

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-090010- -00004-0000

Fecha: 2011-08-19 11:29:00 Dep. 2020 DIR NUEVASOR
Tra. 11 PATENTE/III Evt: 379 FASENACIONALII
Act. 400 CPOSIGBSERVTER Folios: 28

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: 10-090010

Solicitante: GRUNENTHAL GMBH

Apoderado: HUMBERTO RUBIO CAMACHO

Título de la nueva creación o denominación del signo: "FORMA DE
DOSIFICACION FARMACEUTICA DE LIBERACION CONTROLADA"

Gaceta: 628

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: LABORATORIOS SYNTHESIS S.A.S.	IDENTIFICACIÓN	
	Dirección: Carrera 44 N° 20 C 73 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BOGOTA	C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual <u> </u>	
	Teléfono: 3692222 Fax: 3693542 E-mail: <u> </u>	Número <u>860.060.760-1</u>	
REPRESENTANTE O APODERADO	Nombre: ELINA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 104 N°119-95 OF 104 Teléfono: 2131213 Fax: 6121979 E-mail: negocios@optimum-co.com	C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual <u> </u>	
		Número <u>51.975.664</u> TP <u>83823</u>	

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

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

⑤ Comprobante de pago No.

414 0030800

Fecha

26-05-11

⑥ ANEXOS

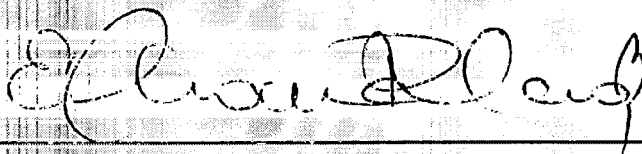
- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE:

ELIANA ISAURA MORENO BOHORQUEZ

FIRMA:



C.C. 51'975.664

TP. 83823

Señor Director,

DIRECCIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 10 090.010

Asunto : Oposición a la solicitud de patente de Invención titulada
*"FORMA DE DOSIFICACIÓN FARMACÉUTICA DE
LIBERACIÓN CONTROLADA"*

Solicitante : GRUNENTHAL GMBH

Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 628 del 20 de mayo de 2011

Yo, *ELIANA ISAUKA 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 Bogotá, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada *"FORMA DE DOSIFICACIÓN FARMACÉUTICA DE LIBERACIÓN CONTROLADA"*, cuyo titular es **GRUNENTHAL GMBH**, 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 en general comprenden sistemas de liberación controlada. 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 23 de julio de 2010, reivindicando prioridad bajo la solicitud EP20080001415 del 2008-01-25, y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 628 del 20 de mayo de 2011, cuya publicación internacional corresponde a la WO2009092601 del 2009-07-30.

2.2. La solicitud colombiana 10 090.010 objeto de la presente oposición, se refiere a una forma de dosificación farmacéutica con liberación controlada de un compuesto (A) farmacológicamente activo contenido en ella, teniendo la forma de dosificación una resistencia a la ruptura B1 de por lo menos 500 N en la dirección de extensión E1 y teniendo una resistencia a la ruptura B2 de menos de 500 N en la dirección de extensión E2.

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

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel*

inventivo y sean susceptibles de aplicación industrial". Así las cosas, las invenciones objeto de parente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: US2006002860 publicada el 5 de enero de 2006.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela una forma de dosificación oral con opioides de liberación controlada para la administración una vez al día, que se caracteriza porque comprende al menos un opioide de entrega (A), al menos un polímero sintético o natural (C), opcionalmente, de liberación retardada de la matriz auxiliares, sustancias auxiliares fisiológicamente aceptable (B), de manera opcional una cera (D) y opcionalmente al menos un recubrimiento de liberación retardada, donde el componente (C) o (D) en cada caso presentan una resistencia a la rotura de al menos por lo menos 500 N, preferentemente de al menos 1000 N. D1 revela en los párrafos 0008; 0014; 0075; 0080; y, 0081 y reivindicaciones 1 a 14, ejemplo 1 y tabla 1 revela formas de dosificación oral con liberación controlada de opiáceos presentan una resistencia a la rotura de al menos 500 N donde los comprimidos comprenden polímeros tales como los óxidos de polietileno en combinación con hidroxipropilmetilcelulosa. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 10 090010 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que*

haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”. A la fecha de prioridad, 25 de enero de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, una forma de dosificación farmacéutica con liberación controlada de un compuesto (A) farmacológicamente activo contenido en ella, teniendo la forma de dosificación una resistencia a la ruptura B1 de por lo menos 500 N, sobre el cual busca protección en el capítulo reivindicatorio.

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

2.9. 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 dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada ***“FORMA DE DOSIFICACIÓN FARMACÉUTICA DE LIBERACIÓN CONTROLADA”***, cuyo titular es GRUNENTHAL GMBH, solicitud

Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N°
628 del 20 de mayo de 2011.

3. PRUEBAS

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

- D1: US2006002860 publicada el 5 de enero de 2006.

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: US2006002860 publicada el 5 de enero de 2006.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1934 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 ISAUERA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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

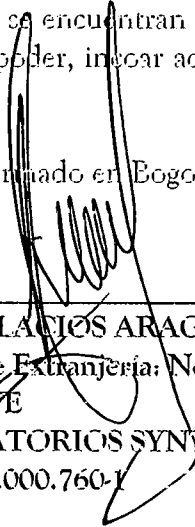
PODER ESPECIAL

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. 10 090.010, titulada "**FORMA DE DOSIFICACION FARMACEUTICA DE LIBERACION CONTROLADA**", cuyo titular **GPUINENTHAL GMEH** publicada en la gaceta No. 628 del 20 de mayo de 2011.

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

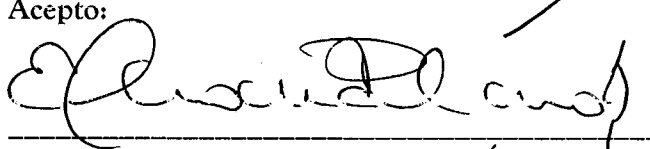
De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Bogotá (Colombia) a los 09 días del mes de agosto de 2011.



LUIS PALACIOS ARAGÓN
Cédula de Extranjería: No. E319788.
GERENTE
LABORATORIOS SYNTHESIS S.A.S.
NIT: 860.000.760-1

Acepto:



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





DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Circulo de Bogotá.

Palacios Aragon
quien exhibio la C.E. *319788*

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

BOGOTA, D.C. **10 AGO 2011**

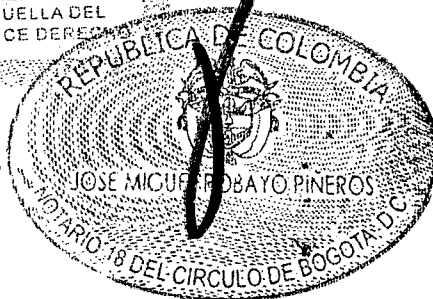
FIRMA

EL NOTARIO



HUELLA DEL
INDICE DERECHO

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



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

Industria y Comercio

SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0050500

Bogotá D.C., Mayo 26 de 2011 - 10:25:46

RECIBIDO DE : LABORATORIOS SYNTHESIS S.A.S.

III 660.000.760

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	Nº PAGO	FECHA PAGO	VE PAGO
CONSIGNACION	BANCO DE BOGOTA	062754337	435179146	25/05/2011	2.128.000.00

*** Conceptos Pagados ***

CAUSAL FENOTIPICO	CONCEPTO	VL. LUDITARIO	VL. CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 MARCAS Y LEMAS COMERCIALES	304.000.00	304.000.00
			\$304.000.00

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-090010- -00004-0000

Fecha: 2011-05-19 11:29:00 Dep. 2020 DIR.NUEVASOR
 Tra. 11 PATENTE/II Evs: 379 FASENACIONALII
 Act. 400 GPS/OBSERVTER Folios: 28

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

Web: www.slc.gov.co e-mail: info@slc.gov.co Conmutador: (571) 5070000 Fax: (571) 5070233 Línea: 012000-916165 Call Center: (571) 6513240

Mayo 26 de 2011 - 10:25:47



01



* 1 0 7 1 1 7 1 6 5 *

CAMARA DE COMERCIO DE BOGOTA

SEDE PALOQUEMAO

10 DE AGOSTO DE 2011

HORA 14:13:06

R032272233

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: "LABOPATORIOS 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 "LABOPATORIOS 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
18-XII-1.956	8 BTA.	22-XII-1.956 NO. 36.077
31-XII-1.958	8 BTA.	12-I-1.959 NO. 42.034
22-IX-1.961	8 BTA.	29-IX-1.961 NO. 51.161
2-II-1.967	6 BTA.	24-II-1.967 NO. 71.304
16-XII-1.967	6 BTA.	26-I-1.968 NO. 75.041
20-XII-1.967	8 BTA.	26-I-1.968 NO. 75.042
14-V-1.968	6 BTA.	30-V-1.968 NO. 76.244
4-V-1.970	6 BTA.	18-V-1.970 NO. 84.983
13-VII-1.970	6 BTA.	13-VIII-1.970 NO. 86.126
15-VII-1.971	3 BTA.	29-VII-1.971 NO. 90.980
10-VII-1.984	11 BTA.	27-VIII-1.984 NO.157.001
14-III-1.985	11 BTA.	26- III-1.985 NO.167.627
11- II-1.985	1 BTA.	21- II-1.985 NO.165.940
11-VIII-1986	1 BTA.	23- IX -1.986 NO.197.784
15- IX -1986	1 BTA.	23- IX -1.986 NO.197.784
16- X -1987	1 BTA.	23- X -1.987 NO.221.604
21-VIII-1990	1 BTA.	3- IX -1.990 NO.303.579
23-XII- 1991	1 STAFE.BTA.	8-I -1.992 NO.351.255
15- X - 1992	1 STAFE.BTA.	16- X-1.992 NO.382.488
26- III-1993	1 STAFE.BTA.	19- III-1993 NO.399972
01-VI-1.995	1A.STAFE BTA	23-VI- 1.995 NO.498.060
17-IX-1.996	1A.STAFE BTA	30-IX- 1.996 NO.556.909
17-IX-1.996	1A.STAFE BTA	01- X- 1.996 NO.557.146
17-IX-1.996	1A.STAFE BTA	02- X- 1.996 NO.557.301
7-X -1.996	1A.STAFE BTA	11- X- 1.996 NO.558.222
24-X--1.996	1A.STAFE BTA	07-XI--1.996 NO.561.207
25-XI-1.996	1A.STAFE BTA	12-XII-1.996 NO.565.961
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
139	2011/06/07	0000	BOGOTA D.C.	2011/06/20	01489422

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 CONDUCENTES 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 : \$18,091,180,000.00
NO. DE ACCIONES : 18,091,180.00
VALOR NOMINAL : \$1,000.00

**** CAPITAL PAGADO ****

VALOR : \$18,091,180,000.00
NO. DE ACCIONES : 18,091,180.00
VALOR NOMINAL : \$1,000.00

CERTIFICA:

REPRESENTACION LEGAL: LA SOCIEDAD CONTARÁ CON UN GERENTE, QUIEN TENDRÁ DOS SUPLENTE DENOMINADOS SUBGERENTES, QUIENES LO REEMPLAZARÁN EN LAS FALTAS OCASIONALES, TEMPORALES O ABSOLUTAS DE AQUÉL.

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
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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
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SUBGERENTE	
MUÑOZ MARTINEZ ORLANDO	C.C. 000000008317044

QUE POR ACTA NO. 139 DE ASAMBLEA DE ACCIONISTAS DEL 7 DE JUNIO DE 2011, INSCRITA EL 20 DE JUNIO DE 2011 BAJO EL NUMERO 01489425 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
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SUBGERENTE	
PICART LAURENZ FRANCISCO JAVIER	P.P. 000000036717704

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)



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CONSTITUIR, PARA CASOS ESPECIALES, APODERADOS JUDICIALES O EXTRAJUDICIALES. D) CELEBRAR LOS ACTOS, OPERACIONES Y CONTRATOS CONDUCENTES 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 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 CEDULA DE CIUDADANIA NO. 9.317.044 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 PARTÍCIPE ACTIVA O COMO PARTÍCIPE 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 COMO 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 NACIONALES 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



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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. 00013604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE 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 CAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.303 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 COMPADRORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C. ADELANTAR 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. I. 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
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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 SUPERINTENDENCIA 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 RESERVA, A SU VALOR NOMINAL DE CIEN PESOS (\$100.00) M/CTE., CADA UNA.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DE REPRESENTANTE LEGAL DEL 28 DE JUNIO DE 2011, INSCRITO EL 1 DE JULIO DE 2011 BAJO EL NUMERO 01492789 DEL LIBRO IX, SE COMUNICO QUE SE HA CONFIGURADO UNA SITUACION DE CONTROL POR PARTE DE LA SOCIEDAD MATRIZ: LABORATORIOS SYNTHESIS S A S, RESPECTO DE LAS SIGUIENTES SOCIEDADES SUBORDINADAS:

- SOCIEDAD PARA LA ENSEÑANZA DE LA HOMEOPATIA CLINICA S A S QUIEN SE IDENTIFICARA CON LA SIGLA S E C H

DOMICILIO: BOGOTA D.C.

FECHA DE CONFIGURACION DE LA SITUACION DE CONTROL : 2011-05-31

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DE REPRESENTANTE LEGAL DEL 9 DE MARZO DE 2011, INSCRITO EL 18 DE MARZO DE 2011 BAJO EL NUMERO 01462396 DEL LIBRO IX, COMUNICO LA SOCIEDAD MATRIZ:

- EUROPEAN CHEMICALS & CO

DOMICILIO: (FUERA DEL PAIS)

QUE SE HA CONFIGURADO UNA SITUACION DE CONTROL CON LA SOCIEDAD DE LA



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REFERENCIA.

CERTIFICA:

*** ACLARACIÓN SITUACIÓN DE CONTROL Y DE GRUPO EMPRESARIAL ***
SE ACLARA LA SITUACIÓN DE CONTROL Y GRUPO EMPRESARIAL INSCRITA CON EL
NO. 01462396 DEL 9 DE MARZO DE 2011 DEL LIBRO IX EN EL SENTIDO DE
INDICAR QUE SE CONFIGURÓ DESDE EL 19 DE NOVIEMBRE DE 2010.

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 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GENERICS

MATRICULA NO : 00664623 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : MASCOTT

MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : ONCOPHARM

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GASTROPHARM

MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GYNECOPHARM

MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : ENTEROPHARM

MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : EQUIPHARMA

MATRICULA NO : 00556630 DE 21 DE JULIO DE 1993

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

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,
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





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(54) **ABUSE-PROOFED ORAL DOSAGE FORM**

Publication Classification

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(57) **ABSTRACT**

The present invention relates to an abuse-proofed, oral dosage form with controlled opioid-release for once daily administration, characterised in that it comprises at least one opioid with potential for abuse (A), at least one synthetic or natural polymer (C), optionally delayed-release matrix auxiliary substances, physiologically acceptable auxiliary substances (B), optionally a wax (D) and optionally at least one delayed-release coating, component (C) or (D) in each case exhibiting a breaking strength of at least 500 N, preferably of at least 1000 N.

ABUSE-PROOFED ORAL DOSAGE FORM

[0001] The present invention relates to an abuse-proofed oral dosage form with controlled opioid release for once daily administration, comprising at least one opioid with potential for abuse (A), at least one synthetic or natural polymer (C), optionally delayed-release matrix auxiliary substances, optionally physiologically acceptable auxiliary substances (P), optionally a wax (D) and optionally a delayed-release coating, component (C) or (D) in each case exhibiting a breaking strength of at least 500 N, preferably of 1000 N.

[0002] The name opioids is taken according to the invention to mean compounds which interact with at least one opioid receptor. In particular, with the exception of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, the physiologically acceptable salts or derivatives thereof, opioids are taken to mean those compounds which exhibit a potential for abuse.

[0003] Preferably, opioids are used for combating pain. To this end, analgesics are frequently used in long-term treatment, for example in the case of chronic pain or pain caused by tumours. In long-term treatment, in particular, it is important to enable the patient to enjoy a good quality of life. The measures which improve the quality of life of a patient include dosage forms which allow once daily administration. However, because of the relatively large quantity of opioid, such dosage forms, which provide delayed release of the active ingredient, are particularly attractive to the abuser who wishes to induce the desired state of narcosis or euphoria as quickly as possible.

[0004] Since, however, delayed-release dosage forms containing opioids with potential for abuse do not usually give rise to the kick desired by the abuser when taken orally even in abusively high quantities, these dosage forms for example in the form of tablets or capsules are also comminuted, e.g. ground, and sniffed by the abuser for the purpose of abuse or the active ingredients are extracted from the powder obtained in this way by means of an aqueous liquid and the resultant solution is administered parenterally, in particular intravenously, optionally after filtration through cotton wool or cellulose wadding. This type of administration produces even more accelerated increase in opioid levels than with oral or nasal abuse, with the result desired by the abuser, namely the "kick" or "rush".

[0005] U.S. Pat. No. 4,070,494 proposed adding a swellable agent to the dosage form in order to prevent abuse. When water is added to extract the opioid, this agent swells and ensures that the filtrate separated from the gel contains only a small quantity of active ingredient.

[0006] The multilayer tablet disclosed in WO 95/20947 is based on a similar approach to preventing parenteral abuse, said tablet containing the opioid with potential for abuse and at least one gel former, each in different layers.

[0007] WO 03/015531 A2 discloses another approach to preventing parenteral abuse. A dosage form containing an analgesic opioid and a dye as an aversive agent is described therein. The colour released by tampering with the dosage form is intended to discourage the abuser from using the dosage form which has been tampered with. Another known option for complicating abuse involves adding to the dosage form an antagonist to the opioid, such as for example

naloxone or naltrexone, or compounds which cause a physiological defence response, such as for example ipecacuanha (ipecac) root, or bitter substances.

[0008] However, since in most cases of abuse of dosage forms with delayed-release of an opioid, it is still necessary to pulverise the dosage form, it was the object of the present invention to complicate or prevent the pulverisation preceding abuse of the dosage form comprising the means conventionally available for potential abuse and accordingly to provide a dosage form with controlled release of opioids with potential for abuse which ensures the desired therapeutic effect when correctly administered once daily, but from which the opioids cannot be converted into a form suitable for abuse simply by pulverisation.

[0009] This object was achieved by the preparation of the abuse-proofed oral dosage form, according to the invention, with controlled release of at least one opioid for once daily administration, which dosage form comprises, in addition to at least one opioid and/or at least one of the physiologically acceptable compounds thereof, preferably salts or derivatives, preferably esters or ethers, with potential for abuse (A), at least one synthetic or natural polymer (C), optionally delayed-release matrix auxiliary substances, optionally physiologically acceptable auxiliary substances (B), optionally a wax (D), and optionally at least one delayed-release coating, component (C) or (D) in each case exhibiting a breaking strength of at least 500 N, preferably of 1000 N.

[0010] By using components (C) and optionally (D) with the stated minimum breaking strength, preferably in such quantities that the dosage form also exhibits such a minimum breaking strength, pulverisation of the dosage form with conventional means and thus subsequent abuse, preferably nasal or parenteral abuse, may be complicated considerably or prevented.

[0011] Preferably, the components (C) and optionally (D) are present in such quantities that the dosage form exhibits a breaking strength of at least 500 N, preferably of at least 1000 N.

[0012] Without sufficient comminution of the dosage form, non-hazardous parenteral, in particular intravenous or nasal administration is impossible or extraction of the active ingredient takes the abuser too long, or no or an inadequate kick is obtained on abusive oral administration, since spontaneous release does not occur.

[0013] According to the invention, comminution is taken to mean pulverisation of the dosage form with conventional means which are available to an abuser, such as for example a pestle and mortar, a hammer, a mallet or other usual means for pulverisation by application of force.

[0014] The dosage form according to the invention is thus suitable for preventing parenteral, nasal and/or oral abuse of opioids with potential for abuse.

[0015] Opioids with potential for abuse are known to the person skilled in the art, as are the dosages thereof to be used and processes for the production thereof, and may be present in the dosage form according to the invention as such, in the form of the corresponding derivatives thereof, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof, as racemates or stere-

oisomers. The dosage form according to the invention is also suitable for the administration of a plurality of opioid. Preferably it is used to administer to humans or mammals, preferably to humans, a particular opioid for combatting pain for a duration of at least 24 hours.

[0016] The dosage forms according to the invention are very particularly suitable for preventing the abuse of an opioid which is selected from the group consisting of N-[1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl]propionanilide (alfentanil), allylprodine, alphaprodine, amileridine, bemidone, benzylmorphine, bezitramide, 17-cyclopropylmethyl-4,5a-epoxy-7a[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-methoxy-6,14-endocinanomorphinan-3-ol (buprenorphine), butorphanol, carfentanil, clonidine, clonitazene, (-)-methyl-[3 β -benzoyloxy-2 β -(1aH,5aH)-tropane carboxylate] (cocaine), 4,5a-epoxy-3-methoxy-17-methyl-7-morphinen-6a-ol (codeine), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl)propionate (dextropropoxyphene), dezocine, diampromide, diamorphine, 4,5a-epoxy-3-methoxy-17-methyl-6a-morphinan-3-ol (dihydrocodeine), 4,5a-epoxy-17-methyl-3,6a-morphinan-3-ol (dihydromorphine), dimenoxadol, dimethylphenol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, dihydromorphine, eptazocine, ethohexazine, ethylmethylthiambutene, 4,5a-epoxy-3-methoxy-17-methyl-7-morphinen-6a-ol (ethylmorphine), etonitazene, 4,5-epoxy-7-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-endo-etheno-morphinan-3-ol (etorphine), fentanyl, fentanyl-N-(1-phenethyl-4-piperidyl)propionanilide (fentanyl), heroin, 4,5-epoxy-3-methoxy-17-methyl-6-morphinan-3-ol (hydrocodone), 4,5a-epoxy-3-hydroxy-17-methyl-6-morphinan-3-ol (hydromorphone), hydroxypethidine, isomethadone, hydroxymethylmorphinan, 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3S,6S)-6-dimethylamino-3,4-diphenylheptan-3-yl acetate (levacetylmethadol), (-)-6-dimethylamino-4,4-diphenol-3-heptanone (levomethadone), (-)-17-methyl-3-morphinan-3-ol (levorphanol), levophenacetylmorphine, levorphanol, lofentanil, meperidine, 2-methyl-2-propylpiperidine dicarbamate, meptazinol, metazocine, methadone, methylmorphine, metapone, 3-methylfentanyl, 4-methylfentanyl, 4,5a-epoxy-17-methyl-7-morphinen-3,6a-diol (morphine), myrophine, nalbuphene, nalorphine, naltrexone, nalmorphine, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpiperidine, the exudation from plants belonging to the species *Papaver somniferum* (opium), 4,5a-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinan-3-ol (oxycodone), oxymorphone, plants and parts of plants belonging to the species *Papaver somniferum* (including the subspecies *setigerum*) (*Papaver somniferum*), papaveretum, 1,2,3,4,5,6-hexahydro-4,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), ethyl-(1-methyl-4-phenyl-4-piperidinecarboxylate) (pethidine), phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, pholcodeine, 1'-3-cyano-3,3-diphenylpropyl[1,4'-bipiperidine]-4'-carboxamide (piritramide), propheptazine, promedol, properidine, propoxyphene, methyl {3-[4-methoxycarbonyl-4-(11-phenylpropanamido)piperidino]-propanoate} (racalfentanil), 11-[4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide (sufentanil), ethyl (2-dimethylamino-1-phenyl-cyclohexene-1-carboxylate) (tilidine, cis and trans), tramadol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluorobenzoyloxy)-1-(m-methoxy-

phenyl)cyclohexanol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(2-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1R,3R,6R)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, preferably as racemate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutoxy-phenyl)propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)propionate, (RR-SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl ester, (RR-SS)-2-hydroxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl ester, (RP-SS)-2-hydroxy-4-chloro-2-hydroxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl ester, (RP-SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RP-SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RP-SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester together with corresponding stereoisomeric compounds, in each case the corresponding derivatives thereof, in particular amides, esters or ethers, and in each case the physiologically acceptable compounds thereof, in particular the salts and solvates thereof, particularly preferably hydrochlorides.

[0017] The dosage form according to the invention is particularly suitable for preventing abuse of an opioid active ingredient selected from among the group comprising oxycodone, hydromorphone, morphine, tramadol and the physiologically acceptable derivatives or compounds thereof, preferably the salts and solvates thereof, preferably the hydrochlorides thereof.

[0018] Furthermore, the dosage form according to the invention is particularly suitable for preventing the abuse of an opioid active ingredient selected from among the group comprising (2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1R,3R,6R)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3 diol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, the physiologically acceptable salts thereof, preferably hydrochlorides, physiologically acceptable enantiomers, stereoisomers, diastereomers and racemates and the physiologically acceptable derivatives thereof, preferably ethers, esters or amides.

[0019] These compounds and the process for the production thereof are described in EP-A-693475 and EP-A-780369 respectively. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

[0020] The dosage in the delayed-release dosage form is selected such that once daily administration is ensured. The corresponding dosages are known to the person skilled in the art.

[0021] In order to achieve the necessary breaking strength of the dosage form according to the invention, at least one

synthetic, semi-synthetic or natural polymer (C) is used which has a breaking strength, measured using the method disclosed in the present application, of at least 500 N, preferably of 1000 N. Preferably, at least one polymer is selected for this purpose from among the group comprising polyalkylene oxides, preferably polymethylene oxides, polyethylene oxides, polypropylene oxides, polyolefins, preferably polyethylenes, polypropylenes, polyvinyl chlorides, polycarbonates, polystyrenes, polymethacrylates, the copolymers thereof, and mixtures of at least two of the stated polymer classes or polymers. Particularly preferably, a water-soluble or water-swellaible polymer is used. The polymers are distinguished by a molecular weight of at least 0.5 million, preferably of at least 1 million to 15 million, determined by rheological measurement. Particularly preferably suitable are thermoplastic polyalkylene oxides, such as polyethylene oxides, with a molecular weight of at least 0.5 million, preferably of at least 1 million to 15 million, determined by rheological measurement. The polyethylene oxides have a viscosity at 25° C. of 4500 to 17600 cP, measured on a 5 wt. % aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2/rotational speed 2 rpm), of 400 to 4000 cP, measured on a 2 wt. % aqueous solution using the stated viscosimeter (but with spindle no. 1 or 3/rotational speed 10 rpm) or of 1650 to 10000 cP, measured on a 1 wt. % aqueous solution using the stated viscosimeter (but with spindle no. 2/rotational speed 2 rpm).

[0022] The polymers are preferably used as powder to produce the dosage form according to the invention.

[0023] Moreover, in addition to the above-stated polymers, at least one natural, semi-synthetic or synthetic wax (D) with a breaking strength, measured using the method disclosed in the present application, of at least 500 N, preferably of 1000 N, may additionally be used to achieve the necessary breaking strength of the dosage form according to the invention. Waxes with a softening point of at least 60° C. are preferred. Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred. Carnauba wax is a natural wax which is obtained from the leaves of the carnauba palm and has a softening point of at most 90° C. When additionally using the wax component, the latter is used together with at least one polymer (C), preferably a polyethylene oxide, in such quantities that the dosage form exhibits a breaking strength of at least 500 N, preferably of 1000 N, measured using the method stated in the present application.

[0024] The dosage forms according to the invention are distinguished in that, they cannot be pulverised using conventional comminution tools, such as grinders, due to their hardness. Oral, parenteral, in particular intravenous, or nasal abuse is complicated a very great deal thereby, if not ruled out altogether. However, in order to prevent any possible abuse of the dosage forms according to the invention, in a preferred embodiment, the dosage forms according to the invention may contain further abuse-complicating or -preventing agents as auxiliary substances (B).

[0025] Thus, the abuse-proofed dosage form according to the invention may comprise, in addition to at least one opioid, at least one polymer (C) and optionally at least one wax (D), at least one of the following components (a)-(f) as auxiliary substances (B):

[0026] (a) at least one substance which irritates the nasal passages and/or pharynx,

[0027] (b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, preferably as an aqueous extract obtained from the dosage form, forms a gel which preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

[0028] (c) at least one antagonist for the present opioids with potential for abuse,

[0029] (d) at least one emetic,

[0030] (e) at least one dye as an aversive agent,

[0031] (f) at least one bitter substance.

[0032] The components (a) to (f) are each suitable on their own as additional protection of the dosage form according to the invention against abuse. Accordingly, component (a) is preferably suitable for proofing the dosage form against nasal, oral and/or parenteral, preferably intravenous, abuse, component (b) is preferably suitable for proofing against parenteral, particularly preferably intravenous and/or nasal abuse, component (c) is preferably suitable for proofing against nasal and/or parenteral, particularly preferably intravenous, abuse, component (d) is preferably suitable for proofing against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (e) is suitable as a visual deterrent against oral or parenteral abuse and component (f) is suitable for proofing against oral or nasal abuse. Through the co-use of at least one of the above-stated components, it is possible to complicate abuse even more effectively for the dosage forms according to the invention.

[0033] In one embodiment, the dosage form according to the invention may also comprise two or more of components (a)-(f) in a combination, preferably in the combinations (a), (b) and optionally (c) and/or (f) and/or (e) or (a), (b) and optionally (d) and/or (f) and/or (e).

[0034] In another embodiment, the dosage form according to the invention may comprise all of components (a)-(f).

[0035] If the dosage form according to the invention comprises component (a) as additional protection against abuse, substances which irritate the nasal passages and/or pharynx which may be considered according to the invention are any substances which, when administered via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the abuser that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteracts taking of the corresponding opioid(s) and/or opiate(s), for example due to increased nasal secretion or sneezing. These substances which conventionally irritate the nasal passages and/or pharynx may also bring about a very unpleasant sensation or even unbearable pain when administered parenterally, in particular intravenously, such that the abuser does not wish to or cannot continue taking the substance.

[0036] Particularly suitable substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli.

Appropriate substances and the quantities thereof which are conventionally to be used are known per se to the person skilled in the art or may be identified by simple preliminary testing.

[0037] The substance which irritates the nasal passages and/or pharynx of component (a) is preferably based on one or more constituents or one or more plant parts of at least one hot substance drug.

[0038] Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie—Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pages 82 et seq.. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

[0039] One or more constituents of at least one hot substance drug selected from the group consisting of *Allii sativi bulbus* (garlic), *Asari rhizoma cum herba* (Asarum root and leaves), *Calami rhizoma* (calamus root), *Capsici fructus* (capsicum), *Capsici fructus acer* (cayenne pepper), *Curcumae longae rhizoma* (turmeric root), *Curcumae xanthorrhizae rhizoma* (Javanese turmeric root), *Galangae rhizoma* (galangal root), *Myristicae semen* (nutmeg), *Piperis nigri fructus* (pepper), *Sinapis albae semen* (white mustard seed), *Sinapis nigri semen* (black mustard seed), *Zedoariae rhizoma* (zedoary root) and *Zingiberis rhizoma* (ginger root), particularly preferably from the group consisting of *Capsici fructus* (capsicum), *Capsici fructus acer* (cayenne pepper) and *Piperis nigri fructus* (pepper) may preferably be added as component (a) to the dosage form according to the invention.

[0040] The constituents of the hot substance drugs preferably comprise o-methoxy(methyl)phenol compounds, acid amide compounds, mustard oils or sulfide compounds or compounds derived therefrom.

[0041] Particularly preferably, at least one constituent of the hot substance drugs is selected from the group consisting of myristicin, elemicin, isoeugenol, a-sasarone, safrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, capsaicin derivatives, such as N-vanillyl-9E-octadecanamide, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, norcapsaicin and homonorcapsaicin, piperine, preferably trans-piperine, glucosinolates, preferably based on non-volatile mustard oils, particularly preferably based on p-hydroxybenzyl mustard oil, methylmercapto mustard oil or methylsulfonyl mustard oil, and compounds derived from these constituents.

[0042] The dosage form according to the invention may preferably contain the plant parts of the corresponding hot substance drugs in a quantity of 0.01 to 50 wt. %, particularly preferably of 0.1 to 0.5 wt. %, in each case relative to the total weight of the dosage unit. If one or more constituents of corresponding hot substance drugs are used, the quantity thereof in a dosage unit according to the invention preferably amounts to 0.001 to 0.005 wt. %, relative to the total weight of the dosage unit. A dosage unit is taken to mean a separate or separable administration unit, such as for example a tablet or a capsule.

[0043] Another option for preventing abuse of the dosage form according to the invention consists in adding at least

one viscosity-increasing agent as a further abuse-preventing component (b) to the dosage form, which, with the assistance of a necessary minimum quantity of an aqueous liquid, preferably an aqueous extract obtained from the dosage form, forms a gel which is virtually impossible to administer safely and preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid.

[0044] For the purposes of the present application, visually distinguishable means that the opioid- or opiate-containing gel formed with the assistance of a necessary minimum quantity of aqueous liquid, when introduced, preferably with the assistance of a hypodermic needle, into a further quantity of aqueous liquid at 37° C., remains substantially insoluble and cohesive and cannot straightforwardly be dispersed in such a manner that it can safely be administered parenterally, in particular intravenously. The material preferably remains visually distinguishable for at least one minute, preferably for at least 10 minutes.

[0045] Increasing the viscosity to a gel makes it more difficult or even impossible for it to be passed through a needle or injected. If the gel remains visually distinguishable, this means that the gel obtained on introduction into a further quantity of aqueous liquid, for example by injection into blood, initially remains in the form of a largely cohesive thread, which, while it may indeed be broken up mechanically into smaller fragments, cannot be dispersed or even dissolved in such a manner that it can safely be administered parenterally, in particular intravenously. In combination with at least one further present component (a), (d) to (f), this additionally leads to unpleasant burning, vomiting, bad flavour and/or visual deterrence.

[0046] Intravenous administration of such a gel would most probably result in obstruction of blood vessels, associated with serious damage to the health of the abuser.

[0047] In order to verify whether a viscosity-increasing agent is suitable as component (b) for use in the dosage form according to the invention, the opioid(s) and/or opiate(s) is(are) mixed with the viscosity-increasing agent and suspended in 10 ml of water at a temperature of 25° C. If this results in the formation of a gel which fulfils the above-stated conditions, the corresponding viscosity-increasing agent is suitable for additionally preventing or averting abuse of the dosage forms according to the invention.

[0048] If component (b) is added to the dosage form obtained by the process according to the invention, preferably one or more viscosity-increasing agents are used, which are selected from the group comprising microcrystalline cellulose with 11 wt. % carboxymethylcellulose sodium (Avicel® P.C. 591), carboxymethylcellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), locust bean flour (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), pectins, preferably from citrus fruit or apples (Cespectin® HM Medium Rapid Set), waxy maize starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E401)®), guar flour (Frimulsion BM®, Polygum 26/1-75®), iota-carrageenan (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150®), tara stone flour (Polygum 43/1®), propylene glycol alginate (Protanal-Ester 3D-LB®), sodium-hyaluronate, tragacanth, tara gum (Vidogum 3P 200®), fermented polysaccharide welan gum

(K1A96), xanthans such as xanthan gum (Xantural 130®). Xanthans are particularly preferred. The names stated in brackets are the trade names by which the materials are known commercially. In general, a quantity of 0.1 to 5 wt. %, relative to the total quantity of the dosage form, of the stated viscosity-increasing agent(s) is sufficient to fulfil the above-stated conditions.

[0049] The component (b) viscosity-increasing agents, where provided, are preferably present in the dosage form according to the invention in quantities of ≈ 5 mg per dosage unit, i.e. per administration unit.

[0050] In a particularly preferred embodiment of the present invention, the viscosity-increasing agents used as component (b) are those which, preferably by extraction from the dosage form with the necessary minimum quantity of aqueous liquid, form a gel which encloses air bubbles. The resultant gels are distinguished by a turbid appearance, which provides the potential abuser with an additional optical warning and discourages him/her from administering the gel parenterally.

[0051] The component (C) may also optionally serve as an additional viscosity-increasing agent, which forms a gel with the assistance of a necessary minimum quantity of aqueous liquid.

[0052] It is also possible, to arrange the viscosity-increasing component and the other constituents of the dosage form according to the invention spatially separately from one another.

[0053] Moreover, in order to discourage and prevent abuse, the dosage form according to the invention may furthermore comprise component (c), namely one or more antagonists for the opioid(s) and/or opiate(s) with potential for abuse, wherein the antagonist is preferably spatially separated from the remaining constituents of the dosage form according to the invention and, when correctly used, do not exert any effect.

[0054] Suitable antagonists for preventing the abuse of opioids are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

[0055] The antagonist used is preferably selected from the group comprising naloxone, naltrexone, nalmefene, nalide and nalmexone, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate. The corresponding antagonists, where component (c) is provided, are preferably used in a quantity of ≈ 1 mg, particularly preferably in a quantity of 2 to 100 mg, very particularly preferably in a quantity of 5 to 50 mg per dosage form, i.e. per administration unit.

[0056] The dosage form according to the invention preferably comprises the antagonist component in a conventional therapeutic dose known to the person skilled in the art, particularly preferably in a quantity of twice to three times this dose per administration unit.

[0057] If the combination for additional discouragement and prevention of abuse of the dosage form according to the

invention comprises component (d), it may comprise at least one emetic, which is preferably present in a spatially separated arrangement from the other components of the dosage form according to the invention and, when correctly used, is intended not to exert its effect in the body.

[0058] Suitable emetics for additionally preventing abuse of an opioid are known per se to the person skilled in the art and may be present in the dosage form according to the invention as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof.

[0059] An emetic based on one or more constituents of ipecacuanha (ipecac) root, preferably based on the constituent emetine may preferably be considered for the dosage form according to the invention, as are, for example, described in "Pharmazeutische Biologie—Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebrandt Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, New York 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

[0060] The dosage form according to the invention may preferably comprise the emetic emetine as component (d), preferably in a quantity of ≈ 3 mg, particularly preferably of ≈ 10 mg and very particularly preferably in a quantity of ≈ 20 mg per dosage form, i.e. administration unit.

[0061] Apomorphine may likewise preferably be used as an emetic for additional abuse proofing, preferably in a quantity of preferably ≈ 3 mg, particularly preferably of ≈ 5 mg and very particularly preferably of ≈ 7 mg per administration unit.

[0062] If the dosage form according to the invention contains component (e) as a further abuse-preventing auxiliary substance, the use of such a dye brings about an intense coloration of a corresponding aqueous solution, in particular when the attempt is made to extract the opioid(s) for parenteral, preferably intravenous administration, which coloration may act as a deterrent to the potential abuser. Oral abuse, which conventionally begins by means of aqueous extraction of the opioid(s), may also be prevented by this coloration. Suitable dyes and the quantities required for the necessary deterrence may be found in WO 03/015531, wherein the corresponding disclosure should be deemed to be part of the present disclosure and is hereby introduced as a reference.

[0063] If the dosage form according to the invention contains component (f) as a further abuse-preventing auxiliary substance, this addition of at least one bitter substance and the consequent impairment of the flavour of the dosage form additionally prevents oral and/or nasal abuse.

[0064] Suitable bitter substances and the quantities effective for use may be found in U.S. 2003/0064099, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Suitable bitter substances are preferably aromatic oils, preferably peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, preferably aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate (Bitrex®). Denatonium benzoate is particularly preferably used.

[0065] To ensure once daily administration, the dosage form according to the invention comprises the opioid (s) and/or opiate(s) with potential for abuse at least in part in delayed-release form, wherein the delayed release of the active ingredient may be achieved with the assistance of conventional materials and processes known to the person skilled in the art, for example by embedding the opioid(s) in a delayed-release matrix or by applying one or more delayed-release coatings. Opioid release must, however, be controlled such that the above-stated conditions are fulfilled in each case, for example that, in the event of correct administration of the dosage form, the opioid(s) are virtually completely released before the optionally present component (c) and/or (d) can exert an impairing effect. In particular, release of the opioid must ensure analgesic action for at least 24 hours.

[0066] If release of the opioid(s) from the dosage form according to the invention is controlled with the assistance of at least one delayed-release coating, the delayed-release coating may consist of conventional materials known to the person skilled in the art.

[0067] In a preferred embodiment of the dosage form according to the invention, the delayed-release coating is preferably based on a water-insoluble, optionally modified natural and/or synthetic polymer or on a natural, semi-synthetic or synthetic wax or on a fat or a fatty alcohol or on a mixture of at least two of the above-stated components.

[0068] To produce a delayed-release coating, the water-insoluble polymers preferably comprise poly(meth)acrylates, particularly preferably poly(C₁₋₄)-alkyl(meth)acrylates, poly(C₁₋₄)-dialkylamino-(C₁₋₄)-alkyl(meth)acrylates and/or the copolymers thereof, very particularly preferably copolymers of ethyl acrylate and methyl methacrylate with a molar ratio of monomers of 2:1 (Eudragit NE30D®), copolymers of ethyl acrylate, methyl methacrylate and trimethylammonium methyl methacrylate chloride with a molar ratio of monomers of 1:2:0.1 (Eudragit P3®), copolymers of ethyl acrylate, methyl methacrylate and trimethylammonium methyl methacrylate chloride with a molar ratio of monomers of 1:2:0.2 (Eudragit RL®) or a mixture of at least two of these above-stated copolymers. These coating materials are commercially obtainable as 30 wt. % aqueous latex dispersions, i.e. as Eudragit NS30D®, Eudragit NE30D® or Eudragit RL30D® and are preferably also used as such as coating material.

[0069] Polyvinyl acetates optionally in combination with further auxiliary substances may likewise preferably be used as water-insoluble polymers for the production of a delayed-release coating for the dosage forms according to the invention. These are commercially obtainable as aqueous dispersions containing 27 wt. % of polyvinyl acetate, 2.5 wt. % of povidone and 0.3 wt. % of sodium lauryl sulfate (Kollicoat SR 30 D®).

[0070] In a further preferred embodiment, the delayed-release coatings for the dosage form according to the invention are based on water-insoluble cellulose derivatives, preferably alkylcelluloses such as for example ethylcellulose, or cellulose esters, such as for example cellulose acetate. The coatings of ethylcellulose or cellulose acetate are preferably applied from an aqueous pseudolatex dispersion. Aqueous ethylcellulose pseudolatex dispersions are commercially obtainable as 30 wt. % dispersions (Aqua-coat®) or as 25 wt. % dispersions (Surelease®).

[0071] If the delayed-release coating is based a water-insoluble, optionally modified natural and/or synthetic polymer, the coating dispersion or solution may comprise, in addition to the corresponding polymer, a conventional physiologically acceptable plasticizer known to the person skilled in the art, in order to reduce the necessary minimum film temperature.

[0072] Suitable plasticisers are for example lipophilic diesters from an aliphatic or aromatic dicarboxylic acid with C₆-C₄₀ and an aliphatic alcohol with C₁-C₈, such as for example dibutyl phthalate, diethyl phthalate, dibutyl sebacate or diethyl sebacate, hydrophilic or lipophilic esters of citric acid, such as triethyl citrate, tributyl citrate, acetyl tributyl citrate or acetyl triethyl citrate, polyethylene glycols, propylene glycol, esters of glycerol, such as for example triacetin, Myvacet® (acetylated mono- and diglycerides, C₂₃H₄₄O₅ to C₂₅H₄₇O₇), medium-chain triglycerides (Miglyol®), oleic acid or mixtures of at least two of the stated plasticisers. Aqueous dispersions of Eudragit FS® and optionally Eudragit RL® preferably contain triethyl citrate.

[0073] Preferably, a delayed-release coating for the dosage form according to the invention contains plasticisers in quantities of 5 to 50 wt. %, particularly preferably of 10 to 40 wt. % and very particularly preferably of 10 to 30 wt. %, relative to the quantity of polymer used. In individual cases, for example for cellulose acetate, it is also possible to use larger quantities of plasticisers.

[0074] Moreover, a delayed-release coating may comprise further conventional auxiliary substances known to the person skilled in the art, such as for example slip agents, preferably talcum or glycerol monostearate, colouring pigments, preferably iron oxides or titanium dioxide, or surfactants, such as for example Tween 80®.

[0075] The release profile obtained for the opioid(s) may furthermore be adjusted by conventional options known to the person skilled in the art, such as for example the thickness of the coating or by the use of further auxiliary substances as constituents of the coating. Suitable auxiliary substances are for example hydrophilic or pH-dependent pore formers, such as for example sodium carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate, lactose, polyethylene glycol or mannitol or water-soluble polymers, such as for example polyvinylpyrrolidone or water-soluble celluloses, preferably hydroxypropylmethylcellulose or hydroxypropylcellulose.

[0076] The dosage forms according to the invention for release of the opioid(s) may additionally also comprise a coating which is resistant to gastric juices, which dissolves in pH-dependent manner. This coating makes it possible to ensure that the dosage forms according to the invention pass through the stomach undissolved and the opioid(s) is(are) not released until it(they) reach(es) the intestine.

[0077] The coating resistant to gastric juices is preferably based on methacrylic acid/alkyl methacrylate copolymers, preferably methyl methacrylate, such as methacrylic acid or ethylene methacrylate copolymers with a molar ratio of the particular monomers of 1:1 to 1:2, such as Eudragit L®, Eudragit S®, Eudragit L30D-55®, Eudragit FS®.

[0078] A delayed-release coating may be applied by conventional methods known to the person skilled in the art, such as for example by spraying of solutions, dispersions or

suspensions, by melt methods or by powder application methods. The solutions, dispersions or suspensions may be used in the form of aqueous or organic solutions or dispersions. Aqueous dispersions are preferably used in this connection. Organic solvents which may be used are alcohols, for example ethanol or isopropanol, ketones, such as for example acetone, esters, for example ethyl acetate, wherein alcohols and ketones are preferably used. The coating methods are known from the prior art, for example H. Suchter, Georg Thieme Verlag, 1991, pages 347 et seq.. They are hereby introduced as a reference and are accordingly deemed to be part of the disclosure.

[0079] If the dosage form according to the invention is in multiparticulate form, the delayed-release coating is preferably applied in such a manner that the multiparticulate forms containing the opioid(s) are coated, after the production thereof, with the particular polymers and optionally further auxiliary substances from aqueous and/or organic media, preferably from aqueous media, with the assistance of the fluidised bed method and the coating is preferably simultaneously dried at conventional temperatures in the fluidised bed.

[0080] A poly(meth)acrylate-based coating is preferably dried at temperatures in the range from 30 to 50° C., particularly preferably from 35 to 45° C. For cellulose-based coatings, such as for example ethylcellulose, drying preferably proceeds at a temperature in the range from 50 to 80° C., particularly preferably in the range from 55 to 65° C. If necessary, drying may additionally be followed by a temperature-controlled treatment in order to obtain a stable release profile. Delayed release of the active ingredient from the dosage form according to the invention may also be achieved by embedding the opioid(s) in a delayed-release matrix.

[0081] Materials which may be used for a delayed-release matrix are preferably physiologically acceptable, hydrophilic polymers, preferably cellulose ethers, cellulose esters and/or acrylic resins. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof, are particularly preferably used.

[0082] Where hydrophobic compounds are used as the delayed-release matrix, fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof may be used. Mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic compounds.

[0083] It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic matrix materials.

[0084] Component (b) as a viscosity-increasing agent may preferably also serve as a material for a delayed-release matrix, if this is permitted by the structure of the dosage form according to the invention.

[0085] Component (C) and the optionally present component (D), which serve to obtain the breaking strength of at least 500 N, preferably of 1000 N, which is necessary according to the invention, may optionally also serve as additional delayed-release matrix materials.

[0086] Corresponding delayed-release compounds and methods for the delayed release of the dosage forms accord-

ing to the invention and for the application of coatings which are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical Dosage Forms—Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Ostertwald, Rothergang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

[0087] The dosage form according to the invention may assume multiparticulate form, preferably the form of microtablets, micropellets, granules, spheroids, beads or pellets, optionally packaged in capsules or press-moulded into tablets. The multiparticulate forms preferably have a size or size distribution in the range from 0.1 to 3 mm, particularly preferably in the range from 0.5 to 2 mm. Depending on the desired dosage form, conventional auxiliary substances (E) are optionally also used for the formulation of the dosage form.

[0088] In a particularly preferred embodiment, the dosage form according to the invention assumes the form of a tablet, a capsule or is in the form of an oral osmotic therapeutic system (OROS), preferably if at least one further abuse-preventing component (a)-(f) is also present.

[0089] The abuse-proofed, solid dosage form according to the invention is preferably produced by mixing components (A), (C) and optionally (D), optionally at least one of the additional abuse-preventing components (a)-(f) and optionally further auxiliary substances (E), in particular the delayed-release matrix compounds, and, with preceding or simultaneous exposure to heat, forming the resultant mixture, optionally after pelletisation, into the dosage form by application of force.

[0090] Pelletisation may be performed by a melt method or by wet pelletisation.

[0091] Mixing of components (A), (C) and optionally (D) and of the optionally present further components (a)-(f) and optionally the further auxiliary substances (E), in particular the delayed-release matrix compounds, may proceed in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

[0092] The resultant mixture is preferably directly formed into the dosage form according to the invention by application of force with preceding or simultaneous exposure to heat. The mixture may, for example, be formed into tablets by direct tableting. In direct tableting with preceding exposure to heat, the material to be press-moulded is heated immediately prior to tableting at least to the softening temperature of component (C) and then pressed.

[0093] The resultant mixture of components (A), (C), optionally (D), the optionally present components (a) to (f) and optionally further auxiliary substances (E), in particular the delayed-release matrix compounds, may also first be pelletised and then formed into the dosage form according to the invention by application of force with preceding or simultaneous exposure to heat.

[0094] It is also possible to form the resultant mixture containing one or more opioid(s) with potential for abuse

(A) and optionally physiologically acceptable auxiliary substances (B), such as components (a) to (f) and optionally the delayed-release matrix compounds and at least one synthetic or natural polymer (C) and optionally a wax (D), into the dosage form by application of force, optionally to singulate the formed articles and optionally in each case to grade them by size and, after or during heating to at least the softening point of component (C), to expose them to force until the formed articles exhibit a breaking hardness of at least 500 N, preferably of 1000 N, optionally to provide them with a cover, which optionally has delayed-release properties, and optionally to mix all the formed articles together again.

[0095] If components (c) and/or (d) and/or (f) are present in the dosage form according to the invention, care must be taken to ensure that they are formulated in such a manner or are present in such a low dose that, when correctly administered, the dosage form is able to bring about virtually no effect which impairs the patient or the efficacy of the opioid(s).

[0096] If the dosage form according to the invention contains component (d) and/or (f), the dosage must be selected such that, when correctly orally administered, no negative effect is caused. If, however, the intended dosage of the dosage form is exceeded inadvertently, in particular by children, or in the event of abuse, nausea or an inclination to vomit or a bad flavour are produced. The particular quantity of component (d) and/or (f) which can still be tolerated by the patient in the event of correct oral administration may be determined by the person skilled in the art by simple preliminary testing.

[0097] If, however, irrespective of the fact that the dosage form according to the invention is virtually impossible to pulverise, the dosage form containing the components (c) and/or (d) and/or (f) is provided with protection, these components should preferably be used at a dosage which is sufficiently high that, when abusively administered, they bring about an intense negative effect on the abuser. This is preferably achieved by spatial separation of at least the opioid(s) from components (c) and/or (d) and/or (f), wherein the opioid(s) is/are present in at least one subunit (X) and components (c) and/or (d) and/or (f) is/are present in at least one subunit (Y), and wherein, when the dosage form is correctly administered, components (c), (d) and (f) do not exert their effect on taking and/or in the body and the remaining components of the formulation, in particular component (C), are identical.

[0098] If the dosage form according to the invention comprises at least 2 of components (c) and (d) or (f), these may each be present in the same or different subunits (Y). Preferably, when present, all the components (c) and (d) and (f) are present in one and the same subunit (Y).

[0099] In the case of spatial separation into subunit(s) (X) and subunit(s) (Y) and irrespective of the arrangement of these subunits in the dosage form, a subunit (X) contains the active ingredient in delayed-release form, such that said active ingredient ensures controlled release with once daily administration.

[0100] For the purposes of the present invention, subunits are solid formulations, which in each case, apart from conventional auxiliary substances known to the person skilled in the art, contain the opioid(s), at least one polymer

(C) and optionally at least one of the optionally present components (a) and/or (b) and/or (e) or in each case at least one polymer (C) and the antagonist(s) and/or emetic(s) and/or component (e) and/or component (f) and optionally at least one of the optionally present components (a) and/or (b) and optionally the delayed-release matrix compounds. Care must here be taken to ensure that each of the subunits is formulated in accordance with the above-stated process.

[0101] One substantial advantage of the separated formulation of the opioid(s) from components (c) or (d) or (f) in subunits (X) and (Y) of the dosage form according to the invention is that, when correctly administered, components (c) and/or (d) and/or (f) are hardly released on taking and/or in the body or are released in such small quantities that they exert no effect which impairs the patient or therapeutic success or, on passing through the patient's body, they are only liberated in locations where they cannot be sufficiently absorbed to be effective. When the dosage form is correctly administered, preferably hardly any of components (c) and/or (d) and/or (f) is released into the patient's body or they go unnoticed by the patient.

[0102] The person skilled in the art will understand that the above-stated conditions may vary as a function of the particular components (c), (d) and/or (f) used and of the formulation of the subunits or the dosage form. The optimum formulation for the particular dosage form may be determined by simple preliminary testing. What is vital is that each subunit contains the polymer (C) and has been formulated in the stated manner.

[0103] Should, contrary to expectations, the abuser succeed in comminuting such a dosage form according to the invention, which comprises components (c) and/or (e) and/or (d) and/or (f) in subunits (Y), for the purpose of abusing the opioid(s) and obtain a powder which is to be extracted with a suitable extracting agent, not only the opioid(s) but also the particular component (c) and/or (e) and/or (f) and/or (d) will be obtained in a form in which it cannot readily be separated from the opioid(s), such that when the dosage form which has been tampered with is administered, in particular by oral and/or parenteral administration, it will exert its effect immediately on taking and/or in the body combined with an additional negative effect on the abuser corresponding to component (c) and/or (d) and/or (f) or, when the attempt is made to extract the active ingredient, the coloration will act as a deterrent and so prevent abuse of the dosage form.

[0104] A dosage form according to the invention, in which the opioid(s) is/are spatially separated from components (c), (d) and/or (e), preferably by formulation in different subunits, may be formulated in many different ways, wherein the corresponding subunits may each be present in the dosage form according to the invention in any desired spatial arrangement relative to one another, provided that the above-stated conditions for the release of components (c) and/or (d), on the one hand, and for release of the opioid, namely controlled release for once daily administration, on the other, are fulfilled.

[0105] The person skilled in the art will understand that component(s) (a) and/or (b) which are optionally also present may preferably be formulated in the dosage form according to the invention both in the particular subunits (X) and (Y) and in the form of independent subunits (Y')

corresponding to subunits (X) and (Y), provided that neither the abuse-proofing nor the opioid release over 24 hours in the event of correct administration is impaired by the nature of the formulation and the polymer (C) is included in the formulation and formulation is carried out in accordance with the above-stated processes.

[0106] In a preferred embodiment of the dosage form according to the invention, subunits (X) and (Y) are present in multiparticulate form, wherein microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets are preferred and the same form, i.e. shape, is selected for both subunit (X) and subunit (Y), such that it is not possible to separate subunits (X) from (Y) by mechanical selection. The multiparticulate forms are preferably of a size in the range from 0.1 to 3 mm, preferably of 0.5 to 2 mm.

[0107] The subunits (X) and (Y) in multiparticulate form may also preferably be packaged in a capsule or be press-moulded into a tablet, wherein the final formulation in each case proceeds in such a manner that the subunits (X) and (Y) are also retained in the resultant dosage form.

[0108] The multiparticulate subunits (X) and (Y) of identical shape should also not be visually distinguishable from one another so that the abuser cannot separate them from one another by simple sorting. This may, for example, be achieved by the application of identical coatings which, apart from this disguising function, may also incorporate further functions, such as, for example, controlled release of one or more opioid(s) or provision of a finish resistant to gastric juices on the particular subunits.

[0109] In a further preferred embodiment of the present invention, subunits (X) and (Y) are in each case arranged in layers relative to one another.

[0110] The layered subunits (X) and (Y) are preferably arranged for this purpose vertically or horizontally relative to one another in the dosage form according to the invention, wherein in each case one or more layered subunits (X) and one or more layered subunits (Y) may be present in the dosage form, such that, apart from the preferred layer sequences (X)-(Y) or (Y)-(X), any desired other layer sequences may be considered, optionally in combination with layers containing components (a) and/or (b).

[0111] Another preferred dosage form according to the invention is one in which subunit (Y) forms a core which is completely enclosed by the delayed-release subunit (X), wherein a separation layer (Z) may be present between said layers. Such a structure is preferably also suitable for the above-stated multiparticulate forms, wherein both subunits (X) and (Y) and an optionally present separation layer (Z), which must satisfy the hardness requirement according to the invention, are formulated in one and the same multiparticulate form.

[0112] In a further preferred embodiment of the dosage form according to the invention, the subunit (X) forms a core, which is enclosed by subunit (Y), wherein the latter comprises at least one channel which leads from the core to the surface of the dosage form.

[0113] The dosage form according to the invention may comprise, between one layer of the subunit (X) and one layer of the subunit (Y), in each case one or more, preferably one,

optionally swellable separation layer (Z) which serves to separate subunit (X) spatially from (Y).

[0114] If the dosage form according to the invention comprises the layered subunits (X) and (Y) and an optionally present separation layer (Z) in an at least partially vertical or horizontal arrangement, the dosage form preferably takes the form of a tablet, a coextrudate or a laminate.

[0115] In one particularly preferred embodiment, the entirety of the free surface of subunit (Y) and optionally at least part of the free surface of subunit(s) (X) and optionally at least part of the free surface of the optionally present separation layer(s) (Z) may be coated with at least one barrier layer (Z') which prevents release of component (c) and/or (e) and/or (d) and/or (f). The barrier layer (Z') must also fulfil the hardness conditions according to the invention.

[0116] Another particularly preferred embodiment of the dosage form according to the invention comprises a vertical or horizontal arrangement of the layers of subunits (X) and (Y) and at least one push layer (p) arranged therebetween, and optionally a separation layer (Z), in which dosage form the entirety of the free surface of the layer structure consisting of subunits (X) and (Y), the push layer and the optionally present separation layer (Z) is provided with a semipermeable coating (E), which is permeable to a release medium, i.e. conventionally a physiological liquid, but substantially impermeable to the opioid(s) and to component (c) and/or (d) and/or (f), and wherein this coating (E) comprises at least one opening for release of the opioid(s) in the area of subunit (X).

[0117] A corresponding dosage form is known to the person skilled in the art, for example under the name oral osmotic therapeutic system (OROS), as are suitable materials and methods for the production thereof, inter alia from U.S. Pat. No. 4,612,002, U.S. Pat. No. 4,765,939 and U.S. Pat. No. 4,783,337. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

[0118] An osmotic dosage form containing an analgesic opioid and a dye as an aversive agent is likewise known to the person skilled in the art from the prior art (WO 03/015531). The tablet core preferably consists of two layers, an opioid-containing layer and a push layer, wherein the push layer contains the dye as the aversive agent. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

[0119] In a further preferred embodiment of the claimed invention, the subunit (X) of the dosage form according to the invention is in the form of a tablet, the edge face and optionally one of the two main faces of which is covered with a barrier layer (Z') containing component (c) and/or (d) and/or (f).

[0120] The person skilled in the art will understand that the auxiliary substances of the subunit(s) (X) or (Y) and of the optionally present separation layer(s) (Z) and/or of the barrier layer(s) (Z') used in formulating the dosage form according to the invention will vary as a function of the arrangement thereof in the dosage form according to the invention, the mode of administration and as a function of the particular opioid, of the optionally present components (a) and/or (b) and/or (e) and of component (c) and/or (d)

and/or (f), while maintaining release of the active ingredient over 24 hours. The materials which have the requisite properties are in each case known per se to the person skilled in the art.

[0121] If release of component (c) and/or (d) and/or (f) from subunit (Y) of the dosage form according to the invention is prevented with the assistance of a cover, preferably a barrier layer, the subunit may consist of conventional materials known to the person skilled in the art, providing that it contains at least one polymer (C) to fulfil the hardness condition of the dosage form according to the invention.

[0122] If a corresponding barrier layer (Z') is not provided to prevent release of component (c) and/or (d) and/or (f), the materials of the subunits should be selected such that release of the particular component (c) and/or (d) from subunit (Y) is virtually ruled out.

[0123] The materials which are stated below to be suitable for production of the barrier layer may preferably be used for this purpose. Preferred materials are those which are selected from the group comprising alkylcelluloses, hydroxyalkylcelluloses, glucans, scleroglucans, mannans, xanthans, copolymers of poly[bis(p-carboxyphenoxy)propane: sebacic acid], preferably in a molar ratio of 20:80 (marketed under the name Polifeprosan 20®), carboxymethylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers based on (meth)acrylic acid and the esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, halogenated polyvinyls, polyglycolides, polysiloxanes and polyurethanes and the copolymers thereof.

[0124] Particularly suitable materials may be selected from the group comprising methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose acetate, cellulose propionate (of low, medium or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethylcellulose, cellulose triacetate, sodium cellulose sulfate, polymethyl methacrylate, polyethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyisodecyl methacrylate, polylauryl methacrylate, polyphenyl methacrylate, polymethyl acrylate, polyisopropyl acrylate, polyisobutyl acrylate, polyoctadecyl acrylate, polyethylene, low density polyethylene, high density polyethylene, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl alcohol, polyvinyl isobutyl ether, polyvinyl acetate and polyvinyl chloride.

[0125] Particularly suitable copolymers may be selected from the group comprising copolymers of butyl methacrylate and isobutyl methacrylate, copolymers of methyl vinyl ether and maleic acid of high molecular weight, copolymers of methyl vinyl ether and maleic acid monoethyl ester, copolymers of methyl vinyl ether and maleic anhydride and copolymers of vinyl alcohol and vinyl acetate.

[0126] Further materials which are suitable for formulating the barrier layer are starch-filled polycaprolactone (WO98/20072), aliphatic polyesteramides (DE 19 753 534 A1, DE 19 300 693 A1, EP 0 320 693 A1), aliphatic and aromatic polyester urethanes (DE 19822979), polyhydroxy-

alkanoates, in particular polyhydroxybutyrate, polyhydroxyvalerate, casein (DE 4 309 520), polylactides and copolylactides (EP 0 930 294 A1). The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

[0127] The above-stated materials may optionally be blended with further conventional auxiliary substances known to the person skilled in the art, preferably selected from the group consisting of glyceryl monostearate, semi-synthetic triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinylpyrrolidone, gelatine, magnesium stearate, stearic acid, sodium stearate, talcum, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols and the derivatives thereof.

[0128] If the dosage form according to the invention comprises a separation layer (Z'), said layer, like the uncovered subunit (Y), may preferably consist of the above-stated materials described for the barrier layer. The person skilled in the art will understand that release of the opioid(s) and/or opiate(s) or of component (c) and/or (d) from the particular subunit may be controlled by the thickness of the separation layer.

Method for Determining Breaking Strength

[0129] In order to verify whether a polymer or a wax may be used as component (C) or (D) respectively, the polymer or wax is press-moulded to form a tablet with a diameter of 10 mm and a height of 5 mm using a force of 150 N at a temperature which at least corresponds to the softening point of the polymer or wax and is determined with the assistance of a DSC diagram of the polymer or wax. Using tablets produced in this manner, breaking strength is determined with the apparatus described below in accordance with the method for determining the breaking strength of tablets published in the European Pharmacopoeia 1997, page 143, 144, method no. 2.9.3. The apparatus used for the measurement is a "Zwick Z 2.5" materials tester, Fmax=2.5 kN, draw max. 1150 mm with the setup comprising a column and a spindle, clearance behind of 100 mm, a test speed of 0.1300 mm/min and testControl software. Measurement was performed using a pressure piston with screw-in inserts and a cylinder (diam. 10 mm), a force transducer, (Fmax: 1 kN, diameter=3 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M to DIN 55350-13, Zwick gross force Fmax=1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany).

[0130] The tablets deemed to be resistant to breaking under a specific load include not only those which have not broken but also those which may have suffered plastic deformation under the action of the force.

[0131] The breaking strength of the dosage forms according to the invention is determined using the same measurement method.

[0132] The invention is explained below with reference to Examples. These explanations are given merely by way of example and do not restrict the general concept of the invention.

EXAMPLE 1

a) Production of an Abuse-proofed Tablet Containing Oxycodone

[0133] The quantities of oxycodone hydrochloride, polyethylene oxide powder and hydroxypropylmethylcellulose (Methocel 90 SH 100 000) as the delayed-release matrix material listed in Table 1 were mixed in a free-fall mixer. The tableting tool, which consists of die, top punch and bottom punch with a diameter of 10 mm, was heated to 90° C. in a heating cabinet. 600 mg portions of the powder mixture were press-moulded by means of the heated tool, the pressure being maintained for at least 15 seconds.

TABLE 1

Components	Per tablet	Complete batch
Oxycodone HCl	80.0 mg	40.0 g
Polyethylene oxide, NE, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	470.0 mg	235.0 g
Hydroxypropylmethylcellulose 100 000	50.0 mg	25.0 g
mPas (Methocel 90 SH 100 000)		
Total weight	600.0 mg	300.0 g

[0134] The breaking strength of the tablets is determined using the above-described method. No breakage occurred when a force of 500 N was applied. The tablets could not be comminuted using a hammer, nor with the assistance of a pestle and mortar.

In Vitro Release From the Tablets Produced According to a)

[0135] In vitro release of oxycodone hydrochloride from the tablets produced according to a) was determined in a paddle stirrer apparatus with sinker according to the method described in the European Pharmacopoeia. The temperature of the release medium was 37° C. and the rotational speed of the stirrer 75 min⁻¹. The release medium used was intestinal juice, pH 6.8. The quantity of oxycodone hydrochloride released in each case into the dissolution medium at any one time was determined by spectrophotometry. The percentage released quantity, relative to the total quantity of oxycodone hydrochloride, at each point in time is shown in Table 2.

TABLE 2

Time, minutes	Released quantity, wt. %
30	11
240	40
480	61
720	76
1080	92
1440	97

1. An abuse-proofed oral dosage form with controlled opioid release for once daily administration, characterised in that it comprises at least one opioid with potential for abuse (A) and/or one of the physiologically acceptable compounds thereof, at least one synthetic or natural polymer (C), optionally delayed-release auxiliary substances, optionally physiologically acceptable auxiliary substances (E), optionally a wax (D) and optionally at least one delayed-release

coating, component (C) or (D) in each case exhibiting a breaking strength of at least 500 N, preferably of at least 1000 N.

2. A dosage form according to claim 1, characterised in that the opioid is at least one opioid selected from among the group comprising oxycodone, hydromorphone, morphine, tramadol, the stereoisomers thereof, the enantiomers thereof, the diastereomers thereof in any desired mixtures, the physiologically acceptable compounds thereof, preferably salts and solvates and the derivatives thereof, preferably esters or ethers.

3. A dosage form according to claim 1, characterised in that the opioid used was at least one opioid selected from among the group comprising (2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1R,3R,6R)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexan-1,3-diol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, the physiologically acceptable salts thereof, preferably hydrochlorides, physiologically acceptable enantiomers, stereoisomers, diastereoisomers and racemates and the physiologically acceptable derivatives thereof, preferably ethers, esters or amides.

4. A dosage form according to claim 1, characterised in that it is in the form of a tablet.

5. A dosage form according to claim 1, characterised in that it is in multiparticulate form, preferably in the form of microtablets, micropellets, granules, spheroids, beads or pellets, optionally press-moulded into tablets or packaged in capsules.

6. A dosage form according to claim 1, characterised in that the polymer (C) is at least one polymer selected from among the group comprising polyethylene oxides, polyethylenes, polypropylenes, polyvinyl chlorides, polycarbonates, polystyrenes, polyacrylates, and the copolymers thereof, preferably a polyethylene oxide.

7. A dosage form according to claim 6, characterised in that the polyethylene oxide is of high molecular weight.

8. A dosage form according to claim 6, characterised in that the polymer (C) is a water-soluble or water-swellaible polymer.

9. A dosage form according to claim 1, characterised in that the wax (D) is at least one natural, semi-synthetic or synthetic wax with a softening point of ≥60° C.

10. A dosage form according to claim 9, characterised in that the wax (D) is carnauba wax or beeswax.

11. A dosage form according to claim 1, characterised in that the component(s) (C) and optionally (D) are present in such quantities that the dosage form exhibits a breaking strength of at least 500 N, preferably of 1000 N.

12. A dosage form according to claim 1, characterised in that the active ingredient is present in a delayed-release matrix.

13. A dosage form according to claim 1, characterised in that component (C) and/or component (D) also serves as an additional delayed-release component.

14. A dosage form according to claim 1, characterised in that it comprises a delayed-release coating.

15. A dosage form according to claim 1, characterised in that it comprises at least one of the following components (a)-(f) as the auxiliary substance (B):

- (a) at least one substance which irritates the nasal passages and/or pharynx,

- (b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, preferably as an aqueous extract obtained from the dosage form, forms a gel which preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,
- (c) at least one antagonist for each of the opioids with potential for abuse,
- (d) at least one emetic,
- (e) at least one dye as an aversive agent,
- (f) at least one bitter substance.

16. A dosage form according to claim 1, characterised in that it comprises as the viscosity-increasing agent, at least one polymer selected from among the group comprising carboxymethylcellulose sodium, polyacrylic acid, locust bean flour, pectin, waxy maize starch, alginate, guar flour, iota-carrageenan, karaya gum, gellan gum, galactomannan, tara stone flour, propylene glycol alginate, hyaluronate, tragacanth, tara gum, fermented polysaccharide welan gum and xanthan.

17. A dosage form according to claim 1, characterised in that component (C) serves as an additional viscosity-increasing agent.

18. A process for the production of a dosage form according to claim 1, characterised in that

- (1) components (A), (C), optionally (B) and optionally (D) and optionally delayed-release matrix compounds are mixed and

- (2) the resultant mixture, optionally after pelletisation, is formed into the dosage form by application of force optionally with preceding or simultaneous exposure to heat and is optionally provided with a delayed-release coating.

19. A process according to claim 18, characterised in that pelletisation is performed by a melt method.

20. A process according to claim 18, characterised in that pelletisation is performed by wet method.

21. A process for the production of a dosage form according to claim 1, characterised in that

- (1) a mixture containing components (A), (C), optionally (B) and optionally (D) and optionally delayed-release matrix compounds is formed into formed articles by application of force,

- (2) the formed articles obtained are optionally singulated and optionally in each case graded by size and

- (3) after or during heating to at least the softening point of component (C), the formed articles are exposed to force until the formed articles exhibit breaking hardness of at least 500 N, preferably of 1000 N,

- (4) are optionally provided with an optionally delayed-release coating and the formed articles are optionally all mixed together again.

22. A dosage form obtainable by processes according to claim 18.

* * * * *

2020
Bogotá, D.C.,

Doctor:
Humberto Rubio Camacho
Apoderado

Oficio N°:

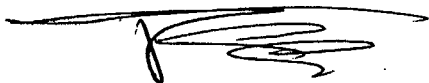
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ASUNTO:	Radicación PCT N°	10-90010
	Trámite	011
	Evento	379
	Actuación	440
	Folios	007

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Laboratorios Synthesis S.A.S., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

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



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C).

23 SET. 2011

El anterior oficio fue notificado por fijación en lista de fecha, _____.

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