

FORMULARIO ÚNICO DE OPOSICIÓN

OPOSICIÓN A

- | | |
|--|---|
| ☒ Patente de Invención | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

**SOLICITUD
PUBLICADA**

Número del expediente 05-007005

Solicitante **GLAXO GROUP LIMITED**

Apoderado CARLOS R. OLARTE.

Título de la nueva creación o denominación del signo "FORMULACIÓN DE LAMOTRIGINA DE LIBERACIÓN PROLONGADA Y USO DE LA MISMA PARA SU PREPARACIÓN"

Gaceta **568**

③ OPOSICIÓN PRESENTADA POR

SOLICITANTE	Nombre PROCAPS S.A Dirección CALLE 80 No. 78b-201 Nacionalidad o Domicilio COLOMBIA Lugar de Constitución BARRANQUILLA	IDENTIFICACIÓN CC ☐ NIT ☒ CE ☐ Otro ☐ Cual _____ Número <u>890 106 527-5</u>
	Teléfono 371 99 00 Fax 373 08 18 E-mail	
REPRESENTANTE O APODERADO	Nombre LAURA CATALINA SILVA BARRERA Dirección CARRERA 13 #119-95 OFICINA 104 Teléfono (571)2131213 Fax (571) 6121979 E-mail.	IDENTIFICACIÓN CC ☒ NIT ☐ CE ☐ Otro ☐ Cual _____ Número <u>52.455 803</u> TP <u>147399</u>
	negocios@optimum-co.com	

④ FUNDAMENTOS DE LA OPOSICIÓN

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

Causa	No cumple con los requisitos de patentabilidad
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Signo opozitor

Justificación

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

⑤ Comprobante de pago No _____ Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE. LAURA CATALINA SILVA BARRERA

FIRMA. *Laura Catalina Silva B*

C.C 52.455.803

TP 147399



Optimum

126
2
Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E S D

Referencia : Expediente N° 05 007.005

Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIÓN DE LAMOTRIGINA DE LIBERACIÓN
PROLONGADA Y USO DE LA MISMA PARA SU
PREPARACIÓN"

Solicitante : GLAXO GROUP LIMITED

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 568 del 29 de Septiembre de 2006

Yo, *Laura Catalina Silva Barrera*, abogada con tarjeta profesional N° 147399 del consejo superior de la judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada **"FORMULACIÓN DE LAMOTRIGINA DE LIBERACIÓN PROLONGADA Y USO DE LA MISMA PARA SU PREPARACIÓN"** solicitada por **GLAXO GROUP LIMITED**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

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Bogotá Colombia

1 INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que pueden contener en particular Lamotrigina. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2 FUNDAMENTOS DE HECHOS

2.1 La solicitud objeto de la presente fue presentada el 28 de enero de 2005, reivindicando prioridad bajo las solicitudes GB0217493 6 del 29-07-2002, GB0217492 8 del 29-07-2002, y, GB0313801 3 del 13-06-2003 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 568 del 29 de septiembre de 2006, página 389, N° publicación 405, cuya publicación internacional corresponde a la WO2004/012741 del 12-02-2004.

2.2 La solicitud colombiana 05 007.005 objeto de la presente oposición, se refiere a una formulación de lamotrigina o de uno de sus derivados farmacéuticamente aceptables caracterizada porque es una formulación de liberación prolongada, donde sustancialmente toda la lamotrigina o uno de sus derivados farmacéuticamente aceptables se libera de la formulación 2 a 20 horas después de la administración al paciente, donde tiene un perfil de disolución in vitro en el que 40 a 65% de la lamotrigina se disuelve en 3 a 8 horas, donde tiene un perfil de disolución in vitro igual o sustancialmente similar al de una cualquiera de las Figuras 3, 4 ó 5, donde tiene un perfil de disolución in vitro en el que el valor del área bajo la curva está entre 80% y 125% del de una cualquiera de las Figuras 3, 4 ó 5, donde la formulación de liberación prolongada de lamotrigina o de uno de sus derivados farmacéuticamente aceptables, también está caracterizada porque la liberación de la lamotrigina o de uno de sus derivados farmacéuticamente aceptables hay al menos dos fases, en las que la velocidad de liberación de la primera fase es diferente de la velocidad de liberación de la segunda fase

2.3 De otra parte el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente

"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial" Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la novedad de la presente solicitud

- D1 WO9714415, 1997-04-24
- D2 WO9847491, 1998-10-29
- D3 US6406716, 2002-06-18

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Bogotá Colombia

2.4 Ahora bien, el documento D1, particularmente en el resumen y en la página 2, líneas 11 a 15 y reivindicaciones, se refiere a una composición farmacéutica para la administración de un antagonista receptor NMDA a un humano o animal donde la composición incluye un antagonista receptor NMDA de liberación inmediata en asociación con un antagonista de receptor NMDA de liberación controlada. Según la descripción del documento D1, la formulación está referida a antagonistas receptores NMDA indicados para ser eficaces en el tratamiento de enfermedades tales como Huntington, esclerosis lateral amiotrófica (ALS), la enfermedad de Alzheimer, la esquizofrenia, enfermedades motoneuronas y desórdenes CNS entre otras. Así las cosas, según se evidencia en el documento D1, la lamotrigina puede formularse en forma de liberación controlada y formulada para el tratamiento de desórdenes DNS. Así las cosas, es claro que este documento D1, revela una misma propuesta como solución que incluye un antagonista de receptor NMDA de liberación controlada para el tratamiento de desórdenes DNS. Por lo tanto, a los ojos de este documento D1, la presente solicitud no es novedosa.

2.5 Por su parte, el documento D2, particularmente en el resumen, página 9, línea 15 y reivindicaciones, especialmente la reivindicación 29, revela una composición farmacéutica de liberación controlada comprendiendo (a) al menos lamotrigina, (b) un primer componente inteligente olímero, y, (c) un segundo componente de polímero inteligente. Por lo tanto, este documento también revela como solución una composición farmacéutica que comprende de liberación controlada que incluye lamotrigina. Según se evidencia en este documento anterior, el problema a ser resuelto fue solucionado con las formulaciones especificadas, especialmente para la lamotrigina. La solución sugerida en la presente solicitud objeto de

oposición, comprende el uso lamotrigina en tabletas mixtas recubiertas o recubiertas por capas de difusión de liberación prolongada, pero dichas soluciones no son diferentes a las formulaciones que incluyen lamotrigina referenciadas en el documento D2. Por lo tanto, este documento objeto de oposición a la luz del documento D2, carece de novedad.

2.6 El documento D3 según el resumen y sus reivindicaciones, especialmente las cláusulas 3 y 4, revela el uso de la lamotrigina dentro de una formulación de liberación controlada para el tratamiento del alivio del dolor neuropático. Por lo tanto, este documento objeto de oposición a la luz del documento D3, carece de novedad.

2.7 En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 05 007 005 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con el requisito más importante para su protección como es el de novedad.

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

2.8.1 **CARECE DE NOVEDAD** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- "Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida." A la fecha de prioridad, 29 de julio de 2002, ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, D2 y D3, una formulación que incluye

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Bogotá Colombia

un antagonista de receptor NMDA tal como lamotrigina de liberación controlada para el tratamiento de desordenes DNS, sobre el cual busca protección en el capítulo reivindicatorio

2 9 Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14 *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."* La solicitud pretendida no cumple con el requisito de novedad necesario para su patentabilidad

2 10 Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMULACIÓN DE LAMOTRIGINA DE LIBERACIÓN PROLONGADA Y USO DE LA MISMA PARA SU PREPARACIÓN"** solicitada por **GLAXO GROUP LIMITED**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 568

3. PRUEBAS

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

• D1 WO9714415, 1997-04-24

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- D2 WO9847491, 1998-10-29
- D3 US6406716, 2002-06-18

4 FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes

- 4 1 Numeral 1 del artículo 586 del Código de Comercio
- 4 2 Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4 3 En las demás normas concordantes

5 ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos

- D1 WO9714415, 1997-04-24
- D2 WO9847491, 1998-10-29
- D3 US6406716, 2002-06-18

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6. NOTIFICACIONES

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

Señor Superintendente,



Laura Catalina Silva Barrera

CC 52'455 803 de Bogotá

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

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Bogotá Colombia



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **LAURA CATALINA SILVA BARRERA**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No 147399, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No **05 007.005**, titulada **"FORMULACIÓN DE LAMOTRIGINA DE LIBERACIÓN PROLONGADA Y USO DE LA MISMA PARA SU PREPARACIÓN"** de **GLAXO GROUP LIMITED**, publicada en la gaceta No 568 del 29 de Septiembre de 2006

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

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

Dado y Firmado en Barranquilla (Colombia) a los 13 días del mes de Diciembre de 2006


PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. N° 16.251 923 de Palmira,
Representante Legal

Acepto:


LAURA CATALINA SILVA BARRERA
C.C. 52'455.803 de Bogotá
T P A. 147399 del C.S. de la J

DILIGENCIA DE RECONOCIMIENTO
ANTE MI: **JUAN ENRIQUE NIÑO GUARÍN** Notario Cuarenta y tres del circuito de Bogotá, D.C. Comprocedo.
Laura catalina silva
Silva
Identificada con C.C. No 52-455 83
24
Declaro que reconozco al contenido del presente documento por ser cierta y que la firma igual que la huella (indica en el presente) en él son suyos.


26 DIC. 2006
JUAN ENRIQUE NIÑO GUARÍN NOTARIO CUARENTA Y TRES

ALTA EN LA FAMILIA SEGURA
Nº 2
NOTARIA ESPECIAL DEL CANTÓN DE NARIÑO
CERTIFICA
Que he(n) firmado(n) con su(s) nombre(s) en el documento que
antecede se asemeja(n) al(s) de WALTER
TANAKA TATEKANA
Que es(es) el/los registrado(s) en esta Notaría previa
confirmación de su/s nombre(s)
(Decreto 2591-71)
Firma en 10 de Oct de 2006

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***** Pag 1
CAMARA DE COMERCIO
DE BARRANQUILLA
12*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S A -----

NIT 890 106 527-5

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Pública No 1 190 del 22 de Julio de 1976, ot rgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No 6 070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA" -----

C E R T I F I C A

Que por Escritura Pública No 1 307 del 28 de Junio de 1979, t rgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No 10 039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S A " PROCAPS S A " -----

C E R T I F I C A

Que por Escritura Pública No 3 810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No 12 705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA" -----

C E R T I F I C A

Que por Escritura Pública No 3 755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No 17 922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S A " PROCAPS S A " -----

C E R T I F I C A

Que por Escritura Pública No 3 615 del 06 de Dic/bre de 1996, torgada en la Notaria 2a de Barranquilla, inscrit (as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No 67 218 del libro respectivo, la sociedad antes mencionada-----

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

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE-
DOCUMENTOS**

PROCAPS S A -----

NIT 890 106 527-5

cambio de razon social, por la denominacion LABORATORIOS PROCAPS S A

C E R T I F I C A

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

C E R T I F I C A

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

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

C E R T I F I C A

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

DENOMINACION O RAZON SOCIAL

PROCAPS S A -----

SIGLA PROCAPS

DOMICILIO PRINCIPAL Barranquilla

NIT No 890 106 527-5

MATRICULA MERCANTIL 24 802

C E R T I F I C A

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



***** Pag 2
 CAMARA DE COMERCIO
 DE BARRANQUILLA
 12*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S A -----

NIT 890 106 527-5

Direccion para notificaciones judiciales

CL 80 No 78 B - 201

De la ciudad de Barranquilla

C E R T I F I C A

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

C E R T I F I C A

OBJETO SOCIAL El objeto principal de la sociedad sera a)-La fabricaci n de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario, b)-La investigacion, desarrollo y fabricacion de t da clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal, c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para l s procesos de fabricacion de sustancias quimicas, farmaceuticas,alimen ticias y cosmeticas, asi como la comercializacion interna y externa de l s productos terminados, d) La compra, venta, importaci n, ex portacion y distribucion de toda clase de elementos instru mentales y equipos medicos, quirurgicos, odontologicos, y hospitalari s para la salud humana y animal e)La compra,venta,exportacion y dis tribucion de dulces, confites, galletas y todo tip de gol sinas o alimentos para el consumo humano f) Actuar como re presentante o agente de personas naturales y juridicas, naci nales y extranjeras en la realizacion de operaciones tran sacci nes relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c) d) y e) antes descritos, g) Prestar los servici s de ases ria y consultoria en las areas administrativas, de mer cade , analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S A , asi como los de publicidad y promocion de product s quimicos, cosmeticos y farmaceuticos para uso humano, animal in dustrial, h)-Adquirir, operar, administrar y explotar, a cualquier titul , empresa o establecimientos dedicados a la investigacion, de sarrollo, fabricacion o comercializacion de productos quimicos, far maceutic s, hospitalari s c smeticos En desarroll de su objet principal, la sociedad podra tomar interes social como accionista, socio fundador de empresas que tengan igual o similar objeto, com-

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S A -----
NIT 890 106 527-5

prar, vender, importar y exportar maquinarias, insumos y repuest s
requeridos para el desarrollo de sus actividades, tomar dinero en
prestamo, financiar y garantizar las operaciones comerciales que ce-
lebre con terceros relativas a su objeto, celebrar y ejecutar todo
tipo de actos y contratos necesarios para desarrollar sus operacio-
nes, girar, aceptar, otorgar y protestar todo tipo de titulos val-
res e instrumentos negociables, comprar, vender y constituir grava-
menes sobre bienes muebles e inmuebles, designar representantes o
apoderados en el pais y en el exterior y, en general, realizar cual-
quier acto o negocio que sea necesario o conveniente para el desa-
rrollo de su objeto social y para la mejor proteccion de sus intere-
ses corporativos o la de sus socios La sociedad podra garantizar
el cumplimiento de obligaciones adquiridas por terceros o por sus
soci s, para lo cual podra inclusive constituir gravámenes reales
sobre sus bienes de cualquier naturaleza -----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2 000 000 000 *****	2 000 000 *****	1 000
Suscrito		
\$*****1 220 000 000 *****	1 220 000 *****	1 000
Pagado		
\$*****1 220 000 000 *****	1 220 000 *****	1 000

C E R T I F I C A

ADMINISTRACION La direccion y administracion de la sociedad corres-
pondera a la Asamblea General de Accionistas, a la Junta Directiva,
al Presidente, al Vicepresidente y a un Gerente General Corresponde
a la Junta Directiva las siguientes funciones y atribuciones entre
tras Autorizar cualquier acto o contrato cuya cuantia sea superi r
al equivalente en pesos Colombianos a doscientos cincuenta mil dola-
res de los Estados Unidos de America (US\$250 000), liquidados a la
tasa de cambio representativa del mercado vigente el dia en que se
surta la transacion Cuando se trate de operaciones en virtud de
las cuales la sociedad garantice obligaciones de terceros o de l s
soci s, se requerira que la operacion sea aprobada con el voto de
por lo menos 2/3 partes de los integrantes de la Junta Directiva
La sociedad tendra un Presidente , quien ejercera la representa-
cion legal de la sociedad y tendra las siguientes atribu-
ciones entre otras Ejecutar las decisiones de la Asamblea
General de Accionistas y de la Junta Directiva Ejercer la Represen-
taci n Legal de la sociedad en todos los actos y contratos que se
requieran para el desarrollo del objeto social, de conformidad c n
lo previsto en las leyes y en los presentes estatutos Constituir
apoderados judiciales y extrajudiciales, recibir notificaciones,
absolver interrogatorios de parte, confesar obligaciones de la
sociedad, transigir, disistir y allanar a la sociedad en cualquier
asunto judicial Aprobar y celebrar en nombre de la socieda t do
act o c ntrato cuya cuantia sea igual inferior al equivalente
en pesos colombianos a doscientos cincuenta mil dolares de los

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



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Estados Unidos de America (US\$250 000), liquidados a la tasa de cambi representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ell acreditar la ausencia del principal La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta separadamente con el Presidente El vicepresidente tendra las siguientes facultades entre otras Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150 000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fij de la sociedad, inclusive de naturaleza muebles, acci nes, cu tas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de l s anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatut s o de la Junta Directiva El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ell acreditar la ausencia del principal La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, c n identicas facultades, pudiendolas ejercer c njunta separadamente c n el Presidente y Vicepresidente, c n identicas facultades que el Gerente General y sin que sea necesari para ell acreditar

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

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la ausencia del titular El Gerente General tendra las siguientes facultades entre otras Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos Aprobar y celebrar en nombre de la s ciudad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de l s Estados Unidos de America (US\$50 000), liquidados a la tasa de cambi representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente -----

C E R T I F I C A

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

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

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

CLASE JUNTA DIRECTIVA

Principales

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

Suplentes

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

C E R T I F I C A

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

Cargo/Nombre	Identificación
Presidente Minski Gontovnik Ruben	CC *****7 463 982

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



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Suplente del Presidente

Minski Minski Abraham

CC *****802 575

Vicepresidente

Minski Gontovnik Meyer

CC *****7 461 324

Suplente del vicepresidente

Minski Gontovnik Jose

CC *****8 671 834

C E R T I F I C A

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

Cargo/Nombre

Identificación

Gerente General

Uribe Ochoa Guillermo Luis

CC *****70 073 754

C E R T I F I C A

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

Cargo/Nombre

Identificación

Suplente del Gerente

Tanaka Walter

CC *****16 251 923

C E R T I F I C A

Que según Acta No 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad PROCAPS S A cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No 82 226 del libro respectivo, fueron hechos los siguientes nombramientos

Cargo/Nombre

Identificación

Revisor Fiscal Ppal

Vargas Pertuz Ana Isabel

CC *****32 696 645

C E R T I F I C A

Que según Acta No 127 del 22 de Marz de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad PROCAPS S A cuya parte pertinente se inscribió en esta Cámara de Comercio,

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DOCUMENTOS

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el 29 de Mayo de 2000 bajo el No 87 250 del libro respectivo,
fueron hechos los siguientes nombramientos

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

C E R T I F I C A

Que por escritura publica No 2 608 del 5 de Octubre del 2 001, otorgada en la Notaria 2a de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2 001, bajo los Nos 95 771, 2 056, 2 057, 2 058, 2 059, 2 060, 2 061, 2 062 y 2 064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No 3 705 de Noviembre 6 de 1 998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad 1 -Se confiere Poder Especial, Amplio y Suficiente a los senores WALTER TANAKA TATEKAWA, C C No 16 251 923, WILLIAM ALBERTO BARROS CERRA, C C No 8 715 941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S A , suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional 2 -Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800 000 oo (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion GUPO A GUILLERMO LUIS URIBE OCHO C C No 70 073 754, LINO LAZALA SILVA VARGAS C C No 19 260 410, JAIRO MOLINA MEJIA C C No 8 706 380, CLAUDIA TANGARIFE CASTILLO C C No 41 660 -293 BRUPO B WALTER TANAKA TATEKAWA C C No 16 251 923, HENRY CARO DIAZ C C No 19 395 298, CARMEN ALICIA FLOREZ C C No 22 434 044, CARMEN ALICIA HERRERA DIAZ GRANADOS C C No 22 377 540 Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B, 3 -Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C C No 33 138 497, a la Doctora MARCELA CARVAJALINO PAGANO C C No 22 579 748, y al Doctor DANIEL MORENO VILLALBA, C C No 19 113 210, para que cada uno representen a PROCAPS S A , ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como Contestar e interponer demandas y requerimientos, comparecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato Para la celebracion de cualquier acuerdo conciliatorio transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la socie-

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dad Los Apoderados podran presentar solicitudes de devoluci n y/
 compensacion de impuestos y recibir los pagos por devoluciones de
 impuestos, firmar, notificarse y realizar todo acto necesario para
 cumplir con el mandato encomendado -----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrit
 en esta Camara de Comercio el 8 de junio de 2000, bajo el No 1 786
 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C C N
 7 463 982 de Barranquilla, actuando como Presidente y Representante
 Legal de la sociedad PROCAPS S A, confiere poder especial, amplio
 y suficiente a KAREN FIGUEROA GARCIA, C C No 32 732 070 de Barran-
 quilla, para que en su nombre y representacion de la sociedad sus-
 criba todas declaraciones cambiarias a que este obligada PROCAPS
 S A, en el giro normal de sus negocios y operaciones sociales --

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2 002, inscrit
 en esta Camara de Comercio el 15 de enero del 2 003 bajo el No 2 290
 del libro respectivo, el señor RUBEN MINSKI GONTOVNIK, C C No 7 463
 982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE
 de PROCAPS S A, mediante el presente documento otorgo PODER ESPE-
 CIAL al Sr MARLON TATIS PAREDES, C C No 72 176 874, para que en
 representacion de PROCAPS S A, suscriba declaraciones, rep rtes y
 cualquier tipo de documentos relacionados con tramites o registros
 de Comercio Exterior ante el Ministerio de Comercio Exteri r y/o
 cualquier entidad del Estado que haga sus veces En consecuencia,
 el Sr MARLON TATIS PAREDES, podra suscribir en representaci n de
 PROCAPS S A declaraciones, reportes y cualquier tipo de documentos
 relacionados con tramites o registros de Comercio Exterior ante el
 Ministerio de Comercio Exterior y/o cualquier entidad del Estado
 que haga sus veces -----

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrit
 en esta Camara de Comercio el 1 de diciembre del 2 004, bajo el No
 2 753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C C
 7 463 982 de Barranquilla, actuando como Presidente y Representante
 Legal de la sociedad PROCAPS S A, confiere poder especial, ampli
 y suficiente a ANTONIO VARELA DIAZ, C C No 72 004 669 de Barran-
 quilla, para que en nombre y representaci n de la sociedad firme
 las declaraciones cambiarias a que este bligada PROCAPS S A, a

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

C E R T I F I C A

Que según documento privado del 22 de Febrero de 2005, inscrito en esta Cámara de Comercio el 28 de Marzo de 2005, bajo el No 2 820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C C 16 251-923 de Palmira, quien actúa como representante legal de la sociedad PROCAPS S A, otorga Poder Especial, Amplio y Suficiente al señor MARLON TATIS PAREDES C C No 72 176 874, para que en representación de PROCAPS S A, suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los trámites o registros de comercio exterior ante la dirección de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de información de las autoridades aduaneras en los órdenes distrital, departamental y nacional -----

C E R T I F I C A

Que por Escritura Pública No 1 613 del 28 de Junio del 2005, otorgada en la Notaría Segunda de Barranquilla, inscrita en esta Cámara de Comercio el 18 de agosto del 2005 bajo el No 2 913 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C C No 7 463 928, en su condición de Presidente y Representante Legal de la sociedad PROCAPS S A, confiere poder especial amplio y suficiente a los siguientes señores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancías y servicios con entidades oficiales, hasta por la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS DE AMERICA (US\$800 000), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción GRUPO A MIRIAM RODRIGUEZ DIAZ, C C No 41 473 569 GRUPO B NELSON SUAREZ CHAVEZ, C C No 79 417 971 -----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad

C E R T I F I C A

Que su última Renovación fue el 29 de Marzo de 2006

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

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03-08036472 024802 PROCAPS S A

Barranquilla, 28 de Nov/bre de 2006

Hr 09 58 04

No 10823978



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ A61K 31/385		A1	(11) International Publication Number WO 97/14415
			(43) International Publication Date 24 April 1997 (24.04.97)
(21) International Application Number PCT/AU96/00658		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 18 October 1996 (18.10.96)		Published With international search report.	
(30) Priority Data PN 6057 19 October 1995 (19.10.95) AU			
(71) Applicant (for all designated States except US): F.H. FAULDING & CO. LIMITED [AU/AU] 160 Greenhill Road, Parkside, S.A. 5063 (AU).			
(72) Inventor; and (73) Inventor/Applicant (for US only): SMITH, Ian, Keith [NZ/AU] 11 Athol Avenue, Blair Athol, S.A. 5084 (AU). HEINICKE, Grant, Wayne [AU/AU]; 14 Bandin Avenue, Fairview Park, S.A. 5126 (AU).			
(74) Agent: PHILLIPS ORMONDE & FITZPATRICK, 367 Collins Street, Melbourne, VIC 3000 (AU)			
(54) Title ANALGESIC IMMEDIATE AND CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION			
(57) Abstract			
The present invention relates to pharmaceutical compositions and is particularly concerned with pharmaceutical compositions containing N-methyl-D-aspartate (NMDA) receptor antagonists and their use in the treatment of pain. Accordingly, there is provided a pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject, the composition including an NMDA receptor antagonist in an immediate release form in association with an NMDA receptor antagonist in a controlled release form. The present invention further provides a method for the therapeutic or prophylactic treatment of pain in a human or animal subject, the method including administering to the subject, a composition in accordance with the present invention. The method of the invention may be used to treat chronic or acute pain. The composition of the invention may be used in the pre-emptive treatment of pain. The NMDA receptor antagonist may be selected from a morphine such as dextromethorphan and dextrorphan, ketamine, amantadine, memantine, aliprodil, ifenprodil, dizocilpine, remacemide, lamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, cefotol, felbamate, spermine, spermidine, levomepamil, a pharmaceutically acceptable salt or ester thereof or a metabolic precursor of any of the foregoing			

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FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

Analgesic immediate and controlled release pharmaceutical composition

The present invention relates to pharmaceutical compositions and is particularly
5 concerned with pharmaceutical compositions containing N-methyl-D-aspartate
(NMDA) receptor antagonists and their use in the treatment of pain

The amino acid glutamate is an excitatory neurotransmitter that is an agonist at
many post-synaptic terminals of the central nervous system. The glutamate
10 receptor complex is termed the NMDA receptor and is a potential target for
therapeutic drugs. This receptor incorporates an ion channel complex which is
novel because it is gated by both dual ligand binding (glutamate and glycine) and
membrane voltage. Because of the novel requirements for activation, it is
believed that the NMDA receptor complex plays only a minor role in routine
15 synaptic transmission. However, the receptor complex may be activated following
repeated afferent stimuli as occurs during trauma such as surgery. Repeated
stimuli cause a temporal summation of C-fibre-mediated responses of dorsal horn
nociceptive neurones, this phenomenon, increased output to a constant input, is
known as wind-up

20

Studies indicate that activation of the NMDA receptor complex in the spinal dorsal
horn leads to increased spontaneous neural discharge, expanded receptive fields
and exaggerated responses to afferent input. These neural mechanisms may be
expressed physically as hyperalgesia (increased pain sensation) and allodynia
25 (pain arising from a stimulus that is not normally painful)

Opioids, through their ability to inhibit release of primary afferent
neurotransmitters or to inhibit interneurons early in nociceptive pathways, initially
reduce or block C-fibre inputs to the deeper dorsal horn nociceptive neurones
30 However, as the peripheral stimulation continues, wind-up breaks through the
input inhibition and the neurones start to respond. Thus at moderate doses
opioids delay the onset of wind-up without inhibiting the process itself

By contrast, NMDA receptor antagonists have no effect on the initial inputs to the cells but diminish or abolish wind-up and convert the potentiated response to a normal response

5

We have found that a particularly effective composition for the administration of an NMDA receptor antagonist to diminish or abolish wind up is one providing both immediate release of an NMDA receptor antagonist and controlled or sustained release of an NMDA receptor antagonist

10

NMDA antagonist receptors have also been indicated to be effective in the treatment of Huntington's disease, amyotrophic lateral sclerosis (ALS), AIDS-related dementia, Alzheimer's disease, schizophrenia, motoneurone diseases and CNS and brain injuries resulting from a number of causes including stroke, trauma and neurosurgery

15

In accordance with one aspect of the present invention there is provided a pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject, the composition including an NMDA receptor antagonist in an immediate release form in association with an NMDA receptor antagonist in a controlled release form

20

The same NMDA receptor antagonist may be used in both the immediate and controlled release forms or they may be different NMDA receptor antagonists

25

The composition of the invention is suitable for the treatment of chronic or acute pain, for example to be administered pre-operatively

Accordingly, the present invention further provides a method for the therapeutic or prophylactic treatment of pain in a human or animal subject the method including administering to the subject, a composition in accordance with the present invention. The method of the invention may be used to treat chronic or acute pain

30

- 3 -

The composition of the invention may be used in the pre-emptive treatment of pain

Preferably the NMDA receptor antagonist may be selected from a morphinan
5 such as dextromethorphan and dextrorphan, ketamine, amantadine, memantine,
eliprodil, ifenprodil, dizocilpine, remacemide, lamotrigine, riluzole, aptiganel,
phencyclidine, flupirtine, cefotel, felbamate, spermine, spermidine, levemopamil,
a pharmaceutically acceptable salt or ester thereof, or a metabolic precursor of
any of the foregoing

10

The formulation may include sufficient NMDA receptor antagonist to provide from
about 1-5000 mg/day, typically 1-1000 mg/day and preferably about 100-800
mg/day of the active ingredient. The composition includes an NMDA receptor
antagonist in an immediate release form in association with a NMDA receptor
15 antagonist in a controlled release form. The composition may include an amount
of NMDA receptor antagonist in the immediate release form of approximately 5%
to 90% of the total NMDA receptor antagonist, preferably 10% to 60%. An
immediate release NMDA receptor antagonist content of about 15% to 50% is
particularly preferred. The controlled release form of the NMDA receptor
20 antagonist may constitute the remainder of the active ingredients.

25

The composition of the invention may be in a form suitable for oral or rectal
administration or for administration by transdermal, intravenous, intramuscular,
subcutaneous, intrathecal, epidural or intracerebroventricular means.

The composition of the invention may or may not be in a single dosage form.
Preferably the composition is in a single dose form.

The composition may be formulated as an oral dosage form such as a tablet,
30 capsule, a liquid, powder, granule or suspension, an injectable solution, a
suppository, implant or transdermal patch.

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Preferably the NMDA receptor antagonist is dextromethorphan (DM) or a pharmaceutically acceptable salt thereof. Preferably the dextromethorphan is in the form of dextromethorphan hydrobromide.

5 The oral form of the pharmaceutical compositions of the invention may be selected from

1) liquids, for example, suspensions, reconstitutable powders, elixirs, oils, solutions, or emulsions,

10

2) confectionery, for example, chewing gums, lozenges or candy bars,

3) powders, for example, drug powder, prilled material, coated actives or granulated materials,

15

4) capsules, for example, soft gelatin, hard gelatin containing, pellets, powders, tablets, granulates, liquids, or combinations of these, said capsules may or may not be coated,

20 5) tablets, for example, disintegrating, chewable effervescent, matrix, osmotic pumps, prepared by multi-layering, contain coated powders in tablets, tablets in tablets, pellets in tablets etc, said tablets may or may not be coated

25 The oral pharmaceutical composition of the invention may be in the form of a "taste-masked" or "taste-neutral" form

The method of manufacture, components and quantities of components used, depend on the particular pharmaceutical composition being considered

30 A suitable immediate release (IR) form of the NMDA receptor antagonist may simply be particles of the antagonist or particles of the antagonist admixed with soluble components for example, sugars (eg sucrose, lactose, fructose, mannitol

- 5 -

etc.), polymers (eg polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, etc), surfactants (sodium lauryl sulphate, chremophor, tweens, spans, pluronics, and the like), insoluble components (microcrystalline cellulose, $\text{Ca}_3(\text{PO}_4)_2$, talc, aerosol and the like), coating material (examples of suitable
5 coating materials are polyethylene glycol, hydroxypropyl methyl cellulose, wax, fatty acids, etc.), dispersions in suitable material (examples are wax, polymers, pharmaceutically acceptable oils, soluble agents etc) or combinations of the above. These mixtures may be prepared by blending, mixing, dissolution and evaporation, or by using suspensions etc. These mixtures may be deposited on
10 inert cores, wet massed and extruded, granulated, spray dried, etc. These mixtures or processed mixtures may be used in suspensions, filled into capsules, tableted, filled into sachets, used in confectionary and so on.

The controlled release may be a sustained release or delayed/modified release

15

A controlled-release dosage form as defined in US Pharmacopeia XXII includes extended release dosage forms which allow at least a twofold reduction in dosing frequency as compared to the drug presented as a conventional dosage form and delayed release dosage forms which release the drug at a time other than
20 promptly after administration.

A core used herein the description contains the active ingredient and other carriers and excipients, fillers, stabilising agents, binders, core seeds or colourants. The active may be present in amounts of approximately 0.1 to 95%
25 by weight based on the weight of the total core element. Preferably the active is present in amounts of 10 to 80% by weight based on the weight of the total core element. The core may be 200 to 1700 μ in diameter.

A pellet is a coated core, the coating being any suitable coating

30

Preferably, the controlled release component is a sustained (or extended) release form.

A suitable sustained release (SR) form of the NMDA receptor antagonist may be a matrix tablet composition. Suitable matrix forming materials are waxes (eg carnauba, bees wax, paraffin wax, cerasine, shellac wax, fatty acids, fatty alcohols), oils, hardened oils or fats (eg hardened rapeseed oil, castor oil, beef tallow, palm oil, soya bean oil), polymers (eg hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, polyethylene glycol) and other excipients known to those familiar with the art. Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, fillers, and excipients known to those familiar with the art. SR tablets may contain granulates, coated powders, pellets, or be multi-layered and the finished tablet may be coated or uncoated.

Suitable coating materials to prepare SR products are any pharmaceutically acceptable polymer such as ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers, polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars including lactose, sucrose, fructose and mannitol, salts including sodium chloride, potassium chloride and derivatives, organic acids including fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof, enteric polymers including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups. These polymers may be applied as solutions or latexes. Other barriers may be used such as waxes.

The coating composition may or may not be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers can be added from 0 to 50% by weight

of the coating composition and at least one may be selected from diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, castor oil and the like

- 5 Cores containing active may be coated directly to produce a SR dose, or tablets or capsules containing active may be coated

A suitable SR form of NMDA receptor antagonist may be an osmotic pump, or combinations of the above

10

These IR or SR forms may be made by pinling, spray drying, pan coating, melt granulation, granulation, wurster coating, tangential coating, top spray, tableting, extruding, coacervation and the like

- 15 The particle sizes of the IR and SR components in the dosage form depends on the technology used. The particle sizes could range from submicron to 500 μm for powder technologies (mixtures, spray drying, dispersions etc), 5-1700 μm for coating technologies (wurster, top spray, bottom spray, spray drying, extrusion, layering etc), to 1-40mm for tableting technologies

20

The IR and SR forms of the NMDA receptor antagonist are then combined into a single dosage such that the amount of NMDA receptor antagonist in the composition of the invention is in the range of about 1 - 5000 mg typically, 1 mg to 1000 mg, and preferably 100 mg to 800 mg. The composition including an NMDA

25 receptor antagonist in an immediate release form in association with a NMDA receptor antagonist in a controlled release form may include an amount of NMDA receptor antagonist in the immediate release form of approximately 5% to 90% of the composition of the invention, preferably 10% to 80%. An immediate release NMDA receptor antagonist content of about 15% to 50% is particularly preferred

- 30 The controlled release form of the NMDA receptor antagonist may constitute the remainder of the active ingredient

As a result the final composition provides an amount of NMDA receptor antagonist for immediate release following administration and an additional amount of NMDA receptor antagonist for sustained release. The SR component is preferably aimed at reducing the dosage interval from 3 to 6 times daily to 1 or 2 times daily

The composition of the invention may exhibit more than one peak in the plasma concentration/time curve in any one dosing interval depending on the particular NMDA receptor antagonist(s) used, the relative amounts of the IR and SR components, and the dissolution properties of the SR component.

The following non-limiting example illustrates the uses of the components listed above in producing a composition in accordance with the invention

Where the composition of the invention is in the form of a pellet product, the pellets may be presented in a sachet, capsule or tablet. The non limiting example below describes pellets (particle sizes 200 - 1 700µm) in a capsule. All the quoted ranges are %w/w

A plurality of elements containing the active ingredients (cores) are prepared by extrusion/spherulisation, or layering the active (or blend of active with other excipients) onto inert carriers by various processes. The cores themselves could be IR or SR depending on the materials and method of manufacture. The cores may contain the drug at the required potency according to the particular NMDA dose (mg), required size and presentation, and subsequent processes (coating etc). The cores may contain drugs in the range 0.1-100% depending on the required dose, potency, manufacturing method, and properties.

An extruded core would typically include a carrier such as microcrystalline cellulose in the range 5-99.9%, a binder such as hydroxypropyl cellulose in the range 0-50%, a filler such as lactose in the range 0-50% and other excipients. An extruded core may only contain drug and binder.

An extruded core with SR properties would typically contain a swelling/gelling polymer such as hydroxypropyl cellulose in the range 0-50% or a hydrophobic material such as cetylalcohol in the range 10-90% with the drug. A layered core would contain an inert carrier such as a sugar sphere in the range 10-90% with a binder in the range 0-50% with the drug. The core may or may not contain fillers, solubilisers and other additives. The binder may be chosen to achieve IR (hydroxypropyl cellulose, hydroxypropyl methyl cellulose etc), or SR (ethyl cellulose, cellulose acetate butyrate etc), or delayed/modified release (ie enteric binding materials such as hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate etc).

A portion of the final dosage form may be IR cores made by the above described processes. Alternatively the IR cores may be coated with a rapidly disintegrating or dissolving coat for aesthetic, handling, or stability purposes. Suitable materials are polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol, polymethacrylates containing free amino groups, each may be with or without plasticisers, and with or without an antitack agent or filler. An addition of about 3% of the weight of the core as coating material is generally regarded as providing a continuous coat for this size range.

The SR portion of the dose may be provided by a SR core as described above, a SR core which is further modified by overcoating, or an IR core which is modified by overcoating. The IR and SR NMDA receptor antagonist need not be the same active, nor are the IR or SR components of a dose themselves limited to just one active.

A typical coating composition for making the SR component would contain an insoluble matrix polymer in amounts approximately 15 - 85% by weight of the coating composition and a water soluble material in an amount of approximately 15 - 85% by weight of the coating composition. Optionally an enteric polymer in amounts from 0 to 100% by weight of the coating composition may be used or

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included Suitable insoluble matrix polymers include ethyl cellulose cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (eg lactose, sucrose, fructose, mannitol and the like), salts (eg sodium chloride, potassium chloride and the like), organic acids (eg fumaric acid, succinic acid, lactic acid, tartaric acid and the like) and mixtures thereof Suitable enterc polymers include hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, polymethacrylates containing carboxyl groups, and the like

The coating composition may or may not be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions Suitable plasticisers can be added from 0 to 50% by weight of the coating composition and at least one may be selected from diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, castor oil and the like

The coating composition may or may not include a filler The filler may comprise 0 to approximately 200% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, polacrillin potassium, and the like

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof Where solutions are applied the solvent is present in amounts from approximate by 25-99% by weight preferably 85-97% by weight based on the total weight of dissolved solids Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones or mixtures thereof

Where latexes are applied, the solvent is present in amounts from approximately 25 - 97% by weight, preferably 60-97% based on the quantity of polymenc material in the latex. The solvent may be predominantly water.

- 5 A suitable tablet formulation may be of a swelling/gelling polymer such as L-hydroxypropyl cellulose admixed with a filler such as MCC and the drug. The tablet excipients may or may not be processed ie spray dried together, prior to use in tableting. The mixture may be compressed directly, or granulated prior to compression. Matrix tablets of this type often exhibit a rapid initial release until the
10 polymers swell and gel, which induces SR for the remainder of the drug.

The quantity of IR and duration of SR can be varied by altering the quantities of the excipients used. If the IR component is not large enough, a quantity of drug can be included in a rapidly dissolving outer coat of polymers such as PEG or
15 hydroxypropyl methyl cellulose. A typical matrix tablet would contain the swelling/gelling polymer in amounts from approximately 15 to 70% by weight based on the total weight of the tablet and filler in amounts from approximately 15 to 70% by weight based on the total weight of the tablet. Additional fillers may be included in amounts from approximately 0 - 60% by weight based on the total
20 weight of the tablet. These may be soluble materials such as lactose, mannitol, sorbitol and the like, or insoluble materials such as tribasic calcium phosphate powdered cellulose or any of the various starches (corn, wheat, potato etc). Additionally, the tablets may contain a lubricant in an amount from 0-8% by weight based on the total weight of the tablet. Lubricants may be selected from
25 metal stearates, stearic acid, hydrogenated oils, such as soya bean oil or castor oil, sodium stearyl fumarate, polytetrafluoroethylene, talc and the like. The tablets may be coated for aesthetic, handling or stability purposes, or to increase the quantity of the IR portion of the drug. In this latter case the drug is dissolved or suspended in the coating solution and sprayed onto the tablets until the desired
30 quantity of drug has been added. Suitable coating materials include polyethylene glycol, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol, polyvinylpyrrolidone, sugar, waxes, or mixtures of these. The material may be

added to any desired thickness but weight gains in the range 1-20% are typical, preferably 2-10%, more preferably 2-5%. The coat may or may not be plasticised. A plasticiser may be present in amounts from about 0-50% by weight based on the total weight of the tablet or the coating material. Examples of plasticisers are diethyl phthalate, citrate esters, acetylated citrate esters, polyethylene glycol glycerol, dibutylsebacate, acetylated monoglycerides, castor oil and the like).

The coating composition may include an antitack agent such as talc, kaolin, titanium dioxide, silicon dioxide, alumina, starch, polacrilin potassium, microcrystalline cellulose or the like).

The coating materials may be applied to the drug particles, processed drug particles (i.e. cores, granules), finished tablets, or finished capsules.

The coating composition may or may not include a filler. The filler may comprise 0 to approximately 200% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, microcrystalline cellulose, polacrilin potassium.

The coat may contain other ingredients such as dyes and waxes.

The coat may be applied as a solution or suspension from aqueous or organic solvents. Solution concentration in equipment familiar to those skilled in the art.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. Where solutions are applied the solvent is present in amounts from approximately 25-99% by weight, preferably 85-97% by weight based on the total weight of dissolved solids. Suitable solvents are water, low molecular weight alcohols, low molecular weight chlorinated hydrocarbons, ketones, or mixtures thereof. Where latexes are applied, the solvent is present in amounts from approximately 25 - 97% by weight, preferably 60-97% based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

Alternatively the SR component of a tablet may be provided in the form of SR pellets and the IR component may be included in the body of the tablet. Such a tablet disintegrates to release the IR drug and the SR pellets. Pellets may be present in amounts from 1 - 60% by weight of the tablet, preferably 5 -50% more preferably 5 -40%. Suitable matrix materials for tablets of this type are microcrystalline cellulose, starches and the like.

The immediate release form of the NMDA receptor antagonist may be presented in a fast dissolving dosage form. The immediate release form may be in the form of a solid or molecular dispersion of the active within a polymer matrix. The polymer matrix may be selected from biologically acceptable polymer such as a cellulose ether, for example ethyl cellulose, or cellulose ester, for example cellulose acetate butyrate etc. The immediate release form may simply be particles of the antagonist or the antagonist deposited on a core containing the antagonist.

The composition of the invention, where it is in a tablet or like form, may include the two forms of the NMDA receptor antagonist as separate components, for example, in a multi-layer tablet, wherein one or more layer include the NMDA receptor antagonist in an immediate release form with one or more layers of the NMDA receptor antagonist in a controlled release form. Alternatively the composition of the invention may be in the form of a tablet wherein the immediate release forms the shell and the controlled release form constitutes the core.

Alternatively, the two forms of the NMDA receptor antagonist may be dispersed throughout the tablet.

The composition of the invention may be produced by providing a core containing the NMDA receptor antagonist controlled release component coated with an enteric or delayed release coating. The core can be in the form of beads compressed to a tablet. The coated core may then be compressed into tablets.

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along with a powder mixture containing additional NMDA receptor antagonist or filled in combination with uncoated NMDA receptor antagonist into a capsule shell. As a result, the final composition provides an amount of NMDA receptor antagonist for immediate release following administration and an additional amount of NMDA receptor antagonist for controlled release.

The controlled release form of the NMDA receptor antagonist is such as to provide sustained release of the antagonist. Preferably the controlled or sustained release form provides a therapeutic effect over a period greater than about 6 hours. More preferably the sustained therapeutic effect is greater than about 8 hours. A sustained therapeutic effect period of 8 to 24 hours being especially preferred. The SR component of the controlled release composition is aimed at reducing the dosage interval from 3 to 6 times daily to 1 to 2 times daily.

The controlled release form of the antagonist may be coated beads or granules of the NMDA receptor antagonist. The coated antagonist may be combined with uncoated or lightly coated antagonist to provide a composition of the present invention. The term "lightly coated" as used in the description means a rapidly disintegrating coating for aesthetic, handling or stability purposes. These then may be filled into capsules or formed into tablets. Microencapsulation may also be used to produce the controlled release form of the NMDA receptor antagonist.

The coating or matrix material may be any suitable material. The coating or matrix material may be a polymer or a wax. The wax may be selected from any suitable wax or wax-like material including natural oil and fat and hardened oils such as hardened rapeseed oil, hardened castor oil, hardened beef tallow, palm oils and the like, waxes such as carnauba wax, bees wax, paraffin wax, ceresine wax, shellac wax or a fatty acid.

The present invention also provides a kit including a plurality of unit dosage forms, in a container or the like, the container including indicia indicative of a

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dosage regimen, at least one of the unit dosages being in the form of a pharmaceutical composition in accordance with the present invention

5 The kit may further include unit dosages which provide immediate and controlled release of one or more actives such as an NMDA receptor antagonist. The kit may also include instructions for use of the kit.

10 Throughout the claims and description of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers and steps.

15 The present invention will now be more fully described with reference to the accompanying example. It should be understood, however, that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention as specified above.

FIGURES

Figure 1 Dissolution rate of Sustained Release Dextromethorphan capsules

5

EXAMPLE 1**A DEXTROMETHORPHAN DISSOLUTION PROFILE****BACKGROUND**

10 Dextromethorphan (DM) is an NMDA receptor which has been in clinical use for many years. Pharmacokinetic data suggest that after a normal 60mg dose the absorption of the drug is quite rapid, reaching maximum plasma levels in 1 to 2 hours. However, the bioavailability of the drug is quite low, probably because of extensive first-pass hepatic metabolism. Once absorbed, DM is converted in the
15 body to a metabolite (dextrophan) which is reported to be pharmacologically active. Both the parent and the metabolite have short half-lives (2 to 4 hours).

Since DM and the active metabolite have short half-lives, a controlled release formulation will be useful to provide up to 24 hour delivery of this NMDA receptor
20 antagonist from a single dose.

METHOD**a) PRODUCTION OF DEXTROMETHORPHAN CAPSULES**

25

Dextromethorphan capsules were prepared according to the following and dissolution profiles were determined on the capsules.

(I) Granulating Dextromethorphan Solution

<u>Ingredient</u>	<u>% (W/W)</u>
Ethanol 96 PC/BP	95.0
5 Hydroxy Propyl Cellulose BP/NF	5.0

Ethanol 96 PC/BP was added to a container. To this, Hydroxy Propyl Cellulose BP/NF was added while shear stirring. The solution was left to stir until all of the polymer was dissolved.

10

(II) Coating SolutionsFormulation 1

<u>Ingredient</u>	<u>% (W/W)</u>
Ethanol 96 PC/BP	95.0
Hydroxy Propyl Methyl Cellulose BP/USP 603	2.0
15 Ethyl Cellulose N50	3.0

20 Ethanol 96 PC/BP and Hydroxy Propyl Methyl Cellulose BP/USP 603 were shear stirred. After the HPMC had dissolved, Ethyl Cellulose N50 was shear stirred into the solution. The solution was shear stirred until the Ethyl Cellulose had completely dissolved.

Formulation 2

	<u>Ingredient</u>	<u>% (W/W)</u>
	Ethanol 96 PC/BP	93.43
5	Diethyl Phthalate BP/USP	0.85
	Methacrylic Acid Copolymer NF, Type C Powder	1.05
	Ethyl Cellulose N50	3.59
	Poly Ethylene Glycol (8000) NF	1.28

10 The above ingredients were combined with stirring to produce Coating Formulation 2

(III) Dextromethorphan Cores

Dextromethorphan Cores Part 1

15

The cores containing dextromethorphan were produced in a fluid bed coater at the following conditions

	Inlet Air Temperature	50°C
20	Air Flow	80 m ³ /hr

Two sets of dextromethorphan containing cores were produced, one with dextromethorphan potency of 57.75% and one with a potency of 80%. Both cores were made in a fluid bed coater with the ingredients listed below using
25 standard methods known to those skilled in the art. The particle size range of the final cores was 710-1400 microns for the low potency cores and 1000-1700 microns for the high potency cores. In order that the desired capsule size would be used, the high potency cores were used in the next part of the process.

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<u>Ingredient</u>		<u>% (W/W)</u>	<u>Typical Amounts (kg)</u>
Ethanol 98 PC/BP		-	0 200
Dextromethorphan Granulating Solution		43 82	1 580
Dextromethorphan HBr		33 71	1 200
5	Sugar Spheres 30-35 Mesh	22 47	0 800

Theoretical Potency at the end of Dextromethorphan Core Part 1 is 57.75%

Dextromethorphan Core Part 2

10

The cores containing dextromethorphan were produced in a fluid bed coated at the following operating conditions

	Inlet Air Temperature	50°C
15	Air Flow	80 m ³ /hr

<u>Ingredient</u>		<u>% (W/W)</u>	<u>Typical Amounts (kg)</u>
Ethanol 98 PC/BP		-	0 200
Dextromethorphan Granulating Solution		43 82	1 580
20	Dextromethorphan HBr	33 71	1 200
Dextromethorphan Cores Part 1		22 47	0 800

Theoretical potency at the end of Dextromethorphan Core Part 2 is 80%

25 The final core will have the following composition

<u>Ingredient</u>	<u>% (W/W)</u>
Dextromethorphan HBr	79.98
Hydroxy Propyl Cellulose BP/NF	5.20
30 Sugar Spheres (30-35) Mesh	14.82

(iv) Dextromethorphan Pellets

The high potency dextromethorphan cores were dispensed with one of the coating formulations and talc in a fluid bed coater to produce the pellets. The process was run with the two different coating formulations and two different theoretical polymer coat weights (TPCW) were produced with Coating formulation 1. The conditions in the fluid bed coater are as follows:

Inlet Air Temperature	50°C
Air Flow	80 m ³ /hr
Dew Point	0°C

The pellets were produced by standard coating methods well known to those skilled in the art. The final pellets within the size range 1000-1700 microns were retained.

Aim Product for A6-048 A1 (8% Theoretical Polymer Coat Weight (TPCW)) A6-048 A1, A6-052 A2, and A6-048 A2 are batch numbers used to identify different pellet compositions.

Ingredient	% (W/W)	Typical Amounts (kg)
Ethanol 96 PC/BP	-	0.2000
Coating Formulation 1	62.51	1.7400
Talc Purified Micronised BP/USP	1.58	0.0435
Dextromethorphan Cores	35.93	1.0000

Aim Product for A6-052 A2 (10% Theoretical Polymer Coat Weight (TPCW))

	<u>Ingredient</u>	<u>% (W/W)</u>	<u>Typical Amounts (kg)</u>
	Ethanol 96 PC/BP	-	0 2000
5	Coating Formulation 2	67 80	2 2222
	Talc Purified Micronised BP/USP	1 89	0 0555
	Dextromethorphan Cores	30 51	1 0000

The resulting Dextromethorphan Pellets have an excipient breakdown as follows

10

Dextromethorphan Pellet A6-052 A2 (10% TPCW)

	<u>Ingredient</u>	<u>% (W/W)</u>
	Dextromethorphan HBr	68 56
15	Hydroxy Propyl Cellulose BP/NF	4 46
	Sugar Spheres (30-35) Mesh	12 70
	Ethyl Cellulose N50	5 20
	Diethyl Phthalate BP/USP	0 94
	Methacrylic Acid Copolymer NF, Type C Powder	1 52
20	Poly Ethylene Glycol (6000) NF	1 86
	Talc Purified Micronised BP/USP	4 78

Dextro Pellet A6-048 A1 (8% TPCW)

25	<u>Ingredient</u>	<u>% (W/W)</u>
	Dextromethorphan HBr	70 75
	Hydroxy Propyl Cellulose BP/NF	4 60
	Sugar Spheres (30-35) Mesh	13 11
	Hydroxy Propyl Methyl Cellulose BP/USP 603	3 08
30	Ethyl Cellulose N50	4 61
	Talc Purified Micronised BP/USP	3 85

Dextro Pellet A6-048-A2 has a 10% TPCW with the same extract coating solution

(v) Capsules

- 5 Capsules were filled by blending cores with pellets. Each size 0, natural / natural capsule contained 250 mg of dextromethorphan. The ratio of core ADS equivalent to pellet ADS equivalent was 25/75. This meant that 62.5 mg of dextromethorphan was contained in the immediate release cores, and 187.5 mg of dextromethorphan was contained in the controlled release pellets. The
10 potencies of each of the cores and pellets was determined by UV assay.

b) MEASUREMENT OF DISSOLUTION OF DEXTROMETHORPHAN CAPSULES

- 15 Dissolution was measured using USPXXIII apparatus and method for dissolution <711>, apparatus 1. The analysis measures the UV absorbance of dextromethorphan at 278nm.

RESULTS

20

DISSOLUTION PROFILE OF DEXTROMETHORPHAN CAPSULES

- Dissolution of the dextromethorphan capsules was measured according to the parameters above. The theoretical dissolution profile is compared with actual
25 dissolution profile in Table 2 and shown in Figure 1. An aim dissolution profile was established with reference to the pharmacokinetic parameters, derived from the literature of immediate release dextromethorphan.

TABLE 2 AIM AND ACTUAL DISSOLUTION

Time (hours)	Aim		Actual		
	% Released	± 20% limit	A6-048 A1	A6-048 A2	A6-052 A2
0.5	27.5	22-33	25.8	24.9	26.7
1	30	24-36	28.0	26.5	27.8
2	35	28-42	33.3	29.5	31.5
4	45	36-54	43.8	38.3	42.2
6	55	44-66	55.2	44.4	53.2
8	65	52-76	66.8	53.3	64.1
12	85	68-100	87.9	71.8	82.0
16	100	>80	99.6	87.7	94.3

Finally, it is to be understood that various other modifications and/or alterations
s may be made without departing from the spirit of the present invention as outlined
herein

CLAIMS

- 1 A pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject, the composition including an NMDA
5 receptor antagonist in an immediate release form in association with an NMDA receptor antagonist in a controlled release form
- 2 A pharmaceutical composition according to claim 1 wherein the controlled release is sustained release or delayed/modified release
- 10 3 A pharmaceutical composition according to claim 1 or 2 providing an NMDA receptor antagonist to a human or animal subject such that the NMDA receptor antagonist is in the range of from about 1 to 5000 mg
- 15 4 A pharmaceutical composition according to claim 3 providing an NMDA receptor antagonist to a human or animal subject such that the NMDA receptor antagonist is in the range of from about 1 to 1000 mg
- 20 5 A pharmaceutical composition according to claim 3 providing an NMDA receptor antagonist to a human or animal subject such that the NMDA receptor antagonist is in the range of from about 100 to 800 mg
- 25 6 A pharmaceutical composition according to any one of claims 1-5 wherein an NMDA receptor antagonist in the immediate release form comprises 5% to 90% of the total weight of the NMDA receptor antagonist
- 7 A pharmaceutical composition according to claim 6 wherein the NMDA receptor antagonist in the immediate release form comprises 10%-80% of the total weight of the NMDA receptor antagonist

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- 8 A pharmaceutical composition according to claim 6 or 7 wherein the NMDA receptor antagonist in the immediate release form comprises 15%-50% of the total weight of the NMDA receptor antagonist
- 5 9 A pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject including an NMDA receptor antagonist in an immediate release form in a single dosage form combined with an NMDA receptor antagonist in a controlled released form
- 10 10 A pharmaceutical composition according to claim 9 wherein the controlled release is sustained release or delayed/modified release
- 11 A pharmaceutical according to claim 9 or 10 wherein the immediate release or sustained release form of the NMDA receptor antagonist are combined
- 15 in a single dosage form such that the amount of NMDA receptor antagonist in the composition is in the range of about 1 mg to 5000 mg
- 12 A pharmaceutical composition according to claim 11 wherein the amount of an NMDA receptor antagonist is in the range of 1 mg to 1000 mg
- 20 13 A pharmaceutical composition according to claim 11 wherein the amount of NMDA receptor antagonist in the range of 100 mg to 600 mg
- 14 A pharmaceutical composition according to any one of claims 9 to 13
- 25 wherein an NMDA receptor antagonist in the immediate release form comprises from 5 to 90% of the total weight of the NMDA receptor antagonist.
- 15 A pharmaceutical composition according to claim 14 wherein the NMDA receptor antagonist in the immediate release form comprises from 10 to 60% of
- 30 the total weight of the NMDA receptor antagonist

- 16 A pharmaceutical composition according to claim 14 wherein the NMDA receptor antagonist in the immediate release form comprises from 15 to 50% of the total weight of the NMDA receptor antagonist.
- 5 17 A pharmaceutical composition according to any one of claims 1 to 16 wherein a portion of the NMDA receptor antagonist is immediately released following administration and a portion is sustained released to provide therapeutic effect over a period of greater than 8 hours to provide a dosage interval of at least 1 to 2 times per day
- 10 18 A pharmaceutical composition according to claim 17 wherein the therapeutic effect is provided over a period of 8 to 24 hours
- 15 19 A pharmaceutical composition according to claim 17 wherein the therapeutic effect is provided over a period of 8 to 12 hours
- 20 20 A pharmaceutical composition according to claim 17 wherein the therapeutic effect is provided over a period of 12 to 24 hours
- 25 21 A pharmaceutical composition according to any one of claims 17 to 20 which exhibits more than one peak in a plasma concentration/time curve in any one dosage interval
- 30 22 A pharmaceutical composition according to any one of claims 1 to 21 wherein the NMDA receptor antagonist in the immediate release or controlled release form is the same or different
- 23 A pharmaceutical composition according to any one of claims 1 to 22 wherein the immediate release or controlled release form are in a form selected from the group including active cores comprising active, tablets, multi-layered tablets, capsules containing active cores, either coated or uncoated, liquids

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powder, granules or pellets, either coated or uncoated, suspensions, an injectable solution, a suppository, implant, transdermal patch or osmotic pump

24 A pharmaceutical composition according to claim 23 wherein the
5 immediate release and controlled release form of the NMDA receptor antagonist are separate components in a multi-layer tablet wherein one or more layers include the NMDA receptor antagonist in an immediate release form and one or more layers include the NMDA receptor antagonist in a controlled release form

10 25 A pharmaceutical composition according to claim 23 wherein the immediate release and controlled release forms of the NMDA receptor antagonist are dispersed throughout a tablet

15 26 A pharmaceutical composition according to claim 23 wherein the immediate release and controlled release form of the NMDA receptor antagonist are separate components in a capsule wherein one or more components include the NMDA receptor antagonist in an immediate release form and one or more components include the NMDA receptor antagonist in a controlled release form

20 27 A pharmaceutical composition according to claim 26 wherein one or more of the components are active cores or pellets and wherein the active cores are uncoated or coated for immediate or controlled release of the active and wherein the pellets are coated for controlled release of the active

25 28 A pharmaceutical composition according to claim 26 or 27 comprising a blend of cores and pellets wherein a ratio of cores to pellets is 25/75

29 A pharmaceutical composition according to any one of claims 1 to 28
30 including dextromethorphan or a salt thereof in a dosage form 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 22% and 33% (by weight) dextromethorphan released after 0.5 hour,

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between 24% and 36% (by weight) dextromethorphan released after 1 hour
between 28% and 42% (by weight) dextromethorphan released after 2 hours,
between 36% and 54% (by weight) dextromethorphan released after 4 hours,
between 44% and 68% (by weight) dextromethorphan released after 6 hours,
5 between 52% and 78% (by weight) dextromethorphan released after 8 hours,
between 68% and 100% (by weight) dextromethorphan released after 12 hours
and greater than 80% (by weight) dextromethorphan released after 16 hours

30 A pharmaceutical composition according to any one of claims 1 to 29
10 wherein the NMDA receptor antagonist is a morphinan selected from the group
including dextromethorphan and dextrophan, ketamine, amantadine, memantine,
eliprodil, fenpropidil, dizocilpine, remacemide, lamotrigine, riluzole, aptiganel,
phencyclidine, flupirtine, cefotol, felbamate, spermine, spermidine, levemopamil,
a pharmaceutically acceptable salt or ester thereof, or a metabolic precursor of
15 any of the foregoing

31 A pharmaceutical composition according to any one of claims 1 to 30
wherein the NMDA receptor antagonist is dextromethorphan (DM) or a
pharmaceutically acceptable salt

20

32 A pharmaceutical composition according to claim 31 wherein the NMDA
receptor antagonist is dextromethorphan hydrobromide

33 A pharmaceutical composition according to any one of claims 1 to 32
25 wherein the immediate release forms of the NMDA receptor antagonist are
particles of the antagonist or particles of the antagonist admixed with soluble
components selected from the group including sugars including sucrose, lactose,
fructose, mannitol, polymers including polyethylene glycol, hydroxypropyl
cellulose, hydroxypropyl methyl cellulose, surfactants including sodium lauryl
30 sulphate, chromophor, tweens, spans, pluronics, insoluble components including
microcrystalline cellulose, $\text{Ca}_3(\text{PO}_4)_2$, talc, aerosol, coating material including
polyethylene glycol, hydroxypropyl methyl cellulose, wax fatty acids, dispersins in

suitable material including wax, polymers, pharmaceutically acceptable oils, soluble agents or combinations thereof

34 A pharmaceutical composition according to any one of claims 1 to 33
5 wherein the controlled release form of the NMDA receptor antagonist is in a matrix composition selected from the group including waxes including carnauba, bees wax, paraffin wax, ceresine, shellac, fatty acids, fatty alcohols, oils, hardened oils or fats including hardened rapeseed oil, castor oil, beef tallow, palm oil, soya bean oil, insoluble matrix polymers including ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers, water soluble matrix materials including polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials including sugars including lactose, sucrose, fructose,
10 mannitol, salts including sodium chloride, potassium chloride, organic acids including fumaric acid, succinic acid, lactic acid, tartaric acid and mixtures thereof

35 A pharmaceutical composition according to claim 34 further including an enteric polymer selected from the group including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zcm, and polymethacrylates containing carboxyl groups or combinations thereof
20

36 A pharmaceutical composition according to any one of claims 1 to 35
25 wherein the composition further includes a binder selected from the group including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, ethyl cellulose, cellulose acetate butyrate, or enteric binding materials such as hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate or combinations thereof

30 37 A pharmaceutical composition according to any one of claims 1 to 36 wherein the immediate release or controlled release forms are coated with a pharmaceutically acceptable coating composition comprising ethyl cellulose,

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cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers, polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars
5 including lactose, sucrose, fructose and mannitol, salts including sodium chloride, potassium chloride and derivatives, organic acids including fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof, enteric polymers including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zern,
10 and polymethacrylates containing carboxyl groups

38 A pharmaceutical composition according to claim 37 wherein the coating composition includes a plasticiser from 0 to 50% by weight selected from the group including silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch,
15 powdered cellulose, MCC, polacrilin potassium, or any combination thereof

39 A pharmaceutical composition according to any one of claims 1 to 38 further including a filler comprising 0 to 200% w/w and selected from the group including silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered
20 cellulose, microcrystalline cellulose, polacrilin potassium, or any combination thereof

40 A pharmaceutical composition according to any one of claims 1 to 39 further comprising a swelling/gelling polymer selected from the group including
25 hydroxypropyl cellulose in the range 0-50% w/w or a hydrophobic material such as cetylalcohol in the range 10-90% w/w

41 A pharmaceutical composition according to any one of claims 1 to 40 in a form suitable for oral or rectal administration or for administration by transdermal,
30 intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular means

42 A method of preparing a pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject, the composition including an NMDA receptor antagonist in an immediate release form in association with an NMDA receptor antagonist in a controlled release form said
5 method including

providing a matrix or coated core containing an NMDA receptor antagonist to provide controlled release of a NMDA receptor antagonist,

providing a mixture containing a NMDA receptor antagonist to provide an immediate release of a NMDA receptor antagonist; and

10 combining the matrix or coated core with the mixture

43 A method according to claim 42 wherein the matrix core is a matrix composition selected from the group including waxes including carnauba, bees wax, paraffin wax, ceresine, shellac, fatty acids, fatty alcohols, oils, hardened oils
15 or fats including hardened rapeseed oil, castor oil, beef tallow, palm oil, soya bean oil, insoluble matrix polymers including ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers, water soluble matrix materials including polymers such as polyethylene glycol, hydroxypropyl
20 cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials including sugars including lactose, sucrose, fructose, mannitol, salts including sodium chloride, potassium chloride, organic acids including fumaric acid, succinic acid, lactic acid, tartaric acid and mixtures thereof

25 44 A method according to claim 42 wherein the coated core is a core of NMDA receptor antagonist coated with a pharmaceutically acceptable polymer including diffusion barrier polymers with or without porosity enhancers selected from the group including ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other
30 pharmaceutically acceptable polymers, polyethylene glycol hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone polyvinyl alcohol, and monomeric materials such as sugars including lactose, sucrose, fructose and

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mannitol, salts including sodium chloride, potassium chloride and derivatives, organic acids including fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof, enteric polymers including hydroxypropyl cellulose hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups

45 A method according to claim 42 wherein the core and the mixture are combined and compressed into a tablet form and wherein the core and the mixture are dispersed throughout the tablet form

46 A method according to claim 42 wherein the core and the mixture are combined and compressed into a tablet form such that the core and the mixture form a multilayer tablet form

15

47 A method according to claim 42 wherein the core and the mixture are combined into a capsule

48 A method for the therapeutic or prophylactic treatment of pain in a human or animal subject, the method including administering to the subject, a composition according to any one of claims 1 to 41

49 A method according to claim 48 for the treatment of chronic or acute pain

50 A method according to claim 48 for the pre-emptive treatment of pain

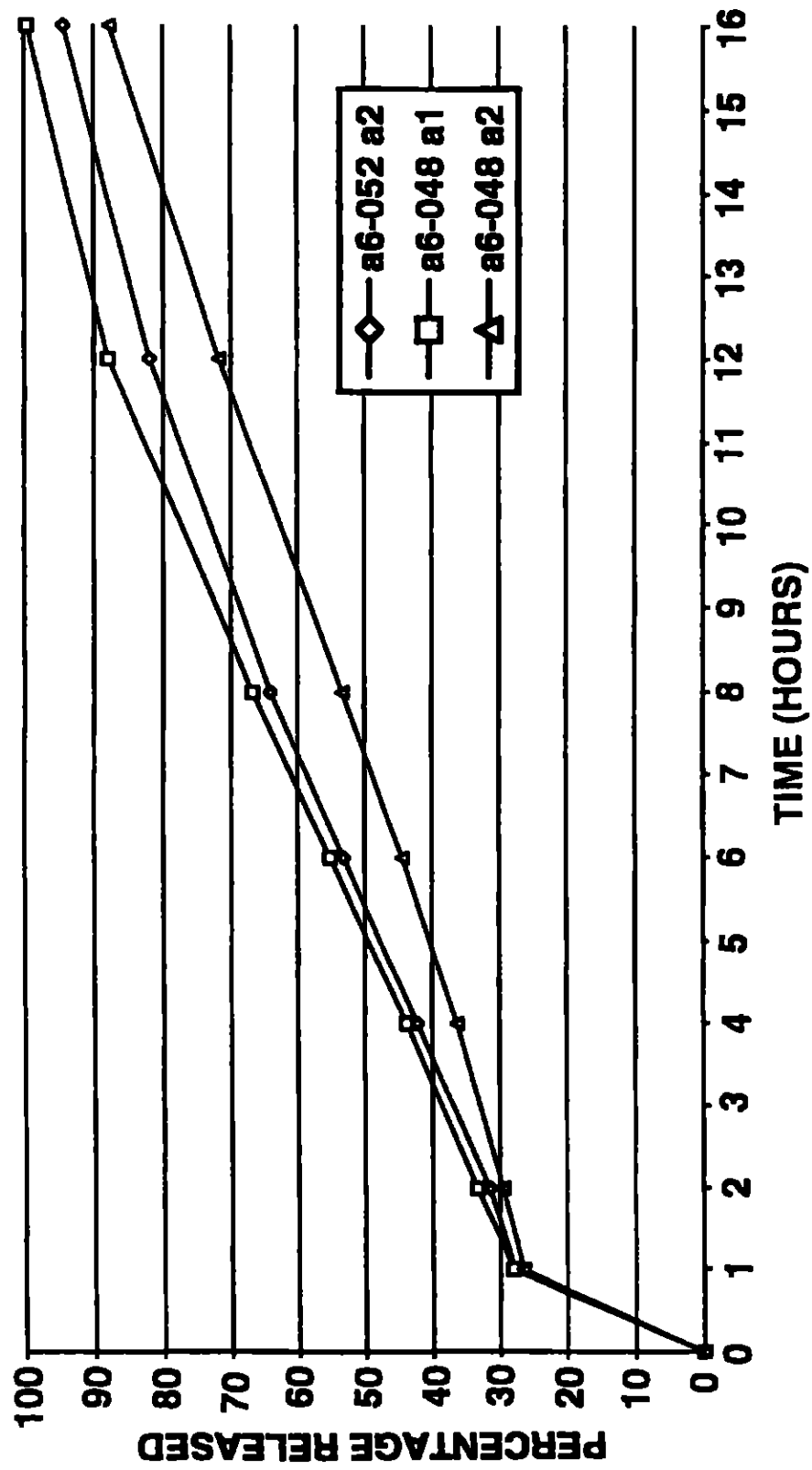
51 A method for the treatment of Huntington's disease amyotrophic lateral sclerosis (ALS), AIDS-related dementia, Alzheimer's disease schizophrenia, motoneurone diseases and CNS and brain injuries resulting from a number of causes including trauma, stroke and neurosurgery in a human or animal subject, the method including administering to the subject, a composition according to any one of claims 1 to 41

52 A kit including a plurality of unit dosage forms, in a container or the like, the container including indicia indicative of a dosage regimen, at least one of the unit dosages being in the form of a pharmaceutical composition according to any one of claims 1 to 41

53 A kit according to claim 52 further including instructions and unit dosage forms providing immediate release and controlled release of NMDA receptor antagonist

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00458

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl^B A61K 31/385

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

B. FIELDS SEARCHED

Maximum documentation searched (classification system followed by classification symbols)
A61K 31/385

Documentation searched other than maximum documentation to the extent that such documents are included in the fields searched
AU IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT, CA (Dextromethorphan, dextropropion, ketamine, amantadine, memantine, eliprodil, fenpropion, dexociprone, remacemide, lamotrigine, rilazole, aptiganel, phencyclidine, flupirtine, cefetol, faldapate, a pertane, spermidine, levamisole, OR NMDA) receptor (antagonist and (control)(release or sustain release)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US A 5238686 (EICHEL et al.) 24 August 1993 see table 1x-B col. 13	1-53
X	US A 5156842 (MULLIGAN et al.) 20 October 1992 see tables 6 and 8 in col. 9-10	1-53
X	US A 5084378 (MEHTA) 28 January 1992 see col. 4 line 63 - col. 5 line 5	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 "E" earlier document but published on or after the international filing date "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) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"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 "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 "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 "A" document member of the same patent family
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Date of the actual completion of the international search
20 December 1996

Date of mailing of the international search report

8 Jan 1997

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/AU 96/00658

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US A 4859462 (CHOW et al) 22 August 1989 see table 1 col.4	1-53
X	US A 4859461 (CHOW et al) 22 August 1989 see table 1 col 4	1-53
X	GB A 2189995 (ALZA CORPORATION) 11 November 1987 see whole document, esp. Example 13	1-53

International Application No
PCT/AU 96/00658

Thus Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
US	5238686	AU	70124/87	CA	1285482	DK	1537/87
		EP	239361	JP	62246513	NO	871243
		ZA	8702154	US	5238686		
US	5156842	CA	1314215	DK	3336/88	EP	295941
		JP	1016717	PH	24979	US	5156842
US	5084278						
US	4859461	AU	70989/87	CA	1283998	DK	3947/87
		EP	254811	FI	872582	IL	82223
		JP	63035527	NO	873031	NZ	219816
US	4859462	AU	72422/87	CA	1283497	DK	3948/87
		EP	254822	FI	872581	IL	82426
		JP	63035526	NO	873184	NZ	219925
		PH	23585	ZA	8703016	US	4859462
GB	2189995	US	4716496				

ANEXO 2



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ A61K 9/22	A2	(11) International Publication Number WO 98/47491 (43) International Publication Date: 29 October 1998 (29.10.98)
(21) International Application Number: PCT/CA98/00274 (22) International Filing Date: 3 April 1998 (03.04.98) (30) Priority Data 60/036,551 21 April 1997 (21.04.97) US (71)(72) Applicants and Inventors: ODIDI, Isa [NG/CA]; 2136 Opal Court, Mississauga, Ontario L5K 2S5 (CA). ODIDI, Amina [NG/CA] 2136 Opal Court, Mississauga, Ontario L5K 2S5 (CA). (74) Agent: BARTOSZEWICZ, Lois, A., Sun & McBurney, 6th floor 330 University Avenue, Toronto, Ontario M5G 1R7 (CA).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (OH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: CONTROLLED RELEASE FORMULATIONS USING INTELLIGENT POLYMERS		
(57) Abstract An extended release dosage composition of pharmaceutically active substances that have a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848 presented as a matrix tablet containing the said pharmaceutically active substances, with/without suitable pharmaceutical excipients in intimate mixture with two groups of intelligent polymers having opposing wettability characteristics, one demonstrating a stronger tendency towards hydrophobicity and the other a stronger tendency towards hydrophilicity the polymer combination being between the ratios of 1:50 and 50:1 amounts effective to control the release of said pharmaceutically active substances in a mathematically predictable manner, wherein the polymer demonstrating a stronger tendency towards hydrophobicity is not less than 5 % w/wt and preferably between 5-70 % w/wt of the final formulation composition. The intelligent polymers being ethylcellulose (EC) as a more strongly hydrophobic and hydroxyethylcellulose (HEC) and/or hydroxypropyl methylcellulose (HPMC) as more strongly hydrophilic (the ratio of HEC to HPMC being between 1:100 and 100:1). The matrix tablet is optionally coated with an enteric coat, 0-5 % - 15 % w/wt to prevent the initial burst effect seen in such systems and to impart gastrointestinal tract (GIT) "stealth" characteristics especially in the presence of food.		

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EE	Estonia						

Controlled Release Formulations Using Intelligent Polymers

5

Field of the Invention

The present invention is directed to novel controlled release formulations of pharmaceutically active substances and methods for their preparation. More particularly, the present invention relates to an easily absorbable, controlled release pharmaceutical formulation utilizing groups of intelligent polymers having opposing wettability characteristics.

Background of the Invention

Controlled release formulations of pharmaceutical agents is an extremely large market in the pharmaceutical and medical fields. A number of types of controlled release dosage forms are known, including matrix tablet systems incorporating active ingredients, fillers and various types of excipients. The very different properties of numerous different types of pharmaceutically active ingredients has necessitated the development of a number of different drug delivery systems utilizing polymer technology in order to provide an appropriate release of a particular medicament after oral ingestion by a patient.

U S Patents 4,601,894 and 4,687,757 describe a controlled release drug delivery system which contains hydroxypropyl cellulose (HPMC) and a second polymer such as ethylcellulose, methylcellulose, sodium carboxymethyl cellulose or other cellulose ethers. U S Patent 4,680,323 describes a carrier system comprising hydroxypropyl cellulose and a carboxy vinyl polymer. U S Patent 4,695,591 describes the use of HPMC for mediating controlled release of pharmaceutically active substances. U.S. Patent 4,994,276 teaches a free-flowing directly compressible granulation useful as a slow release pharmaceutical excipient. The excipient includes a hydrophilic matrix which includes a heteropolysaccharide and a polysaccharide material capable of cross-linking the heteropolysaccharide.

U S Patent 4,167,558 teaches a novel sustained release tableted formulation for oral administration. The formulation is hydrodynamically balanced to be buoyant in gastric juice thereby remaining in the stomach for an extended period of time. U S Patent 4,259,314 teaches a method and composition for the preparation of controlled long-acting pharmaceuticals using a dry carrier or base material comprising an effective amount of hydroxypropyl methylcellulose and hydroxypropyl cellulose.

suitable for use with both hygroscopic and non-hygroscopic materials. The controlled long-acting products of the invention are suitable for use in the form of lozenges, buccal tablets, oral tablets or suppositories.

U S Patent 4,308,251 teaches a tablet formulation comprising an effective amount of an active acidic therapeutic agent, a release-controlling agent and an erosion-promoting agent in relative amounts to provide a criticality factor of less than 450, and in proportions of release-controlling and erosion-promoting agent, respectively, between 0.8-1.6 and 1.0-7.5 weight percent per tablet. The tablets of this invention exhibit zero order release *in vitro* and closely approximate zero order absorption *in vivo*.

U S Patent No 4,361,545 teaches a class of solid pharmaceutical formulations which provides slow, zero order *in vivo* release of a wide range of pharmaceutically active ingredients upon oral administration. A broad range of release rates can be preselected by suitable adjustments of tablet properties. The formulations are based upon control of active ingredient release from the surface of the tablet via a controlled surface erosion mechanism.

U S Patent 4,389,393 teaches a carrier base material combined with a therapeutically active medicament and shaped and compressed to a solid unit dosage form having a regular and prolonged release pattern upon administration, the carrier base material being one or more hydroxypropylmethylcelluloses or a mixture of one or more hydroxypropylmethylcelluloses having a methoxy content of 16-24 weight%, a hydroxypropoxyl content of 4-32 weight% and an average molecular weight of at least 50,000.

U S Patent 4,525,345 teaches a constant release rate indomethacin formulation in tablet unit dosage form containing an admixture of from 50 to 200 mg of indomethacin, from about 1.7 to 3.7 weight percent of a slow-dissolving, water-insoluble cellulose derivative, from about 1.5 to 5.0 weight percent of a tableting disintegrant, and from about 40 to 80 weight percent of a pharmaceutically acceptable bulking agent or diluent.

U S Patent 4,556,678 teaches a tablet consisting essentially of a therapeutically effective amount of propranolol to provide a sustained release thereof over a prolonged period of time. The tablet comprises compressed granules having from about 0.1 to about 10 parts by weight hydroxypropyl methylcellulose and about one part by weight hydroxypropyl cellulose.

U S Patent 4,692,337 teaches a sustained release pharmaceutical tablet comprising theophylline and ethyl cellulose uniformly dispersed therein in an amount

of 5 to 200 parts by weight of ethyl cellulose based on 100 parts by weight of the theophylline

U S Patent 4,756,911 teaches a controlled release pharmaceutical formulation in the form of a coated tablet, containing a core portion from which medicament, such as procainamide hydrochloride, is slowly released over a controlled length of time. The core also includes one or more primary hydrocolloid gelling agents which is a hydropropylmethyl cellulose having a viscosity of within the range of from about 1,000 to about 6,000 centipoises in 2% solution at 20°C, a methoxyl content of 28-30% and optionally a secondary hydrocarbon gelling agent, such as hydroxypropyl cellulose and/or methyl cellulose.

U S Patent 5,073,380 teaches a pharmaceutical sustained release tablet containing a pharmaceutical active, hydroxyethyl cellulose, a wicking agent, povidone, pregelatinized starch, lubricant and a glidant

U S Patent 5,417,982 teaches a controlled release formulation for use with a variety of drugs or hormones in microspherical form. The drug or hormone, e.g. bovine somatotropine, is suspended in a polymer matrix formed from at least two highly water soluble biodegradable polymers. The microspheres are coated with a (δ,1 lactide-glycolide) copolymer

U S Patent 4,968,509 teaches an acetaminophen-sustained release tablet formed by making a wet granulation, using Povidone (PVP) in water or alcohol-water as the granulating fluid which is mixed with acetaminophen, hydroxyethyl cellulose, a wicking agent e.g. microcrystalline cellulose, then drying and milling the granulation and blending with dry powdered erosion promoter, e.g. pregelatinized starch, wicking agent, lubricant e.g. magnesium stearate and glidant e.g. silicon dioxide, and compressing the resultant granulation.

U S Patent 5,462,747 teaches a pharmaceutical sustained release homogeneous tablet formed by making a wet granulation using povidone (PVP) in alcohol as the granulating fluid mixed with a pharmaceutical active, ethylcellulose, a wicking agent, e.g. microcrystalline cellulose, an erosion promoter, e.g. pregelatinized starch, then drying and milling the granulation and blending with a dry powdered erosion promoter, wicking agent, lubricant and glidant

U S Patent 5,543,154 teaches a device for the controlled delivery of a beneficial agent as a gelatinous dispersion consisting of a core which contains a beneficial agent, a polymer which forms gelatinous microscopic particles upon hydration and if desired an agent to modulate the hydration of the polymer; and an impermeable, insoluble coating which adheres to and surrounds the core and contains apertures which provides an area for the hydration and release of a dispersion comprising gelatinous microscopic particles.

U S Patent No 5,439,687 teaches pharmaceutical dosage forms for the daily oral administration of nifedipine or of another calcium antagonist of the dihydropyridine type, characterised by the homogeneous matrix containing 2-50% by weight of hydroxypropylmethylcellulose having an average molecular weight of 20,000-250,000, 5-60% by weight of a calcium antagonist of the dihydropyridine type, as well as excipients compatible with the formulation.

U S Patent 5,264,446 teaches a solid pharmaceutical composition of nifedipine crystals having specific surface area of 1-4 m²/g in the form of tablets, pills, drages, capsules, suppositories, sachets or two layer tablets resulting in sustained release

While these systems can provide for sustained release of a selected active ingredient, most of these systems have the disadvantage of being affected by the presence of food and gastrointestinal enzymes in the gastrointestinal (GI) tract. Therefore, the active ingredient is often not delivered in a consistent and reproducible manner. In addition, osmotic and press coated tablets are particularly difficult and expensive to manufacture

It is therefore particularly desirable to design an efficient drug delivery system that is capable of controlled drug delivery of both high dose, highly soluble, hydrophilic and low dose, poorly soluble, hydrophobic pharmaceutically active substance(s) into the gastrointestinal tract (GIT) in order to provide sustained therapeutic effects for over 24 hours with only a single dose and without any food effect. It is also highly desirable to develop a drug delivery system that is relatively easy and inexpensive to manufacture and more efficient in providing a sustained release of pharmaceutical agents than the known controlled delivery systems.

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Summary of the Invention

An object of the present invention is to provide a novel controlled sustained release delivery composition which may contain a wide variety of pharmaceutically active ingredients and which demonstrates good absorbability of the selected active ingredient and a maintenance of the therapeutically effective blood level of the pharmaceutically active ingredient for a long duration of time by one time administration. This novel controlled release composition and system has been named IntelliGITransporter™

According to an object of the present invention there is provided a novel controlled release delivery composition comprising at least one selected pharmaceutically active ingredient incorporated within a homogeneous matrix comprising effective amounts of two intelligent polymers having opposing wettability characteristics, wherein one polymer is selected which demonstrates a stronger

tendency towards hydrophobicity and the other polymer is selected which demonstrates a stronger tendency towards hydrophilicity

Preferably, the active pharmaceutical ingredient selected has a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848. Also, preferably the intelligent polymer demonstrating a stronger tendency towards hydrophobicity is ethylcellulose (EC) whereas the intelligent polymer demonstrating a stronger tendency towards hydrophilicity is hydroxyethylcellulose (HEC) and/or hydroxypropyl methylcellulose (HPMC)

It is still further objective of the present invention to provide a controlled release delivery composition wherein the selection of the pharmaceutically active ingredient, the physicochemical properties, the proportion of polymer blend and the wettability of the pharmaceutically active substance(s) provides effective controlled release of the pharmaceutically active substance(s)

It is yet a further object of the present invention to provide an effective drug delivery composition that is capable of controlled drug delivery of both high dose, highly soluble hydrophilic or low dose poorly soluble hydrophobic pharmaceutically active substance(s) to the gastrointestinal tract with a zero or first order kinetics

In accordance with a further object of the present invention is a device for providing a controlled release of a pharmaceutically active ingredient contained therein, the device comprising at least one selected pharmaceutically active ingredient incorporated within a homogeneous matrix comprising effective amounts of two intelligent polymers having opposing wettability characteristics, wherein one polymer is selected which demonstrates a stronger tendency towards hydrophobicity and the other polymer is selected which demonstrates a stronger tendency towards hydrophilicity

The composition and device of the present invention can be provided as a tablet and may be optionally encased in a coating material which prevents the burst and/or food effect associated with orally ingested medicaments and imparts gastrointestinal stealth characteristics. The coated matrix providing controlled release kinetics comparable to those of osmotic or press coated controlled release devices. The composition may be provided for oral administration or as a suppository depending on the chosen pharmaceutical active agent selected therein.

It is yet a further objective of the present invention to provide a controlled release drug delivery system for the effective delivery of one or more of the following pharmaceutically active ingredients: nifedipine, nicardipine, felodipine, captopril, naproxen, diclofenac, terfenadine, pentoxifylline, fenofibrate, glipizide, buspirone, cisapride, verapamil, diltiazem, aciclovir, zidovudine, pilocarpine, moclobemide, lamotrigine, risperidone, clonazepam, nefazodone, lovastatin, simvastatin, pravachol,

ketorolac, hydromorphone, morphine, ticlopidine, seligiline, venlafaxine, alprazolam, carbamazepine, divalproex and phenytoin

It is also a further objective of the present invention to provide controlled delivery of therapeutic agents selected from the group consisting of anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arthritis, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, hypoglycemic agents, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infectives, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diabetes agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors and vertigo agents, acetaminophen, acetic acid, acetylsalicylic acid, buffered acetylsalicylic acid, albuterol, albuterol sulfate, ethanol isopropanol, allantoin, aloe, aluminum acetate, aluminum carbonate, aluminum chlorohydrate, aluminum hydroxide, alproazolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoylperoxide, biotin, bisacodyl, bornyl acetate, brompheniramine maleate, bupropion, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, cefaclor, cefadroxil, cephalixin, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorcyclizine hydrochloride, chlorhexidine gluconate, chloroxylenol, chloropentostatm, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine hydrochloride, citalopram, citric acid, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, clorfibrate, ciprofloxacin HCl, cyanocobalamin, cyclizine hydrochloride, danthron, dexbrompheniramine maleate, dextromethorphan hydrobromide, diazepam, dibucaine diclofenac sodium, digoxin, dimethicone, dioxybenzone, diphenhydramine citrate, diphenhydramine hydrochloride, docusate calcium, docusate potassium, docusate sodium, doxycycline hyclate, doxylamine succinate, efavoxan, enalapril, enoxacin, erythromycin, estropipate, ethinyl estradiol, ephedrine, epinephrine bitartrate, erythropoietin, eucalyptol, ferrous fumarate, ferrous gluconate, ferrous sulfate, folic acid,

fosphenytoin, fluoxetine HCl, furosemide, gaba entan gentamicin, gemfibrozil,
 glipizide, glycerin, glyceryl stearate, gnaseofulvin, guaifenesin, hexylresorcinol,
 hydrochlorothiazide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate,
 8-hydroxyquinotone sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac,
 5 iron, isoxicam, ketamine, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine
 hydrochloride, lifinopril, liotrix, lovastatin, magnesium carbonate, magnesium
 salicylate, magnesium trisilicate, mefenamic acid, meclofenamic acid, meclofenamate
 sodium, medroxyprogesterone acetate, methenamine mandelate, menthol, mependine
 hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate,
 10 methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride,
 metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen
 sodium, neomycin sulfate, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin,
 nonoxynol-9, norethindone, norethindone acetate, nystatin, octoxynol, octyl dimethyl
 PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omeprazole,
 15 oxolinic acid, oxybenzone, oxtriphylline, para-aminobenzoic acid (PABA), padimate,
 paramethadione, pentastatin, peppermint oil, pentaerythritol tetranitrate, pentobarbital
 sodium, pheniramine maleate, phenobarbital, phenol, phenolphthalein, phenylephrine
 hydrochloride, phenylpropanolamine, phenylpropanolamine, hydrochloride,
 phenytoin, phenelzine, sulfate, pirmenol, piroxicam, polymycin B sulfate, potassium
 20 chloride, potassium nitrate, prazepam, procainamide hydrochloride, procaterol,
 propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetin, pramoxine,
 pramoxine hydrochloride, propranolol HCl, pseudoephedrine hydrochloride,
 pseudoephedrine sulfate, pyridoxine, quinapril, quinidine gluconate, quinesol
 ralitoline, ramitadine, resorcinol, riboflavin, salicylic acid, sesame oil, shark liver oil,
 25 simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium
 monofluorophosphate, sulfanethoxazole, sulfur, tacrine, tacrine HCl, theophylline,
 tramadol, terfenadine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin,
 tetracycline hydrochloride, tolmetin, tolnaftate, triclosan, triprolidine hydrochloride,
 undecylenic acid, vancomycin, vidarabine phosphate, vitamin A, vitamin B, vitamin
 30 C, vitamin D, vitamin E, vitamin K, witch hazel, xylometazoline hydrochloride, zinc,
 zinc sulfate, and zincundecylenate.

In accordance with another aspect of the present invention is a method for
 preparing a device for the controlled release of selected pharmaceutically active
 ingredients, the method comprising blending at least one selected pharmaceutically
 35 active substance having a water contact angle (θ) such that $\cos \theta$ is between +0.9848
 and -0.9848 with about 5 to 25% by weight hydrophilic polymer and about 1 to 25%
 hydrophobic polymer, adding suitable pharmaceutical excipients, surface active
 agents and lubricants, granulating the mixture with isopropyl alcohol, drying the

granular mixture, milling the dried mixture, adding about 5 to 70% ethylcellulose, adding a lubricant and optionally a glidant and compressing the granules into tablets. The tablets are optionally encased in a gastrointestinal stealth encasement or a pharmaceutically acceptable film coat.

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Detailed Description of the Preferred Embodiments

The present invention provides a composition which provides controlled sustained release of pharmaceutically active ingredients and demonstrates stealth characteristics. The composition of the present invention provides a pseudo first order, first order or zero order release of pharmaceutically active substances that have a water contact angle (θ) such that $\cos \theta$ is between +0.9948 and -0.9848. The composition may be presented as a matrix tablet in which the pharmaceutically active ingredients are intimately mixed with two groups of intelligent polymers having opposing wettability characteristics, one demonstrating a stronger tendency towards hydrophobicity for example ethylcellulose (EC) and the other possessing a stronger tendency towards hydrophilicity, for example ethoxyethylcellulose (HEC) or hydroxypropyl methylcellulose (HPMC). The composition can be made with suitable pharmaceutically acceptable excipients, suitable surface active agents, lubricants, channeling agents and compression enhancers.

The amount of ethylcellulose in the composition should not be less than about 5% wt/wt, and preferably, is about 5% to about 70% wt/wt of the final formulation. The HEC and HPMC are present in a ratio of about 1:100 to about 100:1, the preferred ratio being from about 1:50 to about 50:1. Together, the intelligent polymers provide a homogeneous matrix for the pharmaceutically active ingredient and have the following single and three-component calculated solubility parameters ($\text{MPa}^{0.5}$) using the group contribution method.

Wettability of polymer	δ	δ_t	δ_d	δ_p	δ_h	δ_a
More hydrophilic	18-50	18-45	12-17	2-8	12-20	13-20
More hydrophobic	15-25	14-24	12-17	2-7	5-15	6-13

Where δ is the conventional Hildebrand parameter, t = total, d = dispersion, p = polar, h = hydrogen bond and a = association interactions.

Preferred excipients for use in the compositions of the present invention include glidants such as silicon dioxide which may be present in an amount of about 0.25% to 5% wt/wt. Suitable surface active agents may be present in the amount of about 0.5% to 15% wt/wt and include sodium lauryl sulfate. Channeling agents may be present in an amount of about 10% to 70% wt/wt and include anhydrous lactose. Suitable lubricants for use in the composition are present in an amount of about 0.1% to 5% and include magnesium stearate. An optional compression enhancer may be present in an amount of

ANEXO 1

about 5% to 30% wt/wt and includes microcrystalline cellulose. Although the preferred excipients, surface active agents, lubricants, channeling agents, and compression enhancers are listed herein, it is understood by those skilled in the art that other suitable excipients, surface active agents, lubricants, channeling agents, and compression enhancers may also be used in the present invention. One skilled in the art would clearly understand the different types of excipients, surface active agents, channeling agents, and compression enhancers suitable for use in the present invention.

The pharmaceutically active ingredients are selected from those substances that have a water contact angle (θ) such that $\cos \theta$ is between +0.9948 and -0.9848. The composition may contain one or more such active ingredients in an amount to provide therapeutically effective dosages. The pharmaceutically active ingredients may be selected from but are not limited to nifedipine, nifedipine, felodipine, captopril, naproxen, diclofenac, terfenadine, pentoxifylline, fenofibrate, glipizide, buspirone, cisapride, verapamil, diltiazem, aciclovir, zidovudine, pilocarpine, moclobemide, lamotrigine, risperidone, clonazepam, nefazodone, lovastatin, simvastatin, pravachol, ketorolac, hydromorphone, morphine, ticlopidine, seligiline, venlafaxine, alprazolam, carbamazepine, divalproex and phenytoin.

A most preferred pharmaceutically active ingredient is nifedipine which provides coronary vasodilating and hypotensive effects. As this medicament is hardly water soluble, has little absorbability in body fluids and is rapidly metabolized and excreted, it is highly advantageous to provide nifedipine in the controlled release composition of the present invention. Also, most preferred as pharmaceutically active ingredients are glipizide and diltiazem, verapamil, buspirone, tramadol and bupropion hydrochlorides.

Not to be bound by any theory, it is believed that the release of the pharmaceutically active ingredient within the present composition is provided due to the unique mixture of the rate controlling constituents and excipients in the selected ratios. When the composition is used as a matrix tablet, the solid nifedipine dissolves from the outer surface of the matrix tablet first. When this surface becomes exhausted of nifedipine, the underlying material begins to be depleted by dissolution and diffusion through the matrix to the external solution. During dissolution, some of the rate controlling constituents (the polymer blend) have a tendency towards swelling and thus act as a focus for cleavage or erosion of the matrix tablet. This leads to a cleavage of discrete amounts of nifedipine in combination with the rest of the excipients in the composition at the point of contact or interface between the rate controlling constituents and the other ingredients. In this manner, the interface between the region containing dissolved nifedipine and that containing dispersed nifedipine recedes into the interior as a front. As the cleavage occurs, the nifedipine

is readily absorbed. The release rate becomes smaller towards the end of dissolution due to a reduction in volume of the tablet.

When the composition is made and encased in coating material, the release of nifedipine is due to the encasement coat surrounding the homogeneous matrix tablet and the unique mixture of the rate controlling constituents and excipients in carefully selected ratios within the matrix tablet. Stepwise ionization of the surface groups of the encasement coat triggered by the pH of the surrounding media and the resulting gradual dissolution of the encasement coat over time exposes the matrix tablet to the fluids of the GI system. The solid nifedipine when in contact with the fluids of the GI system dissolves from the outer surface of the matrix tablet first. When this surface becomes exhausted of nifedipine, or other selected pharmaceutically active agent, the underlying material begins to be depleted by dissolution and diffusion through the matrix to the external solution.

The present composition provides controlled release of pharmaceutically active ingredient over an extended period of time (up to at least 20 hours) with minimal initial dumping effects, such that the active ingredient is still being released from the composition 20 hours later.

Furthermore, therapeutic agents may also be used in the composition of the present invention and are selected from the group consisting of anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arthritis, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, hypoglycemic agents, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infectives, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diabetes agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors and vertigo agents, acetaminophen, acetic acid, acetylsalicylic acid, buffered acetylsalicylic acid, albuterol, albuterol sulfate, ethanol isopropanol, allantoin, aloe, aluminum acetate, aluminum carbonate, aluminum chlorohydrate, aluminum hydroxide, alproazolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoylperoxide, biotin, bisacodyl, bornyl

acetate, brompheniramine maleate, buspirone, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, cefaclor, cefadroxil, cephalexin, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorcyclizine hydrochloride, chlorhexidine gluconate, chloroxylenol, chloropentostatin, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine hydrochloride, citalopram, citric acid, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, cloribrate, ciprofloxacin HCl, cyanocobalamin, cyclizine hydrochloride, danthron, dexbrompheniramine maleate, dextromethorphan hydrobromide, diazepam, dibucaine, diclofenac sodium, digoxin, dimethicone, dioxybenzone, diphenhydramine citrate, diphenhydramine hydrochloride, docusate calcium, docusate potassium, docusate sodium, doxycycline hyclate, doxylamine succinate, efavoxan, enalapril, enoxacin, erythromycin, estropipate, ethinyl estradiol, ephedrine, epinephrine bitartrate, eucalyptol, ferrous fumarate, ferrous gluconate, ferrous sulfate, folic acid, fosphenytoin, fluoxetine HCl, furosemide, gabapentin, gentamicin, gemfibrozil, glipizide, glycerin, glyceryl stearate, griseofulvin, guaifenesin, hexylresorcinol, hydrochlorothiazide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate, 8-hydroxyquinoline sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, ketamine, kolin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lisinopril, liotrix, lovastatin, magnesium carbonate, magnesium salicylate, magnesium trisilicate, mefenamic acid, meclofenamic acid, meclofenamate sodium, medroxyprogesterone acetate, methenamine mandelate, menthol, meperidine hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen sodium, neomycin sulfate, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxonyl-9, norethindone, norethindone acetate, nystatin, octoxynol, octyl dimethyl PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omeprazole, oxolinic acid, oxybenzone, oxtriphylline, para-aminobenzoic acid (PABA), padimate, paramethadione, pentastatin, peppermint oil, pentaerythritol tetranitrate, pentobarbital sodium, pheniramine maleate, phenobarbital, phenol, phenolphthalein, phenylephrine hydrochloride, phenylpropanolamine, phenylpropanolamine hydrochloride, phenytoin, phenelzine, sulfate, pirfenol, piroxicam, polymyxin B sulfate, potassium chloride, potassium nitrate, prazepam, procainamide hydrochloride, procaterol, propoxyphene, propoxyphene HCl, propoxyphene napsylate, pramiracetam, pramoxine, pramoxine hydrochloride, propranolol HCl, pseudoephedrine hydrochloride, pseudoephedrine sulfate, pyridoxine, quinapril, quinidine gluconate, quincestrol, raltitoline, ranitidine,

resorcinol, riboflavin, salicylic acid, sesame oil, shark liver oil, simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium monofluorophosphate, sulfamethoxazole, sulfur, tacrine, tacrine HCl, theophylline, terfenadine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin, tetracycline hydrochloride, 5 tolmetin, tolnaftate, triclosan, triprolidine hydrochloride, undecylenic acid, vancomycin, vidarabine phosphate, vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, vitamin K, witch hazel, xylometazoline hydrochloride, zinc, zinc sulfate, and zincundecylenate

The compositions of the invention may be formulated in a tablet form or as a 10 suppository. For both formulations, a coating composition can be optionally applied. Such a coating composition comprises anionic copolymers based on methacrylic acid and methyl methacrylate and are provided in an amount sufficient to obtain 0.5 to 15 mg per cm² on the tablet or suppository. This encasement coat, 0.5% - 15% wt/wt, acts to 15 minimize the initial burst effect seen in administered tableted compositions and also imparts gastrointestinal tract (GIT) "stealth" characteristics especially in the presence of food.

The present invention also provides a method for the manufacture of the novel controlled release pharmaceutical compositions in which the order and rate of drug 20 release is dependant on the physicochemical properties and proportion of polymer blend and the wettability of the pharmaceutically active substance(s) such that sustained release effects are obtained therapeutically.

In a preferred embodiment, a two step granulation technique is used to prepare a desired controlled release device containing at least one selected active ingredient. The method comprises intragranulation by wet granulation and extragranulation by 25 dry granulation. In the intragranulation process the pharmaceutically active substance is blended with about 5-25% hydroxypropyl methylcellulose (preferably METHOCEL® premium grade type K4M PREM), about 1-20% hydroxyethylcellulose (preferably NATROSOL® 250HHX), together with suitable pharmaceutical excipients such as glidants e.g., silicone dioxide about (0.25-5%), surface active agents e.g., sodium 30 lauryl sulfate about (0.5-15%), channelling agents such as anhydrous lactose about (10-70%) and optionally a compression enhancer e.g., microcrystalline cellulose, AVICEL® 101 about (5-30%) until a homogeneous mixture is obtained. Blending can be done in a V-blender but preferably in a planetary or high shear mixer. The homogeneous blend is then granulated with isopropyl alcohol (99%) in a planetary or 35 high shear mixer. It is preferred that the granulating solvent is a non aqueous solvent.

The wet granules are dried in a fluid bed or in tray dryers to a loss on drying of <3% and organic volatile impurities of isopropyl alcohol about <15000 ppm. The dry

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granules are milled to about < 1500 microns using a cone mill. Thereafter the extragranular addition of 5-70% of ethylcellulose having 30-60% ethoxyl content and viscosity 60- 100 cps (preferably ETHOCEL™ type N100) to the dry milled granules is undertaken in a V-blender until a homogeneous blend is obtained. To this blend may be added a glidant preferably talc and a lubricant preferably magnesium stearate. This final mixture is intimately blended and compressed into a matrix tablet using a rotary tablet press.

The matrix tablet can be used as is if no stealth characteristics are required. Under certain circumstances and for certain drugs, GIT stealth characteristics are desirable, e.g., in situations where dose dumping, burst or food effects are to be avoided. Stealth characteristics can be obtained by encasing the matrix tablet in a special coat composition consisting of anionic copolymer(s) based on methacrylic acid and methyl methacrylate. The preferred copolymers are the type A and/or Type B. This special composition may contain one or more of the following, plasticiser about (0-25%), pigment about (0-25%), glidant about (0-30%), lubricant about (0-30%). The values of dry polymer(s) encasing the matrix tablet in mg per cm² of surface area of tablet is about 0.5-15 mg per cm². This special stealth encasement may be applied using a fluid bed or a conventional coating pan. It is preferable to use a side vented perforated coating pan in order to obtain a more uniform and efficient encasement. The coating composition may be aqueous based, however, a solvent based composition is preferred.

EXAMPLES

The examples are described for the purposes of illustration and are not intended to limit the scope of the invention.

- 5 Methods of synthetic chemistry, and pharmacology referred to but not explicitly described in this disclosure and examples are reported in the scientific literature and are well known to those skilled in the art

Example 1 - Glipizide ER 5 mg

	<u>% composition</u>
10 Glipizide	1 83
Hydroxypropyl methylcellulose	20
Ethylcellulose	16 17
Hvdroxyethylcellulose	4
Lactose	30
15 Microcrystalline cellulose	23
Silicone dioxide	0 6
Sodium Lauryl sulfate	4
Magnesium stearate	0 4

Example 2 - Diltiazem hydrochloride ER 60 mg

	<u>% composition</u>
Diltiazem hydrochloride	58 82
Hydroxypropyl methylcellulose	5
Ethylcellulose	5
25 Hydroxyethylcellulose	15
Lactose	5
Microcrystalline cellulose	9 18
Talc	1
Magnesium stearate	1

Example 3 - Nifedipine ER 60 mg

	<u>% composition</u>
Nifedipine	20
5 Hydroxypropyl methylcellulose	20
Ethylcellulose	29
Hydroxyethylcellulose	3.8
Lactose	14
Microcrystalline cellulose	10
10 Silicone dioxide	1.2
Na lauryl sulfate	1
Magnesium stearate	1

Example 4 - Verapamil hydrochloride ER 60 mg

	<u>% composition</u>
15 Verapamil HCl	50
Hydroxypropyl methylcellulose	10
Ethylcellulose	5
Hydroxyethylcellulose	8
20 Lactose	16
Microcrystalline cellulose	10
Magnesium stearate	1

Example 5 - Diltiazem hydrochloride/Hydrochlorothiazide ER 60/12.5 mg

	<u>% composition</u>
25 Diltiazem hydrochloride	48
Hydrochlorothiazide	10
Hydroxypropyl methylcellulose	5.82
30 Ethylcellulose	5
Hydroxyethylcellulose	15
Lactose	5
Microcrystalline cellulose	9.18
Talc	1
35 Magnesium stearate	1

Example 6 - Manufacturing method and composition of GIT "stealth" encasement

	<u>% composition</u>
Methacrylic acid copolymer type A/B	12
5 PEG 600	2
water	5
Talc	8
Titanium dioxide	5
Pigment	8
10 Ethanol	60

Eudragit L/S was added to ethanol using a silverson high shear mixer (solution A) Secondly, PEG 600 was added to water using a propeller stirrer (solution B) Talc, pigment and titanium dioxide were added to ethanol (suspension C) using a propeller mixer Solution B was added into suspension C and mixed vigorously This mixture was then added to solution A under high shear mixing conditions to obtain the GIT "stealth" encasement.

Example 7 - Bupropion ER

	<u>% composition</u>
20 Bupropion	39
Hydroxypropyl methylcellulose	35
Ethylcellulose	5
Hydroxyethylcellulose	5
25 Lactose	10
Microcrystalline cellulose	5
Silicone dioxide	0.6
Caprylocaproyl or oleoyl or linoleoyl macrogolglycerides	5
30 Magnesium stearate	0.4

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Example 8 - Buspirone hydrochloride ER 20 mg

	<u>% composition</u>
Buspirone HCl	5
5 Hydroxypropyl methylcellulose	35
Ethylcellulose	6
Hydroxyethylcellulose	15
Lactose	30
Microcrystalline cellulose	8
10 Magnesium stearate	1

Example 9 - Tramadol hydrochloride ER 200 mg

	<u>% composition</u>
Tramadol hydrochloride	37
15 Hydroxypropyl methylcellulose	33
Ethylcellulose	5
Hydroxyethylcellulose	5
Lactose	10
Microcrystalline cellulose	8
20 Magnesium stearate	1
Talc	1

25 Although preferred embodiments have been described herein in detail, it is understood by those skilled in the art that variations may be made thereto without departing from the scope of the invention or the spirit of the appended claims

We Claim

- 1 A controlled release pharmaceutical composition comprising
(a) at least one pharmaceutically active substance having a water contact
angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848
- 5 (b) a first intelligent polymer component, and
(c) a second intelligent polymer component having opposite wettability
characteristics to said first intelligent polymer component, the first and second
polymer components being present in a ratio in the range of about 1:100 to about
100:1 by weight, the polymer components being effective for controlled release of
10 said pharmaceutically active substance from said composition.
- 2 The composition of claim 1, wherein the first intelligent polymer component is
more hydrophobic than the second intelligent polymer component
- 15 3 The composition of claim 2, wherein the first intelligent polymer component is
present in an amount not less than 5% by weight
- 4 The composition of any of claims 1 to 3 wherein the first intelligent polymer
component is ethylcellulose and the second intelligent polymer component is a
20 mixture of hydroxyethyl cellulose and hydroxypropyl methyl cellulose
- 5 The composition of any of claims 1 to 4 further comprising at least one
pharmaceutically acceptable excipient
- 25 6 The composition of claim 5, wherein the excipient comprises 0.25% to 5% by
weight of the composition
- 7 The composition of claim 4, wherein the at least one excipient is silicon
dioxide
- 30 8 The composition of any one of claims 1 to 7, wherein said composition further
comprises 0.5% to 15% by weight of at least one surface active agent.
- 9 The composition of claim 8, wherein said surface active agent is sodium lauryl
35 sulfate
- 10 The composition of claim 1, wherein said composition further comprises 10%
to 70% by weight channeling agents

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- 11 The composition of claim 10, wherein said channeling agent is anhydrous lactose.
- 5 12 The composition of claim 1, wherein said composition further comprises 5% to 30% compression enhancer
- 13 The composition of claim 10, wherein said compression enhancer is microcrystalline cellulose
- 10 14 A controlled release pharmaceutical composition comprising
- (a) from about 0.5% to about 70% of a pharmaceutically active substance having a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848,
- (b) not less than about 5% wt/wt ethylcellulose,
- 15 (c) about 1:100 to 100:1 hydroxycellulose and hydroxypropyl methyl cellulose,
- (d) about 0.25% to 5% excipients, and
- (e) about 0.5% to 15% surface active agents
- 20 15 The composition of claim 14, wherein said composition additionally comprises
- about 10% to 70% channeling agents, and
- about 5% to 30% compression enhancers
- 25 16 The composition as claimed in any one of claims 1 to 15, made in the form of a compressed tablet.
- 17 The tableted composition of claim 16, wherein said tableted composition has a anionic copolymer coating
- 30 18 The tableted composition of claim 17, wherein said copolymer coating comprises methacrylic acid and methyl methacrylate, from about 0% to 25% plasticizer, from about 0% to 25% pigment, from about 0% to 30% glidant and from about 0% to 30% lubricant
- 35 19 A controlled release composition, the composition comprising a therapeutically effective amount of a pharmaceutically active ingredient having a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848, two groups of

intelligent polymers having opposing wettability characteristics, one group demonstrating a stronger tendency towards hydrophobicity and present in an amount not less than 5% wt/wt and the other group having a stronger tendency towards hydrophilicity and present in the ratio of about 1:100 and 100:1, the polymers being
5 ethylcellulose (EC) as a more strongly hydrophobic and hydroxyethylcellulose (HEC) and hydroxypropyl methylcellulose (HPMC) as more strongly hydrophilic, about 0.25% to 5% silicon dioxide, and about 0.5% to 15% sodium lauryl sulfate.

20 The composition of claim 19, wherein said composition additionally
10 comprises about 10% to 70% anhydrous lactose and about 5% to 30% microcrystalline cellulose

21 The composition of claim 18 or 20, wherein said composition is provided as a
15 tablet and has a coating composition comprising anionic copolymers sufficient to obtain about 0.5 to 15 mg per cm² of tablet.

22 The composition of claim 21, wherein said coating composition additionally
comprises from about 0 to 25% plasticizer, about 0 to 25% pigment, about 0 to 30%
and about 0 to 30% lubricant

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23 A process for the manufacture of a sustained release composition of
pharmaceutically active substance, said process comprising

(a) admixing a pharmaceutically active substance having a water contact angle
(θ) such that $\cos \theta$ is between +0.9848 and -0.9848

25 (b) blending the pharmaceutically active ingredient with about 5 to 25%
hydroxypropyl methylcellulose, about 1 to 25% hydroxyethylcellulose, about 0.25%
to 5% suitable pharmaceutical excipients, about 0.5% to 15% suitable surface active
agents, and about 10% to 70% channelling agents in a high shear mixer until a
homogeneous mixture is obtained,

30 (c) granulating the homogeneous blend with isopropyl alcohol (99%) in a
planetary or high shear mixer,

(d) drying the wet granules to a loss on drying of about <3% and organic
volatile impurities of isopropyl alcohol about <15000 ppm,

(e) milling the dry granules to about <1500 microns,

35 (f) adding and blending about 5% to 70% of ethylcellulose having 30-60%
ethoxyl content and a viscosity of 60-100 cps to the dry milled granules until a
homogeneous blend is obtained,

- (g) adding and intimately mixing a lubricant, preferably magnesium stearate and optionally a glidant preferably talc and optionally a compression enhancer;
- (h) compressing the lubricated granules into tablets having a hardness of 5-30 Strong Cobb units and a moisture content of about <5% with a rotary tablet press, and
- 5 (i) optionally encasing the matrix tablet in a GIT "stealth" encasement or a pharmaceutically acceptable film coat

24 The process according to claim 23, wherein said "stealth" encasement comprises anionic copolymer(s) of methacrylic acid and methyl methacrylate and one
10 or more of the following, plasticiser (about 0-25%), titanium dioxide (about 0-25%), pigment (about 0-25%), glidant (about 0-30%), and lubricant (about 0-30%)

25 A process for preparing a "stealth" encasement, said process comprising preparing a first solution of methacrylic acid copolymer type A and/or type B in
15 ethanol, preparing a second solution of PEG 600 in water, adding talc, pigment and titanium dioxide to the first solution and then incorporating the second solution and mixing vigorously under high shear mixing conditions

26 The composition of claim 1, wherein said pharmaceutically active substance
20 is nifedipine having a specific surface area of <0.5 M²/gram or >6 m²/gram

27 The composition of claim 1, wherein the composition is provided as a tablet which demonstrates the following cumulative percent release dissolution criteria using a pH gradient method of dissolution, 0-40% released in 1 hour in dissolution media of
25 pH 1.5, 0-50% released in 2 hours in dissolution media of pH 4.5, 5-70% released in 2 hours in dissolution media of pH 6.5, 20-100% released in 15 hours in dissolution media of pH 7.5

28 The composition of claim 1, wherein the pharmaceutically active substance is
30 selected from the group consisting of glipizide, diltiazem hydrochloride, bupropion, buspirone hydrochloride, Tramadol hydrochloride and verapamil HCl

29 The composition of claim 1, wherein the pharmaceutically active substance is selected from the group consisting of nifedipine, felodipine, captopril, naproxen,
35 diclofenac, terfenadine, pentoxifylline, fenofibrate, glipizide, buspirone, cisapride, verapamil, diltiazem, aciclovir, zidovudine, pilocarpine, moclobemide, lamotrigine, risperidone, clonazepam, nefazodone, lovastatin, simvastatin, pravachol, ketorolac,

hydromorphone, morphine, ticlopidine, seligiline, venlafaxine, alprazolam,
carbamazepine, divalproex and phenytoin

ANEXO 3



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208(19) **United States**(12) **Patent Application Publication**
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COMPOSITION FOR TREATING
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424/709**(57) **ABSTRACT****The analgesic effectiveness of an tramadol is significantly
enhanced by administering tramadol prior to with or fol
lowing the administration of an analgesia enhancer which is
a nontoxic NMDA receptor blocker and/or a nontoxic sub-
stance that blocks at least one major intracellular conse-
quence of NMDA receptor activation.**

ANTICONVULSANT CONTAINING COMPOSITION FOR TREATING NEUROPATHIC PAIN

BACKGROUND OF THE INVENTION

[0001] This invention relates to a composition and method for alleviating neuropathic pain. More particularly this invention is directed to a composition and method for alleviating neuropathic pain in which a neuropathic pain alleviating amount of an anticonvulsant is combined with an anticonvulsant potentiating amount of a nontoxic antagonist, or blocker for the N-methyl-D-aspartate (NMDA) receptor or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation.

[0002] Neuropathic pain is pain that is due to functional abnormalities of the nervous system. Fields "Pain", McGraw-Hill Inc (1987), pp 133 et seq. There are a variety of possible mechanisms by which nerve dysfunction can cause neuropathic pain: hyperactivity in primary afferent or central nervous system (CNS) nociceptive neurons; loss of central inhibitory connections; and increased activity in sympathetic efferents. Neuropathic pain typically occurs following injury to elements of the nervous system involved in nociception, such as peripheral nerve injury in which the lesions deafferent the nociceptive pathway, the resultant pain sometimes being referred to as deafferentation pain. Neuropathic pain is much more likely to occur with peripheral than with central nervous system damage. Examples of causes of painful nerve injury are accidental trauma, tumors, cervical or lumbar spine disease, and surgical procedures. These injuries usually involve one or two peripheral nerves or nerve roots, and the pain is felt in the body region normally innervated by the damaged nerves. Additionally there are also toxic, metabolic, and hereditary causes of painful polyneuropathies, e.g., alcohol abuse, diabetes mellitus. These tend to be symmetrical and are most severe on the distal limbs.

SUMMARY OF THE INVENTION

[0003] In accordance with the present invention a drug composition is provided which comprises a neuropathic pain-alleviating amount of at least one anticonvulsant in combination with an anticonvulsant potentiating amount of at least one nontoxic antagonist for the NMDA receptor or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation.

[0004] Further in accordance with the present invention a method of alleviating neuropathic pain is provided which comprises administering to a mammal exhibiting neuropathic pain (a) a neuropathic pain alleviating amount of at least one anticonvulsant and (b) an anticonvulsant potentiating amount of at least one nontoxic antagonist for the NMDA receptor or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation with (a) being administered prior to, with or following the administration of (b).

[0005] The expression "N-methyl-D-aspartate receptor" shall be understood to include all of the binding site subcategories associated with the NMDA receptor, e.g., the glycine-binding site, the phenylcycidine (PCP)-binding site, etc., as well as the NMDA channel. Thus, the invention herein contemplates the use of nontoxic substances that

block an NMDA receptor binding site, e.g., dextrorphan or the NMDA channel, e.g., a source of magnesium such as magnesium sulfate.

[0006] The term "nontoxic" as used herein shall be understood in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or in keeping with established regulatory criteria and practice is susceptible to approval by the FDA for administration to humans. The term "nontoxic" is also used herein to distinguish the NMDA receptor antagonists, or blockers that are useful in the practice of the present invention from NMDA receptor antagonists such as MK 801 (the compound 5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine) CPP (the compound 3-[2-carboxy piperazin-4-yl] propyl 1-phosphonic acid) and PCP (the compound 1-(1-phenylcyclohexyl)piperidine) whose toxicities effectively preclude their therapeutic use.

[0007] The expression "neuropathic pain-alleviating" shall be understood herein to include the expressions "neuropathic pain-suppressing" and "neuropathic pain inhibiting" as the invention is applicable to the alleviation of existing neuropathic pain as well as the suppression or inhibition of neuropathic pain which would otherwise ensue from an imminent neuropathic pain-causing event.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0008] Any of the pain alleviating anticonvulsants can be used herein. For extensive listings of anticonvulsants, see e.g., Goodman and Gilman's "The Pharmacological Basis of Therapeutics" 8th ed. McGraw-Hill, Inc. (1990), pp. 436-462, and "Remington's Pharmaceutical Sciences" 17th ed. Mack Publishing Company (1985), pp. 1075-1083. Specific neuropathic pain alleviating anticonvulsants that can be used herein include lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethosuximide, mephobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phenosuximide, trimethadione, benzodiazepine, phenacetamide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadione, phenytoin sodium, valproate sodium, clobazam, sulthiame, dilantin, diphenylan, and L-5-hydroxytryptophan.

[0009] Among the nontoxic substances that block the NMDA receptor and as such are useful for potentiating the neuropathic pain-alleviating activity of the anticonvulsant in accordance with this invention are dextromethorphan ((+)-3-hydroxy-N-methylmorphinan), its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), amantadine (1-aminoadamantine), memantine (3,5-dimethylaminoadamantane), their mixtures and their pharmaceutically acceptable salts. Other useful nontoxic substances that block the NMDA receptor include pyrroloquinoline quinone and cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid.

[0010] In addition to, or in place of a blocker for the NMDA receptor, at least one nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation can also be used. Activation of the NMDA receptor, a subtype of excitatory amino acid receptors, induces a number of changes in the functional activity of nerve cells and, in particular, their capacity for excitability or inhibition.

in the presence of an addictive substance via an increase in intracellular Ca^{++} concentration. The major consequences of NMDA receptor activation include the following sequences, or cascades, of events occurring within nerve cells:

- [0011] a) translocation and activation of protein kinases such as protein kinase C $\rightarrow$ phosphorylation of substrate proteins (such as cytosolic enzymes, channel proteins, receptor proteins, etc $\rightarrow$ changes in functional activity
- [0012] b) initiation of early gene (c-fos, c-jun, etc) expression by either increased intracellular Ca^{++} or Ca^{++} -activated protein kinases $\rightarrow$ expression of functional genes responsible for production of cellular enzymes (such as protein kinases), receptor proteins (such as the NMDA receptor), ion channel proteins (such as K^+ , Na^+ , Ca^{++} channels), neuropeptides (such as dynorphin), etc $\rightarrow$ changes in functional activity
- [0013] c) Ca^{++} /calmodulin (or other Ca^{++} binding proteins) induced activation of enzymes and other cellular components $\rightarrow$ activation of Ca^{++} /calmodulin-protein kinase systems such as Ca^{++} /calmodulin kinase II $\rightarrow$ autophosphorylation of enzymes (e.g. Ca^{++} /calmodulin kinase II) or other functional proteins $\rightarrow$ changes in functional activity
- [0014] d) Ca^{++} /calmodulin induced activation of constitutive nitric oxide synthase as well as induction of inducible nitric oxide synthase $\rightarrow$ production of nitric oxide $\rightarrow$ i) production of cyclic guanosine monophosphate via activation of guanosine cyclase resulting in activation of protein kinases and early gene expression, ii) direct protein modification such as enzymes, receptor and/or channel proteins, iii) lipid membrane modification and/or nucleic acid modification via scavenging of free radicals, iv) induction of neurotoxicity at higher nitric oxide levels, v) retrograde actions in adjacent neurons or glial cells such as facilitation of glutamate release/NMDA receptor activation and/or inhibition of post-synaptic NMDA receptors $\rightarrow$ changes in functional activity
- [0015] e) interactions with the cyclic adenosine monophosphate/protein kinase A system, the phospholipase C inositol triphosphate- Ca^{++} /diacylglycerol-protein kinase system, the phospholipase A2-arachidonic acid/prostanoids/leukotrienes system $\rightarrow$ changes in functional activity induced by second messenger systems other than NMDA receptor/ Ca^{++} /calmodulin/protein kinase systems, and,
- [0016] f) interactions with other excitatory amino acid receptor subtypes including non NMDA receptors and metabotropic receptors as well as intracellular events subsequent to the activation of these excitatory amino acid receptor subtypes $\rightarrow$ changes in functional activity induced by the non NMDA and metabotropic receptor activation

[0017] A substance that blocks the NMDA receptor will effectively prevent all of the foregoing major intracellular sequences of events from taking place. However, even with activation of the NMDA receptor, it is still possible to treat

neuropathic pain in accordance with this invention by administering the anticonvulsant and a nontoxic substance that blocks at least one of the foregoing major intracellular sequences of events brought about by activation of the NMDA receptor. Thus, e.g., a substance that interferes with translocation and activation of protein kinase C or with calmodulin induced activation of constitutive nitric oxide synthase as well as induction of inducible nitric oxide synthase is also useful for the practice of this invention.

[0018] Nontoxic substances that block a major intracellular consequence of NMDA receptor activation and are therefore useful in the practice of the invention include inhibitors of protein kinase C, e.g. gangliosides such as ganglioside GM_1 (monosialoganglioside) and ganglioside GT_1 (trisialoganglioside), amphipathic long chain bases such as sphingosine, N,N,N-trimethylsphingosine, sphingosine and psychosine, quinolyloxazole-2-ones such as 4-methyl-5-(3-quinolinyl)-2-(3H)-oxazolone and phenyl-5-(2-quinolinyl)-2-(3H)-oxazolone, 1,4-bis-(aminohydroxyalkylamino)-anthraquinones such as 1,4-bis-(3-propylamino-2-hydroxypropylamino)-9,10-anthracenedione and 1,4-bis-(3-benzylamino-2-hydroxypropylamino)-9,10-anthracenedione and mixtures and pharmaceutically acceptable salts of any of the foregoing.

[0019] Additional nontoxic substances that block a major intracellular consequence of NMDA receptor activation and as such are useful in the practice of the invention include inhibitors of calmodulin such as the phenothiazines, in particular chlorpromazine, chlorpromazine sulfoxide, prochlorperazine dimaleate, perphenazine, trifluoperazine, fluphenazine, fluphenazine enanthate, fluphenazine decanoate, thioridazine, mesoridazine besylate, piperacelazine, acetophenazine dimaleate, carphenazine dimaleate, butaperazine dimaleate and phenothiazine sulfoxide, naphthalenesulfonamides such as N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide, N-(6-aminohexyl)-5-chloro-2-naphthalenesulfonamide and N-(6-aminohexyl)-5-bromo-2-naphthalenesulfonamide, 4-substituted-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepines such as 1,3-dihydro-1-[1-(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)methyl]-4-piperidinyl]-2H-benzimidazol-2-one, benzhydryls such as N-[2-(diphenylmethylthioethyl)]-2-(trifluoromethyl)benzenecethanamine, N-[2-(bis(4-fluorophenyl)methylthio)ethyl]-2-(trifluoromethyl)benzenecethanamine and N-[2-(bis(4-fluorophenyl)methylthio)ethyl]-3-(trifluoromethyl)benzenecethanamine, tricyclic antidepressant drugs such as imipramine, 2-chloroimipramine and amitriptyline, penfluridol, haloperidol, pimozide, clozapine, calmidazolol, and, mixtures and pharmaceutically acceptable salts of any of the foregoing.

[0020] Of the two groups, the NMDA receptor antagonists are preferred and of these dextromethorphan is especially preferred due to its wide use in over-the-counter medications where it functions as a cough suppressant.

[0021] With regard to dosage levels, the anticonvulsant must be present in a neuropathic pain-alleviating amount, e.g., at a level corresponding to the generally recommended adult human dosages for a particular anticonvulsant, and the NMDA receptor blocker or substance that blocks a major intracellular consequence of NMDA activation must be present at a level that potentiates the neuropathic pain-alleviating effectiveness of the anticonvulsant. Specific dos-

age levels for the anticonvulsants that can be used herein as given, *inter alia* in the "Physicians Desk Reference" 1996 Edition (Medical Economics Data Production Company Montvale, N.J.) as well as in other reference works including Goodman and Gilman's "The Pharmaceutical Basis of Therapeutics" and "Remington's Pharmaceutical Sciences" both of which as referred to above. Given the wide variation in dosage level of the anticonvulsant which depends to a large extent on the specific anticonvulsant being administered there can similarly be a wide variation in the dosage level of the NMDA receptor blocker or substance that blocks a major intracellular consequence of NMDA receptor activation. These amounts can be determined for a particular drug combination in accordance with this invention employing routine experimental testing. In case of the anticonvulsant phenobarbital and the NMDA receptor blocker dextromethorphan, dosages of from 50 to 300 mg/day of the former coadministered with from 30 to 120 mg/day of the latter will usually provide acceptable results.

[0022] While the neuropathic pain-alleviating anticonvulsant and anticonvulsant-potentiating nontoxic NMDA receptor blocker or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation need not be administered together, they must both be present in the patient at effective levels at the same time. While it is within the scope of the invention to separately administer the anticonvulsant and the NMDA receptor blocker or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation, as a matter of convenience it is preferred that these drugs be coadministered in a single dosage form. All modes of administrations are contemplated e.g. orally rectally parenterally intranasally and topically.

[0023] A therapeutic composition containing the anticonvulsant and nontoxic NMDA receptor blocker or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation will ordinarily be formulated with one or more pharmaceutically acceptable ingredients in accordance with known and established practice. Thus, the composition can be formulated as a liquid powder elixir injectable solution etc. Formulations for oral use can be provided as tablets or hard capsules wherein the pharmacologically active ingredients are mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin or as soft gelatin capsules wherein the active ingredients are mixed with an oleaginous medium e.g. liquid paraffin or olive oil.

[0024] Aqueous suspensions can include pharmaceutically acceptable excipients such as suspending agents, e.g. sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide e.g. lecithin, or condensation products of an alkylene oxide with fatty acids, e.g. polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, e.g. heptadecaethylene-oxyoctanol or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g. polyoxyethylene sorbitol monooleate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g. polyoxyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives,

e.g. ethyl-or-n-propyl-p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin or sodium or calcium cyclamate.

[0025] In addition to anticonvulsant and nontoxic NMDA receptor blocker or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation, the therapeutic composition herein can optionally contain at least one other pharmacologically active substance e.g. a non narcotic analgesic such as acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) such as aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, and the like.

What is claimed is:

1. A therapeutic composition comprising (a) a neuropathic pain-alleviating amount of at least one anticonvulsant and (b) an anticonvulsant potentiating amount of at least one nontoxic antagonist for the NMDA receptor or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation.

2. The therapeutic composition of claim 1 wherein anticonvulsant (a) is at least one member selected from the group consisting of lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethosoin, mephobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phenoximide, trimethadione, benzodiazepine, phenacetamide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadione, phenytoin sodium, valproate sodium, clobazam, sulthiame, dilantin, diphenylan and L-5-hydroxytryptophan.

3. The therapeutic composition of claim 1 wherein nontoxic NMDA receptor blocker (b) is at least one member selected from the group consisting of dextromethorphan, dextrothorphan, amantadine, memantine and pharmaceutically acceptable salt thereof.

4. The therapeutic composition of claim 1 wherein (a) and (b) each is present in the same or different sustained release carrier.

5. The therapeutic composition of claim 1 containing a therapeutically effective amount of at least one other pharmacologically active substance (c).

6. The therapeutic composition of claim 1 containing a therapeutically effective amount of at least one other pharmacologically effective substance (c) selected from the group consisting of acetaminophen and nonsteroidal anti-inflammatory drug.

7. The therapeutic composition of claim 1 wherein anticonvulsant (a) is at least one member selected from the group consisting of lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethosoin, mephobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phenoximide, trimethadione, benzodiazepine, phenacetamide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadione, phenytoin sodium, valproate sodium, clobazam, sulthiame, dilantin, diphenylan and L-5 hydroxytryptophan and nontoxic NMDA receptor blocker (b) is dextromethorphan, or pharmaceutically acceptable salt thereof.

8. A method of alleviating neuropathic pain which comprises administering to a mammal exhibiting neuropathic pain (a) a neuropathic pain-alleviating amount of at least one anticonvulsant and (b) an anticonvulsant potentiating amount of at least one nontoxic antagonist for the NMDA receptor or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation with (a) being administered prior to with or following the administration of (b)

9 The method of claim 8 wherein anticonvulsant (a) is at least one member selected from the group consisting of lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethosuximide, methsuximide, phenasuximide, trimethadione, benzodiazepine, phenacetamide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadione, phenytoin sodium, valproate sodium, clobazam, sulthiame, dilantin, diphenylan and L-5 hydroxytryptophan

10 The method of claim 8 wherein nontoxic NMDA receptor blocker (b) is at least one member selected from the group consisting of dextromethorphan, dextrorphan, amantadine, memantine and pharmaceutically acceptable salt thereof

11 The method of claim 8 wherein (a) and (b) are coadministered as a sustained release dosage form

12 The method of claim 8 wherein anticonvulsant (a) is at least one member selected from the group consisting of lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethosuximide, methsuximide, phenasuximide, trimethadione, benzodiazepine, phenacetamide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadione, phenytoin sodium, valproate sodium, clobazam, sulthiame, dilantin, diphenylan and L-5-hydroxytryptophan and nontoxic NMDA receptor blocker (b) is at least one member selected from the group consisting of dextromethorphan, dextrorphan, amantadine, memantine and pharmaceutically acceptable salt thereof and (a) and (b) are coadministered as a single dosage unit

13 The method of claim 8 wherein anticonvulsant (a) is at least one member selected from the group consisting of lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethosuximide, methsuximide, phenasuximide, trimethadione, benzodiazepine, phenacetamide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadione, phenytoin sodium, valproate sodium, clobazam, sulthiame, dilantin, diphenylan and L-5 hydroxytryptophan and nontoxic NMDA receptor blocker (b) is dextromethorphan, or pharmaceutically acceptable salt thereof

14 The therapeutic composition of claim 1 further comprising (c) an analgesic.

15 The therapeutic composition of claim 14 wherein the analgesic is a non-narcotic analgesic

16 The therapeutic composition of claim 15 wherein the non narcotic analgesic is at least one member selected from the group consisting of acetaminophen, aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin and zomepirac.

17 The method of claim 8 further comprising (c) an analgesic.

18 The method of claim 17 wherein the analgesic is a non narcotic analgesic

19 The method of claim 18 wherein the non narcotic analgesic is at least one member selected from the group consisting of acetaminophen, aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin and zomepirac

* * * * *

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-7005

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 568

DE FECHA 29 DE SEPTIEMBRE DEL 2006 EL TERMINO HABIL SEÑALADO

POR LA LEY EXPIRA EL 29 DE DICIEMBRE DEL 2006

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS

SI ___ X ___

NO ___ _ _ _ _

Bogotá D C, ENERO DE 2007

2020
Bogotá, D C ,

Doctor
Carlos Reinaldo Olarte García
Apoderado

Oficio N° 2027

ASUNTO	Radicación PCT N°	05-7005
	Trámite	011
	Evento	379
	Actuación	440
	Folios	010

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

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del título primero de la Circular Unica N° 10 de 2001


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

09 FEB 2007

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

202021

Retro Copio Hasbete

~~Justus~~