

Q.F.



Industria y Comercio

SUPERINTENDENCIA

DELEGATURA PROPIEDAD INDUSTRIAL

PCT

SOLICITUD

PATENTE DE INVENCION

PCT

21 EXPEDIENTE No.

04-9486

54 TITULO

FORMULACIONES AGONISTAS OPIOIDES CON ANTAGINISTAS

LIBERABLES Y SECUESTRADOS

51 CLASIFICACION INTERNACIONAL

A6131/44

71 SOLICITANTE

EURO CELTIQUE, S A

DOMICILIO

122 BOULEVARD DE LA PETRUSSE, L-2330, LUXEMBURGO

LUXEMBURGO

74 APODERADO

LUZ HELENA ADARVE GOMEZ

22 SANTAFE DE BOGOTA, D.C.

SS

Industria y Comercio
SUPERINTENDENCIA

04 009486

ATORIO

SUPERINDUSTRIA Y COMERCIO

Radicación : 04009486 00000000

Folios: 143

Fecha (MM): 2004-02-06 15:04:12

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAR

Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

①

SOLICITUD DE:

☒ Patente de Invención

☐ Patente de Modelo de Utilidad

☐ Capítulo I

☒ Capítulo II

②

SOLICITANTE
(71)

Nombre: EURO CELTIQUE, S.A.

Dirección: 122 Boulevard de la Petrusse, L-2330
Luxemburgo, Luxemburgo

Nacionalidad o Domicilio: LUXEMBURGO

Lugar de Constitución: LUXEMBURGO

Teléfono: 3123600 Fax: 3122410

E-mail: general@cardenasycardenas.com

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☒

Cual _____
Número _____

③

REPRESENTANTE
O APODERADO

Nombre: LUZ HELENA ADARVE GOMEZ

Dirección: Carrera 7 No 71-52 Torre B Piso 9

Teléfono: 3123600 Fax: 3122410

E-Mail: general@cardenasycardenas.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____
Número 41.575.435 TP 14.884
BTA

④

INVENTOR(ES)
(72)

Nombre: 1. CHRISTOPHER BREDER
2. BENJAMIN OSHLACK
3. CURTIS WRIGHT

Dirección: 1. 5 ANNJIM DRIVE, GREENWICH, CT 06830, ESTADOS UNIDOS DE AMERICA
2. 351 EAST 84 TH STREET, NEW YORK, NEW YORK 10028, ESTADOS UNIDOS DE AMERICA

Nacionalidad o Domicilio: 3. 1 JARVIS STREET, NORWALK, CT 06881, ESTADOS UNIDOS DE AMERICA
1. GREENWICH, CONNECTICUT, ESTADOS UNIDOS DE AMERICA
2. NEW YORK, NEW YORK, ESTADOS UNIDOS DE AMERICA
3. NORWALK, CONNECTICUT, ESTADOS UNIDOS DE AMERICA

⑤ PCT (86)

Solicitud Internacional No. PCT/ US02/ 24944 Fecha Agosto 6 de 2002

Publicación Internacional No. WO/ 03/013525 A1 Fecha Febrero 20 de 2003

⑥

Título(54):

FORMULACIONES AGONISTAS OPIOIDES CON ANTAGONISTAS LIBERABLES Y
SECUESTRADOS

⑦

Clasificación Internacional (51): A61K31/44

⑧

Prioridad

SI ☒ NO ☐

(33) País de Origen

Estados Unidos

América

(32) Fecha

Agosto 6 de 2001

(31) N° de Solicitud

80/310,538

⑨

Comprobante de Pago No.: 04-8.815 / 04-8.816

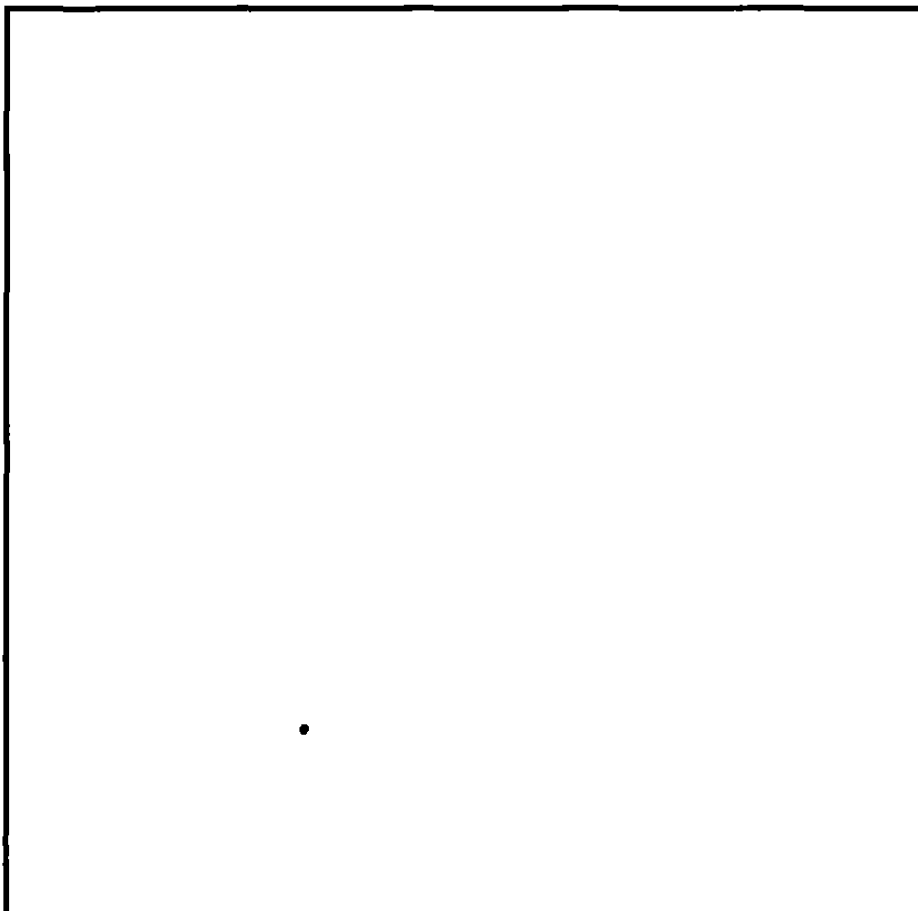
Fecha Febrero 4, 2004

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros. Recibo Examen de Patentabilidad Capítulo II (Solicitó expresamente que se realice el examen de patentabilidad)

11 FIGURA CARACTERISTICA



12

Solicito la Concesión de la patente,

NOMBRE: LUZ HELENA ADARVE GOMEZ

FIRMA:

C.C. 41.575.435 BTA TP. 14.884 C.S.J.

3 3

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04009486 00000000 Folios: 143
Fecha (MM): 2004-02-06 15:04:12
Tramite : 011 PCT-PATENT 379 FASE NRCI 411 PRESENTM
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 090170250 2

RECIBO OFICIAL DE CAJA : 04 - 0,015
FECHA : FEBRERO 4 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PASO	BANCO	CUENTA	Nº. PASO	FECHA PASO	Vr. PASO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO POPULAR	050 00110-6	7972074	04/02/2004	14,400,000.00

***** C O N C E P T O *****

CANT. RECHISTRO	CONCEPTO	TOTAL CONCEPTO
1 50005 01 01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
	TOTAL :	400,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RECIBIBLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Formulaciones Agonistas Opioides con
Antagonistas Liberales y Secuestrados.

RECEIVED
FEB 10 2004

SUPERINDUSTRIA Y COMERCIO
Radacion : 04009486 00000000 Folios: 143
Fecha (MM): 2004-02-06 15:04:12
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

HIT : 000176/00-2

RESERVO OFICIAL DE CAJA : 04 0,81%
FECHA : FEBRERO 4 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO POPULAR	050-00110-6	7772774	04/02/2004	14,400,000.00

***** CONCEPTO *****

CANT. PATENTADO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-11 EXAMEN DE PATENTABILIDAD	177,000.00
	TOTAL :	\$ 177,000.00

CON: CIENTO SETENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RESERVO DE CAJA APLICADO AL EXPEDIENTE No. _____

RECEBIDO

Formulaciones Agonistas
Opioides con Antagonistas
Liberables y Sequestrados.

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

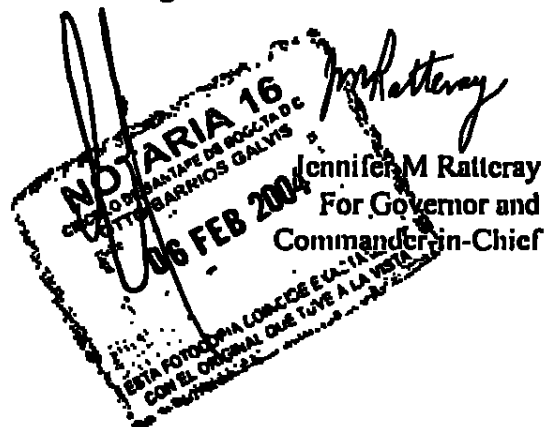
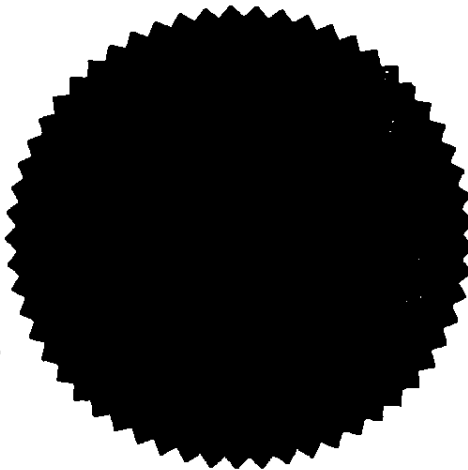
1. Country: United Kingdom in respect of Bermuda

This Public Document

2. Has been signed by James M Keyes
3. Acting in the capacity of Notary Public
4. Bears the seal/stamp JAMES M KEYES, NOTARY PUBLIC, BERMUDA

Certified

5. At Bermuda
6. On 26 January 2004
7. By the Governor and Commander-in-Chief of the Bermudas or Somers Islands or any member of his staff, signing on his behalf and using his official seal.
8. Number: 1585
9. Seal
10. Signature:



8
6

NOTARIAL CERTIFICATE

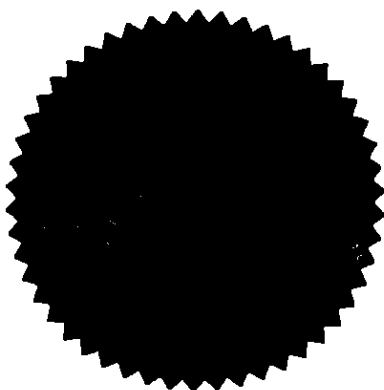
TO ALL TO WHOM THESE PRESENTS SHALL COME:

I, **JAMES KEYES**

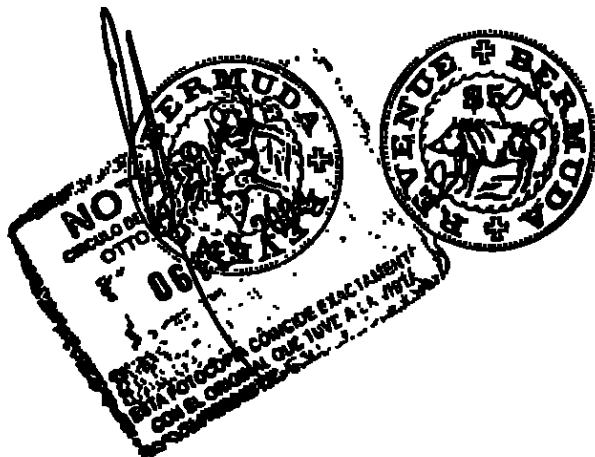
of the City of Hamilton in the Islands of Bermuda, a Notary Public duly commissioned and qualified in and for the Islands of Bermuda, DO HEREBY CERTIFY AND DECLARE that the signature "Douglas Docherty" appearing on the Power of Attorney attached hereto is the signature and handwriting of the said Douglas Docherty to me known to be a Director of Euro-Celtique S.A. a Company formed under the laws of Luxembourg having its address at 122 Boulevard de la Petrusse, L-2330 Luxembourg.

IN TESTIMONY WHEREOF
I, the said Notary Public, have
hereto set my hand and
Official Notarial Seal this 23rd
day of January, 2004.

NOTARY PUBLIC



JAMES M. KEYES
NOTARY PUBLIC
CANON'S COURT
22 VICTORIA STREET
HAMILTON, HM 12
BERMUDA



- Colombia -

POWER OF ATTORNEY

In the city of Buenavista, Medellin on the 23 day of the month of January, two thousand and four (2004) before me, James M. L. L. L. Notary Public, appeared Diego L. L. L. of age, and domiciled at _____ and stated:

FIRST: That he/she acts in his/her capacity of Director of **EURO-CELTIQUE S.A.**, a company legally constituted and in existence in accordance with the laws of Luxembourg, and domiciled at 122, Boulevard de la Petrusse, L-2330 Luxembourg, Luxembourg, as evidenced in the By Laws, documents which I have examined.

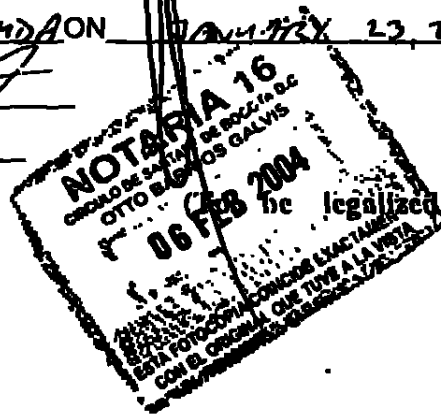
SECOND: That in such capacity he/she grants hereby special, ample and sufficient Power of Attorney to DARIO CARDENAS-NAVAS and/or EDUARDO CARDENAS-CABALLERO and/or BERNARDO P. CARDENAS-MARTINEZ and/or LUZ HELENA ADARVE-GOMEZ, and/or JUANITA ACOSTA GOMEZ and/or ANA MARIA RUIZ RUEDA registered lawyers of the firm CARDENAS & CARDENAS ABOGADOS PROPIEDAD INTELECTUAL LTDA, domiciled at Carrera 7 No. 71-52, Torre B, Piso 9 Bogotá, D.C., Colombia, to carry before the corresponding Colombian national Offices and authorities the proceedings to obtain trademarks, patents, utility models, industrial drawings and designs, deposits of commercial names and ensigns, as well as processing of renewals, assignments, change of name or domicile of the owner, cancellation actions, waivers and licenses of the same for which purpose they are empowered to take before said authorities all necessary actions for the indicated purposes; to file applications, statements, claims, formulate descriptions, amendments, oppositions and appeals; pay all taxes and installments and make any other payments determined by law; to receive every document and values issuing the respective discharge; to fulfill any other requirements and take, in general, every measure that they shall deem opportune for the defense and protection of the Industrial Property of the company in the event of infringements, oppositions, proceedings for cancellation or annulment, imposition of fines, passing the antecedents to the courts; they are empowered to appear as plaintiff or defendant before the competent judges, being entitled to transact, submit to arbitration, waive, receive, resign, withdraw, appeal and all other legal powers which may be necessary, and it is hereby declared ever since now valid and good whatever such attorneys do for its benefit, granting them also power to substitute this proxy and if necessary to revoke such substitutions.

THIRD: That for purposes of articles 597 and 543 of the Colombian code of Commerce the attorneys are empowered to receive service of notice and designate judicial and extrajudicial attorneys.

SIGNED AT Medellin, Antioquia January 23, 2004

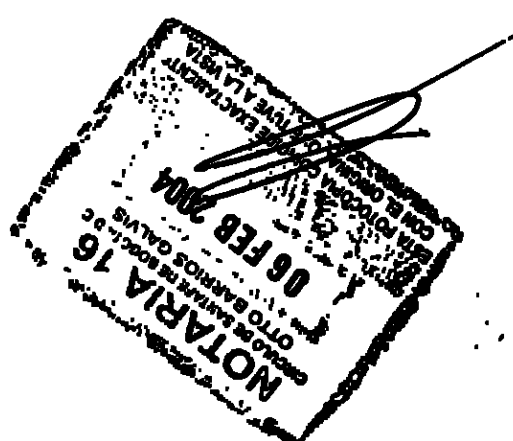
BY [Signature]
Diego L. L. L.

NOTARY PUBLIC





From Minnesota
21-16



TRADUCCION OFICIAL No. 04/071 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Juan Pablo Piedrahita Aguilera, Traductor e Intérprete Oficial debidamente reconocido de conformidad con la resolución número 718 de 2003 expedida por el Ministerio del Interior y de Justicia.

(Se traduce un Poder otorgado por la compañía EURO-CELTIQUE S.A. con fecha Enero 23, 2004, una Certificación Notarial y la Apostilla No. 1585 todo escrito en inglés.)

PODER

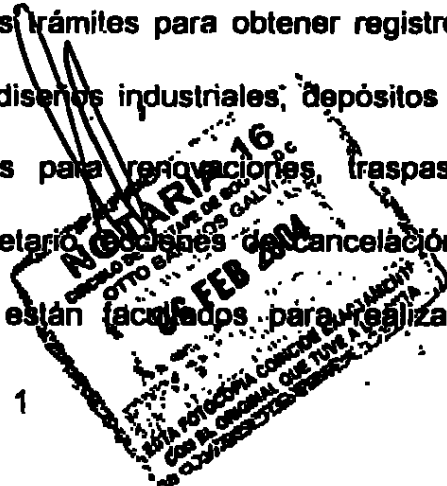
-Colombia-

En la ciudad de Hamilton, Bermudà el día 23 del mes de Enero del año Dos Mil Cuatro (2004), ante mi, JAMES KEYES, Notario Público, compareció Douglas Docherty, mayor de edad y domiciliado en (en blanco) y manifestó:

PRIMERO: Que el/ella obra en su calidad de Director de **EURO-CELTIQUE S.A.**, compañía constituida legalmente y existente de conformidad con las leyes de Luxemburgo y con domicilio en 122, Boulevard de la Petrusse, L-2330 Luxemburgo, según lo evidencian los Estatutos, documentos que he examinado.

SEGUNDO: Que en tal calidad el/ella otorgo por el presente poder especial amplio y suficiente a **DARÍO CÁRDENAS-NAVAS y/o EDUARDO CÁRDENAS CABALLERO, y/o BERNARDO P. CÁRDENAS-MARTÍNEZ, y/o JAMES VALDIRI REYES y/o LUZ HELENA ADARVE-GOMEZ, y/o JUANITA ACOSTA GÓMEZ y/o ANA MARÍA RUIZ RUEDA**, abogados registrados de la firma **CÁRDENAS & CÁRDENAS ABOGADOS PROPIEDAD INTELECTUAL ABOGADOS**, domiciliada en la Carrera 7 No. 71-52, Torre B, Piso 9, Santafé de Bogotá D.C., Colombia, para llevar a cabo ante las correspondientes Oficinas Nacionales Colombianas y autoridades los trámites para obtener registros de marcas, patentes, modelos de utilidad, diseños y diseños industriales, depósitos de nombres y señas comerciales, así como trámites para renovaciones, traspasos, cesiones, cambios de nombre o domicilio del propietario, solicitudes de cancelación, renunciaciones de los mismos para cuyo fin están facultados para realizar ante dichas

04/071
TRADUCCION OFICIAL No. 04/071
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
M.I. 718 DE MAYO 2003
DEL MINISTERIO DEL INTERIOR Y DE JUSTICIA



9

autoridades todas las acciones necesarias para los fines indicados; para presentar solicitudes, declaraciones, reivindicaciones, reclamos, formular descripciones, modificaciones, oposiciones, y apelaciones; pagar todos los impuestos y derechos y hacer cualesquiera otros pagos que la ley determine; recibir todos los documentos y valores con expedición del respectivo descargo; llenar cualesquiera otros requisitos y tomar en general todas las medidas que juzguen oportunas para la defensa y protección de la Propiedad Industrial de la compañía en el evento de infracciones, oposiciones, procesos de cancelación o anulación, imposición de multas, incluyendo recurrir a litigio y presentar antecedentes ante las cortes; quedan facultados para comparecer en calidad de demandante o demandado ante los jueces competentes, con las facultades de transar, someterse a arbitraje, renunciar, recibir, renunciar, desistir, apelar y todas las demás facultades legales que puedan requerirse, y por el presente declara desde ahora válido y satisfactorio lo que dichos abogados hagan en nuestro beneficio, otorgándoles también poder para sustituir este poder y si fuere necesario para revocar tales sustituciones.

TERCERO: que para fines de los artículos 597 y 543 del Código Colombiano de Comercio, los abogados están facultados para recibir notificaciones y para designar apoderados judiciales y extrajudiciales

FIRMADO EN: HAMILTON BERMUDA

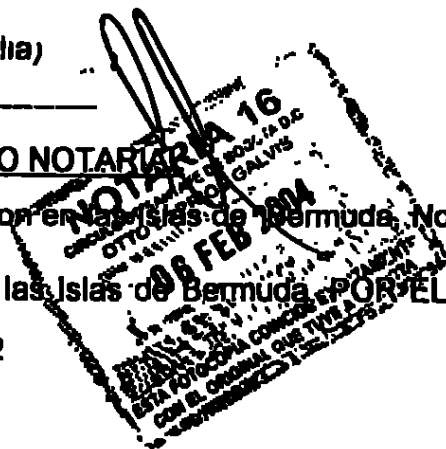
El: 23 de Enero, 2004.

POR: (Firmado) Ilegible Douglas Docherty

Notario Público (legalizar mediante Apostilla)

CERTIFICADO NOTARIAL

NOTARIO, JAMES KEYES, de la Ciudad de Hamilton en las Islas de Bermuda, Notario Público debidamente nombrado e idóneo en y para las Islas de Bermuda, **POR EL PRESENTE**



CERTIFICO Y DECLARO, que la firma de "Douglas Docherty" que aparece en el Poder adjunto al presente es la firma y caligrafía de dicho Douglas Docherty a quien conozco y quien sé que es uno de los Directores de Euro-Celtique S.A., Compañía constituida bajo las leyes de Luxemburgo con domicilio en 122 Boulevard de la Petrusse, L-2330, Luxemburgo.

EN TESTIMONIO DE LO CUAL, YO, el mencionado Notario Público, he estampado mi firma y Sello Notarial hoy día 23 de Enero, 2004.

(Firmado) Ilegible Notario Público

(Sello Notarial Rojo de Oblea en Relieve) (Estampillas)

(Sello Notarial: JAMES M. KEYES, NOTARIO PÚBLICO, CANON'S COURT, 22 VICTORIA STREET, HAMILTON, HM, 12, BERMUDA)

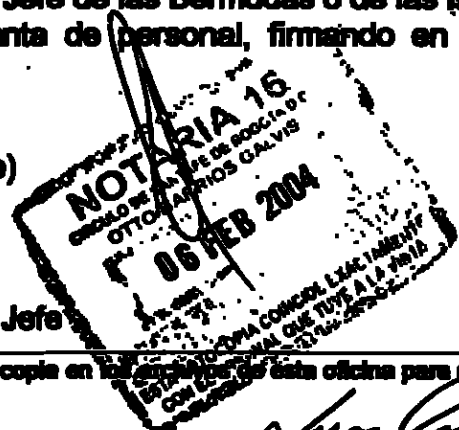
APOSTILLA

(Convención de la Haya de Octubre 5 de 1961)

1. País: Reino Unido respecto de Bermuda
Este documento público
2. Ha sido firmado por James M Keyes
3. Obrando en calidad de Notario Público
4. Lleva el sello/estampilla de James M Keyes Notario Público, Bermuda

CERTIFICADO

5. En Bermuda
6. Hoy 26 de Enero, 2004
7. Por el Gobernador y Comandante en Jefe de las Bermudas o de las Islas Somers o por cualquier funcionario de su planta de personal, firmando en su nombre y usando su sello oficial.
8. Número 1585
9. Sello (Sello Rojo de Oblea en Relieve)
10. Firma (Firmado)
Jennifer M. Ratteray
Por el Gobernador y Comandante en Jefe



ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en la presente para su confrontación y a la cual me remito.
Bogotá, Febrero 4, 2004.

TRADUCCION ORCIAL No. 061071
JUAN PABLO MEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE ORCIAL

RES. 718 DE MAYO 2003
DEL MIN. INTERIOR Y DE JUSTICIA

SECRETARIO Y OFICIALES DE OFICIO

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NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2004 FEB 14

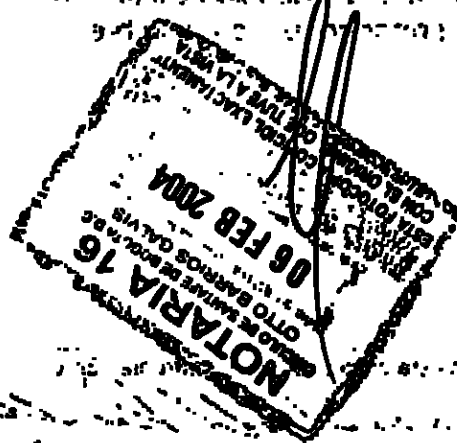
JEFE DE LEGALIZACIONES
SANTAFE DE BUENOS AIRES

MINISTERIO DE RELACIONES
EXTERIORES

Forma presentada

0418

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES DE



TRADUCCION OFICIAL No.
RUBEN FABIO NEGRANHA AGUIRRE

TRADUCCION E INTERPRETE OFICIAL

BO. 212 DE MAYO 2001

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



INTERNATIONAL PATENT COOPERATION TREATY

(43) International Publication Date
20 February 2003 (20.02.2003)

PCT

(10) International Publication Number
WO 03/013525 A1

- (51) International Patent Classification: A61K 31/44, 31/445 (74) Agents: DAVIDSON, Clifford, M. et al.; Davidson, Davidson & Kappel, LLC, 14th Floor, 485 Seventh Avenue, New York, NY 10018 (US).
- (21) International Application Number: PCT/US02/24944 (81) Designated States (national): AR, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GR, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 6 August 2002 (06.08.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/310,536 6 August 2001 (06.08.2001) US (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (for all designated States except US): EURO-CELTIQUE S.A. (LU/LU); 122, Boulevard de la Petrosse, L-2330 Luxembourg (LU).
- (72) Inventors; and (73) Inventors/Applicants (for US only): BREDER, Christopher (US/US); 5 Annapolis Drive, Greenwich, CT 06830 (US). OSHLACK, Benjamin (AU/US); 351 East 84th Street, New York, NY 10028 (US). WRIGHT, Curtis (US/US); 1 Jarvis Street, Norwalk, CT 06851 (US).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



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(54) Title: OPIOID AGONIST FORMULATIONS WITH RELEASABLE AND SEQUESTERED ANTAGONIST

(57) Abstract: Disclosed are oral dosage forms, comprising (i) a therapeutically effective amount of an opioid agonist; (ii) an opioid antagonist-in releasable form; and (iii) a sequestered opioid antagonist which is not released when the dosage form is administered intact, and methods thereof.

5 OPIOID AGONIST FORMULATIONS WITH RELEASABLE AND SEQUESTERED
ANTAGONIST

BACKGROUND OF THE INVENTION

10 Opioid formulations are sometimes the subject of abuse. A particular dose of oxycodone may be more potent when administered parenterally as compared to the same dose administered orally. Also, some formulations can be tampered with in order to provide the opioid agonist contained therein better available for illicit use. For example, a controlled release opioid agonist formulation can be crushed in order to provide the opioid contained therein available for
15 immediate release upon oral or parenteral administration. An opioid formulation can also be abusable by administration of more than the prescribed dose of the drug.

Opioid antagonists have been combined with certain opioid agonists in order to deter the parenteral abuse of opioid agonists. In the prior art, the combination of immediate release pentazocine and naloxone has been utilized in tablets available in the United States,
20 commercially available as Talwin^{Nx} from Sanofi-Winthrop. Talwin^{Nx} contains immediate release pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base. A fixed combination therapy comprising tilidine (50 mg) and naloxone (4 mg) has been available in Germany for the management of pain since 1978 (Valoron^N, Goedecke). A fixed combination of buprenorphine and naloxone was introduced in 1991 in New
25 Zealand (Temgesic^{Nx}, Reckitt & Colman) for the treatment of pain.

Purdue Pharma L.P. currently markets sustained-release oxycodone in dosage forms containing 10, 20, 40 and 160 mg oxycodone hydrochloride under the tradename OxyContin.

U.S. Patent Nos. 5,266,331; 5,508,042; 5,549,912 and 5,656,295 disclose sustained release oxycodone formulations.

30 U.S. Patent No. 4,769,372 and 4,785,000 to Kreek describe methods of treating patients suffering from chronic pain or chronic cough without provoking intestinal dysmotility by administering 1 to 2 dosage units comprising from about 1.5 to about 100 mg of opioid analgesic or antitussive and from about 1 to about 18 mg of an opioid antagonist having little to no systemic antagonist activity when administered orally, from 1 to 5 times daily.

35 U.S. Patent No. 6,228,863 to Palermo et al. describes compositions and methods of preventing abuse of opioid dosage forms.

WO99/32119 to Kaiko et al. describes compositions and methods of preventing abuse of opioid dosage forms.

5 U.S. Patent No. 5,472,943 to Crain et al. describes methods of enhancing the analgesic potency of bimodally acting opioid agonists by administering the agonist with an opioid antagonist.

All documents cited herein, including the foregoing are incorporated by reference in their entireties for all purposes.

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OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the invention to provide an oral dosage form of an opioid agonist that is useful for decreasing the potential for abuse of the opioid agonist contained therein.

15 It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid agonist that is useful for decreasing the potential abuse of the opioid agonist without effecting the analgesic effects of the opioid agonist or incurring the risk of precipitating withdrawal if taken intact.

20 It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid agonist that is resistant to misuse, abuse or diversion, wherein said resistance does not depend on individual patient-specific differences in the effects of co-administered opioid agonist and antagonist mixtures.

25 It is an object of certain embodiments of the invention to provide an oral dosage form containing an effective dose of an opioid agonist along with a dose of opioid antagonist which does not change the analgesic efficacy of the opioid agonist when the dosage form is orally administered intact, but which can prevent abuse if the dosage form is tampered with by interfering with the effect of the opioid agonist.

30 It is an object of certain embodiments of the invention to provide a method for preventing abuse of an oral opioid dosage form where the dosage form also includes a dose of opioid antagonist which is sequestered, e.g., is not bioavailable when the dose is administered intact but is bioavailable when the dosage form is tampered with (e.g., in an attempt to misuse the dose of opioid analgesic) and a dose of antagonist which is releasable to provide a desired effect.

35 It is an object of certain embodiments of the invention to provide oral dosage forms that are intended for or are suitable for use in the management of acute or chronic pain where alteration of the opioid agonist's analgesic affects must be avoided such as in cases of tolerance; physical dependence or individual variability in hepatic metabolism or physiology.

It is a further object of a preferred embodiment of the invention to provide a method of treating pain in human patients with an oral dosage form of an opioid agonist while reducing its

5 misuse by oral, parenteral, intranasal and/or sublingual route.

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less abuse potential via the oral route than prior commercially available dosage forms.

10 It is an object of certain embodiments of the present invention to provide an oral dosage form of an opioid analgesic and method which provides therapeutic analgesia and which also provides a negative, "aversive" experience when the prescribed amount or a large amount of the opioid, e.g., about 2-3 times the usually prescribed dose, is taken by or administered to a physically dependent subject.

15 It is an object of certain embodiments of the present invention to provide an oral dosage form of an opioid analgesic and a method for providing therapeutic analgesia in a manner which is not as positively reinforcing in non-physically dependent subjects taking the same or more than the usually prescribed dose, e.g., about 2-3 times the usually prescribed dose of the opioid, as compared to the same amount of opioid without the antagonist.

20 It is an object of certain embodiments of the invention to provide a method of treating pain in human patients with an oral dosage form of an opioid analgesic while reducing the oral abuse potential of dosage form.

It is an object of certain embodiments of the invention to provide a method of manufacturing an oral dosage form of an opioid analgesic such that it has less oral abuse potential.

25 It is an object of certain embodiments of the invention to provide a composition and method of enhancing the analgesic potency of opioid agonists by blocking their anti-analgesic side-effects.

30 It is an object of certain embodiments of the invention to provide a composition and method of attenuating physical dependence, tolerance, hyperexcitability, hyperalgesia and other undesirable side-effects caused by the chronic administration of opioid agonists.

It is an object of certain embodiments of the invention to provide a composition and method for detoxifying and treating opiate addicts utilizing opioid receptor antagonists.

35 It is an object of certain embodiments of the invention to provide a composition which enhances the analgesic effects of opioid agonists while simultaneously attenuating undesirable side-effects caused by said opioid agonists, including physical dependence, tolerance, hyperexcitability and hyperalgesia.

Some or all of the above objects are achieved by the present invention which is directed to

5 an oral dosage form, comprising (i) a therapeutically effective amount of an opioid agonist; (ii) an opioid antagonist in releasable form; and (iii) a sequestered opioid antagonist which is not released when the dosage form is administered intact.

Certain embodiments of the invention are directed to an oral dosage form, comprising (i) a first component comprising a therapeutically effective amount of an opioid agonist; (ii) a
10 second component comprising an opioid antagonist in releasable form; and (iii) a third component comprising a sequestered opioid antagonist which is not released when the dosage form is administered intact.

Certain embodiments of the invention are directed to an oral dosage form comprising (i) a first component comprising a therapeutically effective amount of an opioid agonist; (ii) a
15 second component comprising an opioid antagonist in releasable form, and a sequestered opioid antagonist which is not released when the dosage form is administered intact.

Certain embodiments of the invention are directed to an oral dosage form, comprising (i) a first component comprising a therapeutically effective amount of an opioid agonist and an opioid antagonist in releasable form; and (ii) a second component comprising a sequestered
20 opioid antagonist which is not released when the dosage form is administered intact.

Certain embodiments of the invention are directed to an oral dosage form, comprising (i) a first component comprising a therapeutically effective amount of an opioid agonist and an opioid antagonist in releasable form; and (ii) a second component comprising a sequestered opioid antagonist which is not substantially released when the dosage form is administered intact.

25 Certain embodiments of the invention are directed to an oral dosage form, comprising (i) a first component comprising a therapeutically effective amount of an opioid agonist; (ii) a second component comprising an opioid antagonist in releasable form; and (iii) a third component comprising a sequestered opioid antagonist which is not substantially released when the dosage form is administered intact.

30 Certain embodiments of the present invention is directed to a dosage form formulated such that the ratio of the amount of antagonist released from the dosage form after tampering to the amount of the antagonist released from the intact dosage form is about 3:1 or greater, based on the in-vitro dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C.

35 In embodiments of the invention wherein the antagonist in non-releasable form can be in the form of multiparticulates coated with a sequestering material, the multiparticulates can be in the form of inert beads coated with the antagonist and overcoated with the material, or

5 alternatively in the form of a granulation comprising the antagonist and the material. The multiparticulates can be dispersed in a matrix comprising the opioid agonist or contained in a capsule with the opioid agonist.

In embodiments of the invention wherein the antagonist is dispersed in a matrix comprising a sequestering material which substantially prevents the release of the antagonist, the
10 matrix can be in the form of pellets. The pellets can be dispersed in another matrix comprising the opioid agonist or contained in a capsule with the opioid agonist.

In other embodiments of the invention, part of the antagonist is in a matrix and/or part of the antagonist is in a coated bead.

In certain embodiments of the invention which exhibit the above-disclosed ratio of about
15 3:1 or greater concerning the amount of antagonist released from the dosage form after tampering to the amount of said antagonist released from the intact dosage form based on the dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C, the intact dosage form releases 22.5% or less of the antagonist after 1 hour and the tampered dosage form releases 67.5% or more antagonist after 1
20 hour. In another embodiment, the intact dosage form releases 20% or less of said antagonist after 1 hour and the tampered dosage form releases 60% or more antagonist after 1 hour. In another embodiment, the intact dosage form releases 10% or less of said antagonist after 1 hour and the tampered dosage form releases 30% or more antagonist after 1 hour. In another embodiment the intact dosage form releases 5% or less of said antagonist after 1 hour and the tampered dosage
25 form releases 15% or more antagonist after 1 hour.

In certain embodiments of the invention, the ratio of the amount of antagonist released from the dosage form after tampering to the amount of said antagonist released from the intact dosage form based on the dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C is 4:1 or greater, 10:1 or
30 greater, 50:1 or greater or 100:1 or greater.

The invention is also directed to methods of preventing abuse of an opioid agonist utilizing the dosage forms disclosed herein. The method can comprise providing the opioid agonist in an oral dosage form together with an opioid antagonist in non-releasable form upon
digestion when the integrity of the dosage form is maintained until digestion begins, but which
35 becomes bioavailable if subjected to tampering (e.g., crushing, shear forces which break up the dosage form, etc., solvents or temperatures of greater than 45°C).

Another embodiment of the invention is directed to a method of decreasing the abuse of

5 an opioid agonist in an oral dosage form, comprising preparing an oral dosage form as disclosed herein. For example, the method can comprise preparing a dosage form comprising an opioid antagonist in non-releasable form such that said dosage form provides a desired analgesic effect and said antagonist does not substantially block the analgesic effect of the opioid agonist when said dosage form is administered orally intact. In alternative embodiments, the effect of the
10 opioid agonist is at least partially blocked when said dosage form tampered with, e.g., chewed, crushed or dissolved in a solvent, and administered orally, intranasally, parenterally or sublingually.

The invention is also directed to a method of treating pain with the dosage forms disclosed herein.

15 The invention is also directed to methods of preparing the dosage forms disclosed herein. In certain embodiments, the invention comprises a method of preparing an oral dosage form comprising pretreating an opioid antagonist to render it non-releasable; and combining the pretreated antagonist with a releasable form of an opioid agonist and an opioid antagonist in a manner that maintains the integrity of the non-releasable form of the antagonist.

20 Certain embodiments of the invention are directed to formulations wherein the agonist, releasable antagonist and non-releasable antagonist are interdispersed and are not isolated from each other in three distinct layers. Certain embodiments have two of the three agents interdispersed with the third in a separate and distinct layer. In other embodiments, at least two or all of the ingredients are partially interdispersed. The present invention contemplates all
25 combinations of the agents interdispersed or partially interdispersed in any combination.

The term "analgesic effectiveness" is defined for purposes of the present invention as a satisfactory reduction in or elimination of pain, along with a tolerable level of side effects, as determined by the human patient. The phrase "not substantially blocking the analgesic effect of an opioid agonist" means that the opioid antagonist does not block the effects of the opioid
30 agonist in sufficient degree as to render the dosage form therapeutically less effective for providing analgesia.

The term "an opioid antagonist in a substantially non-releasable form" refers to an opioid antagonist that is not released or substantially not released at one hour after the intact dosage form containing both opioid agonist and the opioid antagonist is orally administered (i.e., without
35 having been tampered with). For purposes of the invention, the amount released after oral administration of the intact dosage form may be measured in-vitro via the dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at

5 75 rpm at 37 degrees C. Such a dosage form is also referred to as comprising a "sequestered antagonist".

Although the preferred embodiments of the invention comprise an opioid antagonist in a form that completely prevents the release of the opioid antagonist, the invention also includes an antagonist in a substantially non-releasable form. The term "substantially not released" refers to
10 the antagonist that might be released in a small amount, as long as the amount released does not affect or does not significantly affect analgesic efficacy when the dosage form is orally administered to humans as intended.

In certain preferred embodiments of the invention, the substantially non-releasable form of the antagonist is resistant to laxatives (e.g., mineral oil) used to manage delayed colonic transit
15 and to achlorhydric states.

In certain embodiments, the substantially non-releasable form or non-releasable form of an opioid antagonist comprises an opioid antagonist that is formulated with one or more of pharmaceutically acceptable hydrophobic materials, such that the antagonist is not released or substantially not released during its transit through the gastrointestinal tract when administered
20 orally as intended, without having been tampered with.

In certain embodiments of the present invention, the substantially non-releasable form or non-releasable form of the opioid antagonist is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of crushing, shearing, grinding, chewing and/or dissolution in a solvent in combination with heating (e.g., greater than about 45°C) of the oral
25 dosage form. When thus tampered with, the integrity of the substantially non-releasable form or non-releasable form of the opioid antagonist will be compromised, and the opioid antagonist will be made available to be released. In certain embodiments, when the dosage form is chewed, crushed or dissolved and heated in a solvent, and administered orally, intranasally, parenterally or sublingually, the analgesic or euphoric effect of the opioid is reduced or eliminated. In certain
30 embodiments, the effect of the opioid agonist is at least partially blocked by the opioid antagonist. In certain other embodiments, the effect of the opioid agonist is substantially blocked by the opioid antagonist.

In certain embodiments, the quantity of antagonist released from the dosage form is in a ratio to the agonist which is aversive in physically dependent human subjects when the dosage
35 form is administered at the same amount or at a higher amount than the therapeutically effective amount

In certain embodiments, the quantity of the antagonist released from the first component

5 is in an amount sufficient to be aversive in physically dependent human subjects when the dosage form is administered at the same amount or at a higher amount than the therapeutically effective amount.

In certain embodiments, the quantity of the antagonist released from the first component is less than the amount sufficient to be aversive in physically dependent human subjects when the dosage form is administered at the same amount or at a higher amount than the therapeutically effective amount.

10 In certain embodiments, the amount of the antagonist released from the second component is in an amount sufficient to be aversive in physically dependent human subjects when the dosage form is administered at the same amount or at a higher amount than the therapeutically effective amount.

In certain embodiments, the amount of the antagonist released from the second component is less than the amount sufficient to be aversive in physically dependent human subjects when the dosage form is administered at the same amount or at a higher amount than the therapeutically effective amount.

20 In certain embodiments, the invention comprises a sustained release excipient which provides a sustained release of the opioid agonist.

In certain embodiments, the invention comprises a sustained release excipient which provides a sustained release of the releasable opioid antagonist.

25 In certain embodiments, the invention comprises a sustained release excipient which provides a sustained release of the opioid agonist and the opioid antagonist.

In certain embodiments, the sequestered antagonist is in the form of multiparticulates individually coated with a material that prevents release of the sequestered antagonist.

30 In certain embodiments, the sequestered antagonist is in the form of multiparticulates individually coated with a material that substantially prevents release of the sequestered antagonist.

In certain embodiments, the sequestered antagonist is dispersed in a matrix comprising a sequestering material that prevents the release of the sequestered antagonist.

In certain embodiments, the sequestered antagonist is dispersed in a matrix comprising a sequestering material that substantially prevents the release of the sequestered antagonist.

35 In certain embodiments, the releasable opioid antagonist is the same as the sequestered antagonist.

In certain embodiments, the releasable opioid antagonist is different than the sequestered

5 antagonist.

In certain embodiments, the antagonist is selected from the group consisting of naltrexone, naloxone, nalmeperide, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.

10 In certain embodiments, the releasable antagonist is selected from the group consisting of naltrexone, naloxone, nalmeperide, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof and the sequestered antagonist is selected from the group consisting of naltrexone, naloxone, nalmeperide, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.

15 In certain embodiments, the opioid is selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone, pharmaceutically acceptable salts thereof and mixtures thereof.

20 In certain embodiments, the releasable antagonist is an antagonist with minimal oral activity such as naloxone in releasable or "non-sequestered" form and the sequestered antagonist is an orally bioavailable antagonist such as naltrexone. Such a dosage form would be a deterrent to parenteral, nasal and oral abuse of the dosage form upon administration of a tampered dosage form. The inclusion of the releasable non-orally bioavailable antagonist with the opioid agonist would make the formulation more resistant to abuse by making the formulation resistant to parenteral abuse even if the sequestered antagonist was separated from the dosage form, while not affecting the agonist if administered intact.

25 In certain embodiments, the dosage form has a ratio of releasable opioid antagonist to opioid agonist that is analgesically effective when the combination is administered orally, but which is aversive in physically dependent human subjects when administered at the same amount or at a higher amount than the therapeutically effective amount.

30 In certain embodiments, the ratio of releasable opioid antagonist to opioid agonist maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist relative to the same therapeutic amount of opioid analgesic when administered to human patients without the opioid antagonist.

In certain embodiments, the opioid agonist is oxycodone and the releasable antagonist is naltrexone.

35 In certain embodiments, the ratio of releasable naltrexone to hydrocodone is from about 0.03:1 to about 0.27:1.

In certain embodiments, the ratio of releasable naltrexone to hydrocodone is from about

5 0.05:1 to about 0.20:1.

In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is oxycodone, wherein the ratio of releasable naltrexone to oxycodone is from about 0.037:1 to about 0.296:1.

10 In certain embodiments, the releasable opioid antagonist is naltrexone and the releasable opioid agonist is codeine, wherein the ratio of releasable naltrexone to codeine is from about 0.005:1 to about 0.044:1.

In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is hydromorphone, wherein the ratio of releasable naltrexone to hydromorphone is from about 0.148:1 to about 1.185:1.

15 In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is levorphanol, wherein the ratio of releasable naltrexone to levorphanol is from about 0.278:1 to about 2.222:1.

In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is meperidine, wherein the ratio of releasable naltrexone to meperidine is from about 20 0.0037:1 to about 0.0296:1.

In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is methadone, wherein the ratio of releasable naltrexone to methadone is from about 0.056:1 to about 0.444:1.

25 In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is morphine, wherein the ratio of releasable naltrexone to morphine is from about 0.018:1 to about 0.148:1.

In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is oxycodone, wherein the ratio of releasable naltrexone to oxycodone is from about 0.056:1 to about 0.222:1.

30 In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is codeine, wherein the ratio of releasable naltrexone to codeine is from about 0.0083:1 to about 0.033:1.

In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is hydromorphone, wherein the ratio of releasable naltrexone to hydromorphone is from 35 about 0.222:1 to about 0.889:1.

In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is levorphanol, wherein the ratio of releasable naltrexone to levorphanol is from about

5 0.417:1 to about 1.667:1.

In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is meperidine, wherein the ratio of releasable naltrexone to meperidine is from about 0.0056:1 to about 0.022:1.

10 In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is methadone, wherein the ratio of releasable naltrexone to methadone is from about 0.083:1 to about 0.333:1.

In certain embodiments, the releasable opioid antagonist is naltrexone and the opioid agonist is morphine, wherein the ratio of releasable naltrexone to morphine is from about 0.028:1 to about 0.111:1.

15 In certain embodiments, the releasable antagonist is in an amount to attenuate a side effect of the opioid agonist selected from the group consisting of anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance, and a combination of any of the foregoing.

In certain embodiments, the amount of antagonist released during the dosing interval enhances the analgesic potency of the opioid agonist.

20 In certain embodiments, the amount of the releasable opioid receptor antagonist is about 100 to about 1000 fold less than the amount of the opioid agonist.

In certain embodiments, the ratio of the amount of antagonist released from the dosage form after tampering to the amount of the antagonist released from the intact dosage form is about 3, 4, 10, 50 or 100:1; (w:w) or greater, based on the in-vitro dissolution at 1, 8, 24 and/or
25 36 hours of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C, with or without a switch to Simulated Intestinal Fluid after 1 hour.

The term "tampering" means any manipulation by mechanical, thermal and/or chemical means which changes the physical properties of the dosage form, e.g., to liberate the opioid
30 agonist for immediate release if it is in sustained release form, or to make the opioid agonist available for inappropriate use such as administration by an alternate route, e.g., parenterally. The tampering can be, e.g., by means of crushing, shearing, grinding, chewing, dissolution in a solvent, heating (e.g., greater than about 45°C), or any combination thereof.

The term "at least partially blocking the opioid effect," is defined for purposes of the
35 present invention to mean that the opioid antagonist at least significantly blocks the euphoric effect of the opioid agonist, thereby reducing the potential for abuse of the opioid agonist in the dosage form.

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5 In certain preferred embodiments of the present invention, the substantially non-releasable form or non-releasable form of the opioid antagonist comprises opioid antagonist particles in a coating that substantially prevents or prevents the release of the antagonist. In preferred embodiments, the coating comprising one or more of pharmaceutically acceptable hydrophobic material. The coating is preferably impermeable to the opioid antagonist contained therein and is
10 insoluble in the gastrointestinal system, thus substantially preventing the release of the opioid antagonist when the dosage form is administered orally as intended.

Accordingly, when the oral dosage form is not tampered with as to compromise the integrity of the coating, the opioid antagonist contained therein will not be substantially released during its first hour of transit through the gastrointestinal system, and thus would not be available
15 for absorption. In certain preferred embodiments of the present invention, the hydrophobic material comprises a cellulose polymer or an acrylic polymer that is insoluble in the gastrointestinal fluids and impermeable to the opioid antagonist.

The term "particles" of opioid antagonist, as used herein, refers to granules, spheroids, beads or pellets comprising the opioid antagonist. In certain preferred embodiments, the opioid
20 antagonist particles are about 0.2 to about 2 mm in diameter, more preferably about 0.5 to about 2 mm in diameter.

In certain embodiments of the present invention, the releasable antagonist and the non-releasable antagonist can be contained in the same component. For example, when the opioid antagonist is coated with a coating that substantially prevents its release, and is then mixed with
25 an opioid agonist and compressed into tablets, certain amounts of the coating might be cracked, thus exposing the opioid antagonist to be released upon oral administration. This release can be modified and controlled to provide a desired effect as disclosed herein.

Preferably, the opioid agonist useful for the present invention may be selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone and mixtures thereof. Preferred examples of the opioid antagonist useful
30 for the present invention includes naltrexone, naloxone, nalmeffene, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.

In certain embodiments of the present invention, the ratio of the opioid agonist and the opioid antagonist, present in the entire formulation (including releasable and non-releasable
35 form) is about 1:1 to about 50:1 by weight, preferably about 1:1 to about 20:1 by weight or 15:1 to about 30:1. The weight ratio of the opioid agonist to opioid antagonist, as used in this application, refers to the weight of the active ingredients. Thus, for example, the weight of the

5 opioid antagonist excludes the weight of the coating or matrix that renders the opioid antagonist substantially non-releasable, or other possible excipients associated with the antagonist particles. In certain preferred embodiments, the ratio is about 1:1 to about 10:1 by weight. Since a portion of the opioid antagonist is in a non-releasable form, the amount of such antagonist within the dosage form may be varied more widely than the opioid agonist/antagonist combination dosage
10 forms where both are available for release upon administration as the formulation does not depend on differential metabolism or hepatic clearance for proper functioning. For safety reasons, the amount of the opioid antagonist present in the entire dosage form is selected as not to be harmful to humans even if fully released by tampering with the dosage form.

In certain preferred embodiments of the present invention, the opioid agonist comprises
15 hydrocodone, oxycodone or pharmaceutically acceptable salts thereof and the opioid antagonist, present in a substantially non-releasable form, comprises naloxone, naltrexone or pharmaceutically acceptable salts thereof.

The oral dosage form containing an opioid agonist in combination with the releasable and non-releasable opioid antagonist includes, but are not limited to, tablets or capsules. The dosage
20 forms of the present invention may include any desired pharmaceutical excipients known to those skilled in the art. The oral dosage forms may further provide an immediate release of the opioid agonist. In certain embodiments, the oral dosage forms of the present invention provide a sustained release of the opioid agonist contained therein, or a combination of controlled and immediate release agonist. Such dosage forms of the opioid agonist may be prepared in
25 accordance with formulations/methods of manufacture known to those skilled in the art of pharmaceutical formulation.

The benefits of the abuse-resistant dosage form are especially great in connection with oral dosage forms of strong opioid agonists (e.g., oxycodone or hydrocodone), which provide valuable analgesics but can be the subject of abuse. This is particularly true for sustained release
30 opioid agonist products which have a large dose of a desirable opioid agonist intended to be released over a period of time in each dosage unit. Drug abusers take such sustained-release product and crush, grind, extract or otherwise damage the product so that the full contents of the dosage form become available for immediate absorption. Since such tampering of the dosage form of the invention results in opioid antagonist (in addition to the releasable antagonist) also
35 becoming available for absorption, the present invention provides a means for frustrating such abuse. In addition, the present invention addresses the risk of overdose to ordinary patients from "dumping" effect of the full dose of the opioid agonist if the product is accidentally chewed or

5 crushed.

The term "sustained release" is defined for purposes of the present invention as the release of the opioid agonist from the oral dosage form at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective analgesic concentration or "MEAC") but below toxic levels over a period of 8 to 24 hours, 10 preferable over a period of time indicative of a twice-a-day or a once-a-day formulation.

The invention may provide for a safer product (e.g., less respiratory depression), if the product is misused, as well as one with less risk of abuse.

In certain embodiments, a combination of two opioid agonists is included in the formulation. In further embodiments, one or more opioid agonist is included and a further non- 15 opioid drug is also included. Such non-opioid drugs would preferably provide additional analgesia, and include, for example, aspirin, acetaminophen, non-steroidal anti-inflammatory drugs ("NSAIDS"), NMDA antagonists, and cyclooxygenase-II inhibitors ("COX-II inhibitors").

In yet further embodiments, a non-opioid drug can be included which provides a desired effect other than analgesia, e.g., antitussive, expectorant, decongestant, or antihistamine drugs, 20 and the like.

For purposes of the present invention, the term "opioid agonist" is interchangeable with the term "opioid" or "opioid analgesic" and shall include combinations of more than one opioid agonist, and also include the base of the opioid, mixed agonist-antagonists, partial agonists, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and 25 mixtures thereof.

For purposes of the present invention, the term "opioid antagonist" shall include combinations of more than one opioid antagonist, and also include the base, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and mixtures thereof.

The invention disclosed herein is meant to encompass all pharmaceutically acceptable 30 salts thereof of the disclosed opioid agonists and antagonists. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, sodium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; 35 inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as

5 arginate, aspartate, glutamate and the like.

Some of the opioid agonists and antagonists disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described
10 herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and
15 isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposable
20 on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

25 The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

The present invention is further directed to a method of decreasing the potential for abuse of an opioid agonist in an oral dosage form. The method comprises providing the opioid agonist in an oral dosage form as described herein.

30

DETAILED DESCRIPTION OF THE INVENTION

It has been postulated that there exists at least three subspecies of opioid receptors, designated mu, kappa, and delta. Within this framework, the mu receptor is considered to be involved in the production of supraspinal analgesia, respiratory depression, euphoria, and
35 physical dependence. The kappa receptor is considered to be involved in inducing spinal analgesia, miosis and sedation. Activation of the gamma receptors causes dysphoria and hallucinations, as well as respiratory and vasomotor stimulatory effects. A receptor distinct from

5 the mu receptor and designated gamma has been described in the mouse vas deferens, Lord, et al. Nature, 1977, 267, 495-99. Opioid agonists are thought to exert their agonist actions primarily at the mu receptor and to a lesser degree at the kappa receptor. There are a few drugs that appear to act as partial agonists at one receptor type or another. Such drugs exhibit a ceiling effect. Such drugs include nalorphine, propiram, and buprenorphine. Still other drugs act as competitive
10 antagonists at the mu receptor and block the effects of morphine-like drugs, by exerting their actions at the kappa and omega receptors. The term agonist-antagonist has evolved to describe such mechanism of actions.

The present invention is directed to a controlled release opioid analgesic, similar in analgesic spectrum to existing controlled-release opioid analgesics, which is formulated in order
15 to reduce and minimize misuse, abuse and diversion. In certain embodiments, these characteristics are conferred by the inclusion of an opioid antagonist such as naltrexone HCl, which is itself formulated in a unique controlled release matrix. The properties of this formulation are developed to liberate the antagonist in conditions of misuse or tampering yet a negligible amount of antagonist would be released (an amount which does not affect the
20 analgesia experienced by the patient) under the prescribed conditions of use.

In certain embodiments of the invention, the release for the antagonist component of the formulation is expressed in terms of a ratio of the release achieved after tampering, e.g., by crushing or chewing, relative to the amount released from the intact formulation. The ratio is therefore expressed as [Crushed]/[Whole], and it is desired that this ratio have a numerical range
25 of at least 3:1 or greater (crushed release in 1 hour/ intact release in 1 hour).

In certain preferred embodiments, the opioid antagonist in a substantially non-releasable form comprises opioid antagonist particles coated with a coating that substantially prevents its release. In preferred embodiments, such coating surrounds the antagonist particles and is impermeable to the drug and is insoluble in the gastrointestinal system. When the dosage form of
30 the present invention is orally administered to humans, the opioid antagonist is not substantially released from the coating and is, therefore, not available for absorption into the body. Thus, the opioid antagonist, although present in the dosage form, does not substantially block the analgesic effectiveness of the opioid agonist. However, if the oral dosage form of the present invention is tampered with as to compromise the integrity of the coating, the opioid antagonist contained
35 therein would be made available to at least partially block the effect of the opioid agonist. This characteristic decreases the potential for abuse or diversion of the opioid agonist in the oral dosage form. For example, if one attempts to abuse the drug contained in the oral dosage form of

5 the present invention by, e.g., chewing, crushing, grinding or dissolving it in a solvent with heat (e.g., greater than about 45°C to about 50°C), the coating will be damaged and will no longer prevent the opioid antagonist from being released. Upon administration, the opioid antagonist will be released and significantly block the euphoric effect of the opioid agonist.

10 In certain embodiments of the invention, the ratio of the opioid agonist to the coated opioid antagonist is such that when the oral dosage form is tampered with as to compromise the integrity of the coating that renders the opioid antagonist substantially non-releasable, the euphoric effect of the agonist would be negated by the opioid antagonist when misused by a human subject orally, parenterally, intranasally or sublingually. In certain preferred embodiments of the invention, the euphoric effect of the opioid agonist would be negated by the opioid antagonist when misused parenterally or sublingually.

15 In certain other embodiments of the present invention, the opioid antagonist in a substantially non-releasable form comprises an opioid antagonist dispersed in a matrix that renders the antagonist substantially non-releasable, wherein the matrix comprises one or more of a pharmaceutically acceptable hydrophobic material. The antagonist is substantially not released from the matrix, thus is not made available to be absorbed during its transit through the gastrointestinal system.

20 In certain other embodiments of the present invention, the opioid antagonist in a matrix that renders the antagonist substantially non-releasable comprises an opioid antagonist dispersed in a melt-extruded matrix, wherein the matrix comprises one or more of a pharmaceutically acceptable hydrophobic material.

25 All discussion herein directed to the non-releasable component and its release upon tampering as well as all general discussion is in addition to the releasable antagonist of the intact dosage form. As discussed, the releasable form of the antagonist can be released from the same component as the non-releasable, from a separate component or from a combination of both components.

30 The releasable antagonist of the present invention can comprises an amount of the opioid antagonist such as naltrexone in an amount (i) which does not cause a reduction in the level of analgesia elicited from the dosage form upon oral administration to a non-therapeutic level and (ii) which provides at least a mildly negative, "aversive" experience in physically dependent human subjects, for example, physically dependent addicts (e.g., precipitated abstinence syndrome) when taking one dosage form or more than one dosage form. Preferably, the amount of antagonist included in the intact oral dosage form is (iii) less positively reinforcing (e.g., less

5 "liked") by a non-physically dependent human subject, e.g., opioid addict, than a comparable oral dosage form without the antagonist included.

The amount of antagonist which is useful to achieve parameters (i) - (iii) set forth in the preceding paragraph may be determined at least in part, for example, through the use of "surrogate" tests, such as a VAS scale (where the subject grades his/her perception of the effect
10 of the dosage form) and/or via a measurement such as pupil size (measured by pupillometry). Such measurements allow one skilled in the art to determine the dose of antagonist relative to the dose of agonist which causes a diminution in the opiate effects of the agonist. Subsequently, one skilled in the art can determine the level of opioid antagonist that causes aversive effects in
15 physically dependent subjects as well as the level of opioid antagonist that minimizes "liking scores" or opioid reinforcing properties in non-physically dependent addicts. Once these levels of opioid antagonist are determined, it is then possible to determine the range of antagonist dosages at or below this level which would be useful in achieving parameters (i) - (iii) set forth in the preceding paragraph.

In certain preferred embodiments, the opioid agonist or analgesic is selected from the
20 group consisting of hydrocodone, morphine, hydromorphone, oxycodone, codeine, levorphanol, meperidine, methadone, or salts thereof, or mixtures thereof. In certain preferred embodiments, the opioid agonist is hydrocodone or oxycodone. Equianalgesic doses of these opioids, in comparison to a 15 mg dose of hydrocodone, are set forth in Table 1 below:

25 **Table 1: Equianalgesic Doses of Opioids**

Opioid	Calculated Dose (mg)
Oxycodone	13.5
Codeine	90.0
Hydrocodone	15.0
Hydromorphone	3.375
Leverphanol	1.8
Meperidine	135.0
Methadone	9.0

Morphine	27.0
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Based on a ratio of releasable naltrexone in an amount from about 0.5 to about 4 mg per 15 mg of hydrocodone, the approximate ratio of naltrexone to 1mg of each opioid is set forth in Table 2:

Table 2: Weight Ratio of Naltrexone per Dose Opioid

Opioid	Weight Ratio Naltrexone per 1 mg Opioid
Oxycodone	0.037 to 0.296
Codeine	0.005 to 0.044
Hydrocodone	0.033 to 0.267
Hydromorphone	0.148 to 1.185
Leverphanol	0.278 to 2.222
Meperidine	0.0037 to 0.0296
Methadone	0.056 to 0.444
Morphine	0.018 to 0.148

10

Based on a ratio of about 0.75 mg to about 3 mg naltrexone per 15 mg hydrocodone of naltrexone, the approximate ratio of naltrexone to 1mg of each opioid is set forth in Table 3:

Table 3: Weight Ratio of Naltrexone per Dose Opioid

Opioid	Weight Ratio Naltrexone
Oxycodone	0.056 to 0.222
Codeine	0.0083 to 0.033
Hydrocodone	0.050 to 0.200
Hydromorphone	0.222 to 0.889

Leverphanol	0.417 to 1.667
Meperidine	0.0056 to 0.022
Methadone	0.083 to 0.333
Morphine	0.028 to 0.111

5

Ratios of opioids to other antagonists besides naltrexone can be obtained by comparing equivalent doses of other antagonists to equal doses of naltrexone. The specification and examples of PCT/US98/27257 which discloses releasable opioid antagonist/agonist formulations is hereby incorporated by reference in combination with the sequestered antagonist as disclosed herein.

10

The releasable antagonist of the present invention can comprises an amount of the opioid antagonist which can selectively enhancing the potency of the opioid agonists and simultaneously attenuating undesirable side-effects, including physical dependence, caused by the chronic administration of said opioid agonists. Morphine and other bimodally-acting (inhibitory/excitatory) opioid agonists bind to and activate inhibitory and excitatory opioid receptors on nociceptive neurons mediating pain. Activation of inhibitory receptors by said agonists causes analgesia. Activation of excitatory receptors by said agonists results in anti-analgesic effects, development of physical dependence, tolerance, hyperexcitability, hyperalgesia and other undesirable side-effects. The co-administration of the releasable opioid antagonist which binds to and inactivates excitatory opioid receptors results in the blocking of excitatory anti-analgesic side-effects of said opioid agonists on these neurons, thereby resulting in enhanced analgesic potency which permits the use of lower doses of morphine or other conventional opioid analgesics. The specification and examples of U.S. Patent No. 5,472,943 which describes such formulations and methods is hereby incorporated by reference in combination with the sequestered antagonist as disclosed herein.

15

20

All known references of releasable opioid antagonists with opioid agonists such as U.S. Patent No. 3,773,955 (Pachter, et al.); U.S. Patent No. 3,493,657 (Lewenstein, et al.) U.S. Patent No. 4,457,933 (Gordon, et al.); U.S. Patent No. 4,582,835 (Lewia) U.S. Patent Nos. 5,512,578; 5,472,943; 5,580,876; and 5,767,125 (Crain) and U.S. Patent No. 4,769,372 and 4,785,000 (Kreek) can be combined with a sequestered antagonist as disclosed herein and all of these references are hereby incorporated by reference.

25

30

5 U.S. Provisional Application No. 60/181,369 and 60/181,358 both filed February 6, 2000 are hereby incorporated by reference in combination with the three component invention as disclosed herein.

All commercial products of opioid agonist and releasable antagonists can be combined with a sequestered antagonist as disclosed herein. For example, Talwin NX can be formulated
10 with a sequestered antagonist to reduce oral abuse as well as parenteral abuse of the opioid therein.

In preferred embodiments, opioid agonists useful in the present invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine,
15 diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol,
20 metazocine, methadone, metopon, morphine, myrophine, narcaine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures of any of the foregoing, salts of any of the
25 foregoing, and the like. In certain embodiments, the amount of the opioid agonist in the claimed opioid composition may be about 75 ng to 750 mg.

Although hydrocodone and oxycodone are effective in the management of pain, there has been an increase in their abuse by individuals who are psychologically dependent on opioids or who misuse opioids for non-therapeutic reasons. Previous experience with other opioids has
30 demonstrated a decreased abuse potential when opioids are administered in combination with a narcotic antagonist especially in patients who are ex-addicts. Weinhold LL, et al. Buprenorphine Alone and in Combination with Naltrexone in Non-Dependent Humans, *Drug and Alcohol Dependence* 1992; 30:263-274; Mendelson J., et al., Buprenorphine and Naloxone Interactions in Opiate-Dependent Volunteers, *Clin Pharm Ther.* 1996; 60:105-114; both of which are hereby
35 incorporated by reference. These combinations, however, do not contain the opioid antagonist that is in a substantially non-releasable form. Rather, the opioid antagonist is released in the gastrointestinal system when orally administered and is made available for absorption, relying on

5 the physiology of the host to differentially metabolize the agonist and antagonist and negate the agonist effects.

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple central nervous system and gastrointestinal actions. Chemically, hydrocodone is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-one, and is also known as dihydrocodeinone. Like other opioids, hydrocodone may be habit forming and may produce drug dependence of the morphine type. In excess doses hydrocodone, like other opium derivatives, will depress respiration.

Oral hydrocodone is also available in Europe (Belgium, Germany, Greece, Italy, Luxembourg, Norway and Switzerland) as an antitussive agent. A parenteral formulation is also available in Germany as an antitussive agent. For use as an analgesic, hydrocodone bitartrate is commercially available in the United States only as a fixed combination with non-opiate drugs (i.e., ibuprofen, acetaminophen, aspirin, etc.) for relief of moderate or moderately severe pain.

A common dosage form of hydrocodone is in combination with acetaminophen, and is commercially available, e.g., as Lortab® in the U.S. from UCB Pharma, Inc. as 2.5/500 mg, 5/500 mg, 7.5/500 mg and 10/500 mg hydrocodone/acetaminophen tablets. Tablets are also available in the ratio of 7.5mg hydrocodone bitartrate and 650mg acetaminophen; and 7.5mg hydrocodone bitartrate and 750mg acetaminophen. Hydrocodone in combination with aspirin is given in an oral dosage form to adults generally in 1-2 tablets every 4-6 hours as needed to alleviate pain. The tablet form is 5mg hydrocodone bitartrate and 224mg aspirin with 32mg caffeine; or 5mg hydrocodone bitartrate and 500mg aspirin. A relatively new formulation comprises hydrocodone bitartrate and ibuprofen. Vicoprofen®, commercially available in the U.S. from Knoll Laboratories, is a tablet containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen. The present invention is contemplated to encompass all such formulations, with the inclusion of an opioid antagonist in releasable and non-releasable form.

Oxycodone, chemically known as 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, is an opioid agonist whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria and feelings of relaxation. The precise mechanism of its analgesic action is not known, but specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone is commercially available in the United States, e.g., as Oxycontin® from Purdue Pharma L.P. as controlled-release tablets for oral administration containing 10 mg, 20 mg, 40 mg or 80 mg oxycodone hydrochloride, and as OxyIR™, also from Purdue Pharma L.P.,

5 as immediate-release capsules containing 5 mg oxycodone hydrochloride. The present invention is contemplated to encompass all such formulations, with the inclusion of an opioid antagonist in a substantially non-releasable form.

In preferred embodiments, the opioid antagonist of the present invention includes naltrexone, nalbuphine, cyclazacine, levallorphan and mixtures thereof. In certain preferred
10 embodiments, the opioid antagonist is naloxone or naltrexone. In certain embodiments, the amount of the opioid antagonist, present in a substantially non-releasable form, may be about 10 ng to 275 mg.

Naloxone is an opioid antagonist which is almost void of agonist effects. Subcutaneous doses of up to 12 mg of naloxone produce no discernable subjective effects, and 24 mg naloxone
15 causes only slight drowsiness. Small doses (0.4-0.8 mg) of naloxone given intramuscularly or intravenously in man prevent or promptly reverse the effects of morphine-like opioid agonist. One mg of naloxone intravenously has been reported to completely block the effect of 25 mg of heroin. The effects of naloxone are seen almost immediately after intravenous administration. The drug is absorbed after oral administration, but has been reported to be metabolized into an
20 inactive form rapidly in its first passage through the liver such that it has been reported to have significantly lower potency than as when parenterally administered. Oral dosage of more than 1 g have been reported to be almost completely metabolized in less than 24 hours. It has been reported that 25% of naloxone administered sublingually is absorbed. Weinberg, et al., Sublingual Absorption of selected Opioid Analgesics, Clin Pharmacol Ther. (1988); 44:335-340.

25 Other opioid antagonists, for example, cyclazocine and naltrexone, both of which have cyclopropylmethyl substitutions on the nitrogen, retain much of their efficacy by the oral route and their durations of action are much longer, approaching 24 hours after oral doses.

In the treatment of patients previously addicted to opioids, naltrexone has been used in large oral doses (over 100 mg) to prevent euphorogenic effects of opioid agonists. Naltrexone has
30 been reported to exert strong preferential blocking action against μ over delta sites. Naltrexone is known as a synthetic congener of oxymorphone with no opioid agonist properties, and differs in structure from oxymorphone by the replacement of the methyl group located on the nitrogen atom of oxymorphone with a cyclopropylmethyl group. The hydrochloride salt of naltrexone is soluble in water up to about 100 mg/cc. The pharmacological and pharmacokinetic properties of
35 naltrexone have been evaluated in multiple animal and clinical studies. See, e.g., Gonzalez JP, et al. Naltrexone: A review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy in the Management of Opioid Dependence. Drugs 1988; 35:192-213,

5 hereby incorporated by reference. Following oral administration, naltrexone is rapidly absorbed (within 1 hour) and has an oral bioavailability ranging from 5-40%. Naltrexone's protein binding is approximately 21% and the volume of distribution following single-dose administration is 16.1 L/kg.

Naltrexone is commercially available in tablet form (Revia[®], DuPont) for the treatment of
10 alcohol dependence and for the blockade of exogenously administered opioids. See, e.g., Revia (naltrexone hydrochloride tablets). *Physician's Desk Reference* 51st ed., Montvale, NJ. "Medical Economics" 1997; 51:957-959. A dosage of 50 mg Revia[®] blocks the pharmacological effects of 25 mg IV administered heroin for up to 24 hours.

It is known that when coadministered with morphine, heroin or other opioids on a chronic
15 basis, naltrexone blocks the development of physical dependence to opioids. It is believed that the method by which naltrexone blocks the effects of heroin is by competitively binding at the opioid receptors. Naltrexone has been used to treat narcotic addiction by complete blockade of the effects of opioids. It has been found that the most successful use of naltrexone for a narcotic addiction is with narcotic addicts having good prognosis, as part of a comprehensive occupational
20 or rehabilitative program involving behavioral control or other compliance enhancing methods. For treatment of narcotic dependence with naltrexone, it is desirable that the patient be opioid-free for at least 7-10 days. The initial dosage of naltrexone for such purposes has typically been about 25 mg, and if no withdrawal signs occur, the dosage may be increased to 50 mg per day. A daily dosage of 50 mg is considered to produce adequate clinical blockade of the actions of
25 parenterally administered opioids. Naltrexone has also been used for the treatment of alcoholism as an adjunct with social and psychotherapeutic methods.

In certain embodiments of the present invention, ratio of the opioid agonist to the substantially non-releasable form of an opioid antagonist in the oral dosage form is such that the effect of the opioid agonist is at least partially blocked when the dosage form is chewed, crushed
30 or dissolved in a solvent and heated, and administered orally, intranasally, parenterally or sublingually. Since the oral dosage form of the present invention, when administered properly as intended, would not substantially release the opioid antagonist, the amount of such antagonist may be varied more widely than if the opioid antagonist is available to be released into the gastrointestinal system upon oral administration. For safety reasons, the amount of the antagonist
35 present in a substantially non-releasable form should not be harmful to humans even if fully released. The ratio of particular opioid agonist to antagonist can be determined without undue experimentation by one skilled in the art.

5 The oral dosage form of the present invention may further include, in addition to an opioid agonist and releasable and non-releasable antagonist, one or more drugs that may or may not act synergistically therewith. Thus, in certain embodiments, a combination of two opioid agonists may be included in the dosage form, in addition to the opioid antagonist. For example, the dosage form may include two opioid agonists having different properties, such as half-life, solubility, potency, and a combination of any of the foregoing. In yet further embodiments, one or more opioid agonist is included and a further non-opioid drug is also included, in addition to the opioid antagonist. Such non-opioid drugs would preferably provide additional analgesia, and include, for example, aspirin, acetaminophen; non-steroidal anti-inflammatory drugs ("NSAIDS"), e.g., ibuprofen, ketoprofen, etc.; N-methyl-D-aspartate (NMDA) receptor antagonists, e.g., a morphinan such as dextromethorphan or dextrorphan, or ketamine; cyclooxygenase-II inhibitors ("COX-II inhibitors"); and/or glycine receptor antagonists.

10 In certain preferred embodiments of the present invention, the invention allows for the use of lower doses of the opioid analgesic by virtue of the inclusion of an additional non-opioid agonist, such as an NSAID or a COX-2 inhibitor. By using lower amounts of either or both drugs, the side effects associated with effective pain management in humans are reduced.

20 Suitable non-steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Useful dosages of these drugs are well known to those skilled in the art.

25 N-methyl-D-aspartate (NMDA) receptor antagonists are well known in the art, and encompass, for example, morphinans such as dextromethorphan or dextrorphan, ketamine, d-methadone or pharmaceutically acceptable salts thereof. For purposes of the present invention, the term "NMDA antagonist" is also deemed to encompass drugs that block a major intracellular consequence of NMDA-receptor activation, e.g. a ganglioside such as GM₁ or GT_{1b}, a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(6-aminothexyl)-5-chloro-1-naphthalenesulfonamide. These drugs are stated to inhibit the development of tolerance to and/or dependence on addictive drugs, e.g., narcotic analgesics such as morphine, codeine, etc. in U.S. Pat. Nos. 5,321,012 and 5,556,838 (both to Mayer, et al.), and to treat chronic pain in U.S. Pat. No. 5,502,058 (Mayer, et al.), all of which are hereby incorporated by reference. The

5 NMDA antagonist may be included alone, or in combination with a local anesthetic such as lidocaine, as described in these Mayer, et. al. patents.

The treatment of chronic pain via the use of glycine receptor antagonists and the identification of such drugs is described in U.S. Pat. No. 5,514,680 (Weber, et al.), hereby incorporated by reference.

10 COX-2 inhibitors have been reported in the art and many chemical structures are known to produce inhibition of cyclooxygenase-2. COX-2 inhibitors are described, for example, in U.S. Patent Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,474,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311, all of which are hereby incorporated by reference. Certain preferred COX-2 inhibitors include celecoxib (SC-
15 58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), MK-966 (also known as Vioxx), nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof. Dosage levels of COX-2 inhibitor on the order of from about 0.005 mg to about 140 mg per kilogram of body weight per day are therapeutically effective in combination with an opioid analgesic. Alternatively, about 0.25 mg
20 to about 7 g per patient per day of a COX-2 inhibitor is administered in combination with an opioid analgesic.

In yet further embodiments, a non-opioid drug can be included which provides a desired effect other than analgesia, e.g., antitussive, expectorant, decongestant, antihistamine drugs, local anesthetics, and the like.

25

PREPARATION OF OPIOID ANTAGONIST IN A SUBSTANTIALLY NON-RELEASABLE OR NON-RELEASABLE FORM

In certain embodiments of the present invention, an opioid antagonist in a substantially
30 non-releasable form may be prepared by combining the antagonist with one or more of a pharmaceutically acceptable hydrophobic material. For example, opioid antagonist particles may be coated with coating that substantially prevents the release of the antagonist, the coating comprising the hydrophobic materials(s). Another example would be an opioid antagonist that is dispersed in a matrix that renders the antagonist to be substantially non-releasable, the matrix
35 comprising the hydrophobic materials(s). In certain embodiments, the pharmaceutical acceptable hydrophobic material comprises a cellulose polymer selected from the group consisting of ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular

5 weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate and cellulose triacetate. An example of ethylcellulose is one that has an ethoxy content of 44 to 55%. Ethylcellulose may be used in the form of an alcoholic solution. In certain other embodiments, the hydrophobic material comprises polylactic acid, polyglycolic acid or a co-polymer of the polylactic and polyglycolic acid.

10 In certain embodiments, the hydrophobic material may comprise a cellulose polymer selected from the group consisting of cellulose ether, cellulose ester, cellulose ester ether, and cellulose. The cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit, from greater than zero and up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups present on the anhydroglucose unit comprising the cellulose polymer
15 that are replaced by a substituting group. Representative materials include: a polymer selected from the group consisting of cellulose acrylate, cellulose diacrylate, cellulose triacrylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono, di, and tricellulose alkanylates, mono, di, and tricellulose aroylates, and mono, di, and tricellulose alkenylates. Exemplary polymers include cellulose acetate having a D.S. and an acetyl content up to 21%; cellulose acetate having an
20 acetyl content up to 32 to 39.8%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%.

More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45 and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose
25 acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacrylate having a D.S. of 2.9 to 3 such as cellulose triacetate, cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacrylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, and coesters of
30 cellulose such as cellulose acetate butyrate, cellulose acetate octanoate butyrate and cellulose acetate propionate.

Additional cellulose polymers useful for preparing an opioid antagonist in a substantially non-releasable form includes acetaldehyde dimethyl cellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, and cellulose acetate dimethylaminocellulose
35 acetate.

An acrylic polymer useful for preparation of the opioid antagonist in a substantially non-releasable form includes, but are not limited to, acrylic resins comprising copolymers synthesized

5 from acrylic and methacrylic acid esters (e.g., the copolymer of acrylic acid lower alkyl ester and methacrylic acid lower alkyl ester) containing about 0.02 to 0.03 mole of a tri (lower alkyl) ammonium group per mole of the acrylic and methacrylic monomers used. An example of a suitable acrylic resin is a polymer manufactured by Rohm Pharma GmbH and sold under the Eudragit® RS trademark. Eudragit RS30D is preferred. Eudragit® RS is a water insoluble
 10 copolymer of ethyl acrylate (EA), methyl methacrylate (MM) and trimethylammoniummethyl methacrylate chloride (TAM) in which the molar ratio of TAM to the remaining components (EA and MM) is 1:40. Acrylic resins such as Eudragit® RS may be used in the form of an aqueous suspension.

In certain embodiments of the invention, the acrylic polymer may be selected from the
 15 group consisting of acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate co-
 20 polymers.

When the opioid antagonist in a substantially non-releasable form comprises opioid antagonist particles coated with a coating that renders the antagonist substantially non-releasable, and when a cellulose polymer or an acrylic polymer is used for preparation of the coating composition, suitable plasticizers, e.g., acetyl triethyl citrate and/or acetyl tributyl citrate may also
 25 be admixed with the polymer. The coating may also contain additives such as coloring agents, talc and/or magnesium stearate, which are well known in the coating art.

The coating composition may be applied onto the opioid antagonist particles by spraying it onto the particles using any suitable spray equipment known in the art. For example, a Wuster fluidized-bed system may be used in which an air jet, injected from underneath, fluidizes the
 30 coated material and effects drying while the insoluble polymer coating is sprayed on. The thickness of the coating will depend on the characteristics of the particular coating composition being used. However, it is well within the ability of one skilled in the art to determine by routine experimentation the optimum thickness of a particular coating required for a particular dosage form of the present invention.

35 The pharmaceutically acceptable hydrophobic material useful for preparing an opioid antagonist in a substantially non-releasable form includes a biodegradable polymer comprising a poly(lactic/glycolic acid) ("PLGA"), a polylactide, a polyglycolide, a polyanhydride, a

5 polyorthoester, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, polyesters, polydioxanone, polygluconate, polylactic-acid-polyethylene oxide copolymers, poly(hydroxybutyrate), polyphosphoester or mixtures or blends of any of these.

In certain embodiments, biodegradable polymer comprises a poly(lactic/glycolic acid), a copolymer of lactic and glycolic acid, having molecular weight of about 2,000 to about 500,000
10 daltons. The ratio of lactic acid to glycolic acid is from about 100:0 to about 25:75, with the ratio of lactic acid to glycolic acid of 65:35 being preferred.

Poly(lactic/glycolic acid) may be prepared by the procedure set forth in U.S. Patent No. 4,293,539 (Ludwig et al.), the disclosure of which is hereby incorporated by reference in its entirety. In brief, Ludwig prepares the copolymer by condensation of lactic acid and glycolic acid
15 in the presence of a readily removable polymerization catalyst (e.g., a strong acid ion-exchange resin such as Dowex HCR-W2-H). The amount of catalyst is not critical to the polymerization, but typically is from about 0.01 to about 20 parts by weight relative to the total weight of combined lactic acid and glycolic acid. The polymerization reaction may be conducted without solvents at a temperature from about 100 C to about 250 C for about 48 to about 96 hours,
20 preferably under a reduced pressure to facilitate removal of water and by-products. Poly(lactic/glycolic acid) is then recovered by filtering the molten reaction mixture in an organic solvent such as dichloromethane or acetone and then filtering to remove the catalyst.

Once the opioid antagonist in a substantially non-releasable form is prepared, it may be combined with an opioid agonist and releasable antagonist, along with conventional excipients
25 known in the art, to prepare the oral dosage form of the present invention.

In certain preferred embodiments of the invention, the oral dosage form is a capsule or a tablet. When being formulated as a tablet, the agents may be combined with one or more inert, non-toxic pharmaceutical excipients which are suitable for the manufacture of tablets. Such excipients include, for example, an inert diluent such as lactose; granulating and disintegrating
30 agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate.

The oral dosage form of the present invention may be formulated to provide immediate release of the opioid agonist contained therein. In other embodiments of the invention, however, the oral dosage form provides sustained-release of the opioid agonist.

35 In certain embodiments, the oral dosage forms providing sustained release of the opioid agonist and/or releasable antagonist may be prepared by admixing the opioid antagonist in a substantially non-releasable form with the agonist and releasable antagonist and desirable

5 pharmaceutical excipients to provide a tablet, and then coating the tablet with a sustained-release tablet coating.

In certain embodiments of the invention, sustained release opioid agonist tablets may be prepared by admixing the substantially non-releasable form of an opioid antagonist with a releasable opioid antagonist and agonist in a matrix that provides the tablets with sustained-releasing properties.

Detailed description for preparing sustained-release oral dosage forms according to the present invention is set forth below.

15 **PREPARATION OF CONTROLLED RELEASE DOSAGE FORMS
CONTAINING AN OPIOID AGONIST AND A SUBSTANTIALLY
NON-RELEASABLE FORM OF AN OPIOID ANTAGONIST**

A combination of the opioid agonist and a substantially non-releasable form of an opioid antagonist may be formulated as a controlled or sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may optionally include a sustained release carrier which is incorporated into a matrix along with the opioid agonist and a non-available form of an opioid antagonist, or may be applied as a sustained release coating.

In embodiments in which the opioid agonist comprises hydrocodone, the sustained release oral dosage forms may include analgesic doses from about 8 mg to about 50 mg of hydrocodone per dosage unit. In sustained release oral dosage forms, where hydromorphone is the therapeutically active opioid, it is included in an amount from about 2 mg to about 64 mg hydromorphone hydrochloride. In another embodiment, the opioid agonist comprises morphine, and the sustained release oral dosage forms of the present invention include from about 2.5 mg to about 800 mg morphine, by weight. In yet another embodiment, the opioid agonist comprises oxycodone and the sustained release oral dosage forms include from about 2.5 mg to about 800 mg oxycodone. In certain preferred embodiments, the sustained release oral dosage forms include from about 20 mg to about 30 mg oxycodone. Controlled release oxycodone formulations are known in the art. The following documents describe various controlled release oxycodone formulations suitable for use in the invention described herein, and processes for their manufacture: U.S. Patent Nos. 5,266,331; 5,549,912; 5,508,042; and 5,656,295. The opioid agonist may comprise tramadol and the sustained release oral dosage forms may include from about 25 mg to 800 mg tramadol per dosage unit. The dosage form may contain more than one

42

5 opioid agonist to provide a substantially equivalent therapeutic effect. Alternatively, the dosage form may contain molar equivalent amounts of other salts of the opioid agonists useful in the present invention.

In one preferred embodiment of the present invention, the sustained release dosage form comprises such particles comprising the opioid agonist, wherein the particles have diameter from 10 about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm.

The opioid agonist particles are preferably film coated with a material that permits release of the opioid agonist at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, a desired in-vitro release rate. The sustained release coating formulations of the present invention should be capable of producing a 15 strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

The dosage forms comprising an opioid agonist and a substantially non-releasable opioid antagonist may optionally be coated with one or more materials suitable for the regulation of the opioid agonist release or for the protection of the formulation. In one embodiment, coatings are 20 provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the opioid in desired areas of the gastro-intestinal (GI) tract, e.g., the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release of the opioid regardless of pH- 25 changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

30 Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate 35 (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

5 In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic (with or without the COX-2 inhibitor) is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described, e.g., in detail in U.S. Patent Nos. 5,273,760 and 5,286,493, assigned to the Assignee of the present invention and hereby incorporated by reference.

10 Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include Assignee's U.S. Patent Nos. 5,324,351; 5,356,467, and 5,472,712, hereby incorporated by reference in their entirety.

ALKYLCELLULOSE POLYMERS

20 Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

25 One commercially-available aqueous dispersion of ethylcellulose is Aquacoat[®] (FMC Corp., Philadelphia, Pennsylvania, U.S.A.). Aquacoat[®] is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat[®] with a suitable plasticizer prior to use.

35 Another aqueous dispersion of ethylcellulose is commercially available as Surelease[®] (Colorcon, Inc., West Point, Pennsylvania, U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

5

ACRYLIC POLYMERS

In other preferred embodiments of the present invention, the hydrophobic material comprising the controlled release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit[®] from Rohm Tech, Inc. There are several different types of Eudragit[®]. For example, Eudragit[®] E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit[®] L is a methacrylic acid copolymer which does not swell at about pH < 5.7 and is soluble at about pH > 6. Eudragit[®] S does not swell at about pH < 6.5 and is soluble at about pH > 7. Eudragit[®] RL and Eudragit[®] RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit[®] RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit[®] RL30D and Eudragit[®] RS30D, respectively. Eudragit[®] RL30D and Eudragit[®] RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups,

5 the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in
10 aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS,
15 and 10% Eudragit® RL:Eudragit® 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

PLASTICIZERS

20 In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is
25 preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular
30 coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the
35 aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl

5 phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

10 It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

PROCESSES FOR PREPARING COATED BEADS

15 When a hydrophobic controlled release coating material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, which are already coated with an opioid agonist, a plurality of the resultant solid controlled release beads may thereafter be placed in a gelatin capsule, with the opioid antagonist in a substantially non-releasable form. The dosage form provides an effective controlled release dose of the opioid agonist when ingested and
20 contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

The controlled release bead formulations of the present invention slowly release the opioid agonist, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which
25 the plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with an opioid agonist may be prepared, e.g., by dissolving the
30 drug in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wurster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the opioid to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the
35 solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release

5 coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective
10 amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat[®] or Surelease[®], may be used. If Surelease[®] is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit[®] can be used.

The coating solutions of the present invention preferably contain, in addition to the
15 film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color may be added to Aquacoat[®] via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to
20 water soluble polymer solution and then using low shear to the plasticized Aquacoat[®]. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the
25 coating.

Plasticized hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is
30 sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined controlled release of said therapeutically active agent when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as
35 Opadry[®], is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

5 The release of the therapeutically active agent from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

10 The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

15 The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

 The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

 The release-modifying agent may also comprise a semi-permeable polymer.

20 In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

 The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Patent Nos. 3,345,770; 3,916,889; 4,063,064; and 4,088,864
25 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

MATRIX FORMULATIONS

30 In other embodiments of the present invention, the controlled release formulation is achieved via a matrix having a controlled release coating as set forth above. The present invention also comprises sustained-release tablets comprising an opioid agonist and opioid antagonist particles coated with a coating that renders the antagonist substantially non-releasable, wherein the agonist and the antagonist are dispersed in a controlled release matrix that affords *in-*
35 *vitro* dissolution rates of the opioid agonist within the preferred ranges and that releases the opioid agonist in a pH-dependent or pH-independent manner. The materials suitable for inclusion in a controlled release matrix will depend on the method used to form the matrix.

5 For example, a matrix in addition to the opioid agonist and the substantially non-releasable form of the coated opioid antagonist, may include:

Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials; the list is not meant to be exclusive, and any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting controlled
10 release of the opioid may be used in accordance with the present invention.

Digestible, long chain (C_8 - C_{30} , especially C_{12} - C_{24}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols.

Of these polymers, acrylic polymers, especially Eudragit® RSPO - the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage
15 form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25° and 90°C. Of the long chain hydrocarbon materials, fatty
20 (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, the oral dosage form contains up to 60% (by weight) of at least one polyalkylene glycol.

The hydrophobic material is preferably selected from the group consisting of
25 alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl
30 methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and
35 mixtures of the foregoing.

Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the

5 invention have a melting point from about 30° to about 200°C, preferably from about 45° to about 90°C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol and hydrophobic and
10 hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30° to about 100°C.

Suitable hydrophobic materials which may be used in accordance with the present
15 invention include digestible, long chain (C₈-C₃₀, especially C₁₂-C₂₄), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight)
20 of at least one digestible, long chain hydrocarbon.

Preferably, a combination of two or more hydrophobic materials are included in the matrix formulations. If an additional hydrophobic material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be
25 exclusive.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C₁₂-C₂₄, preferably C₁₄-C₂₂, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy (C₁ to C₆) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially,
30 hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of opioid release required. The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one
35 aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of opioid release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol,

5 the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

10 In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/ polyalkylene glycol determines, to a considerable extent, the release rate of the opioid from the formulation. A ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

15 The at least one polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1,000 and 15,000 especially between 1,500 and 12,000.

Another suitable controlled release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C₁₂ to C₃₆ aliphatic alcohol and, optionally, a polyalkylene glycol.

20 In another preferred embodiment, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials.

In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

25 PROCESSES FOR PREPARING MATRIX - BASED BEADS

In order to facilitate the preparation of a solid, controlled release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by

30 (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and opioid or an opioid salt; (b) mixing the hydroxyalkyl cellulose containing granules with at least one C₁₂ - C₃₆ aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/opioid with water. In a particularly preferred embodiment of this process, the amount of water added during the wet

35 granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the opioid.

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5 In yet other alternative embodiments, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low
10 viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally
15 include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

MELT EXTRUSION MATRIX

20 Sustained release matrices can also be prepared via melt-granulation or melt-extrusion techniques, as long as the techniques used do not damage the integrity of the substantially non-releasable form of the opioid antagonist added during the preparation of the matrix to the extent that sufficient amount of the opioid antagonist becomes available to be released into the gastrointestinal system upon oral administration. Alternatively, the melt extrusion step may be
25 performed with the opioid agonist to produce sustained release particles of the agonist, which may then be combined with the substantially non-releasable form of the opioid antagonist. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose
30 or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Patent No. 4,861,598, assigned to the Assignee of the present invention and hereby incorporated by reference in its entirety.

35 The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the formulation should be

5 substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants,
10 flavorants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in
15 the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

20

MELT EXTRUSION MULTIPARTICULATES

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the opioid analgesic, together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a
25 homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then blended with the opioid antagonist particles coated with a coating that
30 renders the antagonist substantially non-releasable and divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the opioid agonist for a time period of from about 8 to about 24 hours.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, a therapeutically active agent, and an
35 optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and combining the particles with the

5 coated opioid antagonist particles and dividing them into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire
10 cutter, guillotine, etc.

The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a
15 range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic material as described herein. In this regard, the melt-extruded multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range.
20 Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide
25 an effective sustained release dose when ingested and contacted by gastric fluid.

In another preferred embodiment, a suitable amount of the multiparticulate extrudate is combined with the coated opioid antagonist particles and compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also
30 described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980), incorporated by reference herein.

In yet another preferred embodiment, the coated opioid antagonist particles are added during the extrusion process and the extrudate can be shaped into tablets as set forth in U.S. Patent No. 4,957,681 (Klimesch, et al.), described in additional detail above and hereby
35 incorporated by reference.

Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule can be further coated, with a sustained release coating such as the

5 sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2 to about 30 percent, although the overcoat may be greater depending upon the physical properties of the particular opioid analgesic compound utilized and the desired release rate, among other things.

10 The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded multiparticulates containing one or more of the therapeutically active agents disclosed above before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release opioid agonist for prompt therapeutic effect. The immediate release opioid agonist may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the multiparticulates after preparation of the dosage forms (e.g., controlled release coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of controlled release beads and matrix multiparticulates to achieve a desired effect.

20 The sustained release formulations of the present invention preferably slowly release the opioid agonist, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

25 In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the opioid agonist and/or coated opioid antagonist particles, which are added thereafter to the extrudate. Such formulations typically will have the drugs blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release of the opioid agonist. Such formulations may be advantageous, for example, when the therapeutically active agent included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/ or the retardant material.

30

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

35 The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

5

EXAMPLE 1

In Example 1, a substantially non-releasable form of an opioid antagonist (naltrexone HCl) is prepared by coating naltrexone particles with a coating that renders the antagonist substantially non-releasable.

10 **FORMULA:**

<i>Ingredients</i>	<i>Amt/unit (mg)</i>
LOADING	
Naltrexone HCl	5.0
Sugar Spheres (30/35 mesh)	50.0
Opadry White Y-5-7068	2.5
Purified Water	42.5*
OVERCOATING	
Opadry White Y-5-7068	3.02
Purified Water	17.11*
NON-RELEASE COATING (FOR RENDERING OPIOID ANTAGONIST SUBSTANTIALLY NON-RELEASABLE)	
Eudragit RS30D (dry wt.)	12.10
Triethyl Citrate	2.42
Talc	4.84
Purified Water	49.21*
OVERCOATING	
Opadry White Y-5-7068	4.12
Purified Water	23.35*
Total	84.0

* Remains in product as residual moisture only.

15 **PROCESS:**

1. **Solution Preparation** Dissolve the Naltrexone HCl in Purified Water. Once dissolved, add the Opadry White and continue mixing until a homogeneous dispersion is yielded.
- 20 2. **Loading** Apply the above dispersion onto the Sugar Spheres using a fluid bed coating machine.
3. **Overcoating** Prepare an overcoating solution by dispersing Opadry White in Purified Water. Apply this dispersion over the sugar spheres loaded with Naltrexone HCl using a fluid bed coating machine.

- 5 4. Retardant Coating Prepare the non-release coating solution by mixing the Eudragit RS30D, Triethyl Citrate, Talc, and Purified Water. Apply this dispersion over the loaded and overcoated sugar spheres using a fluid bed coating machine.
- 10 5. Overcoating Prepare a second overcoating solution by dispersing Opadry White in Purified Water. Apply this dispersion over the non-release coated naltrexone spheres using a fluid bed coating machine
6. Curing Cure the spheres at 45°C for approximately 48 hours.

15 The multiparticulates of Example 1 can be modified in order to have an amount of naltrexone released which provides a desired pharmacological effect as disclosed herein.

EXAMPLE 2

20 In Example 2, a substantially non-releasable form of an opioid antagonist (naltrexone HCl) is prepared as naltrexone HCl containing granulates. The granulates are comprised of naltrexone HCl dispersed in a matrix that renders the antagonist substantially non-releasable.

FORMULA:

25

<i>Ingredient</i>	<i>Amt/unit (mg)</i>
Naltrexone HCl	5.0
Dicalcium Phosphate	53.0
Poly (DL-Lactide-Co-Glycolide) polymer (PLGA) MW~ 100,000	12.0
Ethyl Acetate	
Total	70.0

* Used as a vehicle for application of PLGA polymer.

PROCESS:

- 30 1. Solution Preparation Dissolve PLGA in Ethyl Acetate by mixing.
2. Granulation Place the Naltrexone HCl, and Dicalcium Phosphate in a fluid bed coating machine and granulate by spraying the above solution.

35 The multiparticulates of Example 2 can be modified in order to have an amount of naltrexone released which provides a desired pharmacological effect as disclosed herein.

5

EXAMPLE 3

In Example 3, a substantially non-releasable form of an opioid antagonist (naltrexone HCl) is prepared as naltrexone HCl extruded pellets.

10

FORMULA:

<i>Ingredient</i>	<i>Amount (mg)</i>
Naltrexone HCl	5.0
Eudragit RSPO	180.0
Stearyl Alcohol	55.0
Total	240.0

PROCESS:

15

1. Milling Pass stearyl alcohol flakes through an impact mill.
2. Blending Mix Naltrexone HCl, Eudragit, and milled Stearyl Alcohol in a twin shell blender.
3. Extrusion Continuously feed the blended material into a twin screw extruder and collect the resultant strands on a conveyor.
4. Cooling Allow the strands to cool on the conveyor.
5. Pelletizing Cut the cooled strands into pellets using a Pelletizer.
6. Screening Screen the pellets and collect desired sieve portion.

20

- 25 The multiparticulates of Example 3 can be modified in order to have an amount of naltrexone Released which provides a desired pharmacological effect as disclosed herein

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EXAMPLE 4

Hydrocodone Bitartrate Controlled Release Tablets with Naltrexone HCl Beads and Releasable Naltrexone

<i>Ingredient</i>	<i>Amt/unit (mg)</i>
Hydrocodone Bitartrate	30.0
Stearyl Alcohol	44.0
Anhydrous Dicalcium Phosphate (Powdered)	62.0
Microcrystalline Cellulose	62.0
Glyceryl Behenate	20.0
Naltrexone HCl Binds (Example 1)	84.0
Magnesium Stearate	2.0
Opadry Red	10.0
Purified Water	56.7*
Total	314.0

* Remains in product as residual moisture only.

PROCESS:

- | | | | |
|----|----|-------------|---|
| 15 | 1. | Milling | Pass the Stearyl Alcohol flakes through an occillating mill. |
| | 2. | Blending | Mix the Hydrocodone Bitartrate, milled Stearyl Alcohol, Anhydrous Dicalcium Phosphate, Microcrystalline Cellulose, and Glyceryl Behenate in a twin shell blender. |
| | 3. | Extrusion | Continuously feed the blended material into a twin screw extruder and collect the resultant heated material on a conveyor. |
| 20 | 4. | Cooling | Allow the extrudate to cool on the conveyor. |
| | 5. | Milling | Mill the cooled extrudate using an occillating mill. |
| | 6. | Blending | Blend the milled extrudate, naltrexone HCl beads (from Example 1), and Magnesium Stearate. |
| 25 | 7. | Compression | Compress the resultant granulation using a tablet press. |
| | 8. | Coating | Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores. |

The releasable naltrexone can be a) overcoated onto the tablet by e.g., including it in the
30 Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c)
including the naltrexone with the opioid agonist; or included in any other method known in the
art. The amount of naltrexone should be in an amount to have a desired pharmacological
effect as disclosed herein and can be immediate or sustained release.

5

EXAMPLE 5

Hydrocodone Bitartrate Controlled Release Tablets with Naltrexone HCl Granulation

<i>Ingredient</i>	<i>Amnt/unit (mg)</i>
Hydrocodone Bitartrate	30.0
Stearyl Alcohol	44.0
Anhydrous Dicalcium Phosphate (Powdered)	62.0
Microcrystalline Cellulose	62.0
Glyceryl Behenate	20.0
Naltrexone HCl Granulation (Example 2)	70.0
Magnesium Stearate	2.0
Opadry Red	10.0
Purified Water	56.7*
Total	300.0

10 * Remains in product as residual moisture only.

PROCESS:

1. Milling Pass the Stearyl Alcohol flakes through an occillating mill.
- 15 2. Blending Mix the Hydrocodone Bitartrate, milled Stearyl Alcohol, Anhydrous Dicalcium Phosphate, Microcrystalline Cellulose, and Glyceryl Behenate in a twin shell blender.
3. Extrusion Continuously feed the blended material into a twin screw extruder and collect the resultant heated material on a conveyor.
- 20 4. Cooling Allow the extrudate to cool on the conveyor.
5. Milling Mill the cooled extrudate using an occillating mill.
6. Blending Blend the milled extrudate, Naltrexone HCl granulation (from Example 2), and Magnesium Stearate.
7. Compression Compress the resultant granulation using a tablet press.
- 25 8. Coating Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

The releasable naltrexone can be a) overcoated onto the tablet by e.g., including it in the Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist, or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

30

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EXAMPLE 6

Oxycodone HCl Controlled Release Tablets with Naltrexone HCl Beads

<i>Ingredient</i>	<i>Amo/unit (mg)</i>
Oxycodone HCl	20.00
Spray Dried Lactose	59.25
Povidone	5.00
Eudragit RS 30D (dry wt.)	10.00
Triacetin	2.00
Stearyl Alcohol	25.00
Talc	2.50
Magnesium Stearate	1.25
Naltrexone HCl Beads (Example 1)	84.00
Opadry Pink	6.00
Purified Water	34.00*
Total	215.00

* Remains in product as residual moisture only.

10

PROCESS:

- 15
- 20
- 25
- 30
1. Solution Preparation Plasticize the Eudragit with Triacetin by mixing.
2. Granulation Place Oxycodone HCl, Spray Dried Lactose, and Povidone into a fluid bed granulator and apply the above solution.
3. Milling Pass the granulation through a rotating impeller mill.
4. Drying Dry granulation if moisture content is too high.
5. Waxing Melt Stearyl Alcohol and wax the above granulation by adding melted Stearyl Alcohol onto granulation while mixing.
6. Cooling Cool the waxed granulation in a fluid bed dryer.
7. Milling Pass the cooled waxed granulation through a rotating impeller mill.
8. Blending Blend the milled waxed granulation, Talc, Magnesium Stearate, and Naltrexone HCl beads (from Example 1).
9. Compression Compress the resultant granulation using a tablet press.
10. Coating Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

The releasable naltrexone can be a) overcoated onto the tablet by e.g., including it in the Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

EXAMPLE 7

Oxycodone HCl Controlled Release Tablets with Naltrexone HCl Granulation

<i>Ingredient</i>	<i>Amount (mg)</i>
Oxycodone HCl	20.00
Spray Dried Lactose	59.25
Povidone	5.00
Eudragit RS 30D (dry wt.)	10.00
Triacetin	2.00
Stearyl Alcohol	25.00
Talc	2.50
Magnesium Stearate	1.25
Naltrexone HCl Granulation (Example 2)	70.00
Opadry Pink	6.00
Purified Water	34.00*
Total	201.00

* Remains in product as residual moisture only.

PROCESS:

- | | | | |
|----|-----|----------------------|--|
| | 1. | Solution Preparation | Plasticize the Eudragit with Triacetin by mixing. |
| 15 | 2. | Granulation | Place Oxycodone HCl, Spray Dried Lactose and Povidone into a fluid bed granulator and apply the above solution. |
| | 3. | Milling | Pass the granulation through a rotating impeller mill. |
| | 4. | Drying | Dry granulation if moisture content is too high. |
| | 5. | Waxing | Melt Stearyl Alcohol and wax the above granulation by adding melted Stearyl Alcohol onto granulation while mixing. |
| 20 | 6. | Cooling | Cool the waxed granulation in a fluid bed dryer. |
| | 7. | Milling | Pass the cooled waxed granulation through a rotating impeller mill. |
| | 8. | Blending | Blend the milled waxed granulation, Talc, Magnesium Stearate, and Naltrexone HCl granulation (from Example 2). |
| 25 | 9. | Compression | Compress the resultant granulation using a tablet press. |
| | 10. | Coating | Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores. |

The releasable naltrexone can be a) overcoated onto the tablet by e.g., including it in the 30 · Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

5

EXAMPLE 8**Hydromorphone HCl Controlled Release Capsules with Naltrexone HCl Extruded Pellets**

10

FORMULA:

<i>Ingredient</i>	<i>Amt/unit (mg)</i>
Hydromorphone HCl	12.0
Eudragit RSPO	76.5
Ethylcellulose	4.5
Stearyl Alcohol	27.0
Naltrexone HCl Pellets (Example 3)	240.0
Hard Gelatin Capsules	✓
Total	360.0

15 PROCESS:

1. Milling Pass Stearyl Alcohol flakes through an impact mill.
2. Blending Mix Hydromorphone HCl, Eudragit, Ethylcellulose and milled Stearyl Alcohol in a twin shell blender.
- 20 3. Extrusion Continuously feed the blended material into a twin screw extruder and collect the resultant strands on a conveyor.
4. Cooling Allow the strands to cool on the conveyor.
5. Pelletizing Cut the cooled strands into pellets using a Pelletizer.
6. Screening Screen the pellets and collect desired sieve portion.
- 25 7. Encapsulation Fill the extruded Hydromorphone HCl pellets at 120 mg and Naltrexone HCl pellets (from Example 3) at 240 mg into hard gelatin capsules.

The releasable naltrexone can be a) overcoated onto the pellets by e.g., including it in the
30 Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

5 **EXAMPLE 9**

Hydrocodone Bitartrate Controlled Release Tablets with Naltrexone HCl Bends

<i>Ingredient</i>	<i>Amo/unit (mg)</i>
Hydrocodone Bitartrate	30.0
Stearyl Alcohol	44.0
Anhydrous Dicalcium Phosphate (Powdered)	62.0
Microcrystalline Cellulose	62.0
Glyceryl Behenate	20.0
Naltrexone HCl Beads (Example 1)	84.0
Magnesium Stearate	2.0
Opadry Red	10.0
Purified Water	56.7*
Total	314

10 * Remains in product as residual moisture only.

PROCESS:

- | | | | |
|----|----|-------------|---|
| | 1. | Milling | Pass the Stearyl Alcohol flakes through an occillating mill. |
| 15 | 2. | Blending | Mix the Hydrocodone Bitartrate, milled Stearyl Alcohol, Anhydrous Dicalcium Phosphate, Microcrystalline Cellulose, and Glyceryl Behenate in a twin shell blender. |
| | 3. | Extrusion | Continuously feed the blended material into a twin screw extruder and collect the resultant heated material on a conveyor. |
| 20 | 4. | Cooling | Allow the extrudate to cool on the conveyor. |
| | 5. | Milling | Mill the cooled extrudate using an occillating mill. |
| | 6. | Blending | Blend the milled extrudate, Naltrexone HCl beads (from Example 1), and Magnesium Stearate. |
| | 7. | Compression | Compress the resultant granulation using a tablet press. |
| 25 | 8. | Coating | Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores. |

The releasable naltrexone can be a) overcoated onto the tablet by e.g., including it in the Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

5

EXAMPLE 10

Hydrocodone Bitartrate Controlled Release Tablets with Naltrexone HCl Granulation

<i>Ingredient</i>	<i>Amt/unit (mg)</i>
Hydrocodone Bitartrate	30.0
Stearyl Alcohol	44.0
Anhydrous Dicalcium Phosphate (Powdered)	62.0
Microcrystalline Cellulose	62.0
Glyceryl Behenate	20.0
Naltrexone HCl Granulation (Example 2)	70.0
Magnesium Stearate	2.0
Opadry Red	10.0
Purified Water	56.7*
Total	300.5

10 * Remains in product as residual moisture only.

PROCESS:

- 15
1. Milling

2. Blending

3. Extrusion

20 4. Cooling

5. Milling

6. Blending

7. Compression

25 8. Coating
- Pass the Stearyl Alcohol flakes through an occillating mill.

Mix the Hydrocodone Bitartrate, milled Stearyl Alcohol, Anhydrous Dicalcium Phosphate, Microcrystalline Cellulose, and Glyceryl Behenate in a twin shell blender.

Continuously feed the blended material into a twin screw extruder and collect the resultant heated material on a conveyor.

Allow the extrudate to cool on the conveyor.

Mill the cooled extrudate using an occillating mill.

Blend the milled extrudate, Naltrexone HCl granulation (from Example 2), and Magnesium Stearate.

Compress the resultant granulation using a tablet press.

Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

The releasable naltrexone can be a) overcoated onto the tablet by e.g., including it in the Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

5

EXAMPLE 11

Oxycodone HCl Controlled Release Tablets with Naltrexone HCl Beads

<i>Ingredient</i>	<i>Amnt/unit (mg)</i>
Oxycodone HCl	20.00
Spray Dried Lactose	58.75
Povidone	5.00
Eudragit RS 30D (dry wt.)	10.00
Triacetin	2.00
Stearyl Alcohol	25.00
Talc	2.50
Magnesium Stearate	1.25
Naltrexone HCl Beads (Example 1)	84.00
Opadry Pink	6.00
Purified Water	34.00*
Total	215.00

10 * Remains in product as residual moisture only.

PROCESS:

- 15
- 20
- 25
- 30
1. Solution Preparation Plasticize the Eudragit with Triacetin by mixing.
2. Granulation Place Oxycodone HCl, Spray Dried Lactose, and Povidone into a fluid bed granulator and apply the above solution.
3. Milling Pass the granulation through a rotating impeller mill.
4. Drying Dry granulation if moisture content is too high.
5. Waxing Melt Stearyl Alcohol and wax the above granulation by adding melted Stearyl Alcohol onto granulation while mixing.
6. Cooling Cool the waxed granulation in a fluid bed dryer.
7. Milling Pass the cooled waxed granulation through a rotating impeller mill.
8. Blending Blend the milled waxed granulation, Talc, Magnesium Stearate, and Naltrexone HCl beads (from Example 1).
9. Compression Compress the resultant granulation using a tablet press.
10. Coating Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

The releasable naltrexone can be a) overcoated onto the tablet by e.g., including it in the Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

5

EXAMPLE 12

Oxycodone HCl Controlled Release Tablets with Naltrexone HCl Granulation

<i>Ingredient</i>	<i>Amt/unit (mg)</i>
Oxycodone HCl	20.00
Spray Dried Lactose	58.75
Povidone	5.00
Eudragit RS 30D (dry wt.)	10.00
Triacetin	2.00
Stearyl Alcohol	25.00
Talc	2.50
Magnesium Stearate	1.25
Naltrexone HCl Granulation (Example 2)	70.00
Opadry Pink	6.00
Purified Water	34.00*
Total	201.00

10 * Remains in product as residual moisture only.

PROCESS:

- 15
- 20
- 25
- 30
1. Solution Preparation Plasticize the Eudragit with Triacetin by mixing.
 2. Granulation Place Oxycodone HCl, Spray Dried Lactose, and Povidone into a fluid bed granulator and apply the above solution.
 3. Milling Pass the granulation through a rotating impeller mill.
 4. Drying Dry granulation if moisture content is too high.
 5. Waxing Melt Stearyl Alcohol and wax the above granulation by adding melted Stearyl Alcohol onto granulation while mixing.
 6. Cooling Cool the waxed granulation in a fluid bed dryer.
 7. Milling Pass the cooled waxed granulation through a rotating impeller mill.
 8. Blending Blend the milled waxed granulation, Talc, Magnesium Stearate, and Naltrexone HCl granulation (from Example 2).
 9. Compression Compress the resultant granulation using a tablet press.
 10. Coating Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet cores.

The releasable naltrexone can be a) overcoated onto the tablet by e.g., including it in the Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

EXAMPLE 13

Hydromorphone HCl Controlled Release Capsules with Naltrexone HCl Extruded Pellets

10 FORMULA:

<i>Ingredient</i>	<i>Amt/unit (mg)</i>
Hydromorphone HCl	12.0
Eudragit RSPO	76.0
Ethycellulose	4.5
Stearyl Alcohol	27.0
Naltrexone HCl Pellets (Example 3)	240.0
Hard Gelatin Capsules	✓
Total	360.0

PROCESS:

- | | | |
|----|------------------|--|
| 15 | | |
| | 1. Milling | Pass stearyl alcohol flakes through an impact mill. |
| | 2. Blending | Mix Hydromorphone HCl, Eudragit, Ethycellulose and milled Stearyl Alcohol in a twin shell blender. |
| | 3. Extrusion | Continuously feed the blended material into a twin screw extruder and collect the resultant strands on a conveyor. |
| 20 | 4. Cooling | Allow the strands to cool on a Conveyor. |
| | 5. Pelletizing | Cut the cooled strands into pellets using a Pelletizer. |
| | 6. Screening | Screen the pellets and collect desired sieve portion. |
| | 7. Encapsulation | Fill the extruded Hydromorphone HCl pellets at 120.0 mg and |
| 25 | | Naltrexone HCl pellets (from Example 3) at 240 mg into hard gelatin capsules. |

The releasable naltrexone can be a) overcoated onto the pellets by e.g., including it in the Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

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EXAMPLE 14

Sequestered Naltrexone HCl beads

In Example 14, Naltrexone HCl beads for incorporation into capsules were prepared
10 having the following formulation in Table 14 below.

TABLE 14

	Ingredients	Am/unit (mg)
Step 1. Drug layering	Naltrexone HCl	2.1
	Non-pareil beads (30/35 mesh)	39.98
	Opadry Clear (Hydroxypropymethyl cellulose)	0.4
	Sodium ascorbate	0.027
	Ascorbic acid	0.05
Step 2. Anionic polymer coat	Eudragit L30D (dry)	2.164
	Triethyl Citrate	0.433
	Cabosil	0.108
Step 3. Sustained release coat	Eudragit RS30D (dry)	17.475
	Triethyl citrate	3.495
	Cabosil	0.874
Step 4. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	1.899
	Cabosil	0.271
Total (on dry basis)		69.287

15

PROCESS:

1. Dissolve naltrexone HCl, ascorbic acid, sodium ascorbate and Opadry Clear in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.
- 20 2. Disperse Eudragit L30D, Triethyl citrate, and Cabosil in water. Spray the dispersion onto the drug-loaded beads in the fluid bed coater.
3. Disperse Eudragit RS30D, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.
4. Dissolve Opadry Clear in water. Spray the solution onto the beads in the fluid bed coater.
- 25 5. Cure the beads at 60°C for 24 hours.

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TABLE 15

Ingredients	Amt/Unit (mg)
Naltrexone HCl	2.0
Eudragit RSPO	88.0
Stearyl alcohol	15.0
Stearic acid	15.0
BHT	1.0
Total	121.0

20

- Powder feed rate—4.2 kg/hr; vacuum—980 mBar**
Conveyor—such that diameter of extrudate is 1mm
Pelletizer—such that pellets are cut to 1mm in length

- 30

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A naltrexone sustained release bead formulation was prepared which can be incorporated into an opioid controlled release granulation and compressed into tablets. The naltrexone controlled release bead formulation is listed in Table 16 below.

5

TABLE 16

	Ingredients	Amt/unit* (mg)
Step 1. Drug layering	Naltrexone HCl	0.609
	Non-pareil beads (30/35 mesh)	67.264
	Opadry Clear	0.547
Step 2. Seal coat	Eudragit L	2.545
	Triethyl citrate	0.636
	Glyceryl monostearate	0.239
Step 3. Sustained release coat	Eudragit RS30D (dry)	43.789
	Triethyl citrate	8.758
	Cabosil	2.189
Step 4. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	2.053
	Cabosil	1.365
Total		130

PROCESS:

10

1. Dissolve naltrexone HCl and Opadry (HPMC) in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.
2. Disperse Eudragit L, Triethyl citrate, and glyceryl monostearate in water. Spray the dispersion onto the drug-loaded beads in the fluid bed coater.
- 15 3. Disperse Eudragit RS, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.
4. Dissolve Opadry in water. Spray the solution onto the beads in the fluid bed coater.
5. Cure the beads at 60°C for 24 hours.

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EXAMPLE 17

Controlled Release Oxycodone 20 mg

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In Example 17, a sustained release 20 mg oxycodone formulation was prepared having the formulation listed in Table 17 below.

TABLE 17

Ingredients	Amt/Unit (mg)
Oxycodone HCl	20.0
Spray Dried Lactose	59.25
Povidone	5.0
Eudragit RS30D (solids)	10.0
Triacetin	2.0

Stearyl Alcohol	25.0
Talc	2.5
Magnesium Stearate	1.25
Opadry Pink Y-S-14518A	4.0
Total	129.0

PROCESS:

1. Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone HCl, Spray Dried Lactose and Povidone using a fluid bed granulator.
2. Milling: Discharge the granulation and pass through a mill.
3. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.
4. Milling: Pass the cooled granulation through a mill.
5. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.
6. Compression: Compress the granulation into tablets using a tablet press.
7. Film coating: Apply an aqueous film coat to the tablets.

EXAMPLE 18

In Example 18, naltrexone beads prepared in accordance with Example 16 are incorporated into the sustained release 20 mg oxycodone tablets prepared in accordance with Example 17 and having the formula listed in Table 18 below.

TABLE 18

	Ingredients	Amt/unit* (mg)
Step 1. Granulation	Oxycodone HCl	20.0
	Spray Dried Lactose	59.25
	Povidone	5.0
	Eudragit RS30D (dry)	10.0
	Triacetin	2.0
	Stearyl alcohol	25.0
	Talc	2.5
	Magnesium	1.25
Step 2. Combination tablet	OxyContin granulation (Example 3)	125
	Naltrexone CR beads (Formula 2)	140

PROCESS:

1. Spray the Eudragit/triacetin dispersion onto the Oxycodone HCl, spray dried lactose and povidone using a fluid bed granulator.
2. Discharge the granulation and pass through a mill.

- 5 3. Melt the stearyl alcohol and add to the milled granulation using a mill. Allow to cool.
4. Pass the cooled granulation through a mill.
5. Lubricate the granulation with talc and magnesium stearate. Using a mixer.
6. Mix naltrexone beads with the above granulation and compress into tablets.

10 **ALTERNATE PROCESS:**

1. Spray the Eudragit/triacetin dispersion onto the Oxycodone HCl, spray dried lactose and povidone using a fluid bed granulator.
2. Discharge the granulation and pass through a mill.
- 15 3. Mix naltrexone beads (example 2) with the above granulation in a Hobar mixer.
4. Melt the stearyl alcohol and add to the above mixture. Allow to cool.
5. Pass the cooled granulation through a mill.
6. Lubricate the granulation with talc and magnesium stearate using a mixer.
7. Compress into tablets.

20 Releasable naltrexone can be a) overcoated onto the tablets by e.g., including it in the Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist, or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect .

25 as disclosed herein and can be immediate or sustained release.

EXAMPLE 19

30 **Controlled Release Hydrocodone**

 A sustained release hydrocodone formulation was prepared having the formula in Table 19 below.

TABLE 19

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Ingredients	Amt/Unit (mg)	Amt/Batch (g)
Hydrocodone Bitartrate	15.0	320.0
Eudragit RSPO	76.0	1520.0
Eudragit RLPO	4.0	80.0
Stearyl Alcohol	25.0	500.0
Total	120.0	2400.0

PROCESS:

- 40 1. Blend milled Stearyl Alcohol, Eudragit RLPO, Hydrocodone Bitartrate, and Eudragit RSPO using a Hobart Mixer.
2. Extrude the granulation using a Powder Feeder, Melt Extruder(equipped with the 6 x 1 mm die head), Conveyor, Lasermike, and Pelletizer.

- 5 Powder feed rate-40g/min; vacuum--980 mBar
Conveyor-such that diameter of extrudate is 1mm
Pelletizer-such that pellets are cut to 1mm in length
3. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen.
- 10 4. Fill size #2 clear gelatin capsules with the pellets. Range: NLT (not less than) 114 mg and NMT (not more than) 126 mg.

The sequestered naltrexone formulation of Example 15 can be incorporated in a capsule with the hydrocodone pellets. Preferably, the sequestered naltrexone pellets are indistinguishable from the hydrocodone pellets.

Releasable naltrexone can be a) overcoated onto the pellets by e.g., including it in an Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist, or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

EXAMPLE 20

Controlled Release Oxycodone HCl beads

A sustained release oxycodone HCl bead formulation was prepared having the formula in Table 20 below.

TABLE 20

	Ingredients	Amt/unit* (mg)
Step 1. Drug layering	Oxycodone HCl	10.5
	Non-pareil beads (30/35 mesh)	45.349
	Opadry Clear	2.5
Step 2. Sustained release coat	Eudragit RS30D (dry)	7.206
	Eudragit RL30D (dry)	0.379
	Triethyl citrate	1.517
	Cabosil	0.379
Step 3. Seal coat	Opadry Clear (Hydroxypropylmethyl cellulose)	1.899
	Cabosil	0.271
Total		70.0

5 PROCESS:

1. Dissolve oxycodone HCl and Opadry (HPMC) in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.
2. Disperse Eudragit RS, Eudragit RL, triethyl citrate, and Cabosil[®] in water. Spray the dispersion onto the beads in the fluid bed coater.
3. Dissolve Opadry in water. Spray the solution onto the beads in the fluid bed coater.
4. Cure the beads at 60°C for 24 hours.

15 The sequestered naltrexone formulation of Example 14 can be incorporated in a capsule with the oxycodone beads. Preferably, the sequestered naltrexone beads are indistinguishable from the oxycodone beads.

Releasable naltrexone can be a) overcoated onto the beads by e.g., including it in an Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

25 **EXAMPLE 21**
Controlled Release Hydromorphone

A sustained release hydromorphone HCl formulation was prepared having the formula in Table 21 below:

TABLE 21

Ingredients	Amt/Unit (mg)
Hydromorphone HCl	12.0
Eudragit RSPO	76.5
Ethocel	4.5
Stearic acid	27.0
Total	120.0

PROCESS:

1. Blend milled Stearic acid, ethocel, Hydrocodone Bitrtrate, and Eudragit RSPO using a V-blender.
2. Extrude the mixture using a Powder Feeder, Melt Extruder(equipped with the 6 x 1 mm die head), Conveyor, Lasermike, and Pelletizer.

Powder feed rate—4.2 kg/hr, vacuum—980 mBar

- 5 Conveyor-such that diameter of extrudate is 1mm
 Pelletizer-such that pellets are cut to 1mm in length
3. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen.
- 10 4. Fill size #2 clear gelatin capsules with the pellets. Range: NLT 114 mg and NMT 126 mg.

15 The sequestered naltrexone formulation of Example 15 can be incorporated in a capsule with the hydromorphone pellets. Preferably, the sequestered naltrexone pellets are indistinguishable from the hydrocodone pellets.

20 Releasable naltrexone can be a) overcoated onto the pellets by e.g., including it in an Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired ph: macological effect as disclosed herein and can be immediate or sustained release.

5 WHAT IS CLAIMED IS:

1. An oral dosage form, comprising
 - (i) a therapeutically effective amount of an opioid agonist;
 - (ii) an opioid antagonist in releasable form; and
 - 10 (iii) a sequestered opioid antagonist which is not released when the dosage form is administered intact.
2. An oral dosage form, comprising
 - (i) a first component comprising a therapeutically effective amount of an
 - 15 opioid agonist;
 - (ii) a second component comprising an opioid antagonist in releasable form; and
 - (iii) a third component comprising a sequestered opioid antagonist which is not released when the dosage form is administered intact.
 - 20
3. An oral dosage form, comprising
 - (i) a first component comprising a therapeutically effective amount of an opioid agonist;
 - (ii) a second component comprising an opioid antagonist in releasable form,
 - 25 and a sequestered opioid antagonist which is not released when the dosage form is administered intact.
4. An oral dosage form, comprising
 - (i) a first component comprising a therapeutically effective amount of an
 - 30 opioid agonist and an opioid antagonist in releasable form; and
 - (ii) a second component comprising a sequestered opioid antagonist which is not released when the dosage form is administered intact.
5. An oral dosage form, comprising
 - (i) a first component comprising a therapeutically effective amount of an
 - 35 opioid agonist and an opioid antagonist in releasable form; and
 - (ii) a second component comprising a sequestered opioid antagonist which is

- 5 not substantially released when the dosage form is administered intact.
6. An oral dosage form, comprising
 - (i) a first component comprising a therapeutically effective amount of an opioid agonist;
 - 10 (ii) a second component comprising an opioid antagonist in releasable form; and
 - (iii) a third component comprising a sequestered opioid antagonist which is not substantially released when the dosage form is administered intact.
- 15 7. The dosage form of claim 1 wherein the quantity of antagonist released from said dosage form is in a ratio to said agonist which is aversive in physically dependent human subjects when the dosage form is administered at the same amount or at a higher amount than said therapeutically effective amount
- 20 8. The dosage form of claim 5 wherein the quantity of said antagonist released from said first component is in an amount sufficient to be aversive in physically dependent human subjects when the dosage form is administered at the same amount or at a higher amount than said therapeutically effective amount.
- 25 9. The dosage form of claim 5 wherein the quantity of said antagonist released from said first component is less than the amount sufficient to be aversive in physically dependent human subjects when the dosage form is administered at the same amount or at a higher amount than said therapeutically effective amount.
- 30 10. The dosage form of claim 6 wherein the amount of said antagonist released from said second component is in an amount sufficient to be aversive in physically dependent human subjects when the dosage form is administered at the same amount or at a higher amount than said therapeutically effective amount.
- 35 11. The dosage form of claim 6 wherein the amount of said antagonist released from said second component is less than the amount sufficient to be aversive in physically dependent human subjects when the dosage form is administered at the same amount

5 or at a higher amount than said therapeutically effective amount.

12. The dosage form of claim 1 further comprising a sustained release excipient which provides a sustained release of said opioid agonist.

10 13. The dosage form of claim 1 further comprising a sustained release excipient which provides a sustained release of said opioid antagonist.

14. The dosage form of claim 1 further comprising a sustained release excipient which provides a sustained release of said opioid agonist and said opioid antagonist.

15 15. The dosage form of claim 1 wherein said sequestered antagonist is in the form of multiparticulates individually coated with a material that prevents release of the sequestered antagonist.

20 16. The dosage form of claim 1 wherein said sequestered antagonist is in the form of multiparticulates individually coated with a material that substantially prevents release of said sequestered antagonist.

25 17. The dosage form of claim 1 wherein said sequestered antagonist is dispersed in a matrix comprising a sequestering material that prevents the release of said sequestered antagonist.

30 18. The dosage form of claim 1 wherein said sequestered antagonist is dispersed in a matrix comprising a sequestering material that substantially prevents the release of said sequestered antagonist.

19. The dosage form of claim 1 wherein said releasable opioid antagonist is the same as the sequestered antagonist.

35 20. The dosage form of claim 1 wherein said releasable opioid antagonist is different than the sequestered antagonist.

- 5 21. The dosage form of claim 19 wherein said antagonist is selected from the group consisting of naltrexone, naloxone, nalmephen, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.
- 10 22. The dosage form of claim 20 wherein said releasable antagonist is selected from the group consisting of naltrexone, naloxone, nalmephen, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof and said sequestered antagonist is selected from the group consisting of naltrexone, naloxone, nalmephen, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof.
- 15 23. The dosage form of claim 1 wherein said opioid is selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, tramadol, meperidine, methadone, pharmaceutically acceptable salts thereof and mixtures thereof.
- 20 24. The dosage form of claim 1 having a ratio of having a ratio of releasable opioid antagonist to opioid agonist that is analgesically effective when the combination is administered orally, but which is aversive in physically dependent human subjects when administered at the same amount or at a higher amount than said therapeutically
- 25 effective amount.
25. The dosage form of claim 24 wherein said ratio of releasable opioid antagonist to opioid agonist maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist relative to the same therapeutic amount of opioid analgesic when
- 30 administered to human patients without said opioid antagonist.
26. The oral dosage form of claim 1 wherein the opioid agonist is hydrocodone and the releasable antagonist is naltrexone.
- 35 27. The oral dosage form of claim 26, wherein the ratio of releasable naltrexone to hydrocodone is from about 0.03:1 to about 0.27:1.

- 5 28. The oral dosage form of claim 27, wherein the ratio of releasable naltrexone to hydrocodone is from about 0.05:1 to about 0.20:1.
- 10 29. The oral dosage form of claim 7, wherein said releasable opioid antagonist is naltrexone and said opioid agonist is oxycodone, wherein the ratio of releasable naltrexone to oxycodone is from about 0.037:1 to about 0.296:1.
- 15 30. The oral dosage form of claim 7, wherein said releasable opioid antagonist is naltrexone and said releasable opioid agonist is codeine, wherein the ratio of releasable naltrexone to codeine is from about 0.005:1 to about 0.044:1.
- 20 31. The oral dosage form of claim 7, wherein said releasable opioid antagonist is naltrexone and said opioid agonist is hydromorphone, wherein the ratio of releasable naltrexone to hydromorphone is from about 0.148:1 to about 1.185:1.
- 25 32. The oral dosage form of claim 7, wherein said releasable opioid antagonist is naltrexone and said opioid agonist is levorphanol, wherein the ratio of releasable naltrexone to levorphanol is from about 0.278:1 to about 2.222:1.
- 30 33. The oral dosage form of claim 7, wherein said releasable opioid antagonist is naltrexone and said opioid agonist is methadone, wherein the ratio of releasable naltrexone to methadone is from about 0.056:1 to about 0.444:1.
- 35 34. The oral dosage form of claim 7, wherein said releasable opioid antagonist is naltrexone and said opioid agonist is morphine, wherein the ratio of releasable naltrexone to morphine is from about 0.018:1 to about 0.148:1.
- 35 35. The oral dosage form of claim 7, wherein said releasable opioid antagonist is naltrexone and said opioid agonist is oxycodone, wherein the ratio of releasable

- 5 naltrexone to oxycodone is from about 0.056:1 to about 0.222:1.
36. The oral dosage form of claim 7, wherein said releasable opioid antagonist is
naltrexone and said opioid agonist is codeine, wherein the ratio of releasable
naltrexone to codeine is from about 0.0083:1 to about 0.033:1.
- 10 37. The oral dosage form of claim 7, wherein said releasable opioid antagonist is
naltrexone and said opioid agonist is hydromorphone, wherein the ratio of releasable
naltrexone to hydromorphone is from about 0.222:1 to about 0.889:1.
- 15 38. The oral dosage form of claim 7, wherein said releasable opioid antagonist is
naltrexone and said opioid agonist is levorphanol, wherein the ratio of releasable
naltrexone to levorphanol is from about 0.417:1 to about 1.667:1.
- 20 39. The oral dosage form of claim 7, wherein said releasable opioid antagonist is
naltrexone and said opioid agonist is meperidine, wherein the ratio of releasable
naltrexone to meperidine is from about 0.0056:1 to about 0.022:1.
- 25 40. The oral dosage form of claim 7, wherein said releasable opioid antagonist is
naltrexone and said opioid agonist is methadone, wherein the ratio of releasable
naltrexone to methadone is from about 0.083:1 to about 0.333:1.
- 30 41. The oral dosage form of claim 7, wherein said releasable opioid antagonist is
naltrexone and said opioid agonist is morphine, wherein the ratio of releasable
naltrexone to morphine is from about 0.028:1 to about 0.111:1.
- 35 42. The oral dosage form of claim 1 wherein the releasable antagonist is in an amount to
attenuate a side effect of said opioid agonist selected from the group consisting of
anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance, and a
combination of any of the foregoing.
43. The controlled release dosage form of claim 1, wherein the amount of antagonist
released during the dosing interval enhances the analgesic potency of the opioid

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agonist.

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44. The controlled-release dosage form of claim 42, wherein the amount of the releasable opioid receptor antagonist is about 100 to about 1000 fold less than the amount of the opioid agonist.

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45. The dosage form of claim 7 wherein the ratio of the amount of antagonist released from said dosage form after tampering to the amount of said antagonist released from said intact dosage form is about 4:1 (w:w) or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C.

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46. The dosage form of claim 7 wherein the ratio of the amount of antagonist contained in said intact dosage form to the amount of said antagonist released from said intact dosage form after 1 hour is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C.

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47. The oral dosage form of claim 45 wherein said ratio is 10:1 or greater.

48. The oral dosage form of claim 45 wherein said ratio is 50:1 or greater.

49. The oral dosage form of claim 45 wherein said ratio is 100:1 or greater.

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50. The oral dosage form of claim 1 wherein said releasable antagonist is naloxone or a pharmaceutically acceptable salt thereof and said non-releasable antagonist is naltrexone or a pharmaceutically acceptable salt thereof.

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51. A method of treating pain comprising administering a dosage form of claim 1.

52. A method of deterring abuse comprising preparing a dosage form of claim 1.

5 53. A method of preparing a dosage form of claim 1 comprising combining an opioid
 agonist with an antagonist in releasable and non-releasable form in a dosage form.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04044

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/44, 31/443

US CL : 514/889, 820

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/889, 820

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,785,000 A (KREEK et al.) 15 November 1988 (15.11.88), see the entire document.	1-53
A	US 5,266,331 A (OSHLACK et al.) 30 November 1993 (30.11.93), see the entire document.	1-53
A	US 5,472,943 A (CRAIN et al.) 05 December 1995 (05.12.95), see the entire document.	1-53



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	-T-	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

13 SEPTEMBER 2002

Date of mailing of the international search report

03 DEC 2002

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Applicant
EURO-CELTIQUE S.A.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
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Form PCT/IPEA/416 (July 1992)

Excluded 5/9 PCT 5/9
1 - 5/23/03 Send Revision letter

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 200.1144PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US02/24944	International filing date (day/month/year) 06 August 2002 (06.08.2002)	Priority date (day/month/year) 06 August 2001 (06.08.2001)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/44, 31/445 and US Cl.: 514/282, 330		
Applicant EURO-CELTIQUE S.A.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>2</u> sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of <u> </u> sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 21 February 2003 (21.02.2003)	Date of completion of this report 20 April 2003 (20.04.2003)	
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer  Raymond J. Hesley, III Telephone No. 703-308-1235	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US02/24944

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed.
- ☒ the description:
 pages 1-65 as originally filed
 pages NONE filed with the demand
 pages NONE filed with the letter of _____
- ☒ the claims:
 pages 66-73 as originally filed
 pages NONE as amended (together with any statement) under Article 19
 pages NONE filed with the demand
 pages NONE filed with the letter of _____
- ☐ the drawings:
 pages NONE as originally filed
 pages NONE filed with the demand
 pages NONE filed with the letter of _____
- ☐ the sequence listing part of the description:
 pages NONE as originally filed
 pages NONE filed with the demand
 pages NONE filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/24944

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)

Claims 1-53

YES

Claims NONE

NO

Inventive Step (IS)

Claims 1-53

YES

Claims NONE

NO

Industrial Applicability (IA)

Claims 1-53

YES

Claims NONE

NO

2. CITATIONS AND EXPLANATIONS

Claims 1-53 meet the criteria under PCT Article 33(2) for novelty because the prior art fails to teach the presently claimed oral dosage forms comprising a therapeutically effective amount of an opioid agonist, an opioid antagonist in releasable form and a sequestered opioid antagonist which is not released when the dosage form is administered intact; method of treating pain in which such dosage form is utilized; method of deterring abuse in which such dosage form is prepared or method of preparing such dosage form.

Claims 1-53 meet the criteria under PCT Article 33(3) for inventive step because the prior art fails to teach or suggest the presently claimed oral dosage forms comprising a therapeutically effective amount of an opioid agonist, an opioid antagonist in releasable form and a sequestered opioid antagonist which is not released when the dosage form is administered intact; method of treating pain in which such dosage form is utilized; method of deterring abuse in which such dosage form is prepared or method of preparing such dosage form.

Claims 1-53 meet the criteria under PCT Article 33(4) because the presently claimed oral dosage forms comprising a therapeutically effective amount of an opioid agonist, an opioid antagonist in releasable form and a sequestered opioid antagonist which is not released when the dosage form is administered intact; method of treating pain in which such dosage form is utilized; method of deterring abuse in which such dosage form is prepared and method of preparing such dosage form would have applicability in the medical industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: CLIFFORD M. DAVIDSON
DAVIDSON, DAVIDSON & KAPPEL, LLC
445 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NEW YORK 10018

RECEIVED
DEC 06 2002

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing (day/month/year) 03 DEC 2002	
Applicant's or agent's address 800.1144PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US08/24044	International filing date (day/month/year) 08 AUGUST 2002
Applicant EURO-CELTIQUE S.A.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicants's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 900.1144PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US09/14944	International filing date (day/month/year) 08 AUGUST 2009	(Earliest) Priority Date (day/month/year) 08 AUGUST 2001
Applicant EURO-CELTIQUE S.A.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 93.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 93.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/04844

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/44, 31/446

US CL : 514/889, 330

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/889, 330

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,785,000 A (KREEK et al.) 15 November 1988 (15.11.88), see the entire document.	1-53
A	US 5,266,331 A (OSHLACK et al.) 30 November 1993 (30.11.93), see the entire document.	1-53
A	US 5,472,943 A (CRAIN et al.) 05 December 1995 (05.12.95), see the entire document.	1-53



Further documents are listed in the continuation of Box C.



See patent family annex.

Special categories of cited documents	
* "A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to substantiate the principle or theory underlying the invention
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"Z" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

18 SEPTEMBER 2002

Date of mailing of the international search report

02 DEC 2002

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim involves one or more amendments.

NOTES TO FORM PCT/ISA/210 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)".

It should not contain any disparaging comments on the international search report or the relevance of citations contained in the report. Reference to citations, relevant to a given claim, contained in the international search report, may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

United States Patent [19]

Kreek et al.

[11] Patent Number: 4,785,000

[45] Date of Patent: Nov. 15, 1988

[34] METHOD OF TREATING PATIENTS
SUFFERING FROM CHRONIC PAIN OR
CHRONIC COUGH

[73] Inventors: Mary J. Kreek; Jack Fishman, both
of New York, N.Y.

[71] Assignee: The Rockefeller University, New
York, N.Y.

[21] Appl. No.: 121,784

[22] Filed: Nov. 16, 1987

Related U.S. Application Data

[62] Division of Ser. No. 875,360, Jan. 12, 1986.

[31] Int. Cl.⁴ A61K 31/22; A61K 31/44
[32] U.S. Cl. 514/282; 514/546
[38] Field of Search 514/282, 546

[36] References Cited

U.S. PATENT DOCUMENTS

1,896,226 7/1973 Lewinstein et al. 514/282

OTHER PUBLICATIONS

Chem Abstr. 78(1973)-47818y.

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Klauber & Jackson

[57] ABSTRACT

A method of treating patients in chronic pain or suffering from chronic cough over a prolonged period to provide systemic analgesia or central antitussive effect while simultaneously avoiding the onset of intestinal hypomotility. The method includes the oral administration to the patient of dosage units comprising in combination opioid analgesics or antitussives and selected opioid antagonists which are substantially devoid of systemic antagonist activity when administered orally.

9 Claims, No Drawings

METHOD OF TREATING PATIENTS SUFFERING FROM CHRONIC PAIN OR CHRONIC COUGH

This is a Division, of application Ser. No. 875,560, filed June 18, 1986.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to methods of treating patients suffering from chronic pain or chronic cough without provoking intestinal dysmotility.

2. Description of the Prior Art

The treatment of patients suffering from severe, chronic pain or chronic cough presents a number of serious clinical difficulties. Narcotic or opioid analgesic agents, such as morphine, methadone, codeine, meperidine and oxycodone are often administered to such patients, e.g. patients suffering from progressive cancer, pulmonary disease, degenerative joint disease and chronic abdominal pain. However, apart from other undesirable side effects of long-term opioid administration, it is well known that chronic usage of long-acting opioid analgesics results in severe constipation and other symptoms of intestinal hypomotility. Although it is believed that tolerance to the constipating effects of chronic narcotic administration does eventually develop, it develops extremely slowly. Indeed, development of tolerance may be of little significance in the case of many elderly or terminal patients because of the limiting time factors or because doses of analgesic must normally be increased as tolerance develops to their analgesic effects.

The constipation and other symptoms of intestinal hypomotility caused by administration of opioid analgesics for chronic pain or cough not only create discomfort for the patient but may also complicate both the treatment program and the patient's underlying condition. In fact, chronic constipation may cause new health risks in and of itself, such as for cardiac patients and geriatric patients.

Traditional methods of relieving constipation in patients on long-term opioid analgesic regimens include the administration of a variety of laxatives, purgatives, stool softeners and lubricants, the regulation of diet, and the like. In some cases, the discomfort and potential danger of intestinal rupture created by constipation may become the limiting factor in the treatment of the pain and the doses of analgesic may have to be held constant at a given level or even reduced in an attempt to improve intestinal motility.

It has been proposed that certain opioid antagonists which have substantial systemic activity upon oral administration might be utilized to counteract the intestinal hypomotility provoked by long term administration of opioid agonists. Of course, in order to be of practical use, any such antagonists to be orally administered as adjuncts to analgesic or antitussive agents must not substantially interfere with the analgesic or antitussive effects of the opioid agonists administered to relieve pain or reduce cough. Thus, in U.S. Pat. No. 4,176,186, a family of compounds containing quaternary derivatives of noroxymorphone are disclosed as being useful to prevent or relieve the intestinal motility-inhibiting side effects of narcotic analgesics without interfering with their analgesic activity.

The compounds disclosed in U.S. Pat. No. 4,176,186 and similar agents suggested in the prior art for alleviat-

ing the constipation problems of chronic pain patients suffer from a number of drawbacks. Although these substances do not cross the blood-brain barrier, and therefore do not substantially interfere with those analgesic effects of the opioid agents that are mediated through the brain, the antagonists suggested by the prior art may well interfere with analgesic activity mediated through the spinal cord, the peripheral sensory system, the pituitary gland and possibly the basal hypothalamus, all of which are believed to contain important opioid receptors. In addition, quaternary antagonists have low affinity for opioid receptors, including the gut receptors, and thus are not effective in counteracting narcotic induced-intestinal hypomotility. Furthermore, the prior art quaternary antagonist compounds have been found to have an unacceptably high degree of toxicity, making them particularly unsuitable for long-term administration to chronic pain patients. No feasible or satisfactory method of treating chronic pain or cough patients utilizing the quaternary compounds has ever been disclosed.

In short, no safe, effective and practical means for alleviating the serious complication of intestinal hypomotility in chronic pain or cough patients undergoing opioid therapy has been heretofore developed, notwithstanding the long felt clinical need for such means.

SUMMARY OF THE INVENTION

Objects of the Invention

It is an object of the present invention to provide safe, effective methods of alleviating the symptoms of chronic pain or cough patients without provoking or aggravating disorders of intestinal motility.

It is another object of the present invention to provide methods as described above which are suitable for patients requiring long term opioid therapy.

A further object of the present invention is to provide methods as described above which comprise the administration of a pharmaceutical agent to chronic pain or cough patients concomitantly with their pain or cough medication to prevent and alleviate constipation and other symptoms of intestinal hypomotility.

Still another object of the present invention is to provide methods described above wherein the pharmaceutical agent administered concomitantly with the analgesic or antitussive medication does not significantly reduce or impair the latter's analgesic or antitussive activity.

Yet a further object of the present invention is to provide methods as described above wherein the agent administered as an adjunct to opioid analgesics can be administered orally and exhibits a low level of toxicity and low incidence of undesirable side effects.

Yet another object of the present invention is to provide methods described above wherein the adjunct agent comprises an opioid antagonist having little or no systemic bio-availability when taken by the oral route yet is effective in preventing and/or alleviating intestinal hypomotility.

Brief Description of the Invention

In keeping with these objects and others that will become apparent hereinafter, the present invention resides, briefly stated, in methods of treating chronic pain or cough patients, e.g. patients suffering from progressive cancer, pulmonary disease or progressive, degenerative joint disease, without provoking or aggravating

disorders of intestinal motility such as constipation. The subject methods comprise the administration in combination or co-administration of an effective amount of an opioid analgesic or antitussive and an opioid antagonist which is systemically bio-available when administered by the parenteral route but is substantially non-bio-available when administered orally. Examples of suitable opioid analgesics include morphine, meperidine, oxycodone, methadone and the like. Among the most commonly used opioid antitussives are codeine and hydrocodone. Examples of suitable antagonists include naloxone, naloxone glucuronide and nalmefene glucuronide.

In accordance with the present invention, chronic pain or cough patients receive per os 1 to 2 dosage units comprising from about 1.5 to about 100 mg of opioid analgesic or antitussive and from about 1 to about 18 mg of suitable opioid antagonists (to be further defined below) 1 to 3 times daily. The two agents can be administered in combination in the form of tablets, capsules, caplets or prepared oral solutions, or can be dissolved or suspended together at time of administration in a suitable liquid vehicle, such as water, juice or other beverage. The two agents can also be co-administered in a non-simultaneous fashion, i.e., one of the agents is administered and, during the duration of its in vivo activity, the other agent is administered. *termed.*

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of treating a patient in chronic pain or with chronic cough over a prolonged period to provide systemic analgesia or central antitussive effect while simultaneously preventing the onset of intestinal hypomotility or alleviating hypomotility which has resulted from use of narcotic alone. These methods comprise the oral administration in combination of pharmaceutically effective amounts of an opioid analgesic or antitussive and an opioid antagonist having little or no systemic bio-availability in active form and, hence, substantially devoid of systemic antagonist activity when administered orally.

Opioid agonists which may be used in the methods of the present invention include all known safe and effective opioid analgesics, both short and long-acting opioid analgesics, for example, morphine, meperidine, oxycodone, methadone, hydromorphone, codeine, hydrocodone and propoxyphene. Because the subject methods relate solely to the oral administration of the agonists and antagonists, the opioid analgesics or antitussives selected must have a high degree of oral activity and be safe for oral administration.

The opioid antagonists which are suitable for use in the methods of the present invention, hereinafter sometimes referred to as "suitable opioid antagonists", must have little to no systemic antagonist activity when administered orally. A low degree of oral systemic activity is a necessary feature of the opioid antagonists used in the present invention because when the antagonists are given in combination with the opioid agonists as taught herein, they have little value if they neutralize or substantially negate the analgesic activity of the opioid agonists.

The suitable opioid antagonists are generally of two types:

1. Agents which exhibit a high degree of antagonist activity when administered parenterally but are substantially (at least 95%) metabolized and lose systemic

antagonist activity when administered orally. Such antagonists include, for example, naloxone (N-allyl-14-hydroxydihydronormorphine).

2. Agents which are in the form of antagonist metabolites, e.g. naloxone glucuronide and nalmefene (6-methylene-6-deoxy-N-cyclopropylmethyl-14-hydroxydihydronormorphine) glucuronide, which are inactive metabolites of parenterally active antagonists.

It has been discovered that certain opioid antagonists which are poorly bio-available when administered orally do reach the gut in substantially unaltered form and are absorbed through the intestinal walls into the portal circulation, but then are quickly metabolized and deactivated in the liver—for example, naloxone is metabolized in the liver to naloxone glucuronide, which has little or no systemic antagonist activity. Yet, by reaching the gut opiate receptors, these antagonists are capable of blocking the hypomotility-causing effects of the opioid agonists on the gastrointestinal tract, and thus can prevent the onset, or alleviate the symptoms, of constipation in patients receiving long term narcotic analgesic therapy, while not interfering with or ablating the analgesic activity of the opioid agonists.

The glucuronide metabolites specified above also prevent the onset of constipation and/or reduce the severity of constipation in chronic pain patients receiving opioid analgesics, perhaps because they are de-glucuronidated by bacterial activity or the activity of enzymes in the intestinal wall and reach the gut wall to some extent in the form of the antagonist bases, i.e., naloxone and nalmefene. Thus, it is believed that these metabolites act as pro-drugs when administered orally. As used herein the term "pro-drug" refers to substances which are inactive in vitro but are converted at least to some extent to a pharmaceutically active form in vivo.

In our co-pending application Ser. No. 680,230 filed Dec. 10, 1984 (continuation of Ser. No. 464,110 filed Feb. 4, 1983), we disclosed the utility of naloxone and other antagonist agents in relieving idiopathic or spontaneous constipation—i.e., constipation not caused by, for example, chronic administration of narcotic agonists. We emphasized on page 3 of that application that the invention therein disclosed did not relate to the use of opioid antagonists to neutralize the effect of opioid agonists such as narcotic drugs. The present invention relates to the use of specific opioid antagonists not to neutralize the systemic effects of narcotic agonists such as opioid analgesics, but only to counteract the gut level effects of the agonists on gastrointestinal motility while not otherwise blocking or interfering with any systemic agonist activity. Moreover, the methods of the present invention provide detailed dosage ranges and ratios for opioid analgesics and antitussives and suitable antagonists to provide a coherent method of acute or chronic treatment for patients with pain or cough which ensures adequate analgesia and antitussive activity while not compounding the patient's discomfort or aggravating the underlying illness with the complications of severe constipation.

In accordance with the novel methods of the present invention, patients suffering from chronic pain or cough, e.g., patients with progressive cancers, pulmonary disease, degenerative joint diseases, patients recovering from severe trauma and the like, receive one or two dosage units of opioid agonists and suitable antagonists 1 to 3 times daily. The opioid analgesics or antitussives utilized according to the present invention can be any short or long acting agents found to be safe and

effective for long term use, such as, by way of example, morphine, meperidine, oxycodone, hydromorphone, methadone, codeine, hydrocodone and propoxyphene.

The dosage range for the opioid agents is from about 1.5 to about 100 mg per dosage unit, with 1 or 2 units being administered 1 to 5 times daily, yielding a daily dosage range of about 1.5 to about 1,000 mg of opioid agonist. The following are illustrative ranges for particular opioid analgesics:

TABLE 1

Opioid Analgesics	Dosage Range Per Unit (mg)
morphine	10 to 30
meperidine	30 to 150
oxycodone	5 to 15
hydromorphone	1.5 to 3
methadone	5 to 15
codeine	40 to 80
propoxyphene	40 to 80

Suitable opioid antagonists for use in the present invention are, as discussed above, those which have little or no systemic antagonist activity when administered orally yet are capable of acting on gut opiate receptors to block the dysmotility provoking effects of opioid agonists. Such suitable antagonists include those which are absorbed from the gastrointestinal tract in non-metabolized form to the extent of 5% or less, such as naloxone. In addition, metabolites of narcotic antagonists which have little or no systemic activity, e.g., naloxone glucuronide and nalbuphine glucuronide, also have been found suitable for purposes of the present invention, probably because they act as pro-drugs. The key qualifications for the opioid antagonists suitable for use in the present invention are that they antagonize the adverse opioid effects on intestinal motility without significantly reducing the analgesic potency of the concomitantly administered opioid agonist.

In accordance with the present invention, chronic pain or cough patients receive a dosage amount of naloxone or other suitable antagonist together with each dosage amount of opioid analgesic, 1 to 5 times daily. Each dosage amount includes one or more dosage units comprising both pharmaceutical agents. The two agents can be combined in a fixed ratio in any pharmaceutically acceptable oral dosage form including, by way of example, capsules, tablets, caplets, syrups, elixirs and the like, with the addition of conventional carriers, binders, excipients, disintegration agents, lubricants, sweeteners and other known pharmaceutically acceptable additives. Alternatively, dosage amounts of opioid agonists and antagonists can be added in powdered form to a compatible beverage, such as fruit juice, for greater patient acceptability. The opioid agonist and suitable antagonist may also be co-administered to the patient in a non-simultaneous fashion with 1-5 dosage units of agonists and antagonists being separately administered to the patient.

The recommended dosage range for the narcotic antagonists suitable for use in the methods of the present invention is about 1 to about 18 mg per dosage unit. It has been found that a higher amount of antagonist, such as 12-18 mg per unit, is required with weaker agents such as codeine and propoxyphene, and a smaller amount of antagonist, such as 1-3 mg, per unit is required with stronger agonists such as morphine and meperidine. The following are typical unit and daily dosages of agonists and antagonists:

TABLE 2

Opioid Analgesics	Representative Unit Dose (mg)	Representative Unit Dose Antagonist (Naloxone)	Typical Total Daily Dose of Agonist-Antagonist
morphine	10	2	1-2 units qid
methadone	10	2	1-3 units qid
meperidine	30	2	1-3 units qid
oxycodone	5	3	1-2 units qid
hydromorphone	1.5	3	1-3 units qid
codeine	60	12	2 units qid
propoxyphene	60	18	2 units qid

The novelty of the present methods of treating chronic pain or cough patients by providing effective analgesia and central antitussive effect without provoking or aggravating constipation and other symptoms of intestinal hypomotility is not detracted from by the fact that combinations of opioid agonists and antagonists (primarily naloxone) are disclosed in the prior art. None of these prior disclosures relates to the utility of opioid agonists and orally ineffective antagonists in combination for purposes disclosed herein, or in any other method of treatment where local antagonism of gut level opioid effects is desired.

For example, in U.S. Pat. No. 3,493,637 it is disclosed that naloxone is useful in conjunction with opiate alkaloids for abating the respiratory depression caused by the opioids. But not only are the beneficial gastrointestinal effects of naloxone not disclosed in that patent, the combination formulations taught therein are only for parenteral use. Parenterally administered agonist-antagonist combinations would be useless in the methods of the present invention because the antagonist would seriously reduce the analgesic effect of the agonist while not improving intestinal motility as effectively as an orally administered preparation.

In U.S. Pat. No. 3,966,940, orally effective compositions are disclosed which comprise opioid analgesics and naloxone in combination. However, these combination formulations are disclosed as useful principally for the prevention of drug abuse because upon parenteral administration they do not produce analgesia, euphoria or physical dependence. This use of naloxone for the purpose of "adulterating" orally administered narcotic drugs to prevent parenteral abuse, such as by heroin and morphine addicts, is well known in the prior art. However, there is no prior disclosure in the patent or medical literature that such combination drugs would be useful in the treatment of chronic pain patients because of the oral effectiveness of naloxone in preventing narcotic induced constipation. Furthermore, it would not have occurred to skilled workers in the art to have utilized the prior art agonist-antagonist oral preparations to treat chronic pain patients where the possibility of parenteral abuse by the patients is not a significant concern.

Other combinations of opioid analgesics and naloxone suitable for prevention of parenteral abuse are disclosed in U.S. Pat. No. 4,512,835.

The following examples illustrate the methods of the present invention, but are in no way intended to indicate techniques, pharmaceutical agents, dosage forms or dosage amounts which must be utilized exclusively in order to come within the scope of the present invention.

The following examples represent titration studies which were performed on the subject patients. Opioid analgesics and antagonists were orally co-administered

in the patients and the dosage ranges adjusted until the point where a significant increase in fecal passage was observed with increased fecal wet weight, and with no sign of narcotic withdrawal symptoms or recrudescence of pain. The dosage regimen discovered by titration to be optimal for achieving the foregoing results is referred to in the examples as the "optimal dosage regimen".

EXAMPLE 1

Patient No. 1 was a 42 year old female with a 9 year history of lower left quadrant abdominal pain, bloating and rectal bleeding, and a 5 year history of seizures. Her optimal dosage regimen was found to be 65 mg of propoxyphene and 18 mg of naloxone administered orally bid (twice daily).

EXAMPLE 2

Patient No. 2 was a 33 year old male with a 15 year history of narcotic addiction and a 5 year history of narcotic methadone maintenance treatment. Two years prior to admission, the patient had suffered a fall from a 30-foot ladder resulting in brain hemorrhaging, a fractured left femur and clavicle and secondary pain. The patient's optimal dosage regimen was found to be 100 mg of methadone, 5 mg of oxycodone and 8 mg of naloxone administered qd (once daily).

EXAMPLE 3

Patient No. 3 was a 59 year old female with a 13 year history of post-auto crash secondary spinal cord lesions, paraplegia, chronic pain and constipation. Her optimal dosage regimen was found to be 10 mg of methadone, 5 mg of oxycodone and 8 mg of naloxone administered tid (thrice daily).

EXAMPLE 4

Patient No. 4 was a 53 year old female with a 13 year history of post left mastectomy and right pneumosctomy secondary pain. Her optimal dosage regimen was found to be 10 mg of oxycodone, administered 5 times daily as well as 10-12 mg of naloxone, 1-4 times daily.

EXAMPLE 5

Patient No. 5 was a 27 year old female with a 13 year history of intermittent small bowel obstruction diagnosed as pseudocobstruction and secondary chronic pain resulting in chronic narcotic dependency and methadone maintenance treatment. Her optimal dosage regimen was found to be 100 mg of methadone together with 4 mg of naloxone administered qd.

It will thus be seen that there are provided novel methods which achieve the various objects of the invention, and which are well adapted to meet the conditions of practical use.

As various possible embodiments might be made of the above invention, and as various changes might be made in the embodiments set forth above, it is to be understood that all matters herein described are to be interpreted as illustrative and not in a limiting sense.

What is claimed as new and desired to be protected by Letters Patent is set forth in the appended claims.

1. A method of treating a patient in chronic pain or suffering from chronic cough over a prolonged period to provide systemic analgesia or central antitussive effect while simultaneously avoiding the onset of intestinal hypomotility, comprising the oral administration to the patient 1-5 times daily of 1-2 dosage units comprising from about 1.5 to about 100 mg of an opioid analgesic or antitussive selected from the group consisting of methadone and propoxyphene and from about 1 to about 18 mg of an opioid antagonist or antagonist pro-drug substantially devoid of systemic antagonist activity when administered orally.

2. A method according to claim 1 which comprises the use of an opioid antagonist absorbed into the bloodstream through the gastrointestinal tract in non-metabolized form to the extent of less than 5%.

3. A method according to claim 2 wherein said opioid antagonist is naloxone.

4. A method according to claim 1 which comprises the use of an antagonist pro-drug in the form of a metabolite of a parenterally active antagonist.

5. A method according to claim 4 wherein said antagonist pro-drug is selected from the group consisting of naloxone glucuronide and nalmeferne glucuronide.

6. A method according to claim 1 wherein at least one dosage unit each of said analgesic or antitussive and antagonist or antagonist pro-drug is administered to the patient in combination in pharmaceutically acceptable oral dosage form.

7. A method according to claim 6 wherein said oral dosage form is selected from the group consisting of capsules, caplets, tablets, syrups and elixirs.

8. A method according to claim 1 wherein a dosage amount comprising at least one dosage unit each of analgesic or antitussive and antagonist or antagonist pro-drug is dissolved or suspended in a liquid beverage at the time of administration to the patient.

9. A method according to claims 6 or 8 wherein said dosage unit of antagonist includes from about 1 to about 18 mg of naloxone.

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[34] CONTROLLED RELEASE OXYCODONE COMPOSITIONS

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[*] Notice: The portion of the term of this patent subsequent to Feb. 5, 2008 has been disclaimed.

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[58] Field of Search 424/464, 465, 468, 469, 424/470, 486, 487, 488, 494, 496, 497, 498

[36] References Cited

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[57] ABSTRACT

A solid controlled release, oral dosage form, the dosage form comprising a therapeutically effective amount of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method of 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 12.5% and 42.5% (by weight) oxycodone released after 1 hour, between 25% and 55% (by weight) oxycodone released after 2 hours, between 45% and 75% (by weight) oxycodone released after 4 hours and between 55% and 85% (by weight) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

17 Claims, No Drawings

CONTROLLED RELEASE OXYCODONE COMPOSITIONS

BACKGROUND OF THE INVENTION

The present invention relates to a solid, controlled release oral dosage form for use in the treatment of moderate to severe pain.

It has previously been known in the art that controlled release compositions of hydromorphone or salts thereof could be prepared in a suitable matrix. For example, U.S. Pat. No. 4,990,341 (Goldie), also assigned to the assignee of the present invention, describes hydromorphone compositions wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C., is between 12.5 and 42.5% (by wt) hydromorphone released after 1 hour, between 25 and 55% (by wt) released after 2 hours, between 45 and 75% (by wt) released after 4 hours and between 55 and 85% (by wt) released after 6 hours.

For example, this patent teaches that controlled release hydromorphone compositions can be prepared by incorporating the drug into a controlled release matrix (e.g. hydrophobic polymers, digestible long chain hydrocarbons, polyalkylene glycols), or by incorporating the drug into a normal release matrix and utilizing a coating that controls the release of the drug (e.g. a film coating comprising a wax, shellac or zein, a water insoluble cellulose, a polymethacrylate). In a particularly preferred embodiment, film coated spheroids of hydromorphone and microcrystalline cellulose are film-coated to obtain the desired controlled release of the hydromorphone.

While controlled release compositions utilizing hydromorphone as the therapeutically active ingredient were obtained, controlled release compositions containing other therapeutically active agents having the same medicinal use (analgesia) and structurally related to hydromorphone, such as oxycodone, were not believed to be obtained when using similar techniques as those set forth in U.S. Patent No. 4,990,341.

It has now been surprisingly discovered that controlled release compositions which include an analgesic other than hydromorphone are indeed obtainable via the methods set forth in U.S. Pat. No. 4,990,341.

SUMMARY OF THE INVENTION

According to the present invention there is provided a solid, controlled release, oral dosage form, the dosage form comprising a therapeutically effective amount of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

Preferably, the dosage form contains an analgesically effective amount of oxycodone or a salt thereof. However, other related analgesically effective agents may also be used, including hydromorphone, dihy-

drocodeine, codeine, dihydromorphine, morphine, buprenorphine, salts thereof, and the like.

USP Paddle Method is the Paddle Method described, e.g., in U.S. Pharmacopoeia XXII (1990).

In the present specification, "independent of pH" means that the difference, at any given time, between the amount of oxycodone released at pH 1.6 and the amount released at any other pH up to, and including, pH 7.2 (when measured in vitro using the USP Paddle Method at 100 rpm in 900 ml aqueous buffer) is 10% (by weight) or less. The amounts released being, in all cases, a mean of at least three experiments.

DETAILED DESCRIPTION

In order to obtain a controlled release drug dosage form having at least a 12 hour therapeutic effect, it is usual in the pharmaceutical art to produce a formulation that gives a peak plasma level of the drug between about 4-8 hours after administration (in a single dose study). The present inventors have surprisingly found that, in the case of oxycodone, a peak plasma level at between 2-4 hours after administration gives at least 12 hours pain relief and, most surprisingly, that the pain relief obtained with such a formulation is greater than that achieved with formulations giving peak plasma levels (of oxycodone) in the normal period of 1-2 hours after administration.

Furthermore, in the case of the present dosage form, therapeutic levels are generally achieved without concurrent side effects, such as nausea, vomiting, constipation and drowsiness, which are often associated with high blood levels of oxycodone. There is also evidence to suggest that the use of the present dosage forms leads to a reduced risk of drug addiction.

A further advantage of the present composition, which releases oxycodone at a rate that is independent of pH between 1.6 and 7.2, is that it avoids dose dumping upon oral administration. In other words, the oxycodone is released evenly throughout the gastrointestinal tract.

The present oral dosage form may be presented as, for example, granules, spheroids or pellets in a capsule or in any other suitable solid form. Preferably, however, the oral dosage form is a tablet.

The present oral dosage form preferably contains between 1 and 30 mg, most especially between 10 and 30 mg, of oxycodone hydrochloride. Alternatively the dosage form may contain molar equivalent amounts of other oxycodone salts or of the oxycodone base.

The present matrix may be any matrix that affords in vitro dissolution rates of oxycodone within the narrow ranges required and that releases the oxycodone in a pH independent manner. Preferably the matrix is a controlled release matrix, although normal release matrices having a coating that controls the release of the drug may be used. Suitable materials for inclusion in a controlled release matrix are

- (a) Hydrophilic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic polymer.
- (b) Digestible, long chain (C₁₂-C₂₄, especially C₁₂-C₁₆), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl

esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25° and 90° C. are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of at least one polyalkylene glycol.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C₁₂-C₁₆, preferably C₁₄-C₁₆, aliphatic alcohol and, optionally, at least one polyalkylene glycol.

The at least one hydroxyalkyl cellulose is preferably a hydroxy (C₁ to C₆) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of oxycodone release required. Preferably however, the oral dosage form contains between 5% and 25%, especially between 6.25% and 15% (by wt) of the at least one hydroxyalkyl cellulose.

The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In a particularly preferred embodiment of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of oxycodone release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In a preferred embodiment, the controlled release composition comprises from about 5 to about 25% acrylic resin and from about 8 to about 40% by weight aliphatic alcohol by weight of the total dosage form. A particularly preferred acrylic resin comprises Eudragit TM RS PM commercially available from Rohm Pharma.

In the present preferred dosage form, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/ polyalkylene glycol determines, to a considerable extent, the release rate of the oxycodone from the formulation. A ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1000 and 15000 especially between 1500 and 12000.

Another suitable controlled release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C₁₂ to C₁₆ aliphatic alcohol and, optionally, a polyalkylene glycol.

In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

As an alternative to a controlled release matrix, the present matrix may be a normal release matrix having a coat that controls the release of the drug. In particularly preferred embodiments of this aspect of the invention, the present dosage form comprises film coated spheroids containing active ingredient and a non-water soluble spheronising agent. The term spheroid is known in the pharmaceutical art and means a spherical granule having a diameter of between 0.5 mm and 2.5 mm especially between 0.5 mm and 2 mm.

The spheronising agent may be any pharmaceutically acceptable material that, together with the active ingredient, can be spheronised to form spheroids. Microcrystalline cellulose is preferred.

A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). According to a preferred aspect of the present invention, the film coated spheroids contain between 70% and 99% (by wt), especially between 80% and 95% (by wt), of the spheronising agent, especially microcrystalline cellulose.

In addition to the active ingredient and spheronising agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose.

The spheroids are preferably film coated with a material that permits release of the oxycodone (or salt) at a controlled rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other ingredients, the in-vitro release rate outlined above (between 12.5% and 42.5% (by wt) release after 1 hour, etc.).

The film coat will generally include a water insoluble material such as

- (a) a wax, either alone or in admixture with a fatty alcohol,
- (b) shellac or zein,
- (c) a water insoluble cellulose, especially ethyl cellulose,
- (d) a polymethacrylate, especially Eudragit®.

Preferably, the film coat comprises a mixture of the water insoluble material and a water soluble material. The ratio of water insoluble to water soluble material is determined by, amongst other factors, the release rate required and the solubility characteristics of the materials selected.

The water soluble material may be, for example, polyvinylpyrrolidone or, which is preferred, a water soluble cellulose, especially hydroxypropylmethyl cellulose.

Suitable combinations of water insoluble and water soluble materials for the film coat include shellac and polyvinylpyrrolidone or, which is preferred, ethyl cellulose and hydroxypropylmethyl cellulose.

In order to facilitate the preparation of a solid, controlled release, oral dosage form according to this in-

vention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, controlled release, oral dosage form according to the present invention comprising incorporating oxycodone or a salt thereof in a controlled release matrix. Incorporation in the matrix may be effected, for example, by

- (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and oxycodone or a oxycodone salt,
- (b) mixing the hydroxyalkyl cellulose containing granules with at least one C₁₂-C₁₈ aliphatic alcohol, and
- (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/oxycodone with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 3 times, especially between 1.75 and 3.5 times, the dry weight of the oxycodone.

The present solid, controlled release, oral dosage form may also be prepared, in the form of film coated spheroids, by

- (a) blending a mixture comprising oxycodone or a oxycodone salt and a non-water soluble spheronizing agent,
- (b) extruding the blended mixture to give an extrudate,
- (c) spheronizing the extrudate until spheroids are formed, and
- (d) coating the spheroids with a film coat.

The present solid, controlled release, oral dosage form and processes for its preparation will now be described by way of example only.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not meant to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Controlled Release Oxycodone HCl 30 mg Tablets Aqueous Manufacture

The required quantities of oxycodone hydrochloride, spray-dried lactose, and Eudragit TM RS PM are transferred into an appropriate-size mixer, and mixed for approximately 5 minutes. While the powders are mixing, the mixture is granulated with enough water to produce a moist granular mass. The granules are then dried in a fluid bed dryer at 60° C., and then passed through an 8-mesh screen. Thereafter, the granules are redried and pushed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°-70° C., and while the granules are mixing, the melted stearyl alcohol is added. The warm granules are returned to the mixer.

The coated granules are removed from the mixer and allowed to cool. The granules are then passed through a 12-mesh screen. The granulate is then lubricated by mixing the required quantity of talc and magnesium stearate in a suitable blender. Tablets are compressed to 375 mg in weight on a suitable tableting machine. The formula for the tablets of Example 1 is set forth in Table 1 below:

TABLE 1

Formula of Oxycodone HCl 30-mg Tablets

Component	mg/Tablet	Percent (by wt)
Oxycodone Hydrochloride	30.0	8
Lactose (spray-dried)	211.75	57
Eudragit ® RS PM	41.0	12
Purified Water	q.s.*	—
Stearyl Alcohol	71.0	20
Talc	7.5	2
Magnesium Stearate	1.75	1
Total:	375.0	100

*Used in manufacture and remains in final product in residual quantity only.

The tablets of Example 1 are then tested for dissolution via the USP Basket Method, 37° C., 100 RPM, first hour 700 ml gastric fluid at pH 1.2, then changed to 900 ml at 7.5. The results are set forth in Table 2 below:

TABLE 2

Dissolution of Oxycodone 30 mg Controlled Release Tablets

Time	% Oxycodone Dissolved
1	11.1
2	43.3
4	58.2
8	71.1
12	81.8
18	81.8
24	89.2

EXAMPLE 2

Controlled Oxycodone HCl 10 mg Release Tablets—Organic Manufacture

The required quantities of oxycodone hydrochloride and spray dried lactose are transferred into an appropriate sized mixer and mix for approximately 6 minutes. Approximately 40 percent of the required Eudragit ® RS PM powder is dispersed in Ethanol. While the powders are mixing, the powders are granulated with the dispersion and the mixing continued until a moist granular mass is formed. Additional ethanol is added if needed to reach granulation end point. The granulation is transferred to a fluid bed dryer and dried at 30° C.; and then passed through a 12-mesh screen. The remaining Eudragit ® RS PM is dispersed in a solvent of 90 parts ethanol and 10 parts purified water; and sprayed onto the granules in the fluid bed granulator/dryer at 30° C. Next, the granulate is passed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°-70° C. The warm granules are returned to the mixer. While mixing, the melted stearyl alcohol is added. The coated granules are removed from the mixer and allowed to cool. Thereafter, they are passed through a 12-mesh screen.

Next, the granulate is lubricated by mixing the required quantities of talc and magnesium stearate in a suitable blender. The granulate is then compressed to 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 2 is set forth in Table 3 below:

TABLE 3

Formula of Oxycodone HCl 10 mg Controlled Release Tablets

Component	Mg/Tablet	Percent (by wt)
Oxycodone hydrochloride	10.00	8
Lactose (spray-dried)	71.25	57
Eudragit ® RS PM	15.00	12
Ethanol	q.s.*	—

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TABLE 3-continued

Formula of Oxycodone HCl 10 mg Controlled Release Tablets		
Component	Mg/Tablet	Percent (by wt)
Purified Water	9.4*	—
Stearyl Alcohol	25.00	20
Talc	2.50	2
Magnesium stearate	1.25	1
Total	125.00 mg	100

*Used only in the manufacture and remains in final product in reduced quantity only.

The tablets of Example 2 are then tested for dissolution via USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric (pH 1.2) then changed to 900 ml at pH 7.5. The results are set forth in Table 4 below:

TABLE 4

Dissolution of Oxycodone 10 mg Controlled Release Tablets	
Hour	% Dissolved
1	33.9
2	47.7
4	58.3
8	67.7
12	74.3
18	76.9
24	81.3

EXAMPLE 3

Controlled Release Oxycodone 10 mg Tablets (Aqueous Manufacture)

Eudragit® RS 30D and Triacetin® are combined while passing through a 60 mesh screen, and mixed under low shear for approximately 5 minutes or until a uniform dispersion is observed.

Next, suitable quantities of Oxycodone HCl, lactose, and povidone are placed into a fluid bed granulator/dryer (FBD) bowl, and the suspension sprayed onto the powder in the fluid bed. After spraying, the granulation is passed through a #12 screen if necessary to reduce lumps. The dry granulation is placed in a mixer.

In the meantime, the required amount of stearyl alcohol is melted at a temperature of approximately 70° C. The melted stearyl alcohol is incorporated into the granulation while mixing. The waxed granulation is transferred to a fluid bed granulator/dryer or trays and allowed to cool to room temperature or below. The cooled granulation is then passed through a #12 screen. Thereafter, the waxed granulation is placed in a mixer/blender and lubricated with the required amounts of talc and magnesium stearate for approximately 3 minutes, and then the granulate is compressed into 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 3 is set forth in Table 5 below:

TABLE 5

Formula of Controlled Release Oxycodone 10 mg Tablets		
Component	Mg/Tablet	percent (by wt)
Oxycodone Hydrochloride	10.0	8.0
Lactose (spray dried)	69.25	55.4
Povidone	3.0	2.4
Eudragit® RS 30D (solid)	10.0*	8.0
Triacetin®	2.0	1.6
Stearyl Alcohol	25.0	20.0
Talc	2.5	2.0
Magnesium Stearate	1.25	1.0

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TABLE 3-continued

Formula of Controlled Release Oxycodone 10 mg Tablets		
Component	Mg/Tablet	percent (by wt)
Total	125.0	100.0

*Approximately 11.13 mg Eudragit® RS 30D aqueous dispersion is equivalent to 10 mg of Eudragit® RS 30D dry substance.

The tablets of Example 3 are then tested for dissolution via the USP Basket Method at 37° C., 100 RPM, first hour 700ml simulated gastric fluid at pH 1.2, then changed to 900ml at pH 7.5.

TABLE 6

Dissolution of Oxycodone 10 mg Controlled Release Tablets	
Hour	% Oxycodone Dissolved
1	34.0
2	47.3
4	62.0
8	79.8
12	91.1
18	94.9
24	98.7

EXAMPLES 4-5

In Example 4, 30 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 1.

In Example 5, 10 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 2.

Thereafter, dissolution studies of the tablets of Examples 4 and 5 are conducted at different pH levels, namely, pH 1.3, 4.56, 6.88 and 7.5.

The results are provided in Tables 7 and 8 below:

TABLE 7

Example 4 Percentage Oxycodone HCl 30 mg Tablets Dissolved Over Time	
pH	1 2 4 8 12 18 24
1.3	29.3 43.7 61.8 78.9 91.0 97.0 97.1
4.56	34.4 49.1 66.4 82.0 93.6 99.4 101.1
6.88	33.8 47.1 64.4 81.9 92.9 100.3 103.0
7.5	27.0 38.6 52.3 70.0 81.8 89.7 96.6

TABLE 8

Example 5 Percentage Oxycodone HCl - 10 mg Tablets Dissolved Over Time	
pH	1 2 4 8 12 18 24
1.3	25.0 41.9 58.5 75.5 85.3 90.7 94.3
4.56	37.1 44.2 59.4 76.4 86.2 91.2 93.7
6.88	34.7 43.2 60.0 75.1 81.4 90.3 93.9
7.5	33.3 40.1 51.3 66.3 73.2 81.7 86.8

EXAMPLES 6-11

In examples 6-11, 4 mg and 10 mg oxycodone HCl tablets were prepared according to the formulations and methods set forth in the assignee's U.S. Pat. No. 4,844,909.

In Example 6, oxycodone hydrochloride (10.00 gm) was wet granulated with lactose monohydrate (417.3 gm) and hydroxyethyl cellulose (100.00 gm), and the granules were sieved through a 12 mesh screen. The

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granules were then dried in a fluid bed dryer at 50° C. and sieved through a 16 mesh screen.

Molten cetostearyl alcohol (300.0 gm) was added to the warmed oxycodone containing granules, and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Purified Tale (15.0 gm) and magnesium stearate (7.5 gm) were then added and mixed with the granules. The granules were then compressed into tablets.

Example 7 is prepared in the same manner as Example 6; however, the formulation includes 10 mg oxycodone HCl/tablet. The formulas for Examples 6 and 7 are set forth in Tables 9 and 10, respectively.

TABLE 9

Formulation of Example 6		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Purified tale	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 10

Formulation of Example 7		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Tale	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 8, 4 mg oxycodone HCl controlled release tablets are prepared according to the excipient formula cited in Example 2 of U.S. Pat. No. 4,844,909. The method of manufacture is the same as set forth in Examples 6 and 7 above. Example 9 is prepared according to Example 8, except that 10 mg oxycodone HCl is included per tablet. The formulas for Examples 8 and 9 are set forth in Tables 11 and 12, respectively.

TABLE 11

Formulation of Example 8		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Anhydrous Lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Tale	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 12

Formulation of Example 9		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Anhydrous Lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Tale	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 10, oxycodone 4 mg controlled release tablets are prepared with the same excipient formula cited in Example 3 of U.S. Pat. No. 4,844,909.

Oxycodone hydrochloride (32.0 gm) was wet granulated with lactose monohydrate (240.0 gm) hydroxyethyl cellulose (80.0 gm) and methacrylic acid copoly-

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mer (240.0 gm, Eudragit® L-100-55), and the granules were sieved through a 12 mesh screen. The granules were then dried in a Fluid Bed Dryer at 50° C. and passed through a 16 mesh screen.

The warmed oxycodone containing granules was added molten cetostearyl alcohol (240.0 gm), and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen. The granules were then compressed into tablets.

Example 11 is prepared in identical fashion to Example 10, except that 10 mg oxycodone HCl is included per tablet. The formulations for Examples 10 and 11 are set forth in Tables 13 and 14, respectively.

TABLE 13

Formulation of Example 10		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	75.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

TABLE 14

Formulation of Example 11		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	80.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

Next, dissolution studies were conducted on the tablets of Examples 6-11 using the USP basket method as described in the U.S. Pharmacopoeia XXII (1990). The speed was 100 rpm, the medium was simulated gastric fluid for the first hour followed by simulated intestinal fluid thereafter, at a temperature of 37° C. Results are given in Table 15.

TABLE 15

DISSOLUTION STUDIES OF EXAMPLES 6-11						
Time (hr)	% Oxycodone Dissolved					
	Ex. 6	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11
1	21.3	23.5	28.1	39.3	31.3	40.9
2	35.6	37.5	41.3	43.2	44.9	55.6
4	51.9	56.4	61.3	63.6	62.1	74.2
8	75.3	79.2	81.7	88.0	82.0	91.9
12	90.7	94.5	95.1	100.0	91.4	100.0

EXAMPLES 12-14

Clinical Studies

In Examples 12-14, randomized crossover bioavailability studies were conducted employing the formulation of Examples 2 (organic manufacture) and 3 (aqueous manufacture).

In Example 12, a single dose fast/fed study was conducted on 24 subjects with oxycodone tablets prepared according to Example 3.

In Example 13, a steady-state study was conducted on 23 subjects after 12 hours with oxycodone tablets prepared according to Example 2, and compared to a 5 mg oxycodone immediate-release solution.

In Example 14, a single dose study was conducted on 8 subjects with 2x10 mg oxycodone tablets prepared

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according to Examples 2 and 3, respectively, compared to a 20 mg oxycodone immediate release solution.

In Example 15, a single dose study was conducted on 22 subjects using oxycodone tablets prepared according to Example 3, and compared to a 20mg oxycodone immediate release solution.

In Example 16, a 12 subject single-dose study was conducted using 3x10mg oxycodone tablets prepared according to Example 3, and compared to a 30mg oxycodone immediate release solution.

The results of Examples 12-16 are set forth in Table 16.

TABLE 16

Example	Dosage	AUC ng/ml/hr	Cmax ng/ml	Tmax hr
12	10 mg CR Fast	43	6.1	2.8
	10 mg CR Fed	44	7.1	1.6
13	5 mg CR q4h	121	17	1.2
	10 mg CR q12h	130	17	1.1
14	20 mg IR	144	24	2.1
	2 x 10 mg CR	117	14	1.1
15	2 x 10 mg CR	129	14	2.6
	20 mg IR	184	40	1.4
16	2 x 10 mg CR	197	18	2.6
	30 mg IR	306	33	1.1
	3 x 10 mg CR	330	31	2.6
	30 mg CR	352	36	2.9

IR denotes immediate-release oxycodone solution.
CR denotes controlled-release tablets

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. A solid, controlled release, oral dosage form, the dosage form comprising an analgesically effective amount of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 12.5% and 42.5% (by wt) oxycodone released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

2. A dosage form according to claim 1 wherein the in vitro dissolution rate is between 17.5% and 38% (by wt) oxycodone released after 1 hour, between 30% and 50% (by wt) oxycodone released after 2 hours, between 50% and 70% (by wt) oxycodone released after 4 hours and between 60% and 80% (by wt) oxycodone released after 6 hours.

3. A dosage form according to claim 2 wherein the in vitro dissolution rate is between 17.5% and 32.5% (by wt) oxycodone released after 1 hour, between 35% and 45% (by wt) oxycodone released after 2 hours, between 55% and 65% (by wt) oxycodone released after 4 hours and between 65% and 75% (by wt) oxycodone released after 6 hours.

4. A dosage form according to claim 1 wherein the peak plasma level of oxycodone occurs between 2.25 and 3.75 hours after administration of the dosage form.

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5. A dosage form according to claim 1 wherein a therapeutically effective amount of an oxycodone salt comprises between 2 and 30 mg of oxycodone hydrochloride.

6. A dosage form according to claim 1 wherein a therapeutically effective amount of an oxycodone salt comprises between 2 and 40 mg of oxycodone hydrochloride.

7. A solid controlled release oral dosage form, comprising an analgesically

- (a) effective amount of oxycodone or a salt thereof;
- (b) an effective amount of a controlled release matrix selected from the group consisting of hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from about 98 to about 50 carbon atoms, and polyalkylene glycole; and

(c) a suitable amount of a suitable pharmaceutical diluent, wherein said composition provides an in vitro dissolution rate of the dosage form when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 12.5% and 42.5% (by wt) oxycodone released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

8. The controlled release composition of claim 7, wherein said controlled release matrix comprises an acrylic resin.

9. The controlled release composition of claim 8 which contains from about 2 to about 30 mg of oxycodone hydrochloride.

10. A solid controlled release oral dosage form, comprising

- (a) an analgesically effective amount of spheroids comprising oxycodone or a salt thereof and either a spheronizing agent or an acrylic polymer or copolymer;
- (b) a film coating which controls the release of the oxycodone or oxycodone salt at a controlled rate in an aqueous medium, wherein said composition provides an in vitro dissolution rate of the dosage form; and

(c) a suitable amount of a suitable pharmaceutical diluent, wherein said composition provides an in vitro dissolution rate of the dosage form when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. between 12.5% and 42.5% (by wt) oxycodone released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

11. The controlled release composition of claim 10, wherein said film coating comprises a water insoluble material selected from the group consisting of shellac or zein, a water insoluble cellulose, or a polymethacrylate.

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12. The controlled release composition of claim 11, which contains from about 2 to about 30 mg of oxycodone hydrochloride.

13. A controlled release tablet for oral administration comprising an analgesically effective amount of oxycodone or an oxycodone salt dispersed in a controlled release matrix, comprising

from about 5% to about 25% of an acrylic resin and from about 8% to about 40% of at least one aliphatic alcohol of 12-36 carbon atoms, by weight, wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 12.5% and 42.5% (by wt) oxycodone released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being independent of pH between 20 pH 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

14. A process for the preparation of a solid, controlled release, oral dosage form comprising incorporating an analgesically effective amount of oxycodone or a salt thereof in a controlled release matrix comprising from about 5% to about 25% of an acrylic resin and from about 8% to about 40% of at least one aliphatic alcohol of 12-36 carbon atoms, by weight, wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method

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of 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 25% and 60% (by weight) oxycodone release after 1 hour, between 45% and 80% (by weight) oxycodone released after 2 hours, between 60% and 90% (by weight) oxycodone released after 3 hours, and between 70% and 100% (by weight) oxycodone released after 4 hours, the in vitro release rate being independent of pH between 1.6 and 7.2 and chosen such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

15. The process of claim 14, further comprising wet granulating said oxycodone or a salt thereof with said acrylic resin in alcohol to form a granulate thereof;

adding said at least one aliphatic alcohol in a substantially liquid state to said granulate to obtain coated granules; and

compressing and shaping the granules.

16. The process of claim 14, further comprising wet granulating said oxycodone or a salt thereof with said acrylic resin in water to form a granulate thereof;

adding said at least one aliphatic alcohol in a substantially liquid state to said granulate to obtain coated granules; and

compressing and shaping the granules.

17. The process of claim 16, wherein a portion of said acrylic resin is dispersed in a suitable solvent and sprayed onto said granulate prior to adding said at least one aliphatic alcohol.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,266,331
DATED : November 30, 1993
INVENTOR(S) : Benjamin Oshlack et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the cover page, the portion reciting "The portion of the term of this patent subsequent to Feb. 5, 2008 has been disclaimed." should recite --The term of this patent shall not extend beyond the expiration date of Patent No. 4,990,341.--

Signed and Sealed this
Sixteenth Day of November, 1999

Attest:



Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

United States Patent [19]
Crain et al.

[11] Patent Number: 5,472,943
[45] Date of Patent: Dec. 5, 1995

[54] METHOD OF SIMULTANEOUSLY
ENHANCING ANALGESIC POTENCY AND
ATTENUATING DEPENDENCE LIABILITY
CAUSED BY MORPHINE AND OTHER
OPIOID AGONISTS

[75] Inventors: Stanley M. Crain, Leonia, N.J.; Ke-Fei
Shen, Flushing, N.Y.

[73] Assignee: Albert Einstein College of Medicine
of Yeshiva University, Bronx, N.Y.

[21] Appl. No.: 97,460

[22] Filed: Jul. 27, 1993

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 947,690, Sep. 21, 1992,
abandoned.

[51] Int. Cl.⁴ _____ A61K 31/44

[52] U.S. Cl. _____ 514/12; 514/13; 514/282

[58] Field of Search _____ 514/12, 13, 282

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Primary Examiner—James H. Reamer
Attorney, Agent, or Firm—Amster, Rothstein & Ebenstein

[57] ABSTRACT

This invention relates to a method of selectively enhancing the analgesic potency of morphine and other clinically used bimodally-acting opioid agonists and simultaneously attenuating development of physical dependence, tolerance and other undesirable side-effects caused by the chronic administration of said bimodally-acting opioid agonists comprising the co-administration of a bimodally-acting opioid agonist which activates inhibitory opioid receptor-mediated functions of neurons in the nociceptive (pain) pathways of the nervous system and an opioid receptor antagonist which selectively inactivates excitatory opioid receptor-mediated side-effects caused by said bimodally-acting opioid agonists. This invention further relates to a method of detoxifying and treating opiate addicts utilizing said opioid receptor antagonists, as well as to a composition comprising an excitatory opioid receptor antagonist of the invention and a bimodally-acting opioid agonist.

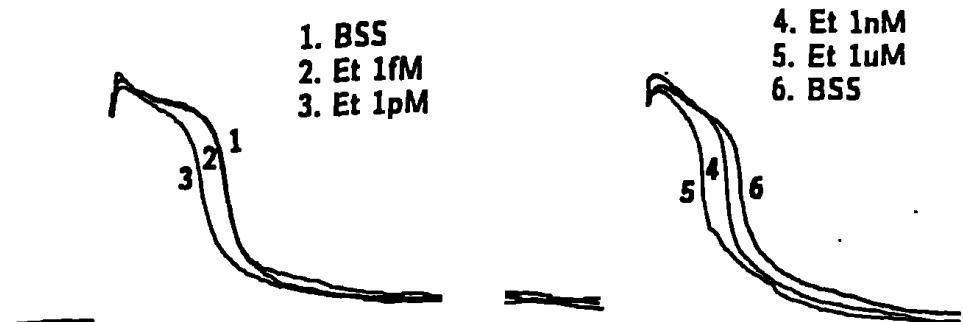


FIG. 1A

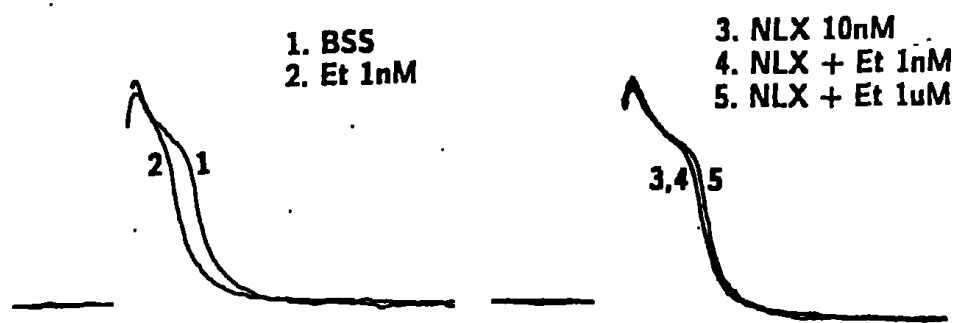


FIG. 1B

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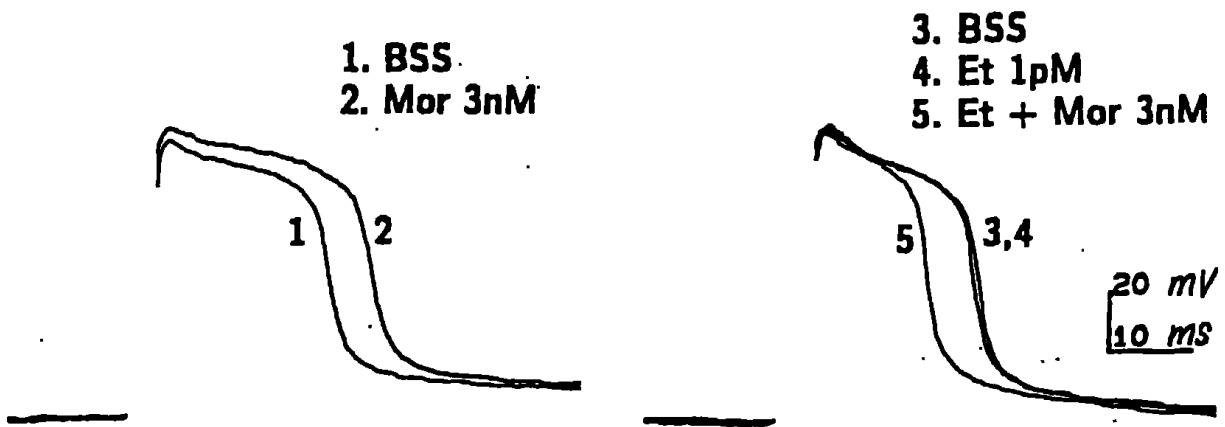


FIG. 1C

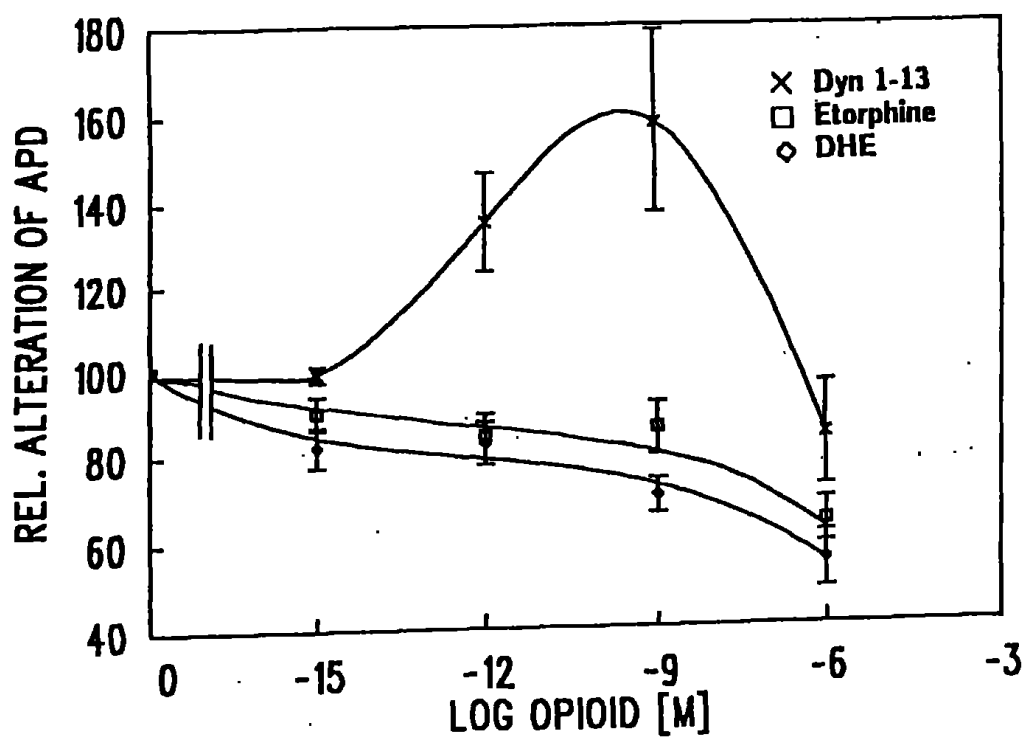


FIG. 2

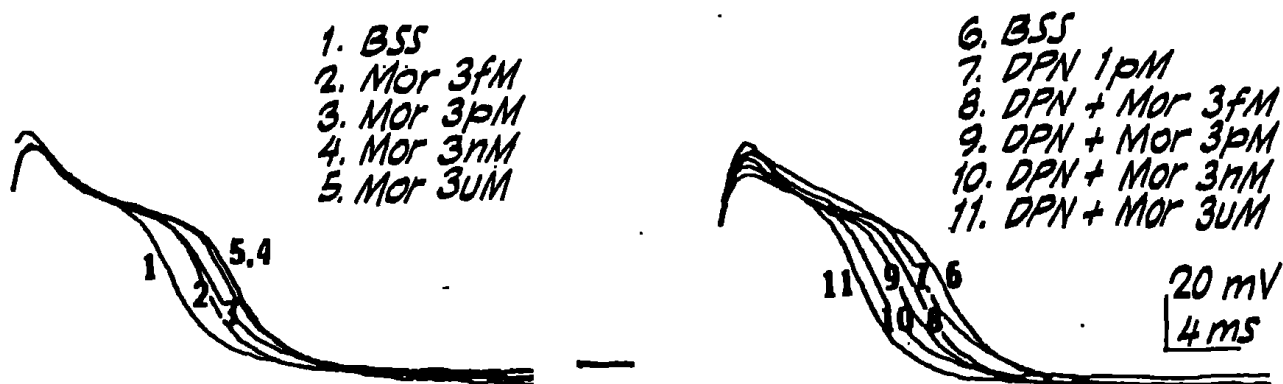


FIG. 3A

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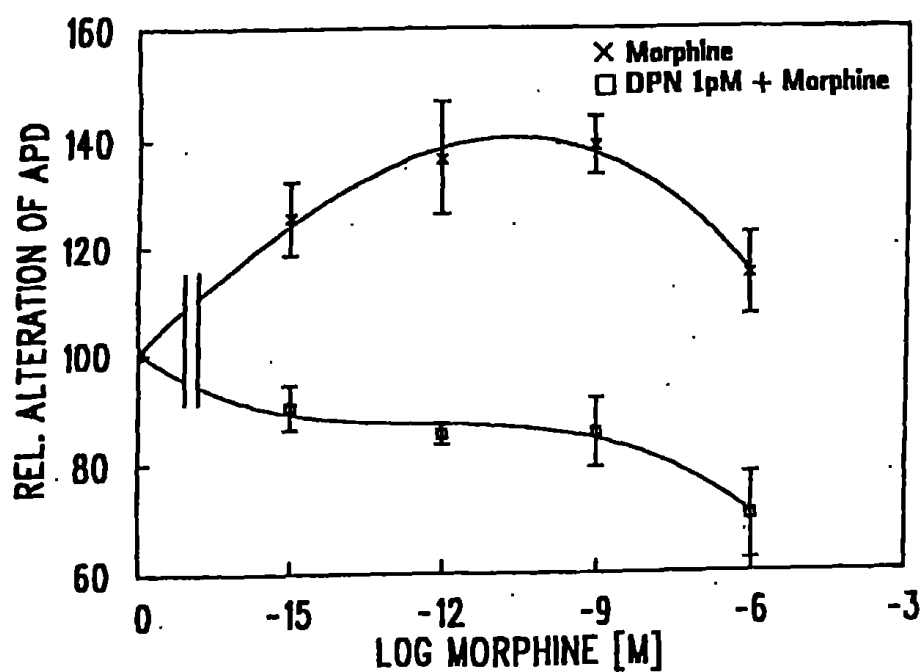


FIG. 3B

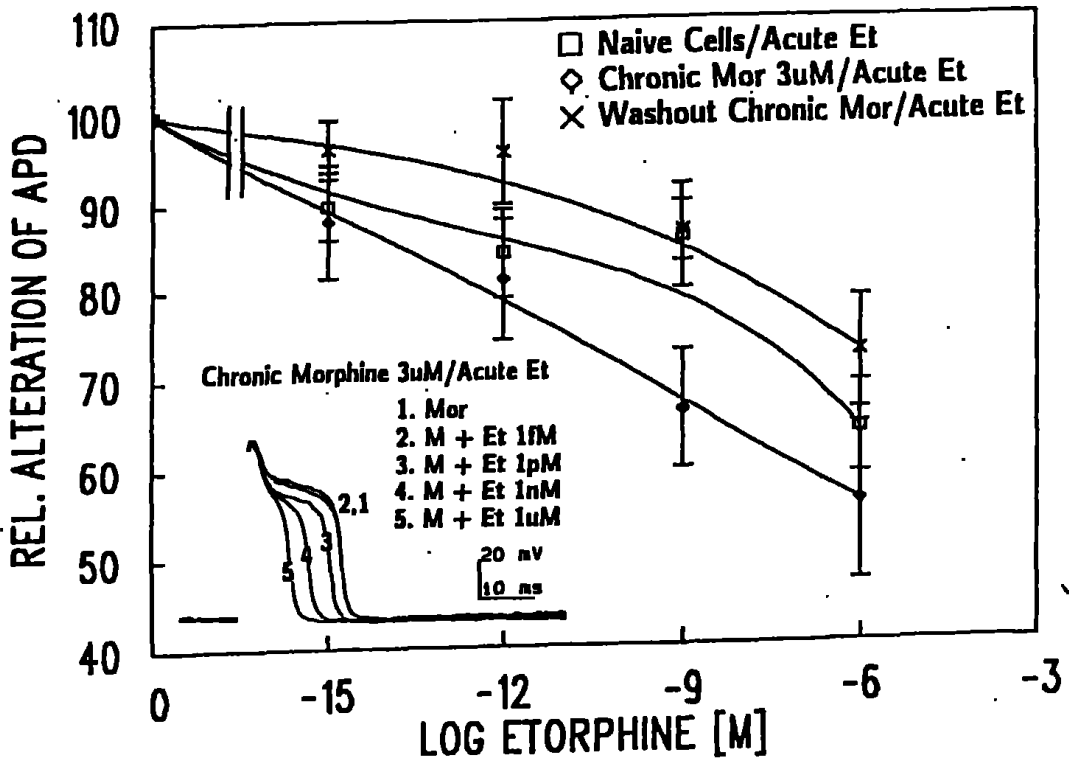
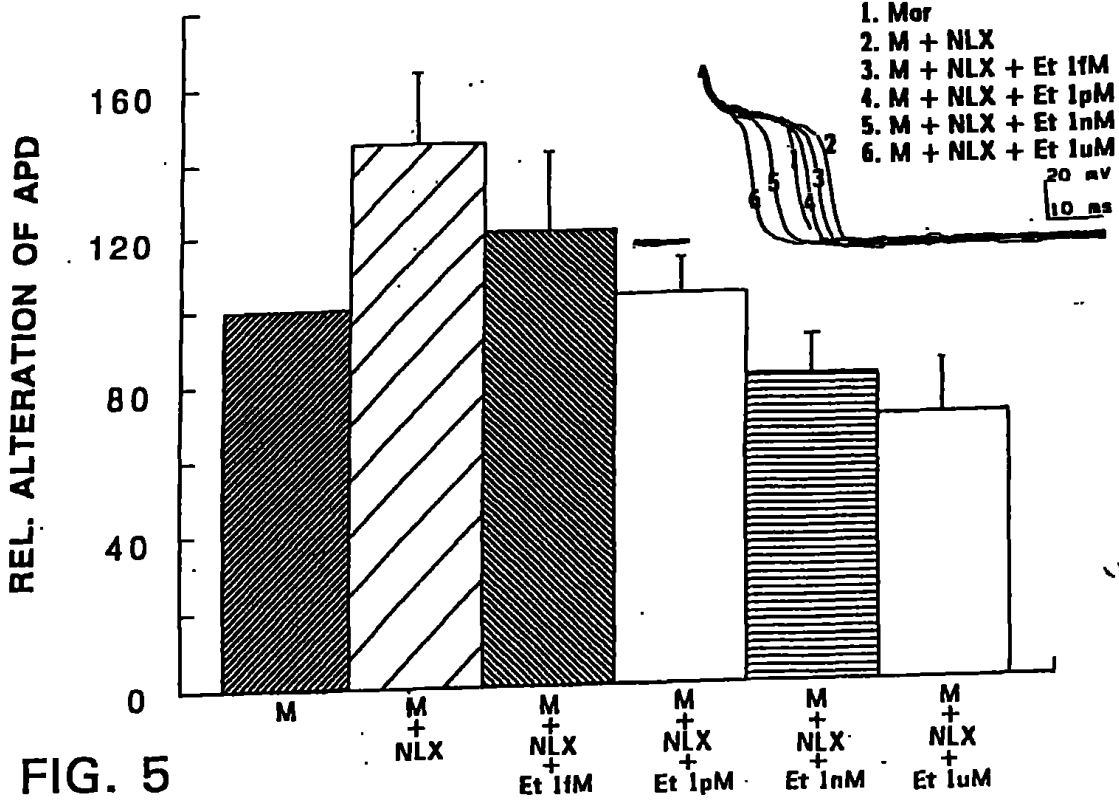


FIG. 4



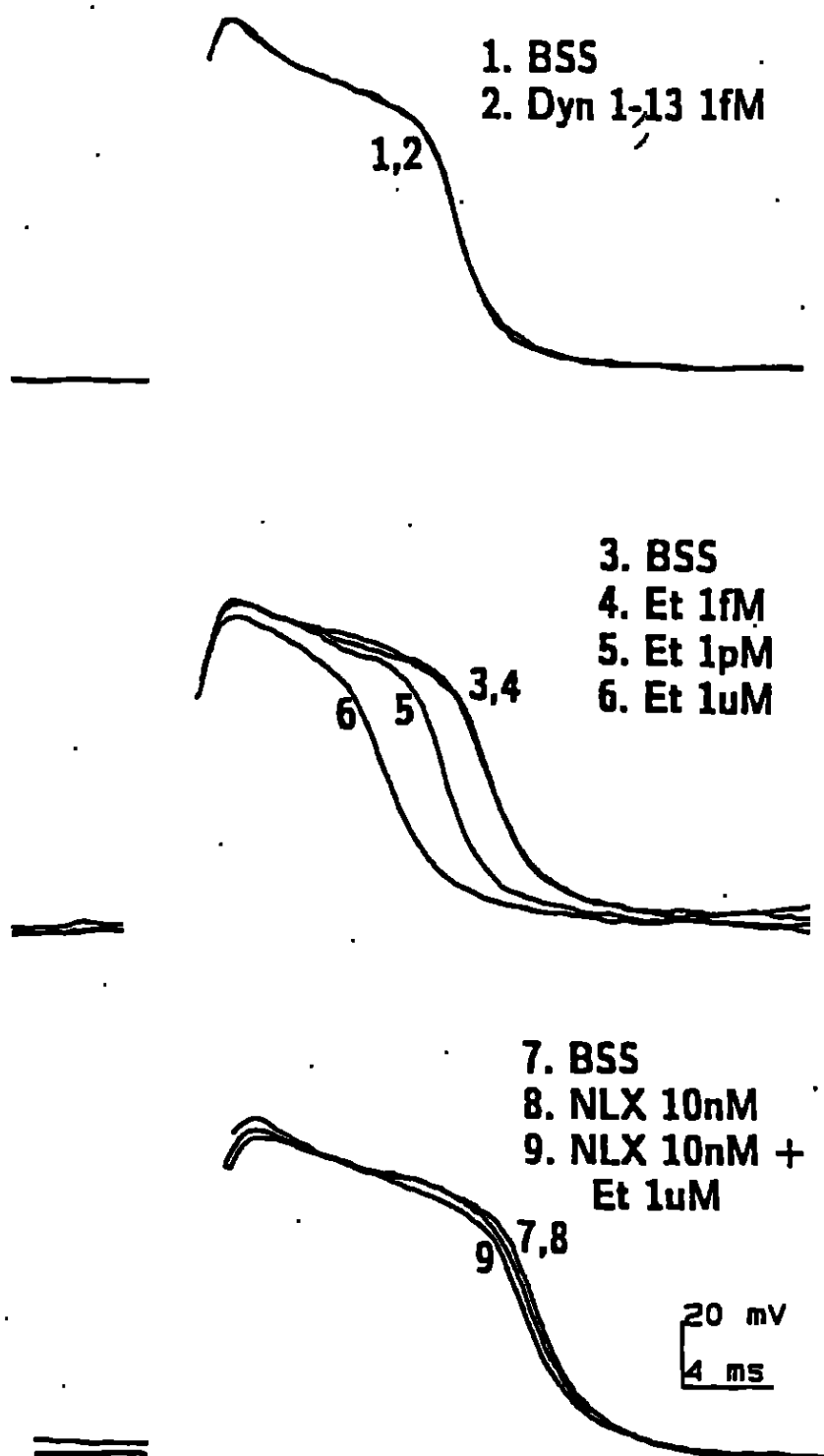


FIG. 6

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METHOD OF SIMULTANEOUSLY ENHANCING ANALGESIC POTENCY AND ATTENUATING DEPENDENCE LIABILITY CAUSED BY MORPHINE AND OTHER OPIOID AGONISTS

STATEMENT OF GOVERNMENT INTEREST

This invention was made with government support under NIDA research grant number DA 02031. As such, the government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

This Application is a Continuation-In-Part of application Ser. No. 07/947,690 filed Sep. 19, 1992, now abandoned, entitled A METHOD OF IDENTIFICATION OF NON-ADDICTIVE OPIOID ANALGESICS AND THE USE OF SAID ANALGESICS FOR TREATMENT OF OPIOID ADDICTION.

FIELD OF THE INVENTION

This invention relates to a method of enhancing the analgesic (inhibitory) effects of bimodally-acting opioid agonists, including morphine and other clinically used opioid analgesics, while at the same time attenuating anti-analgesic effects, physical dependence, tolerance, hyperexcitability, hyperalgesia, and other undesirable (excitatory) side-effects typically caused by chronic use of bimodally-acting opioid agonists. As used herein, the term "opioid" refers to compounds which bind to specific opioid receptors and have agonist (activation) or antagonist (inactivation) effects at these receptors, such as opioid alkaloids, including the agonist morphine and the antagonist naloxone, and opioid peptides, including enkephalins and dynorphins. As used herein, the term "opiate" refers to drugs derived from opium or related analogs.

In the instant invention, a selective excitatory opioid receptor antagonist is combined with a reduced dose of a bimodally-acting opioid agonist so as to elicit the desired degree of analgesia (inhibitory effects) and attenuate undesired side-effects (excitatory effects). Opioid analgesia results from activation (by opioid agonists) of inhibitory opioid receptors on neurons in the nociceptive (pain) pathways of the peripheral and central nervous systems. The undesirable side-effects, including anti-analgesic actions, the development of physical dependence, some types of tolerance, hyperexcitability and hyperalgesia, result from sustained activation (by bimodally-acting opioid agonists) of excitatory opioid receptors on neurons in the nociceptive (pain) pathways of the peripheral and central nervous systems. The administration of selective excitatory receptor antagonists together with bimodally-acting opioid agonists enhances analgesic effects caused by said opioids and attenuates the development of physical dependence, tolerance and other undesirable side-effects which are also caused by said opioids. In addition, combined use of the opioid receptor antagonists and agonists of the invention can be used for more effective detoxification and treatment of opiate addicts.

BACKGROUND OF THE INVENTION

Morphine or other bimodally-acting opioid agonists are administered to relieve severe pain due to the fact that they have analgesic effects mediated by their activation of inhibitory opioid receptors on nociceptive neurons (see North,

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Trends Neurosci., Vol. 9, pp. 114-117 (1986) and Crain and Shen, *Trends Pharmacol. Sci.*, Vol. 11, pp. 77-81 (1990)). However, bimodally-acting opioid agonists also activate opioid excitatory receptors on nociceptive neurons, which attenuates the analgesic potency of said opioids and results in the development of physical dependence thereon and increased tolerance thereto (see Shen and Crain, *Brain Res.*, Vol. 597, pp. 74-83 (1992)), as well as hyperexcitability, hyperalgesia and other undesirable (excitatory) side-effects. As a result, a long-standing need has existed to develop a method of both enhancing the analgesic (inhibitory) effects of bimodally-acting opioid agonists and limiting the undesirable (excitatory) side-effects caused by such opioid agonists.

The parent Patent Application for the instant invention, Ser. No. 07/947,690, relates to a specific group of opioid agonists for use as low/non-addictive analgesics and for the treatment of opioid addiction. In the parent Application, it is stated that this group of opioid agonists (which includes etorphine and dihydroetorphine) bind to and activate inhibitory but not excitatory opioid receptors. (In contrast, morphine and most other opioid alkaloids and peptides elicit bimodal effects by binding to and activating both excitatory and inhibitory opioid receptors.)

To date, no method has been discovered or developed whereby two opioid compounds are administered, one of which binds to and activates inhibitory opioid receptors to cause analgesia and the other of which binds to and inactivates excitatory opioid receptors so as to attenuate undesirable side-effects caused by the administration of bimodally-acting opioid agonists while simultaneously enhancing the analgesic effects of said bimodally-acting opioid agonists.

It is therefore an object of this invention to provide a method of enhancing the analgesic potency of morphine and other bimodally-acting opioid agonists by blocking their anti-analgesic side-effects.

It is a further object of this invention to provide a method of attenuating physical dependence, tolerance, hyperexcitability, hyperalgesia and other undesirable side-effects caused by the chronic administration of bimodally-acting opioid agonists.

It is another object of this invention to provide a method for detoxifying and treating opiate addicts utilizing excitatory opioid receptor antagonists.

It is yet another object of this invention to provide a composition which enhances the analgesic effects of bimodally-acting opioid agonists while simultaneously attenuating undesirable side-effects caused by said opioid agonists, including physical dependence, tolerance, hyperexcitability and hyperalgesia.

It is still a further object of this invention to provide a composition which is useful for detoxification and treatment of opiate addicts.

SUMMARY OF THE INVENTION

This invention is directed to a method of selectively enhancing the potency of morphine and other conventional bimodally-acting opioid agonists and simultaneously attenuating undesirable side-effects, including physical dependence, caused by the chronic administration of said opioid agonists. Morphine and other bimodally-acting (inhibitory/excitatory) opioid agonists bind to and activate inhibitory and excitatory opioid receptors on nociceptive neurons mediating pain. Activation of inhibitory receptors by said agonists causes analgesia. Activation of excitatory receptors

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by said agonists results in anti-analgesic effects, development of physical dependence, tolerance, hyperexcitability, hyperalgesia and other undesirable side-effects. The co-administration of an opioid antagonist which binds to and inactivates excitatory opioid receptors results in the blocking of excitatory anti-analgesic side-effects of said opioid agonists on these neurons, thereby resulting in enhanced analgesic potency which permits the use of lower doses of morphine or other conventional opioid analgesics.

The excitatory opioid receptor antagonists of the invention include etorphine, dihydroetorphine, diprenorphine and similarly acting opioid alkaloids and opioid peptides. The opioid agonists of the invention include morphine or other bimodally-acting (inhibitory/excitatory) opioid alkaloids or opioid peptides that are in clinical use as analgesics, including codeine, fentanyl analogs and endorphins.

In addition, combinations of an excitatory opioid receptor antagonist and morphine or another conventional bimodally-acting opioid analgesic can be used to detoxify and treat opiate addicts.

DESCRIPTION OF THE DRAWINGS

The above brief description, as well as further objects and features of the present invention, will be more fully understood by reference to the following detailed description of the presently preferred, albeit illustrative, embodiments of the present invention when taken in conjunction with the accompanying drawings wherein:

FIG. 1 represents the direct inhibitory effect of etorphine on the action potential duration (APD) of sensory neurons and the blocking effect of etorphine on the excitatory response (APD prolongation) elicited by morphine. Acute application of low (pM-nM) concentrations of etorphine to naive dorsal root ganglion (DRG) neurons elicits dose-dependent, naloxone-reversible inhibitory shortening of the APD. In contrast, morphine and other bimodally-acting opioid agonists elicit excitatory APD prolongation at these low concentrations which can be selectively blocked by cPM levels of etorphine;

FIG. 2 represents dose-response curves of different opioids, showing that etorphine and dihydroetorphine elicit only inhibitory dose-dependent shortening of the APD of DRG neurons at all concentrations tested (fM- μ M). In contrast, dynorphin A (as well as morphine and other bimodally-acting opioids) elicits dose-dependent excitatory APD prolongation at low concentrations (fM-nM) and requires much higher concentrations (about 0.1-1 μ M) to shorten the APD, thereby resulting in a bell-shaped dose-response curve;

FIG. 3 is comprised of FIG. 3A and 3B, and represents the selective blocking of excitatory APD-prolonging effects elicited by morphine in DRG neurons by co-administration of a low (pM) concentration of diprenorphine, thereby unmasking potent dose-dependent inhibitory APD shortening by low concentrations of morphine;

FIG. 4 represents the blocking of supersensitive excitatory APD-prolonging effect of DRG neurons after chronic morphine exposure by the excitatory opioid receptor antagonist, etorphine. After chronic exposure to morphine or other bimodally-acting opioids, DRG neurons become supersensitive to the excitatory APD prolonging effects of these opioids, whereas morphine becomes even more effective in eliciting inhibitory shortening of the APD of the same DRG neurons when tested in the presence of the chronic opioid. The apparent enhancement in inhibitory potency of etorphine on chronic morphine-treated neurons is due to the

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unmasking of inhibitory APD shortening effects of morphine following etorphine-antagonist action at excitatory opioid receptors;

FIG. 5 represents the blocking effect of etorphine on naloxone-precipitated excitatory APD prolongation of DRG neurons after chronic exposure to morphine or other bimodally-acting opioids. Acute application of low concentrations of etorphine can dose-dependently block the excitatory APD-prolonging effects of naloxone on these supersensitive DRG neurons; and

FIG. 6 represents the ability of etorphine to elicit sustained inhibitory effects without causing supersensitivity and tolerance in DRG neurons after chronic treatment. Chronic exposure of etorphine (nM) to DRG neurons did not elicit supersensitive excitatory responses (APD prolongation) to low test concentrations of dynorphin A (1-13) and naloxone nor did these cells develop tolerance to the inhibitory effects of etorphine or other opioid agonists.

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to a method of selectively enhancing the analgesic effect caused by the administration of a bimodally-acting opioid agonist and simultaneously attenuating undesirable side-effects caused by the chronic administration of said bimodally-acting opioid agonists. This is performed by simultaneously inactivating excitatory opioid receptor-mediated functions of neurons in the nociceptive (pain) pathways and activating inhibitory opioid receptor-mediated functions of nociceptive neurons. A bimodally-acting opioid agonist and an excitatory opioid receptor antagonist are co-administered. The bimodally-acting opioid agonist binds to inhibitory receptors on nociceptive neurons so as to activate inhibitory opioid receptor-mediated functions, including analgesia, and concomitantly activates excitatory opioid receptors on nociceptive neurons. The excitatory opioid receptor antagonist binds to excitatory receptors on said neurons and thereby inactivates excitatory opioid receptor-mediated functions, including anti-analgesic effects, physical dependence and tolerance to the opioid agonist, hyperexcitability and hyperalgesia. In addition, this invention is directed to the use of said excitatory opioid receptor antagonists and opioid agonists to detoxify and treat opiate addicts. Further, this invention is directed to a composition comprising an excitatory opioid receptor antagonist and a bimodally-acting opioid agonist.

The inventors have discovered that certain compounds act as excitatory opioid receptor antagonists, that is, they bind to and inactivate excitatory opioid receptors on neurons in the pain pathways. The excitatory opioid receptor antagonists of the invention are preferably selected from the group consisting of etorphine, dihydroetorphine and diprenorphine. The opioid receptor antagonists of the invention inactivate μ , δ , κ and other subtypes of excitatory opioid receptors. They may have varying structures. For example, etorphine and dihydroetorphine have very similar chemical structures and are considered to be potent analgesics which selectively activate inhibitory but not excitatory opioid receptors (see Shen and Crain, *Regulatory Peptides*, in press (1993)). In contrast, diprenorphine has a somewhat different chemical structure than etorphine and dihydroetorphine and has been previously considered to act as a universal opioid receptor antagonist by inactivating all types of inhibitory and excitatory opioid receptors (see Shen and Crain, *Brain Res.*, Vol. 491, pp. 227-242 (1989)). Nevertheless, these

three compounds are all capable of selectively binding to and inactivating excitatory opioid receptors on nociceptive neurons when administered at low concentrations.

The bimodally-acting opioid agonists of this invention preferably include morphine, codeine, fentanyl analogs, endorphins, and other opioid alkaloids and opioid peptides. Typically, the opioid agonists of the invention are mu, delta, kappa or epsilon opioid receptor agonists, and are capable of binding to inhibitory opioid receptors on neurons in the pain pathway. When these bimodally-acting agonists bind to inhibitory opioid receptors, they thereby activate inhibitory opioid receptor-mediated functions, including analgesia.

As discussed below, the inventors have discovered that certain compounds (the excitatory opioid receptor antagonists of the invention), when co-administered with bimodally-acting opioid agonists, are capable at very low dosages of enhancing the analgesic effects of the bimodally-acting opioid agonists at least 10-1000 fold by inactivating excitatory anti-analgesic side-effects of said agonists. In addition, the excitatory opioid receptor antagonists of the invention inactivate other excitatory receptor-mediated functions, and thereby reduce the undesirable side-effects caused by said opioid agonists, including development of physical dependence, tolerance to the opioid agonists, hyperexcitability and hyperalgesia. In addition, the excitatory opioid receptor antagonists of the invention may be administered to detoxify and treat opiate addicts.

Ordinarily, bimodally-acting opioid agonists are administered clinically in pill form and are administered in milligram dosages. By co-administering bimodally-acting opioid agonists with the excitatory opioid receptor antagonists of the invention, it is possible to achieve an analgesic effect with 10-1000 times lower doses of the bimodally-acting opioid agonist than when said opioid agonist is administered alone. This is because the excitatory opioid receptor antagonists of the invention enhance the analgesic effects of the bimodally-acting opioid agonists by attenuating the anti-analgesic excitatory side-effects of said opioid agonists. Hence, bimodally-acting opioid agonists which are administered with the excitatory opioid receptor antagonists of the invention are administered in an amount 10-1000 times less than the amount of that bimodally-acting opioid agonist which has typically been administered for analgesia.

According to the present invention, the dose of excitatory opioid receptor antagonist to be administered is 10-1000 times less than the dose of bimodally-acting opioid agonist to be administered, for example, <1 microgram of said antagonist together with 10-100 micrograms of said agonist. These estimates of dosages are based on studies of neurons in culture. The excitatory opioid receptor antagonists, as well as the opioid agonists, can be administered sublingually, intramuscularly, subcutaneously or intravenously.

The co-administration of the opioid agonists and excitatory opioid receptor antagonists of the invention simultaneously activates inhibitory functions of nociceptive neurons in the pain pathway and inactivates excitatory functions of the same or other nociceptive neurons. In order to demonstrate this, electrophysiologic studies on the effects of opioids on mouse sensory dorsal root ganglion neurons in tissue cultures were performed. It is shown below that this bimodal modulation is mediated by activating putative excitatory opioid receptors in addition to previously characterized inhibitory opioid receptors on sensory neurons.

It is shown that at low pM-nM concentrations, nearly all opioids, including morphine, enkephalins, dynorphins, endorphins and specific mu, delta and kappa opioid agonists,

elicit naloxone-reversible dose-dependent excitatory effects manifested by prolongation of the calcium-dependent component of the action potential duration (APD) of dorsal root ganglia (DRG) neurons. In contrast, the same opioids generally elicit inhibitory APD shortening effects when applied at higher concentrations (0.1-1 μ M).

The excitatory opioid effects on sensory neurons have been shown to be mediated by opioid receptors that are coupled via a cholera-toxin-sensitive stimulatory GTP-binding protein, G_s , to adenylate cyclase/cyclic AMP/protein kinase A-dependent ionic conductances that prolong the APD (resembling, for example, beta-adrenergic receptors). (See Crain and Shen, *Trends Pharmacol. Sci.*, Vol. 11, pp. 77-81 (1990)). On the other hand, inhibitory opioid effects are mediated by opioid receptors that are coupled via pertussis toxin-sensitive inhibitory G proteins: G_i to the adenylate cyclase/cyclic AMP system and G_o to ionic conductances that shorten the APD (resembling, for example, alpha₂-adrenergic receptors). Shortening by opioids of the action potential of primary sensory neurons has generally been considered to be a useful model of their inhibition of calcium influx and transmitter release at presynaptic terminals in the dorsal spinal cord, thereby accounting for opioid-induced analgesia in vivo. (See North, *Trends Neurosci.*, Vol. 9, pp. 114-117 (1986) and Crain and Shen, *Trends Pharmacol. Sci.*, Vol. 11, pp. 77-81 (1990)). Similarly, the delayed repolarization associated with the observed opioid-induced prolongation of action potential has been interpreted as evidence of excitatory effects of opioids on sensory neurons that may result in enhanced calcium influx and transmitter release at presynaptic terminals. This could account for some types of hyperalgesia and hyperexcitatory states elicited by opioids in vivo (see Crain and Shen, *Trends Pharmacol. Sci.*, Vol. 11, pp. 77-81 (1990) and Shen and Crain, *Brain Res.*, Vol. 491, pp. 227-242 (1989)).

Chronic treatment of DRG neurons with typical bimodally-acting (excitatory/inhibitory) opioids (e.g., 1 μ M D-al³-D-leu⁵ enkephalin (DADLE) or morphine for 1 week) results in tolerance to the usual inhibitory APD-shortening effects of high concentrations of these opioids and supersensitivity to the excitatory APD-prolonging effects of these opioid agonists, as well as the opioid antagonist, naloxone (see Crain and Shen, *Brain Res.*, Vol. 575, pp. 13-24 (1992) and Shen and Crain, *Brain Res.*, Vol. 597, pp. 74-83 (1992)). It has been suggested that the latter electrophysiologic effects and related biochemical adaptations are cellular manifestations of physical dependence that may underlie some aspects of opiate addiction (see Shen and Crain, *Brain Res.*, Vol. 597, pp. 74-83 (1992) and Terwilliger et al., *Brain Res.*, Vol. 548, pp. 100-110 (1991)).

In contrast to bimodally-acting opioids, it has been discovered by the inventors that the opioid alkaloids, morphine (see Bentley and Hardy, *Proc. Chem. Soc.*, pp. 220 (1963)) and dihydromorphine (see Bentley and Hardy, *J. Amer. Chem. Soc.*, Vol. 89, pp. 3281-3286 (1967)) uniquely elicit dose-dependent, naloxone-reversible inhibitory effects on sensory neurons in DRG-spinal cord explants, even at concentrations as low as 1 pM, and show no excitatory effects at lower concentrations (see Shen and Crain, *Regulatory Peptides*, in press (1993)). In addition, these potent inhibitory opioid receptor agonists also display unexpected antagonist effects at excitatory opioid receptors on DRG neurons. Acute pretreatment of DRG neurons with morphine or dihydromorphine, at low concentrations (<pM) which do not alter the APD, block the excitatory APD-prolonging effects of morphine and other bimodally-acting opioids and unmask inhibitory APD-shortening effects which normally

require much higher concentrations. The potent inhibitory effect of etorphine and dihydroetorphine may be due to their selective activation of inhibitory opioid receptor-mediated functions while simultaneously inactivating excitatory opioid receptor-mediated functions in sensory neurons. In contrast, bimodally-acting opioids activate high-affinity excitatory as well as inhibitory opioid receptors on DRG neurons, thereby decreasing the net inhibitory effectiveness of these agonists, resembling the attenuation of the inhibitory potency of systemic morphine by the "anti-analgesic" (excitatory) effect of dynorphin A release in spinal cord in mice (see Fujimoto et al., *Neuropharmacol.*, Vol. 29, pp. 609-617, (1990)).

Acute application of μ M etorphine or dihydroetorphine to chronic μ M morphine-treated DRG neurons elicited marked APD shortening (as in naive cells) even when added during naloxone-precipitated APD-prolongation in these sensitized cells, whereas 10 μ M morphine or DADLE were ineffective and in contrast elicited a marked APD prolongation. These potent inhibitory effects of etorphine and dihydroetorphine on the action potential of chronic morphine-treated sensory neurons show remarkable mimicry of the rapid DHE-induced blockade of naloxone-evoked withdrawal syndromes in opiate-addicted animals and humans (see Wang et al., *Chinese J. Pharmacol. Toxicol.*, Vol. 6, pp. 36-40 (1992) and Qin, *Chinese J. Pharmacol. Toxicol.*, Vol. 6 (1992)) and the absence of cross-tolerance to etorphine in chronic morphine-treated mice even when the analgesic ED50 for morphine had increased 15-fold (see Lange et al., *Toxicol. Applied Pharmacol.*, Vol. 34, pp. 177-186 (1980)). Furthermore, chronic treatment of DRG neurons with 10 nM etorphine for >1 week did not result in opioid excitatory supersensitivity, i.e., APD prolongation following acute application of 1M dynorphin A (1-13) or nM naloxone, nor tolerance to opioid inhibitory effects, all of which occur after chronic treatment with bimodally-acting opioids, e.g., DADLE or morphine (see Crain and Shen, *Brain Res.*, Vol. 575, pp. 13-24 (1992) and Shen and Crain, *Brain Res.*, Vol. 597, pp. 74-83 (1992)).

In vitro studies on sensory neurons suggested that an opioid which can selectively activate inhibitory, and inactivate excitatory, opioid receptor functions would be a unique analgesic in vivo with high potency, low dependence liability, and useful for treatment of opiate addicts.

EXAMPLE 1

Etorphine And Dihydroetorphine Act As Potent Selective Antagonists At Excitatory Opioid Receptors On DRG Neurons Thereby Enhancing Inhibitory Effects Of Bimodally-Acting Opioid Agonists

Methods: The experiments described herein were carried out on dorsal root ganglion (DRG) neurons in organotypic explants of spinal cord with attached DRGs from 13-day-old fetal mice after 3 to 5 weeks of maturation in culture. The DRG-cord explants were grown on collagen-coated coverslips in Maximow depression-slide chambers. The culture medium consisted of 65% Eagle's minimal essential medium, 25% fetal bovine serum, 10% chick embryo extract, 2 mM glutamine and 0.5% glucose. During the first week in vitro the medium was supplemented with nerve growth factor (NGF-7S) at a concentration of about 0.5 μ g/ml, to enhance survival and growth of the fetal mouse DRG neurons.

In order to perform electrophysiologic procedures, the culture coverslip was transferred to a recording chamber containing about 1 ml of Hanks' balanced salt solution (BSS). The bath solution was supplemented with 4 mM Ca^{2+} and 5 mM Ba^{2+} (i.e., $\text{Ca}_2\text{Ba}/\text{BSS}$) to provide a prominent baseline response for pharmacological tests. Intracellular recordings were obtained from DRG perikarya selected at random within the ganglion. The micropipettes were filled with 3M KCl (having a resistance of about 60-100 megohms) and were connected via a chloridized silver wire to a neutralized input capacity preamplifier (Axoclamp 2A) for current-clamp recording. After impalement of a DRG neuron, brief (2 msec) depolarizing current pulses were applied via the recording electrode to evoke action potentials at a frequency of 0.1 Hz. Recordings of the action potentials were stored on a floppy disc using the P-clamp program (Axon Instruments) in a microcomputer (IBM AT-compatible).

Drugs were applied by bath perfusion with a manually operated, push-pull syringe system at a rate of 2-3 ml/min. Perfusion of test agents was begun after the action potential and the resting potential of the neuron reached a stable condition during >4 minute pretest periods in control $\text{Ca}_2\text{Ba}/\text{BSS}$. Opioid-mediated changes in the APD were considered significant if the APD alteration was >10% of the control value for the same cell and was maintained for the entire test period of 5 minutes. The APD was measured as the time between the peak of the APD and the inflection point on the repolarizing phase. The following drugs were used: etorphine, diprenorphine and morphine (gifts from Dr. Eric Simon); dihydroetorphine (gift from Dr. B.-Y. Qin, China); naloxone (Endo Labs); DADLE, dynorphin and other opioid peptides (Sigma).

Opioid alkaloids and peptides were generally prepared as 1 mM solutions in H_2O and then carefully diluted with BSS to the desired concentrations, systematically discarding pipette tips after each successive 1-10 or 1-100 dilution step to ensure accuracy of extremely low (fM-pM) concentrations.

Results: The opioid responsiveness of DRG neurons was analyzed by measuring the opioid-induced alterations in the APD of DRG perikarya. A total of 64 DRG neurons (from 23 DRG-cord explants) were studied for sensitivity to progressive increases in the concentration of etorphine ($n=30$) or dihydroetorphine ($n=38$). Etorphine rapidly and dose-dependently shortened the APD in progressively larger fractions of DRG cells at concentrations from 1 fM (30% of cells; $n=26$) to 1 μ M (80% of cells; $n=16$) (see FIGS. 1 and 2).

FIG. 1 shows that acute application of low (pM-nM) concentrations of etorphine to naive DRG neurons elicits dose-dependent, naloxone-reversible inhibitory shortening of the action potential duration (APD). In contrast, dynorphin (and many other bimodally-acting opioid agonists, e.g., morphine, DADLE) elicit excitatory APD prolongation at these low concentrations (see FIG. 2), which can be selectively blocked by μ M levels of etorphine or diprenorphine (see FIG. 3). FIG. 1A record 1 shows the action potential (AP) generated by a DRG neuron in balanced salt solution containing 5 mM Ca^{2+} and 5 mM Ba^{2+} (BSS). AP response in this record (and in all records below) is evoked by a brief (2 msec) intracellular depolarizing current pulse. FIG. 1A records 2-5 show that APD is not altered by bath perfusion with 1 fM etorphine (Et) but is progressively shortened in 1 pM, 1 nM and 1 μ M concentrations (5 minute test periods). FIG. 1A record 6 shows that APD returns to control value after transfer to BSS (5 minute test). FIG. 1B records 1 and

2 show that APD of another DRG neuron is shortened by application of 1 nM etorphine (2 minute test). FIG. 1B record 3 shows that APD returns to control value after transfer to 10 nM naloxone (NLX). FIG. 1B records 4 and 5 show that APD is no longer shortened by 1 nM or even 1 μ M etorphine when co-perfused with 10 nM naloxone (5 minute test periods). FIG. 1C records 1 and 2 show that APD of another DRG neuron is prolonged by application of 3 nM morphine. FIG. 1C record 3 shows that APD returns to control value by 5 minutes after washout. FIG. 1C record 4 shows that application of 1 μ M etorphine does not alter the APD. FIG. 1C record 5 shows that APD is no longer prolonged by 3 nM morphine when co-perfused with 1 μ M etorphine and instead is markedly shortened to a degree which would require a much higher morphine concentration in the absence of etorphine. Similar results were obtained by pretreatment with 1 μ M diprenorphine (see FIG. 3). Records in this and subsequent Figures are from DRG neurons in organotypic DRG-spinal cord explants maintained for 3-4 weeks in culture.

FIG. 2 shows dose-response curves demonstrating that etorphine (Et) (□) and dihydroetorphine (DHE) (○) elicit only inhibitory dose-dependent shortening of the APD of DRG neurons at all concentrations tested (fM- μ M). In contrast, dynorphin A (1-13) (Dya) (X) (as well as morphine and other bimodally-acting opioids) elicits dose-dependent excitatory APD prolongation at low concentrations (fM-nM) and generally requires much higher concentrations (about 0.1-1 μ M) to shorten the APD, thereby resulting in a bell-shaped dose-response curve. Data were obtained from 11 neurons for the etorphine tests, 13 for the DHE tests and 35 for the dynorphin tests; 5, 8 and 9 neurons were tested (as in FIG. 1) with all four concentrations of etorphine, DHE and dynorphin, respectively (from fM to μ M). For sequential dose-response data on the same neuron, the lowest concentrations (e.g., 1 fM) were applied first.

Dihydroetorphine was even more effective (n=38; FIG. 2). Naloxone (10 nM) prevented the etorphine- and dihydroetorphine-induced APD shortening which was previously elicited in the same cells (n=12; FIG. 1B). These potent inhibitory effects of etorphine and dihydroetorphine on DRG neurons at low concentrations are in sharp contrast to the excitatory APD-prolonging effects observed in similar tests with morphine and a wide variety of mu, delta and kappa opioids. None of the DRG neurons tested with different concentrations of etorphine or dihydroetorphine showed prominent APD prolongation.

The absence of excitatory APD-prolonging effects of etorphine and dihydroetorphine on DRG neurons could be due to low binding affinity of these opioid agonists to excitatory opioid receptors. Alternatively, these opioids might bind strongly to excitatory receptors, but fail to activate them, thereby functioning as antagonists. In order to distinguish between these two modes of action, DRG neurons were pretreated with etorphine at low concentrations (fM-pM) that evoked little or no alteration of the APD. Subsequent addition of nM concentrations of morphine, DAGO, DADLE or dynorphin to etorphine-treated cells no longer evoked the usual APD prolongation observed in the same cells prior to exposure to etorphine (n=11; see FIG. 1C). This etorphine-induced blockade of opioid excitatory effects on DRG neurons was often effective for periods up to 0.5-2 hours after washout (n=4).

These results demonstrate that etorphine, which has been considered to be a "universal" agonist at mu, delta and kappa opioid receptors (see Magnus et al., *Naunyn-Schmiedebert's Arch. Pharmacol.*, Vol. 319, pp. 197-205 (1982)), has

potent antagonist actions at mu, delta and kappa excitatory opioid receptors on DRG neurons, in addition to its well-known agonist effects at inhibitory opioid receptors. Pretreatment with dihydroetorphine (fM-pM) showed similar antagonist action at excitatory opioid receptor mediating nM opioid-induced APD prolongation (n=2). Furthermore, after selective blockade of opioid excitatory APD-prolonging effects by pretreating DRG neurons with low concentrations of etorphine (fM-pM), which showed little or no alteration of the APD, fM-nM levels of bimodally-acting opioids now showed potent inhibitory APD-shortening effects (5 out of 9 cells) (see FIG. 1C and FIG. 3). This is presumably due to unmasking of inhibitory opioid receptor-mediated functions in these cells after selective blockade of their excitatory opioid receptor functions by etorphine.

EXAMPLE 2

Diprenorphine At Low Concentration Also Shows Potent Selective Antagonist Action At Excitatory Opioid Receptors

Drug tests: Mouse DRG-cord explants, grown for >3 weeks as described in Example 1, were tested with the opioid antagonist, diprenorphine. Electrophysiological recordings were made as in Example 1.

Results: The "universal" opioid receptor antagonist, diprenorphine was previously shown to block, at nM concentrations, both inhibitory APD shortening of DRG neurons by μ M opioid agonists as well as excitatory APD prolongation by nM opioids. Tests at lower concentrations have revealed that pM diprenorphine acts selectively as an antagonist at mu, delta and kappa excitatory opioid receptors, comparable to the antagonist effects of pM etorphine and dihydroetorphine. In the presence of pM diprenorphine, morphine (n=7) and DAGO (n=7) no longer elicited APD prolongation at low (pM-nM) concentrations (see FIG. 3A). Instead, they showed progressive dose-dependent APD shortening throughout the entire range of concentrations from fM to μ M (see FIG. 3B), comparable to the dose-response curves for etorphine and dihydroetorphine (see FIG. 2 and FIG. 1C). This unmasking of inhibitory opioid receptor-mediated APD-shortening effects by pM diprenorphine occurred even in the presence of 10⁻⁶-fold higher concentrations of morphine (see FIG. 3A, records 11 vs. 5).

FIG. 3 shows that excitatory APD-prolonging effects elicited by morphine in DRG neurons are selectively blocked by co-administration of a low (pM) concentration of diprenorphine, thereby unmasking potent dose-dependent inhibitory APD shortening by low concentrations of morphine. FIG. 3A records 1-4 show that APD of a DRG neuron is progressively prolonged by sequential bath perfusions with 3 fM, 3 pM and 3 nM morphine (Mor). FIG. 3A record 5 shows that APD of this cell is only slightly shortened after increasing morphine concentration to 3 μ M. FIG. 3A records 6 and 7 show that after transfer to BSS, the APD is slightly shortened during pretreatment for 17 minutes with 1 pM diprenorphine (DPN). FIG. 3A records 8-11 show that after the APD reached a stable value in DPN, sequential applications of 3 fM, 3 pM, 3 nM and 3 μ M Mor progressively shorten the APD, in contrast to the marked APD prolongation evoked by these same concentrations of Mor in the absence of DPN (see also FIG. 1C). FIG. 3B dose-response curves demonstrate similar unmasking by 1 pM DPN of potent dose-dependent inhibitory APD shortening by morphine (X) in a group of DRG neurons (n=7), all of which showed only excitatory APD prolongation responses when

tested prior to introduction of DPN (X). Note that the inhibitory potency of morphine in the presence of pM DPN becomes comparable to that of etorphine and diprenorphine (see FIG. 2).

EXAMPLE 3

Enhanced Inhibitory Effect of Etorphine and Dihydroetorphine On Chronic Opioid-Treated Sensory Neurons Which Become Supersensitive To Opioid Excitatory Effects

Drug tests: Mouse DRG-cord explants, grown for >3 weeks as described in Example 1, were chronically exposed to the bimodally-acting (excitatory/inhibitory) delta/mu opioid agonist, DADLE (1 μ M) or morphine (1 μ M) for 1 week or longer and tested acutely with etorphine or dihydroetorphine. Electrophysiological recordings were made as in Example 1.

Results: Acute application of fM etorphine to chronic μ M DADLE- or morphine-treated DRG neurons (for >1 week) was still effective in shortening the APD in 30% of the treated neurons ($n=23$) when tested in the presence of μ M DADLE or morphine (see FIG. 4). Furthermore, pM levels of etorphine shortened the APD in 76% of the cells tested ($n=21$).

FIG. 4 shows that after chronic exposure to morphine (Mor), or other bimodally-acting opioids, DRG neurons become supersensitive to the excitatory APD-prolonging effects of these opioids, whereas etorphine (Et) becomes even more effective in eliciting inhibitory shortening of the APD of the same DRG neurons when tested acutely in the presence of the chronic opioid. Dose-response curves show that after chronic treatment of DRG neurons with 3 μ M Mor for 2-3 weeks in culture, the magnitude of APD shortening elicited by acute application of Et (O) is markedly enhanced at all test concentrations (fM- μ M); see typical records in inset), thereby shifting the dose-response curve sharply to the left, as compared to data obtained from naive DRG neurons (□). In contrast, after washout of the chronic morphine with BSS, retests of sequentially increasing concentrations of Et from fM to μ M result in less prominent APD shortening (X), comparable to, or even weaker than, Et effects on naive cells (□). These results suggest that the apparent enhancement in inhibitory potency of Et on chronic Mor-treated neurons is actually due to unmasking of inhibitory APD-shortening effects of chronic Mor following Et-antagonist action at excitatory opioid receptors, as occurs in tests on naive DRG cells (see FIG. 1C). As shown in the inset, FIG. 4 record 1 shows AP generated by a DRG neuron treated for 3 weeks in culture with 3 μ M Mor and then tested in BSS in the presence of the chronic Mor. FIG. 4 record 2 shows that 1 fM Et does not alter the APD in the presence of 3 μ M Mor. FIG. 4 records 3-5 show that sequential increases in the concentration of Et from 1 pM to 1 μ M progressively shorten the APD in the presence of 3 μ M Mor (whereas dynorphin dose-dependently prolonged the APD of the same chronic opioid-treated cell — not shown; see FIG. 2).

In contrast, morphine, DADLE and other chronic bimodally-acting opioid-treated DRG neurons showed supersensitive excitatory APD-prolonging effects when tested with low (fM-pM) concentrations of dynorphin (1-13) before ($n=13$) or after ($n=6$) washout of the chronic DADLE or morphine. The effectiveness of etorphine in eliciting inhibitory APD-shortening in chronic opioid-treated DRG neurons appeared to be significantly enhanced relative to naive cells.

Whereas nM etorphine moderately shortened the APD of naive DRG neurons (mean decrease to about 86±6%; $n=18$; see FIGS. 1A and 2), this low concentration was much more effective on chronic morphine-treated DRG neurons (mean decrease to 66±7% ($n=9$)), when tested in the presence of morphine (FIG. 4). Dose-response tests of etorphine on chronic DADLE- or morphine-treated DRG neurons showed that the magnitude of the APD was progressively shortened when the acute etorphine concentration was tested sequentially from 1 fM to 1 μ M in the presence of μ M DADLE or morphine (FIG. 4). On the other hand, after washout of the chronic morphine, acute application of etorphine to chronic μ M opioid-treated DRG neurons no longer showed greater inhibitory effectiveness as compared to tests on naive cells ($n=10$) (FIG. 4). These results suggest that the apparent enhancement in inhibitory effectiveness of etorphine (and dihydroetorphine), when tested during chronic exposure to bimodally-acting opioid-treated DRG neurons, is due to their dual synergistic action as agonists at inhibitory opioid receptors and antagonists at excitatory opioid receptors. The latter property results in unmasking of the inhibitory actions of the chronic DADLE or morphine, as occurs in similar tests on naive neurons (see FIG. 1C and FIG. 3). Acute application of dihydroetorphine to chronic μ M morphine-treated DRG neurons indicated that this opioid showed even greater inhibitory potency than etorphine. fM concentrations shortened the APD in 80% of the treated cells ($n=10$) and pM (or higher) levels were effective on all cells tested in the presence of the chronic opioid ($n=10$).

Thus, etorphine and dihydroetorphine show similarly remarkable effectiveness as diprenorphine in antagonizing excitatory opioid receptors even when tested in the presence of 10^4 - 10^5 higher concentrations of morphine or DADLE. As a result of these unusual properties, etorphine and dihydroetorphine showed no cross-tolerance in tests on chronic DADLE- or morphine-treated DRG neurons, just as chronic morphine-treated mice showed no cross-tolerance to etorphine even when the analgesic ED for morphine had increased 15-fold (see Lange et al., *Toxicol. Applied Pharmacol.*, Vol. 54, pp. 177-186 (1980)). The absence of cross-tolerance to etorphine in chronic morphine-treated DRG neurons is in sharp contrast to the attenuated inhibitory effects (i.e., tolerance) and the enhanced excitatory effects (i.e., "dependence") displayed by all bimodally-acting mu, delta and kappa opioid agonists when tested acutely on these chronic opioid-treated cells.

EXAMPLE 4

Etorphine Or Dihydroetorphine Can Block Naloxone-Precipitated Supersensitive Excitatory Effects In Chronic Opioid-Treated DRG Neurons

Drug tests: Mouse DRG-cord explants, grown for >3 weeks as described in Example 1, were chronically exposed to the bimodally-acting (excitatory/inhibitory) delta/mu opioid agonist, DADLE (1 μ M) or morphine (1 μ M) for 1 week or longer. The excitatory opioid supersensitivity of chronic opioid-treated DRG neurons was precipitated by naloxone (1 nM). Electrophysiological recordings were made as in Example 1.

Results: The opioid antagonist, naloxone (1 nM-1 μ M) does not alter the APD of naive DRG neurons. In contrast, after chronic opioid treatment (as well as after acute GMI ganglioside treatment) excitatory opioid receptor functions become so supersensitive that acute application of low concentrations of naloxone prolonged the APD of the treated

sensory neurons, presumably due to weak partial agonist properties of naloxone at excitatory opioid receptors (see Crain and Shen, *Brain Res.*, Vol. 575, pp. 13-24 (1992) and Crain and Shen, *J. Pharmacol. Exp. Ther.*, Vol. 260, pp. 182-186 (1992)). Naloxone (1 nM) elicited excitatory APD-prolonging effects in 92% of the chronic μ M DADLE- or morphine-treated DRG neurons tested in the present study (n=12) (see FIG. 5).

These results provide a novel cellular model to account for naloxone-precipitated withdrawal supersensitivity in opiate addicts in vivo. It should be emphasized that naloxone was not simply blocking the inhibitory effect of residual DADLE or morphine since the treated DRG neurons were already tolerant to these APD-shortening effects. It is therefore of great interest that acute application of remarkably low concentrations of etorphine (fM-nM) to chronic μ M morphine or DADLE-treated cells could effectively block naloxone-induced APD prolongation in all of the treated DRG neurons (n=18) (see FIG. 5), thereby mimicking the potent effects of the related etorphine analog dihydroetorphine in suppressing naloxone-evoked withdrawal symptoms in opiate addicts (see Wang et al., *Chinese J. Pharmacol. Toxicol.*, Vol. 6, pp. 36-40 (1992)).

FIG. 5 shows that after chronic exposure to morphine (Mor) or other bimodally-acting opioids, acute application of low concentrations of etorphine (Et) can dose-dependently block the excitatory APD-prolonging effects of naloxone (NLX) on these supersensitive DRG neurons. Histogram shows that acute application of 1 nM NLX to DRG neurons chronically treated with 3 μ M Mor for 1-4 weeks prolonged the APD by about 50%, tested in the presence of 3 μ M Mor. See also Inset: records 1 and 2. In contrast, NLX (nM- μ M) does not alter the APD of naive DRG neurons. Sequential co-perfusions with 1 fM to 1 μ M Et elicit dose-dependent attenuation of the NLX-induced APD prolongation in these treated neurons, resulting in shortening of the APD to about 70% of the control value in 1 μ M Et. In contrast, NLX-pretreatment of naive DRG neurons blocks Et-induced APD shortening (see FIG. 1B). Inset records 1 and 2 show that 1 nM NLX prolongs the APD of a DRG neuron after chronic 3 μ M Mor treatment for 2 weeks and tested in the presence of 3 μ M Mor (5 minute test). Inset record 3 shows that acute addition of 1 fM Et attenuates the NLX-induced APD prolongation (5 minute test). Inset record 4 shows that increasing the concentration of Et to 1 pM almost completely blocks the NLX-induced APD prolongation. Inset records 5 and 6 show that sequential application of 1 nM and 1 μ M Et in the presence of Mor and NLX results in progressive shortening of the APD well below the initial magnitude in chronic Mor (as shown in FIG. 4).

These results suggest that the potent dose-dependent effects of etorphine and dihydroetorphine in blocking naloxone-evoked APD prolongation in chronic opioid-treated DRG neurons in vitro and withdrawal syndromes in opiate addicts in vivo is due to the strong antagonist actions of these opioids at supersensitive excitatory opioid receptors which have become responsive to the weak agonist properties of naloxone. This is in sharp contrast to the blockade of etorphine-induced APD shortening in naive DRG neurons by naloxone under conditions where it acts primarily as an antagonist at inhibitory opioid receptors (see FIG. 5 and FIG. 1B).

EXAMPLE 5

In The Presence Of Etorphine, Chronic Morphine Treatment Of DRG Neurons No Longer Results In Development Of Opioid Excitatory Supersensitivity And Tolerance

Drug test: Mouse DRG-cord explants, grown for >3 weeks as described in Example 1, were chronically exposed to bimodally-acting opioid agonist, morphine (1 μ M) and opioid excitatory receptor antagonist, etorphine (1 pM) for >1 week and tested for opioid excitatory supersensitivity of DRG neurons at low concentrations of naloxone or dynorphin A (1-13) and tolerance to the opioid inhibitory effects of APD with high concentrations of morphine. Electrophysiological recordings were made as in Example 1.

Results: Co-administration of low (pM) concentrations of etorphine during chronic treatment of DRG neurons with μ M levels of morphine was remarkably effective in preventing development of the opioid excitatory supersensitivity and tolerance that generally occurs after sustained exposure to bimodally-acting opioids. Acute application of 1 fM dynorphin (1-13) (n=10) or 10 nM naloxone (n=8) to DRG neurons chronically exposed to 3 μ M morphine together with 1 pM etorphine (for >1 week) did not evoke the usual excitatory APD prolongation observed in chronic morphine-treated cells, even when tested up to 6 hours after return to BSS. Furthermore, there was little or no evidence of tolerance to the inhibitory effects of μ M morphine: 6 out of 10 cells still showed APD shortening following acute application of μ M morphine similar to tests on naive DRG cells. If etorphine was acting simply as an agonist at inhibitory opioid receptors, one might predict that the addition of 1 pM etorphine together with a 10^6 -fold higher concentration of morphine would have a negligible effect on chronic morphine-treated DRG neurons or would segment development of cellular signs of dependence. On the other hand, the results are readily accounted for by the potent antagonist action of etorphine at excitatory opioid receptors during chronic morphine treatment, thereby preventing development of opioid excitatory supersensitivity and tolerance, just as occurs during chronic opioid treatment of DRG neurons in the presence of cholera toxin-B subunit (see Shen and Crain, *Brain Res.*, Vol. 597, pp. 74-83 (1992)). This toxic subunit selectively interferes with GM1 ganglioside regulation of excitatory opioid receptor functions (see Shen and Crain, *Brain Res.*, Vol. 531, pp. 1-7 (1990) and Shen et al., *Brain Res.*, Vol. 539, pp. 130-138 (1991)).

EXAMPLE 6

Chronic Etorphine-Treated DRG Neurons Do Not Develop Opioid Excitatory Supersensitivity Or Tolerance

Drug tests: Mouse DRG-cord explants, grown for >3 weeks as described in Example 1, were chronically exposed to etorphine (nM) for >1 week and tested for opioid excitatory supersensitivity of DRG neurons to low concentrations of naloxone or dynorphin A (1-13) and tolerance to the inhibitory effects of higher concentrations of etorphine.

Results: Chronic treatment of DRG neurons with etorphine alone even at a relatively high concentration (10 nM) for >1 week in culture also did not result in opioid excitatory supersensitivity when tested acutely with 1 fM dynorphin (1-13) (26 out of 28 cells) or 1-10 nM naloxone (13 out of

14 cells), either before or after withdrawal of the chronic etorphine (FIG. 6).

FIG. 6 shows that after chronic exposure to nM etorphine (Et), DRG neurons do not become supersensitive to the excitatory effects of dynorphin 1-13 (Dyna) and naloxone (NLX), nor do they develop tolerance to the inhibitory effects of etorphine or other opioid agonists. Record 1 shows the action potential (AP) generated by a DRG neuron after chronic 10 nM Et treatment for 20 days and tested in balanced salt solution (BSS) shortly after washout of the Et. Record 2 shows that APD is not altered by 1 fM Dyn. Records 3-6 show that APD is not altered by bath perfusion with 1 fM Et but is progressively shortened by 1 pM and 1 μ M concentrations (5 minute test periods). Records 7 and 8 show that APD of the same neuron is not altered by application of 10 nM NLX. Record 9 shows that APD is no longer shortened by 1 μ M Et when co-perfused with 10 nM naloxone (5 minute test period).

After etorphine withdrawal for about 1 hour, 1 nM dynorphin (1-13) shortened the APD in 3 cells or did not show typical APD prolongation (10 out of 11 cells), resembling the attenuation of opioid excitatory effects and unmasking of opioid inhibition observed in acute tests on naive cells after washout of low (pM) concentrations of etorphine (see FIG. 1C). Furthermore, after washout of the chronic 10 nM etorphine, acute application of pM, nM and μ M etorphine elicited similar APD shortening (in 3 out of 4 cells tested at each concentration) as observed in naive cells. Thus chronic 10 nM etorphine treatment of DRG neurons did not result in the characteristic cellular signs of physical dependence and tolerance that occurred after chronic exposure of these cells to morphine and other bimodally-acting opioids.

Estimates Of Specific In Vivo Dosages Of Excitatory Opioid Receptor Antagonists That May Enhance Analgesic Potency And Reduce Dependence Liability (And Other Side-Effects) Of Morphine Or Other Conventional Opioid Analgesics When Administered In Combination

Electrophysiological studies on DRG neurons indicated that pre-treatment with low fM-pM concentrations of etorphine, dihydroetorphine and diprenorphine are remarkably effective in blocking excitatory APD-prolonging effects of morphine bimodally-acting opioid agonists by selective antagonist actions at mu, delta and kappa excitatory opioid receptors. The potency of these three excitatory opioid receptor antagonists is clearly shown by their ability to unmask inhibitory opioid receptor-mediated APD-shortening effects, even in presence of 10^4 -fold higher concentrations of morphine other bimodally-acting opioid agonists (FIGS. 3-5).

In the presence of these selective excitatory opioid receptor antagonists, morphine and other clinically used opioids showed markedly increased potency in evoking the inhibitory effects on the action potential of sensory neurons which are generally considered to underlie opioid analgesic action in vivo. These bimodally-acting opioid agonists became effective in shortening, instead of prolonging, the APD at pM-nM (i.e., 10^{-12} - 10^{-9} M) concentrations, whereas 0.1-1 μ M (i.e., 10^{-7} - 10^{-6} M) levels were generally required to shorten the APD (FIG. 2). Selective blockade of the excitatory side-effects of these bimodally-acting opioid agonists eliminates the attenuation of their inhibitory effectiveness that would otherwise occur. Hence, according to this invention, the combined use of a relatively low dose of one of

these selective excitatory opioid receptor antagonists, together with morphine or other bimodally-acting mu, delta or kappa opioid agonists, will markedly enhance the analgesic potency of said opioid agonists, and render said opioid agonist comparable in potency to etorphine or dihydroetorphine, which, when used alone at higher doses, are >1000 times more potent than morphine in eliciting analgesia.

Co-administration of one of these excitatory opioid receptor antagonists at low concentration (about 10^{-12} M) during chronic treatment of sensory neurons with 10^{-6} M morphine or other bimodally-acting opioids (>1 week in culture) prevented development of the opioid excitatory supersensitivity, including naloxone-precipitated APD-prolongation, as well as the tolerance to opioid inhibitory effects that generally occurs after chronic opioid exposure. This experimental paradigm was previously utilized by the inventors on sensory neurons in culture to demonstrate that co-administration of 10^{-7} M cholera toxin-B subunit, which binds selectively to GM1 ganglioside and thereby blocks excitatory GM1-regulated opioid receptor-mediated effects, but not opioid inhibitory effects (see Shen and Crain, *Brain Res.*, Vol. 531, pp. 1-7 (1990)) during chronic opioid treatment prevents development of these plastic changes in neuronal sensitivity that are considered to be cellular manifestations related to opioid dependence/addiction and tolerance in vivo (see Shen and Crain, *Brain Res.*, Vol. 597, pp. 74-83 (1992)). Hence, according to this invention, the sustained use of a relatively low clinical dose of one of these selective excitatory opioid receptor antagonists, e.g., <1 microgram of etorphine, dihydroetorphine or diprenorphine, in combination with 10-100 micrograms of morphine or other conventional bimodally-acting opioid analgesics will result in analgesia comparable to that elicited by said analgesics when administered alone in milligram doses and will attenuate or even prevent development of physical dependence and other undesirable excitatory side-effects generally associated with said analgesics.

Estimates Of Specific In Vivo Dosages That Provide Improved Detoxification And Treatment Of Opiate Addicts

Acute application of one of these excitatory opioid receptor antagonists, e.g., etorphine or dihydroetorphine, at a low concentration (about 10^{-12} M) to chronic opioid-treated sensory neurons prevented the excitatory APD-prolonging effects precipitated by naloxone (10^{-6} M) (FIG. 5). The latter effects provide a novel cellular model to account for naloxone-evoked withdrawal supersensitivity in opiate addicts in vivo. The potent effects of etorphine and dihydroetorphine in blocking naloxone-evoked APD prolongation in chronic opioid-treated sensory neurons in vitro (FIG. 5) is due to their blockade of supersensitive excitatory opioid receptors which have become responsive to the weak agonist properties of naloxone. A similar mechanism may account for the efficacy of dihydroetorphine in suppressing naloxone-evoked withdrawal syndromes in opiate-addicted animals and humans (see Lange, *Toxicol. Applied Pharmacol.*, Vol. 54, pp. 177-186 (1992) and Qiu, *Chinese J. Pharmacol. Toxicol.*, Vol. 6, (1992)). Hence, according to this invention, appropriately low doses of one of these selective excitatory opioid receptor antagonists, e.g., about 1 microgram in combination with a 10-1000 fold lower than standard dose of one of the opioids currently used for the treatment of opioid dependence, e.g., methadone, buprenorphine, will provide an improved method for detoxifying and weaning addicts from dependence on opiates.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of various aspects of the invention. Thus, it is to be understood that numerous modifications may be made in the illustrative embodiments and other arrangements may be devised without departing from the spirit and scope of the invention.

We claim:

1. A method for selectively enhancing the analgesic potency of a bimodally-acting opioid agonist selected from the group consisting of morphine, codeine, fentanyl, buprenorphine, methadone, enkephalin, dynorphin, and endorphin and simultaneously attenuating the undesirable excitatory side-effects caused by said bimodally-acting opioid agonist in a subject treated with said bimodally-acting opioid agonist comprising administering to the subject in combination with said bimodally-acting opioid agonist an amount of an excitatory opioid receptor antagonist selected from the group consisting of etorphine, dihydroetorphine and diprenorphine effective to enhance the analgesic potency of said bimodally-acting opioid agonist and attenuate the undesirable excitatory side-effects caused by said bimodally-acting opioid agonist.

2. The method of claim 1 wherein the undesirable excitatory side-effect is selected from the group consisting of anti-analgesic effects, physical dependence, tolerance, hyperexcitability and hyperalgesia.

3. The method of claim 1 wherein the dose of bimodally-acting opioid agonist to be administered is 10-1000 times less than the amount of that bimodally-acting opioid agonist which is typically administered clinically for analgesia.

4. The method of claim 1 wherein the dose of opioid receptor antagonist to be administered is 10-1000 times less than the dose of bimodally-acting opioid agonist administered.

5. The method of claim 1 wherein the mode of administration is selected from the group consisting of sublingual,

intramuscular, subcutaneous and intravenous.

6. A method for detoxifying and treating an opiate addict comprising administering to the opiate addict an analgesic amount of a bimodally-acting opioid agonist selected from the group consisting of methadone and buprenorphine in combination with an amount of an excitatory opioid receptor antagonist selected from the group consisting of etorphine, dihydroetorphine and diprenorphine effective to enhance the analgesic potency of said bimodally-acting opioid agonist and attenuate the undesirable excitatory side-effects caused by said bimodally-acting opioid agonist, thereby detoxifying and treating said opiate addict.

7. The method of claim 6 wherein the dose of bimodally-acting opioid agonist to be administered is 10-1000 times less than the amount of that bimodally-acting opioid agonist which is typically administered clinically for analgesia.

8. The method of claim 6 wherein the dose of opioid receptor antagonist to be administered is 10-1000 times less than the dose of bimodally-acting opioid agonist administered.

9. The method of claim 6 wherein the mode of administration is selected from the group consisting of sublingual, intramuscular, subcutaneous and intravenous.

10. A composition comprising an analgesic amount of a bimodally-acting opioid agonist selected from the group consisting of morphine, codeine, fentanyl, enkephalin, dynorphin, endorphin, methadone and buprenorphine and an amount of an excitatory opioid receptor antagonist selected from the group consisting of etorphine, dihydroetorphine and diprenorphine effective to enhance the analgesic potency of said bimodally-acting opioid agonist and attenuate undesirable excitatory side-effects caused by said bimodally-acting opioid agonist in a subject administered said composition.

* * * * *

FORMULACIONES AGONISTAS OPIOIDES CON ANTAGONISTAS LIBERABLES Y SECUESTRADOS

ANTECEDENTES DE LA INVENCION

Las formulaciones opioides son algunas veces sujeto de abuso. Una dosis particular de oxycodona puede ser más potente cuando se administra parenteralmente comparada con la misma dosis administrada oralmente. También, algunas formulaciones pueden ser violadas con el fin de suministrarle al agonista opioide contenido allí mejor disponibilidad para uso ilícito. Por ejemplo, una formulación agonista opioide de liberación controlada puede ser molida con el fin de dejar el opioide contenido allí disponible para liberación inmediata mediante administración oral o parenteral. Una formulación opioide puede ser abusable por administración de más de la dosis prescrita de la droga.

Los antagonistas opioides se han combinado en ciertos antagonistas opioides con el fin de desestimular el abuso parenteral de los agonistas opioides. En la técnica anterior, la combinación de la pentazocina de liberación inmediata y naloxona se ha utilizado en tabletas disponibles en los Estados Unidos, comercialmente disponibles como Talwin® Nx de Sanofi -Winthrop. El Talwin® Nx contiene clorhidrato de pentazocina de liberación inmediata equivalente a 50 mg de base y clorhidrato de naloxona equivalente a 0,5 mg de base. Una terapia de combinación fija que comprende

tilidina (50 mg) y naloxona (4 mg) ha estado disponible en Alemania para el manejo del dolor desde 1978 (Valoron® N, Goedecke). Una combinación fija de buprenorfina y naloxona se introdujo en 1991 en Nueva Zelanda (Temgesic® Nx, Reckitt & Colman) para el tratamiento del dolor.

Purdue Pharma L.P. eventualmente comercializa oxycodona de liberación sostenida en formas de dosis que contienen 10, 20, 40 y 160 mg de clorhidrato de oxycodona bajo el nombre comercial OxyContin.

Las Patentes estadounidenses Nos. 5,266,331; 5,508,042; 5,549,912 y 5,656,295 describen formulaciones de oxycodona de liberación sostenida.

La Patente estadounidense No. 4,769,372 y 4,785,000 de Kreek describe métodos para tratar pacientes que sufren de dolor crónico o crónica sin provocar desmotilidad intestinal al administrar 1 a 2 unidades de dosis que comprenden desde aproximadamente 1,5 a aproximadamente 100 mg del analgésico opioide o antitusivo y desde aproximadamente 1 a aproximadamente 18 mg de un antagonista opioide que tiene poca o ninguna actividad antagonista sistémica cuando se administra oralmente, desde 1 a 5 veces diariamente.

La Patente estadounidense No. 6,228,863 de Palermo et al

describe composiciones y métodos para evitar el abuso de formas de dosis opioides.

La WO99/32119 de Kaiko et al describe composiciones y métodos para evitar el abuso de formas de dosis opioide.

La Patente estadounidense No. 5,472,943 de Crain et al describe métodos para mejorar la potencia analgésica de agonistas opioides que actúan bimodalmente al administrar el agonista con un antagonista opioide.

Todos los documentos citados aquí, incluyendo los anteriores se incorporan como referencia en su totalidad para todos los propósitos.

OBJETOS Y RESUMEN DE LA INVENCION

Es un objeto de la invención proporcionar una forma de dosis oral de un agonista opioide que es útil para disminuir el potencial de abuso del agonista opioide contenido allí.

Es un objeto de ciertas modalidades de la invención proporcionar una forma de dosis oral de un agonista opioide que es

útil para disminuir el potencial abuso del agonista opioide sin afectar los efectos analgésicos del agonista opioide o incurrir en el riesgo de un retiro precipitado si se toma intacto.

Es un objeto de ciertas modalidades de la invención proporcionar una forma de dosis oral de un agonista opioide que es resistente al mal uso, abuso o diversión, en donde dicha resistencia no depende de diferencias específicas de pacientes individuales en los efectos de agonistas opioides coadministrados y mezclas de antagonistas.

Es un objeto de ciertas modalidades de la invención proporcionar una forma de dosis oral que contiene una dosis efectiva de un agonista opioide junto con una dosis de antagonista opioide que no cambia la eficacia analgésica del agonista opioide cuando la forma de dosis es administrada oralmente intacta, pero la cual puede evitar el abuso si la forma de dosis es violada al interferir con el efecto del agonista opioide.

Es un objeto de ciertas modalidades de la invención proporcionar un método para evitar el abuso de una forma de dosis oral opioide donde la forma de dosis también incluye una dosis de antagonista opioide que es secuestrada, por ejemplo, no está biodisponible cuando la dosis se administra intacta pero está biodisponible cuando la forma de dosis es violada (por ejemplo en un

intento de mal uso de la dosis de analgésico opioide) y una dosis de antagonista que es liberable para suministrar un efecto deseado.

Es un objeto de ciertas modalidades de la invención proporcionar una forma de dosis oral que están destinadas o son adecuadas para el uso en el manejo de dolor agudo o crónico cuando la alteración de los efectos analgésicos del Agonista opioide se deben evitar tal como en casos de tolerancia, dependencia física o variabilidad individual con el metabolismo o fisiología hepática.

Es un objeto adicional de una modalidad preferida de la invención proporcionar un método para tratar dolor en pacientes humanos con una forma de dosis oral de un agonista opioide aunque reduciendo su

REIVINDIVCACIONES

1. Una forma de dosis oral, que comprende
 - (i) una cantidad terapéuticamente efectiva de un agonista opioide;
 - (ii) un antagonista opioide en forma liberable;
 - (iii) un antagonista opioide secuestrado que no es liberado cuando la forma de dosis se administra intacta.

2. Una forma de dosis oral, que comprende
 - (i) un primer componente que comprende una cantidad terapéuticamente efectiva de un agonista opioide;
 - (ii) un segundo componente que comprende un antagonista opioide en forma liberable;
 - (iii) un tercer componente que comprende un antagonista opioide secuestrado que no es liberado cuando la forma de dosis se administra intacta.

3. Una forma de dosis oral, que comprende
 - (i) un primer componente que comprende una cantidad terapéuticamente efectiva de un agonista opioide;
 - (ii) un segundo componente que comprende un antagonista opioide en forma liberable, y un antagonista opioide secuestrado que no es liberado cuando la forma de dosis se administra intacta.

4. Una forma de dosis oral, que comprende

(i) un primer componente que comprende una cantidad terapéuticamente efectiva de un agonista opioide y un antagonista opioide en forma liberable;

(ii) un segundo componente que comprende un antagonista opioide secuestrado que no es liberado cuando la forma de dosis se administra intacta.

5. Una forma de dosis oral, que comprende

(i) un primer componente que comprende una cantidad terapéuticamente efectiva de un agonista opioide y un antagonista opioide en forma liberable;

(ii) un segundo componente que comprende un antagonista opioide secuestrado el cual no es sustancialmente liberada cuando la forma de dosis se administra intacta.

6. Una forma de dosis oral, que comprende

(i) un primer componente que comprende una cantidad terapéuticamente efectiva de un agonista opioide;

(ii) un segundo componente que comprende un antagonista opioide en forma liberable; y

(iii) un tercer componente que comprende un antagonista opioide secuestrado que no es sustancialmente liberado cuando la forma de dosis se administra intacta.

7. La forma de dosis de la reivindicación 1 en donde la cantidad del antagonista liberado de dicha forma de dosis esta en una proporción a dicho antagonista que es aversivo en sujetos humanos físicamente dependientes cuando la forma de dosis se administra en la misma cantidad o en una cantidad mayor que dicha cantidad terapéuticamente efectiva.

8. La forma de dosis de la reivindicación 5 en donde la cantidad de dicho antagonista liberado de dicho primer componente es una cantidad suficiente para ser aversiva en sujetos humanos físicamente dependientes cuando la forma de dosis se administra en la misma cantidad o en mayor cantidad que dicha cantidad terapéuticamente efectiva.

9. La forma de dosis de la reivindicación 5 en donde la cantidad de dicho antagonista liberado de dicho primer componente es menor que la cantidad suficiente para hacer aversiva en sujetos humanos físicamente dependientes cuando la forma de dosis se administra en la misma cantidad o en mayor cantidad que dicha cantidad terapéuticamente efectiva.

10. La forma de dosis de la reivindicación 5 en donde la cantidad de dicho antagonista liberado de dicho segundo componente está en una cantidad suficiente para ser aversiva en sujetos humanos físicamente dependientes cuando la forma de dosis se administra en la misma cantidad o en una cantidad mayor que dicha cantidad

terapéuticamente efectiva.

11. La forma de dosis de la reivindicación 6 en donde la cantidad de dicho antagonista liberado de dicho segundo componente es menor que la cantidad suficiente para ser aversiva en sujetos humanos físicamente dependientes cuando la forma de dosis se administra en la misma cantidad o en una cantidad mayor que dicha cantidad terapéuticamente efectiva.

12. La forma de dosis de la reivindicación 1 que comprende además un excipiente de liberación sostenida que proporciona una liberación sostenida de dicho agonista opiode.

13. La forma de dosis de la reivindicación 1 que comprende además un excipiente de liberación sostenido que proporciona una liberación sostenida de dicho antagonista opiode.

14. La forma de dosis de la reivindicación 1 que comprende además un excipiente de liberación sostenida que proporciona una liberación sostenida de dicho agonista opiode y dicho antagonista opiode.

15. La forma de dosis de la reivindicación 1 en donde dicho antagonista secuestrado esta en la forma de multipartículas individualmente recubiertas con un material que evita la liberación

del antagonista secuestrado.

16. La forma de dosis de la reivindicación 1 en donde dicho antagonista secuestrado esta en la forma de multipartículas individualmente recubiertas con un material que evita sustancialmente la liberación de dicho antagonista secuestrado.

17. La forma de dosis de la reivindicación 1 en donde dicho antagonista secuestrado se dispersa en una matriz que comprende un material secuestrante que evita la liberación de dicho antagonista secuestrado.

18. La forma de dosis de la reivindicación 1 en donde dicho antagonista secuestrado se dispersa en una matriz que comprende un material secuestrante que evita sustancialmente la liberación de dicho antagonista secuestrado.

19. La forma de dosis de la reivindicación 1 en donde dicho antagonista opioide liberable es el mismo que el antagonista secuestrado.

20. La forma de dosis de la reivindicación 1 en donde dicho antagonista opioide liberable es diferente del antagonista secuestrado.

21. La forma de dosis de la reivindicación 19 en donde dicho antagonista se selecciona del grupo que consiste de naltrexonanaloxona, nalmeveno, ciclazocina, levalorfono, sales farmacéuticamente aceptables de estos y mezclas y mezclas de estos.
22. La forma de dosis de la reivindicación 20 en donde dicho antagonista liberable se selecciona del grupo que consiste de naltrexona, naloxona, nalmeveno, ciclazocina, levalorfono, sales farmacéuticamente aceptables de estos y mezclas de estos y dicho antagonista secuestrado se selecciona del grupo que consiste de naltrexona, naloxona, nalmeveno, ciclazocina, levalorfono, sales farmacéuticamente aceptables de estos y mezclas de estos.
23. La forma de dosis de la reivindicación 1 en donde dicho opioide se selecciona del grupo que consiste de morfina, hidromorfona, hidrocodona, oxicodona, codeína, levorfanol, tramadol, meperidina, metadona, sales farmacéuticamente aceptables de estos y mezclas de estos.
24. La forma de dosis de la reivindicación 1 que tiene una proporción de antagonista opioide liberable a agonista opioide que es analgésicamente efectivo cuando la combinación se administra oralmente, pero que es aversivo en sujetos humanos físicamente dependientes cuando se administra en la misma cantidad o en una cantidad mayor que dicha cantidad terapéuticamente efectiva.

25. La forma de dosis de la reivindicación 24 en donde dicha proporción de antagonista opioide liberable a agonista opioide mantiene un efecto analgésico pero no incrementa la eficacia analgésica del agonista opioide con relación a la misma cantidad terapéutica del analgésico opioide cuando se administra a pacientes humanos sin dicho antagonista opioide.

26. La forma de dosis oral de la reivindicación 1 en donde el agonista opioide es hidrocodona y el antagonista liberable es naltrexona.

27. La forma de dosis oral de la reivindicación 26, en donde la proporción de naltrexona liberable a hidrocodona va de aproximadamente 0,03:1 a aproximadamente 0,27:1.

28. La forma de dosis oral de la reivindicación 27, en donde la proporción de naltrexona liberable a hidrocodona va de aproximadamente 0,05:1 a aproximadamente 0,20:1.

29. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es oxicodona, en donde la proporción de naltrexona liberable a oxicodona va de aproximadamente 0,037:1 a aproximadamente 0,296:1.

30. La forma de dosis oral de la reivindicación 7, en donde dicho

antagonista opioide liberable es naltrexona y dicho agonista opioide liberable es codeína, en donde la proporción de naltrexona liberable a codeína va de aproximadamente 0,005:1 a aproximadamente 0,044:1.

31. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es hidromorfona, en donde la proporción de naltrexona liberable a hidromorfona va de aproximadamente 0,148:1 a aproximadamente 1,185:1.

32. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es levorfanol, en donde la proporción de naltrexona liberable a levorfanol va de aproximadamente 0,278:1 a aproximadamente 2,222:1.

32. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es meperidina, en donde la proporción de naltrexona liberable a meperidina va de aproximadamente 0,0037:1 a aproximadamente 0,0296:1.

33. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es metadona, en donde la proporción de naltrexona liberable a metadona va de aproximadamente 0,056:1 a aproximadamente 0,444:1.

34. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es morfina, en donde la proporción de naltrexona liberable a morfina va de aproximadamente 0,018:1 a aproximadamente 0,148:1.
35. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es oxycodona, en donde la proporción de naltrexona liberable a oxycodona va de aproximadamente 0,056:1 a aproximadamente 0,222:1.
36. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es codeína, en donde la proporción de naltrexona liberable a codeína va de aproximadamente 0,0083:1 a aproximadamente 0,033:1.
37. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es hidromorfona, en donde la proporción de naltrexona liberable a hidromorfona va de aproximadamente 0,222:1 a aproximadamente 0,889:1.
38. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es levorfanol, en donde la proporción de naltrexona liberable

a levorfanol va de aproximadamente 0,417:1 a aproximadamente 1,667:1.

39. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es meperidina, en donde la proporción de naltrexona liberable a meperidina va de aproximadamente 0,0056:1 a aproximadamente 0,022:1.

40. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es metadona, en donde la proporción de naltrexona liberable a metadona va de aproximadamente 0,083:1 a aproximadamente 0,333:1.

41. La forma de dosis oral de la reivindicación 7, en donde dicho antagonista opioide liberable es naltrexona y dicho agonista opioide es morfina, en donde la proporción de naltrexona liberable a morfina va de aproximadamente 0,028:1 a aproximadamente 0,111:1.

42. La forma de dosis oral de la reivindicación 1, en donde el antagonista liberable esta en una cantidad para atenuar un efecto colateral de dicho agonista opioide seleccionado del grupo que consiste de anti -analgesia, hiperalgesia, hiperexcitabilidad, dependencia física, tolerancia y una combinación de cualquiera de los anteriores.

43. La forma de dosis de liberación controlada de la reivindicación 1, en donde la cantidad de antagonista liberado durante el intervalo de dosificación mejora la potencia analgésica del agonista opioide.

44. La forma de dosis de liberación controlada de la reivindicación 42, en donde la cantidad de antagonista receptor opioide liberable es aproximadamente 100 a aproximadamente 1000 veces menor que la cantidad de agonista opioide.

45. La forma de dosis de la reivindicación 7 en donde la proporción de la cantidad del antagonista liberado de dicha forma de dosis después de violación a la cantidad de dicho antagonista liberado de dicha forma de dosis intacta es aproximadamente 4:1 (p:p) o mayor, basada en la disolución in vitro a una hora de dicha forma de dosis en 900 ml de Fluido Gástrico Simulado USP tipo II (paleta) a 75 rpm a 37°C.

46. La forma de dosis de la reivindicación 7 en donde la proporción de la cantidad del antagonista contenido en dicha forma de dosis intacta a la cantidad de dicho antagonista liberado de dicha forma de dosis intacta después de una hora es aproximadamente 4:1 o mayor, basado en la disolución in vitro a una hora de dicha forma de dosis en 900 ml de Fluido Gástrico Simulado utilizando un aparato USP tipo II (paleta) a 75 rpm a 37°C.

47. La forma de dosis oral de la reivindicación 45 en donde dicha proporción es 10:1 o mayor.

48. La forma de dosis oral de la reivindicación 45 en donde dicha proporción es 50:1 o mayor.

49. La forma de dosis oral de la reivindicación 45 en donde dicha proporción es 100:1 o mayor.

50. La forma de dosis oral de la reivindicación 1 en donde dicho antagonista liberable es naloxona o una sal farmacéuticamente aceptable de esta y dicho antagonista no liberable es naltrexona o una sal farmacéuticamente aceptable de esta.

51. Un método para tratar el dolor que comprende administrar una forma de dosis de la reivindicación 1.

52. Un método para desestimular el abuso que comprende preparar una forma de dosis de la reivindicación 1.

53. Un método para preparar una forma de dosis de la reivindicación 1 que comprende combinar un agonista opioide con un antagonista en una forma liberable y no liberable en una forma de dosis.

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()

- | | | |
|---|-----|-----|
| - Indicación de que se solicita la concesión de una patente. | () | () |
| - Datos de identificación del solicitante o de la persona que se presenta la solicitud. | () | () |
| - Descripción de la invención. | () | () |
| - Dibujos de ser estos pertinentes. | () | () |
| - Comprobante de Pago de las tasas establecidas. | () | () |

COMPLETA ()	INCOMPLETA ()	()
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DISEÑO INDUSTRIAL ()

- | | | |
|--|-----|-----|
| - Indicación de que se solicita el registro de Diseño Industrial | () | () |
| - Datos de identificación del solicitante o de la persona que presenta la solicitud. | () | () |
| - Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. | () | () |
| - Comprobante de pago de las tasas establecidas | () | () |

COMPLETA ()	INCOMPLETA	()	()
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ESQUEMA DE TRAZADO ()

- | | | |
|--|-----|-----|
| - Indicación de que solicita el registro de un Esquema de trazado. | () | () |
| - Datos de identificación del solicitante o de la persona que presenta La solicitud. | () | () |
| - Representación gráfica del esquema de trazado | () | () |
| - Comprobante de pago de las tasas establecidas. | () | () |

COMPLETA ()	INCOMPLETA	()	()
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Firma Responsable:



Fecha:

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04009406 00000000 Folios: 143
Fecha (AMD): 2004-02-06 15:04:12
Tramite : 011 PCT-PATENT 279 FIDE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES



2020
Bogotá, D.C.,

Doctora:
Luz Helena Adarve Gómez
Apoderada
Euro Certique S.A

Oficio N° 02168

ASUNTO:	Radicación N°	04-8488
	Solicitud Internacional	PCT/US02/24944
	Fecha inicio fase nacional	06/03/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

27 FEB. 2004

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