffe mit "P" gekennzeichnet. Bei der Kapsel 14 ist noch eine dritte Art sonstiger Inhaltsstoffe vorhanden, die mit "S" bezeichnet sind.

Die aus Fig. 1 ersichtliche Kapsel 11 ist als Weichgelatinekapsel ausgebildet. Sie weist je ein in sich abgeschlossenes Behältnis 15 und 16 auf, die bei der Herstellung der Kapsel 11 aus dem Werkstoff für Kapseln geformt werden, wobei die Wandungen der beiden Behältnisse 15 und 16 noch während des Füllvorganges in sich dicht verschlossen werden. Bei diesem Herstellungsvorgang wird zwischen den beiden kugelförmigen oder langrunden Behältnissen 15 und 16 aus demselben Werkstoff wie diese zugleich ein Steg 17 angeformt oder, genauer ausgedrückt, zwischen den beiden Behältnissen 15 und 16 stehengelassen. Dieser Steg 17 verbindet die beiden Behältnisse 15 und 16 zu einer Doppelkammerkapsel.

Die Kapsel 11 wird vor allem dann verwendet, wenn die Inhaltsstoffe P und L in fließfähiger Form, d.h. in flüssiger oder in pastöser Form, vorliegen.

Die aus Fig. 2 ersichtliche Kapsel 12 ist dreiteilig ausgebildet. Der äußere Teil ist eine Hartgelatinekapsel mit den beiden Kapselteilen 18 und 19. Der innere Teil ist als in sich abgeschlossenes Behältnis 21 in Form einer Weichgelatinekapsel ausgebildet.

Das Behältnis 21 nimmt vorzugsweise die lipophilen Inhaltsstoffe L auf, die im allgemeinen in fließfähiger Form, d.h. in flüssiger oder pastöser Form vorliegen. Von den beiden Kapselteilen 18 und 19 nimmt der beim Zusammenfügen innen gelegene Kapselteil 18 vorzugsweise die polaren Inhaltsstoffe P auf, und zwar insbesondere dann, wenn diese in rieselfähiger Form, also im allgemeinen in getrockneter Form, vorliegen. Die Handhabung des Kapselteils 18 nach dem Befüllen mit den polaren Inhaltsstoffen P wird dadurch erleichtert, daß ein Deckel 22 eingesetzt wird, der die Füllung im Kapselteil 18 festhält. Soweit die Füllung mit den polaren Inhaltsstoffen P trocken ist, genügt es, den Deckel 22 mit einer entsprechenden Passung herzustellen und einfach hineinzudrücken. Falls das nicht ausreichend sein sollte, insbesondere dann, wenn die Inhaltsstoffe P eben-

falls in fließfähiger Form vorliegen oder wenn sie aus anderen Gründen schon vor dem Verschließen der Kapsel 12, d.h. vor dem Aufstecken des zweiten Kapselteils 19, vor den Einflüssen der Umgebung geschützt werden sollen, dann kann der Deckel 22 auch eingeklebt oder eingeschweißt werden. In diesem Falle bildet der Deckel 22 eine feste Trennwand zwischen den beiden Aufnahmeteilen für die Inhaltsstoffe P und L. Wenn der polare Inhaltsstoff in thixotroper Form vorliegt oder wenn er durch kurzzeitiges Erwärmen verflüssigt werden kann und er dadurch in fließfähiger Form abgekühlt werden kann, wonach er wieder erstarrt, dann kann auf den Deckel 22 verzichtet werden.

Wenn nach dem Einfüllen der polaren Inhaltsstoffe P und gegebenenfalls nach dem Einsetzen des Deckels 22 auch noch das Behältnis 21 mit den lipophilen Inhaltsstoffen L eingebracht wurde, wird der äußere zweite Kapselteil 19 auf den ersten Kapselteil 18 aufgesteckt und die Kapsel damit verschlossen.

Die aus Fig. 3 ersichtliche Kapsel 13 ist vierteilig ausgebildet. Der äußere Teil ist wiederum eine Hartgelatinekapsel mit den beiden Kapselteilen 23 und 24. Im Inneren befinden sich die beiden in sich abgeschlossenen Behältnisse 25 und 26. Darin sind die lipophilen Inhaltsstoffe L und die polaren Inhaltsstoffe P je getrennt voneinander untergebracht. Für die beiden Behältnisse 25 und 26 bildet die Kapsel 13 eine gemeinsame Hülle.

Diese Ausführungsform der Kapsel kommt vor allem dann in Betracht, wenn die Inhaltsstoffe beider Phasen in fließfähiger Form vorliegen, die zwei in sich abgeschlossene Behältnisse erfordern, und dafür aber aus irgendwelchen Gründen die Ausführungsform der Kapsel 11 nach Fig. 1 nicht in Betracht kommt. Das kann z.B. dann der Fall sein, wenn die Inhaltsstoffe beider Phasen an unterschiedlichen Orten oder zu unterschiedlichen Zeiten verarbeitet werden müssen und unabhängig voneinander in ein Behältnis eingefüllt werden müssen.

Die aus Fig. 4 ersichtliche Kapsel 14 stellt eine Abwandlung der Kapsel 13 dar. Ihr äußerer Teil ist ebenfalls eine Hartgelatinekapsel mit den Kapselteilen 27 und 28. Im inneren Kapselteil 27 ist eine dritte Art Inhaltsstoffe S untergebracht. Wie schon zuvor bei der Kapsel 12, werden diese Inhaltsstoffe S - bei Bedarf - durch einen Deckel 29 festgehalten und gegenüber dem übrigen Innenraum der Kapsel 14 abgeschlossen. In diesem übrigen Innenraum befinden sich zwei in sich abgeschlossene Behältnisse 31 und 32 in Form je einer Weichgelatinekapsel. Darin sind, wie bei der Kapsel 13, die lipophilen Inhaltsstoffe L und die polaren Inhaltsstoffe P je getrennt voneinander untergebracht. Auch hier dient die Kapsel 14 als Hülle für die beiden Behältnisse 31 und 32 und zugleich als

Aufnahmeteil für die Inhaltsstoffe S.

Diese Ausführungsform kommt vor allem für die gleichzeitige Verabreichung von drei verschiedenen Arten Inhaltsstoffe in Betracht. Dabei sind auch andere Abwandlungen möglich. Beispielsweise kann auch der äußere Kapselteil 28 unmittelbar mit Inhaltsstoffen in rieselfähiger oder thixotroper Form befüllt werden und erforderlichenfalls mit einem Deckel verschlossen werden. Es könnten aber auch drei (oder mehr) in sich abgeschlossene Behältnisse in Form von Weichgelatinekapseln in die Kapsel 14 als gemeinsame Hülle eingebracht werden.

Ansprüche

1. Kapsel für pharmazeutisch wirksame Inhaltsstoffe einer Droge,

gekennzeichnet durch die Merkmale:

- die Inhaltsstoffe (L) lipophiler Phase und die Inhaltsstoffe (P) polarer Phase sind in je einem Aufnahmeteil (21, 18; 19) der Kapsel (12) getrennt voneinander untergebracht,
- die Wand zumindest des einen Aufnahmeteils (21) ist für den Durchtritt der Inhaltsstoffe (L) beider Phasen undurchlässig.

2. Kapsel für pharmazeutisch wirksame Inhaltsstoffe einer Droge,

gekennzeichnet durch die Merkmale:

- die Inhaltsstoffe (L) lipophiler Phase und die Inhaltsstoffe (P) polarer Phase sind in je einem eigenen Aufnahmeteil (26; 25) der Kapsel (13) getrennt voneinander untergebracht,
- die Wand jedes der beiden Aufnahmeteile (25; 26) der Kapsel (13) ist in Bezug auf das Austreten der darin befindlichen Inhaltsstoffe (P; L) undurchlässig.

3. Kapsel für pharmazeutisch wirksame Inhaltsstoffe einer Droge,

gekennzeichnet durch die Merkmale:

- die Inhaltsstoffe (L) lipophiler Phase und die Inhaltsstoffe (P) polarer Phase sind in je einem eigenen Aufnahmeteil (15; 16) der Kapsel (11) getrennt voneinander untergebracht,
- die beiden Aufnahmeteile sind als Teilräume (15; 16) der Kapsel (11) ausgebildet, die mittels einer Trennwand (17) abgetrennt sind, die für den Durchtritt der Inhaltsstoffe (L; P) beider Phasen undurchlässig ist.

4. Kapsel nach Anspruch 1.

gekennzeichnet durch die Merkmale:

- der eine Aufnahmeteil ist als abgeschlossenes Behältnis (21) ausgebildet,
- der andere Aufnahmeteil wird durch die Kapsel (12) gebildet, die neben den zugeordneten Inhaltsstoffen (P) zugleich auch das eine Behältnis (21) aufnimmt.

5. Kapsel nach Anspruch 1 oder 2,

gekennzeichnet durch das Merkmal,

- die beiden Aufnahmeteile der Kapsel (11) werden durch je ein abgeschlossenes Behältnis (15; 16) gebildet, die beide mittels eines äußeren Steges (17) miteinander verbunden sind, der vorzugsweise aus dem gleichen Werkstoff wie die Behältnisse (15; 16) ist.

6. Kapsel nach Anspruch 2,

gekennzeichnet durch die Merkmale,

- die beiden Aufnahmeteil der Kapsel (13) werden durch je ein abgeschlossenes Behältnis (25; 26) für die zugeordneten Inhaltsstoffe (P; L) gebildet,
- die beiden Behältnisse (25; 26) sind von der Kapsel (13) als gemeinsame Hülle umschlossen.

Fig.1

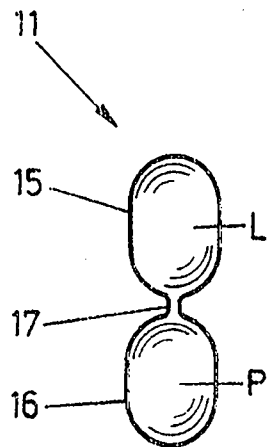


Fig.2

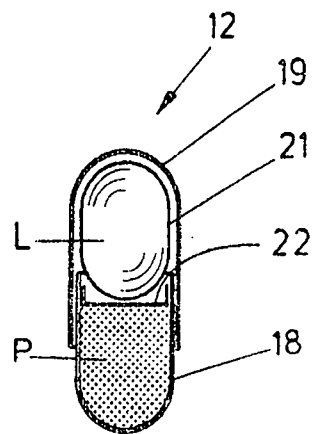


Fig.3

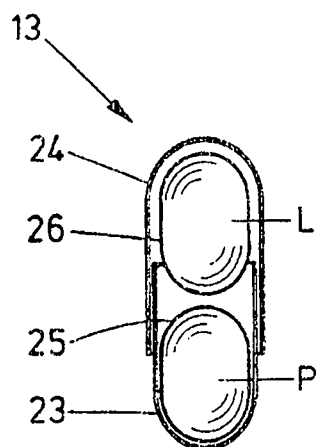
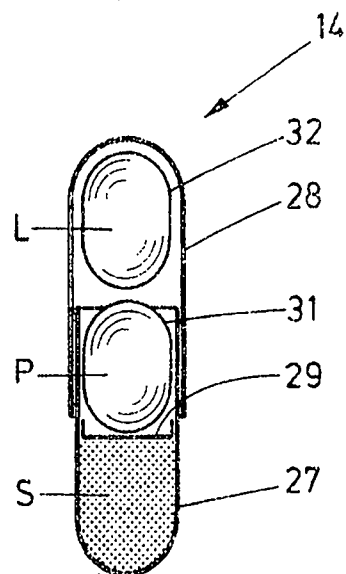


Fig.4





Europäisches
Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 88 11 2688

EINSCHLÄGIGE DOKUMENTE			
Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.4)
X	DERWENT PUBLICATIONS LTD, Datenbank: WPI; Ref.Nr. 78-24571a, London, GB; & NL-A-76 10 038 (TAPANAHONY) 09/09/1976 * Zusammenfassung *	1,2	A 61 K 9/48 A 61 J 3/07
X	EP-A-0 211 079 (FUJISAWA) * Ansprüche 1-4; Seite 2, Zeilen 15-18; Seite 3, Zeilen 5-15 *	1,2	
			RECHERCHIERTE SACHGEBIETE (Int. Cl.4)
			A 61 K A 61 J
Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt			
Recherchenort DEN HAAG		Abschlußdatum der Recherche 06-12-1988	Prüfer SCARPONI U.
KATEGORIE DER GENANNTEN DOKUMENTE			
X : von besonderer Bedeutung allein betrachtet Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie A : technologischer Hintergrund O : mündliche Offenbarung P : Zwischenliteratur		I : der Erfindung zugrunde liegende Theorien oder Grundsätze E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist D : in der Anmeldung angeführtes Dokument L : aus andern Gründen angeführtes Dokument & : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument	

Señor Jefe,

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-070672- -00003-0000

Fecha: 2011-01-18 11:52:26 Dep. 2020 DIR.NUEVASCR
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Act. 400 OPOSIOBSERVTER Folios: 85

Referencia : Expediente N° 09 70672
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIONES CON FORMA DE DOSIFICACION
SIMPLE PARA LIBERAR MULTIPLES FARMACOS A
DIFERENTES VELOCIDADES DE LIBERACION"
Solicitante : WYETH
Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 621 del 20 de octubre de 2010

Yo, *ELIANA ISaura MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *83823* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** 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 "COMPOSICIONES CON FORMA DE DOSIFICACION SIMPLE PARA LIBERAR MULTIPLES FARMACOS A DIFERENTES VELOCIDADES DE

LIBERACION", 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 ESTROGENOS. 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 08 de julio de 2009 reivindicando prioridad bajo la solicitud US20070884801 del 2007-01-12; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 621 del 20 de octubre de 2010, cuya publicación internacional corresponde a la WO2008089087 del 2008-07-24.

2.2. La solicitud colombiana 09 70672 objeto de la presente oposición se refiere a composiciones de tableta en tableta que comprenden uno o más estrógenos en una

primera capa y un agente terapéutico en una segunda capa y con procesos para su producción, en donde la composición de tableta en tableta, es caracterizada porque comprende: a) una tableta central que comprende: uno o más estrógenos; un componente rellenedor/ diluyente central; un componente rellenedor/aglomerante central; un componente polimérico de formación de gel hidrofílico central; y opcionalmente, un componente lubricante central; y b) una capa de tableta exterior comprimida que comprende uno o más agentes terapéuticos seleccionados del grupo que consiste de modulador del receptor de estrógeno selectivos y agentes progestacionales; un componente rellenedor/diluyente de la capa exterior; un componente rellenedor/aglomerante de la capa; un componente de polímero de formación de gel hidrofílico de la capa exterior; opcionalmente, un componente antioxidante; y opcionalmente, un componente lubricante de la capa exterior.

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

- D1: WO2005120466 publicada el 22 de diciembre de 2005.
- D2: EP0308637 publicada el 29 de marzo de 1989.

2.4. Ahora bien, el documento D1, se refiere a composiciones particularmente útiles como revestimientos para formas de dosis en sólidos de agentes terapéuticos, que se encuentran como formas de dosis en sólidos que comprenden dichos revestimientos, procedimientos para la preparación de dichas formas de dosis en

sólidos, y los productos de esos procedimientos; las composiciones para revestimiento generalmente proveen una excelente fuerza y resistencia a la fragmentación, incluso cuando se aplica a núcleos de tabletas flexibles que se pueden hinchar tales como núcleos tipo hidrogel; Dicho documento D1 describe una tableta comprimida que comprende los estrógenos conjugados en el núcleo, recubierta con una capa externa que comprende un agente terapéutico como acetato de medroxiprogesterona; el mismo documento D1 se refiere a la utilización de capas y/o revestimientos en tabletas, o similares para obtener diferentes beneficios, y revela particularmente que los revestimientos de película también han sido utilizados para modificar la liberación de los constituyentes de núcleo de tableta como, por ejemplo, vía revestimientos entéricos en los cuales el polímero empleado en el revestimiento es esencialmente impermeable al PH gástrico pero es soluble en el PH incrementado de los intestinos, mas adelante el documento D1 menciona ventajas del revestimiento de película como la formulación de revestimientos de liberación extendida que ayudan a eliminar la necesidad de regímenes de dosis múltiples de un agente terapéutico particular. El documento D1 se refiere también al perfil de liberación del agente terapéutico anotando que se puede modificar mediante diferentes métodos conocidos como la inclusión de sustancias solubles al agua dentro de las membranas, o revestimientos, sustancias que se disuelven por los fluidos gastrointestinales, creando poros dentro de la película que permiten que los fluidos gastrointestinales pasen a través de la membrana y disuelvan el agente terapéutico dentro del núcleo de la tableta, etc. Finalmente el documento D1 menciona que la velocidad de difusión se puede controlar de varias formas, como por ejemplo mediante el grosor y composición de la membrana para difusión.

2.5.El documento D2 por su parte revela una cápsula, compuesta por dos capsulas individuales, las cuales pueden tener características diferentes, considerando las necesidades de los ingredientes activos o las necesidades relativas a las afecciones que se desee tratar; ingredientes activos, lubricantes y similares, en cada capsula. Dicho documento D2 describe características de diferenciación de capsulas y fases, considerando si es necesario una capa para evitar que los componentes se mezclen de forma indeseada, y particularmente el documento D2 menciona el uso de diferentes compuestos adyuvantes, excipientes, o similares conocidos como rellenos, estabilizadores de PH, formadores de gel, diluyentes, etc.

2.6. Tomando los documentos D1 y D2 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir del documento D1 en combinación con D2, concebir composiciones de tableta en tableta que comprenden uno o más estrógenos en una primera capa y un agente terapéutico en una segunda capa y a procesos para su producción, en donde la composición de tableta en tableta, es caracterizada porque comprende: a) una tableta central que comprende: uno o más estrógenos; un componente relleno/ diluyente central; un componente relleno/aglomerante central. Un componente polimérico de formación de gel hidrofílico central; y opcionalmente, un componente lubricante central; y b) una capa de tableta exterior comprimida que comprende uno o más agentes terapéuticos seleccionados del grupo que consiste de modulador del receptor de estrógeno selectivos y agentes progestacionales; un componente relleno/diluyente de la capa exterior; un componente relleno/aglomerante de la capa; un componente de polímero de formación de gel hidrofílico de la capa exterior; opcionalmente, un componente antioxidante; y opcionalmente, un

componente lubricante de la capa exterior. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 70672 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.

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

2.8.1. 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, 12 de enero de 2007, a partir del documento D1, en combinación con D2 un experto en la materia puede llegar de manera evidente a composiciones de tableta en tableta que comprenden uno o más estrógenos en una primera capa y un agente terapéutico en una segunda capa, en donde la composición de tableta en tableta, es caracterizada porque comprende: a) una tableta central que comprende: uno o más estrógenos u otros activos; un componente rellenedor/diluyente central, un componente rellenedor/aglomerante central, y/o similares. Un componente polimérico de formación de gel hidrofílico central; y opcionalmente, un componente lubricante central; y b) una capa de tableta exterior comprimida que comprende uno o más agentes terapéuticos seleccionados del grupo que consiste de moduladores del receptor de estrógeno selectivos y agentes progestacionales; un componente rellenedor/diluyente de la

capa exterior; un componente rellenedor/aglomerante de la capa; un componente de polímero de formación de gel hidrofílico de la capa exterior, o componentes similares, opcionalmente un componente antioxidante; y opcionalmente, un componente lubricante de la capa exterior; sobre lo cual busca protección en el capítulo reivindicatorio.

2.9. 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.

2.10. 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 **“COMPOSICIONES CON FORMA DE DOSIFICACION SIMPLE PARA LIBERAR MULTIPLES FARMACOS A DIFERENTES VELOCIDADES DE LIBERACION”**, cuyos titulares son WYETH, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 621 del 20 de octubre de 2010.

3. PRUEBAS

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

D1: WO2005120466 publicada el 22 de diciembre de 2005.

D2: EP0308637 publicada el 29 de marzo de 1989.

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 **LABORATORIOS SYNTHESIS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

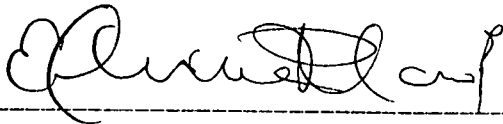
D1: WO2005120466 publicada el 22 de diciembre de 2005.

D2: EP0308637 publicada el 29 de marzo de 1989.

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,



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

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 09-70672

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **621** DE

FECHA **20 DE OCTUBRE DE 2010** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **18 DE ENERO DE 2011**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI X

NO