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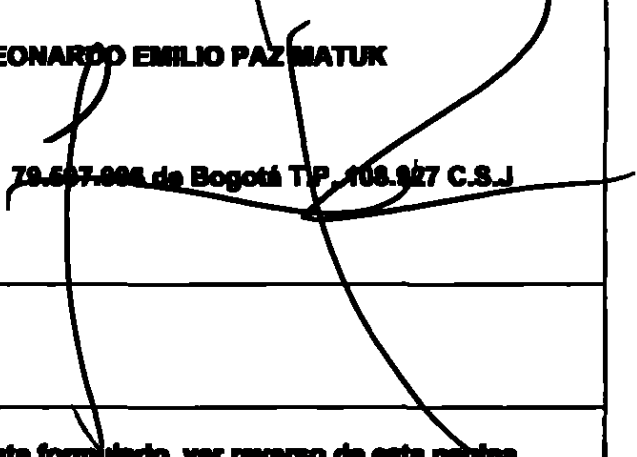
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-007005-00005-0000
Fec: 2008-11-15 12:10:57 Dep: 2000 NUEVE ALFONOS
1ra. 11 PATENTERIA
Evo 3/01 PASADUACIONALN
Act 400 OPOSICION SERVTER Folios 05

FORMULARIO UNICO DE OPOSICION
2000-12

1 OPOSICION A		
☒ Patente de invención Patente Modelo de Utilidad Diseño Industrial Esquema de trazado para circuitos integrados Marcas de productos o servicios		
2 Numero del expediente 05-007005 SOLICITUD Solicitante GLAXO WELLCOME FUNDATION LIMITED PUBLICADA GACETA 588 Apoderado CARLOS OLARTE Titulo de la nueva creacion o denominación del signo LAMOTRIGINA DE LIBERACION PROLONGADA		
3 OPOSICION PRESENTADA POR LEONARDO EMILIO PAZ MATUK		
OPOSITOR	Nombre LEONARDO EMILIO PAZ MATUK Direccion Calle 38 No. 8 - 56 oficina 1105 telefono 2878198 Fax 4150086 E-mail lepazmatuk@hotmail.com Domicilio Bogotá D.C	IDENTIFICACION C.C 79.597.996 NIT C.E. Otro Numero
REPRESENTANTE O APODERADO (74)	Nombre LEONARDO PAZ MATUK Direccion Calle 38 No. 8 - 56 oficina 1105 Bogotá Telefono 2878198 Fax 2878198 E-mail	IDENTIFICACION C.C. X NIT C.E. Otro Numero 79.597.996 Btá T.P 108.927 C.S.J.
4 FUNDAMENTOS DE LA OPOSICION <u>Ver anexo</u>		

5 Comprobante de pago No 06 87537	Fecha 14 NOV DE 2008
6 ANEXOS ☒ Comprobante de pago de la tasa Podemos, si fuere el caso ☒ Pruebas de los fundamentos de la oposición Documentos que acrediten el legítimo interés, si fuere el caso. Certificado de Existencia y Representación legal de las partes, cuando sean personas jurídicas	

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7	NOMBRE LEONARDO EMILIO PAZ MATUK
	FIRMA  C.C 79.597.886 de Bogotá T.P. 108.927 C.S.J
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.	

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Javeriana Colegio Mayor de Nuestra
Señora del Rosario. Propiedad
Industrial, Derechos de Autor y Nuevas
Tecnologías. Universidad Externado de
Colombia.

GIOVANNA FERNANDEZ ORJUELA
LEONARDO EMILIO PAZ MATUK
ABOGADOS ASOCIADOS

ÁREAS DE PRÁCTICA. PROPIEDAD INTELECTUAL, PROPIEDAD INDUSTRIAL, NUEVAS
TECNOLOGÍAS, PROTECCIÓN AL CONSUMIDOR, DERECHO SANITARIO, DERECHO DE LAS
TELECOMUNICACIONES, NORMAS TÉCNICAS, DERECHO COMERCIAL, DERECHO SOCIETARIO,
PROCESOS CONCÚRBALES, DERECHO LABORAL Y DERECHO DE FAMILIA.

Calle 38 No. 8-56 oficina 1105 Bogotá D.C; Telefax 2878198
Celulares 3112361824 - 3156035898

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Delegatura de la Propiedad Industrial

NUEVAS CREACIONES

Ciudad

E. S. D.

Referencia: Expediente 05 007005

Presentación de oposición a la solicitud
indicada en el formulario

LEONARDO EMILIO PAZ MATUK, abogado en
ejercicio, identificado civil y profesionalmente tal y
como aparece al pie de mi firma, obrando en nombre
propio, de la manera más atenta manifiesto a su
d espacho que presento observación (oposición) a la
solicitud de la proteccion indicada, solicitando de
antemano, se declare fundada esta oposición,
negando la protección del privilegio de patente de

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invención Lo anterior en consideración a los hechos y fundamentos que a continuación se refieren

**HECHOS Y FUNDAMENTOS QUE ORIGINAN LA
OPOSICIÓN (OBSERVACIÓN)**

1. La solicitud en curso reivindica como materia de su propiedad:

1.1 La solicitud pretende obtener patente sobre Lamotrigina de liberación prolongada, reclamada como "Una formulación de Lamotrigina o uno de sus derivados farmacéuticamente aceptables caracterizada porque es una formulación de liberación prolongada".

1.2 Una formulación de liberación prolongada según la reivindicación 1, caracterizada porque 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

1.3-Una formulación de liberación prolongada según las reivindicaciones 1 o 2, caracterizada porque tiene un perfil de disolución in Vitro en el que 40 a 65% de la lamotrigina se disuelve en 3 a 8 horas.

1.4-Una formulación de liberación prolongada según las reivindicaciones 1 a 3, caracterizada porque tiene un perfil de disolución in Vitro igual o sustancialmente similar al de una cualquiera de las Figuras 3,4 ó 5.

1.5-Una formulación de liberación prolongada según las reivindicaciones 1 a 4, caracterizada porque 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.

1.6- Una formulación de liberación prolongada de lamotrigina o uno de sus derivados farmacéuticamente aceptables según la reivindicación 1, caracterizada porque la liberación de la lamotrigina o 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. Las ideas no son patentables.

Frente a la pretensión de obtener privilegio sobre "Una formulación de Lamotrigina o uno de sus derivados farmacéuticamente aceptables caracterizada porque es una formulación de liberación prolongada", como tal, sea lo primero anotar que no existe definida técnicamente ninguna formulación de lamotrigina, simplemente esta presentada como un idea, y las ideas en propiedad intelectual, de acuerdo a los derechos de propiedad industrial e intelectual no protegen las ideas en sí mismas. Nadie puede apropiarse de ellas. Nadie puede reivindicar su propiedad y, por ello, tampoco la protección de una idea como tal, sino sólo su materialización en el mundo real

También se define la idea de "formulación de liberación de lamotrigina" en características que les gustaría que el producto tuviera más no una definición técnica de lo que comprende la formulación de manera clara, contraviniendo lo dispuesto en el artículo 30 de la Decisión 486

3. Análisis de Novedad

También es necesario recordar que no es la primera vez en el acervo tecnológico, que se presenta una composición de liberación prolongada, en el estado de la técnica se puede observar un sinnúmero de composiciones de liberación prolongada para innumerables principios activos. Existen específicamente de tres (3) anterioridades que afectan la novedad y el nivel inventivo de la solicitud colombiana 05-007.005, las cuales serán referidas a continuación:

a) Publicación internacional W097/15316, publicada el 24-04-1997, ya que se refiere a composiciones farmacéuticas, que comprenden un principio activo antagonista de (NMDA) que puede ser presentado en forma de liberación inmediata o de liberación prolongada, y puede ser usada para el tratamiento de desordenes del CNS, se muestra sus paginas 1 a 2, y se reclama en sus reivindicaciones 1 a 30. Esta publicación nos enseña diáfamanamente, que la idea de presentar una composición de liberación modificada no es nueva, como tampoco es nueva su materialización para la lamotrigina, ya que esta descrita y se reclama en esta publicación W097/15316.

b) Del mismo modo, la publicación W098/47491, publicada el 29-10-1998, revela en paginas 1 a 4 múltiples patentes que aportan al acervo tecnológico novedad en formulaciones para la liberación controlada de sustancias activas y los métodos para su preparación, lo que claramente nos muestra que la idea de presentar composiciones de liberación controlada ya se había materializado. Igualmente esta publicación enseña composiciones de liberación

pr longada que conti nen lamotrigina,(pag 9 renglón 15), y se reclaman composicion s técnicamente definidas, de liberación sostenida

c) De la misma forma la patente US 6,406,716, publicada el 18-06-2002, representa una vez más que, este tipo de composiciones no son nuevas, es decir que las composiciones de liberación modificada, no sólo sirven para un determinado principio activo, sino para cualquier principio activo, para el tratamiento de enfermedades inflamatorias y su amplio uso en composiciones farmacéuticas, sino que claramente de acuerdo al principio activo esta patente ya contenía la descripción de las composiciones de liberación retardada que contienen lamotrigina.

Lo anterior muestra las composiciones de liberación "retardada" ya eran de conocimiento general del stado de la técnica, y además se conocen múltiples procesos para su obtención, al igual que la idea y la forma materializada de presentar la lamotrigina en composiciones de liberación retardada las cuales fueron enseñadas en las publicaciones referidas arriba. Entonces la solución sugerida para la presentación de composiciones de liberación r tardada no se observa el aporte al acervo tecnológico, o el salto cualitativo, ni la diferencia con las formulaciones enseñadas del estado de la técnica, ni la dificultad real superada con la solución técnica presentada.

El simple hecho de conocerse la existencia de todas las posibles formas de formulación en que existe la lamotrigina en estado de la técnica, que es bastante amplio, podemos ver en cual de ellas no se ha presentado y posteriormente presentar formulaciones de liberación retardada de lamotrigina y conociéndose



muy bien sus propiedades inconvenientes para su formulación, conducirían de manera obvia a una persona medianamente versada en la materia técnica, basada en documentos generales y en presencia de métodos experimentales conocidos, a combinar las enseñanzas descritas y a derivar efectivamente la posibilidad de obtener las formulaciones de liberación modificada, pues es ampliamente conocido en la literatura científica los procesos y las formulaciones que presentan una velocidad de disolución más rápida o menos para ser ajustada de acuerdo con las necesidades, sin que por ello se haga un aporte técnico significativo o salto cualitativo al acervo tecnológico.

4. CONCLUSIONES

Es claro que la presente solicitud de patente CO 05-007.005 se encuentra afectada tanto en novedad como en nivel inventivo, teniendo en cuenta los argumentos expuestos en el escrito de oposición presentada ante ese Despacho el 29 de mayo de 2003 y en lo establecido en el Informe Internacional de Búsqueda practicado por la Oficina Europea de Patentes a la aplicación internacional PCTIW001/42221 equivalente

5. PRUEBAS

Además de las solicitadas en el escrito de oposición, y de aquellas que oficiosamente considere el despacho, ruego que se tengan como tales las siguientes



5.1 Copia d la publicación internacional
WO97/14415

5.2. Copia de la publicación internacional
WO98/47491 páginas 1 a 11 y 18 a 22.

5 3 Copia de la patente US 6,406,716

5 4 Las publicaciones del estado de la técnica, de
todas las "formas de presentación de lamotrigina"

PETICIONES

Sírvase negar el beneficio patentario a la solicitud
contenida en el expediente 05-007.005, por no
cumplir con lo dispuesto en los artículos 14, 16 y 18
de la Decisión 486 de 2000, con base en los
fundamentos expuestos en el presente escrito

NOTIFICACIONES

Las recibo en la Calle 38 No 8 -56 Oficina 1105 de la
Ciudad de Bogotá D.C

Del Señor Superintendente,

LEONARDO EMILIO PAZ MATUK
C.C. No. 79.597.996
T.P.A. 108.927 del C. S de la J.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT 860176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-007005-00006-0000
Fec: 2006-11-15 12:00:00 Dep: 2460 MIL DOLARACIONES
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Lec: 370 PASADONALIA
Act: 400 OMISION/SENYTER Fobor: 08

RECIBO OFICIAL DE CAJA 06 - 87,537
FECHA NOVIEMBRE 14 DE 2006

***** CONSIGNACION *****

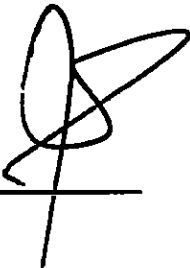
DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PAGO	Vr PAGO
IRMA MENDOZA	CONSIGNACION	BANCO POPULAR	050 00110-6	17248143	14/11/2006	246,000 00

***** CONCEPTO *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEYAS COMERCIALES	246,000 00
		TOTAL :	\$ 246,000 00

● DOSCIENTOS CUARENTA Y SEIS MIL PESOS

RESPONSABLE _____



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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 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 (22) International Filing Date 18 October 1996 (18.10.96) (30) Priority Data PN 6057 19 October 1995 (19.10.95) AU (71) Applicant (for all designated States except US): F.H. FAULD- ING & CO. LIMITED [AU/AU] 160 Greenhill Road, Park- side, S.A. 3063 (AU). (72) Inventors; and (73) Inventors/Applicants (for US only): SMITH, Ian, Keith [NZ/AU]; 11 Athol Avenue, Blair Athol, S.A. 3084 (AU). HEINICKE, Grant, Wayne [AU/AU]; 14 Baudin Avenue, Fairview Park, S.A. 5126 (AU). (74) Agent: PHILLIPS ORMONDE & FITZPATRICK, 367 Collins Street, Melbourne, VIC 3000 (AU).	(51) 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), European 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). Published With international search report.	
(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, eliprodil, ifenprodil, dizocilpine, remacemide, lamotrigine, riluzole, apigenin, phenylcyclidine, flupirtine, cefetol, felbamate, spermine, spermidine, levamisole, a pharmaceutically acceptable salt or ester thereof, or a metabolic precursor of any of the foregoing.		

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.

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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

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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

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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

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

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

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- 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, apbganel,
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.

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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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- 4 -

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,

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

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

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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

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

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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



etc), polymers (eg polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, etc), surfactants (sodium lauryl sulphate, chromophor, 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 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 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 confectionery and so on.

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

A controlled-release dosage form as defined in US Pharmacopela 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 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% 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.

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, ceresine, 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.

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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

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These IR or SR forms may be made by prilling, 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

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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 - 1 700 μ m) in a capsule. All the quoted ranges are %w/w.

A plurality of elements containing the active ingredients (cores) are prepared by extrusion/manumerisation, 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

21

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.

- 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 - 80% 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 (ie 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.

20

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.

23

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.

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
5 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
10 about 8 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.

15 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
20 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
25 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.

30 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

26

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.

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(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

15	<u>Ingredient</u>	<u>% (W/W)</u>
	Ethanol 96 PC/BP	95.0
	Hydroxy Propyl Methyl Cellulose BP/USP 603	2.0
	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	0.65
	Methacrylic Acid Copolymer NF, Type C Powder	1.05
	Ethyl Cellulose N50	3.59
	Poly Ethylene Glycol (6000) 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.

Ann Product for A8-048 A1 (8% Theoretical Polymer Coat Weight (TPCW)) A8-048 A1, A8-052 A2, and A8-048 A2 are batch numbers used to identify different pellet compositions.

20

<u>Ingredient</u>	<u>% (W/W)</u>	<u>Typical Amounts (kg)</u>
Ethanol 96 PC/BP	-	0.2000
Coating Formulation 1	62.51	1.7400
Talc Purified Micronised BP/USP	1.56	0.0435
Dextromethorphan Cores	35.93	1.0000

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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 98 PC/BP	-	0 2000
5	Coating Formulation 2	67 80	2 2222
	Talc Purified Micronised BP/USP	1 69	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 76

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

3/2

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	A8-048 A1	A8-048 A2	A8-052 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	36.3	42.2
6	55	44-66	55.2	44.4	53.2
8	65	52-78	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
 5 may be made without departing from the spirit of the present invention as outlined
 herein

TABLE 2 AIM AND ACTUAL DISSOLUTION

Time (hours)	Aim		Actual		
	% Released	$\pm 20\%$ 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	36.3	42.2
6	55	44-66	55.2	44.4	53.2
8	65	52-78	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

35

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
- 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
25 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%-60% 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.

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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 6 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 A pharmaceutical composition according to claim 17 wherein the therapeutic effect is provided over a period of 12 to 24 hours

20 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

22 A pharmaceutical composition according to any one of claims 1 to 21
25 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
30 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 66% (by weight) dextromethorphan released after 6 hours,
s 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 dextrorphan, ketamine, amantadine, memantine,
eliprodil, ifenprodil, 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, cerasine, 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
10 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,
15 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,
20 hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups or combinations thereof

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 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

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, powdered cellulose, MCC, polacrillin 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 cellulose, microcrystalline cellulose, polacrillin 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 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, intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular means

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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

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

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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
5 of claims 1 to 41

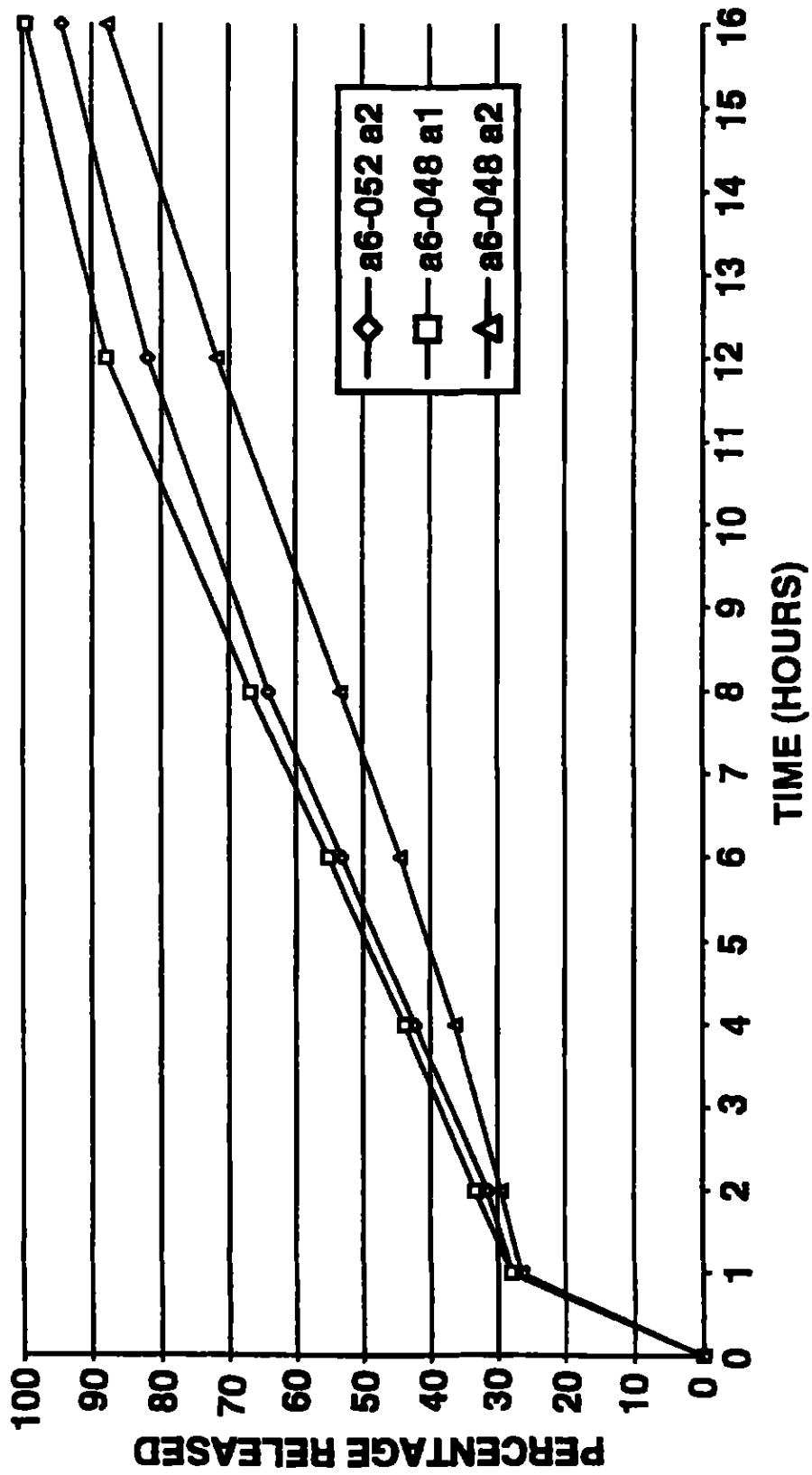
53 A kit according to claim 52 further including instructions and unit dosage forms providing immediate release and controlled release of NMDA receptor antagonist
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(12) **United States Patent**
Caruso et al.

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(54) **ANTICONVULSANT CONTAINING COMPOSITION FOR TREATING NEUROPATHIC PAIN**

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(*) **Notice** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(51) **Int. Cl.⁷** A61K 9/22 A61K 9/52

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(58) **Field of Search** 424/457, 468, 424/489, 455, 464, 423, 451 456

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(57) **ABSTRACT**

The effectiveness of an anticonvulsant such as gabapentin for alleviating neuropathic pain is potentiated by a nontoxic antagonist for the N-methyl-D-aspartate receptor or nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation.

46 Claims, No Drawings

**ANTICONVULSANT CONTAINING
COMPOSITION FOR TREATING
NEUROPATHIC PAIN**

This is a continuation of application Ser No 09/253,598 filed Feb 22, 1999 now U.S. Pat. No 6,187,338, which is a continuation of application Ser No PCT/US97/14680 filed Aug. 21, 1997. This application claims benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 60/024,508 filed Aug. 23, 1996.

BACKGROUND OF THE INVENTION

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.

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

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.

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).

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 phenylcyclichine (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., dextropropanolol, or the NMDA channel, e.g., a source of magnesium such as magnesium sulfate.

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-carboxypiperazin-4-yl]propyl-1-phosphonic acid) and PCP (the compound 1-(1-phenylcyclohexyl)piperidine) whose toxicities effectively preclude their therapeutic use.

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**

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, mephentoin, ethosuximide, mephobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phenisuximide, trimethadione, benzodiazepine phenacetamide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadone, phenytoin sodium, valproate sodium, clobazam, sulthame, dilantin, diphenylan and L-5-hydroxytryptophan.

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 dextropropanolol ((+)-3-hydroxy-N-methylmorphinan), amantadine (1-amino adamantane), memantine (3,5-dimethylaminoadamantane), their mixtures and their pharmaceutically acceptable salts. Other useful nontoxic substances that block the NMDA receptor include pyrrolidine quinone and cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid.

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

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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.

- 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
- b) initiation of early gene (c-fos, c-jun, zif-268, 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
- 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.
- 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 postsynaptic NMDA receptors $\rightarrow$ changes in functional activity.
- 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/prostaglandin/leukotrienes system $\rightarrow$ changes in functional activity induced by second messenger systems other than NMDA receptor/ Ca^{++} / Ca^{++} -calmodulin/protein kinase systems, and,
- 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

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.

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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 GM₁ (monosialoganglioside) and ganglioside GT_{1b} (trisialoganglioside), amphipathic long chain bases such as sphingosine, N,N,N-trimethylsphingosine, sphinganine and psychoamine, quinolyloxazole-2-ones such as 4-methyl-5-(3-quinolyl)-2-(3H)-oxazolone and phenyl-5-(2-quinolyl)-2-3(3H)-oxazolone, 1,4-bis-(amino-hydroxyalkylamino) 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.

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, piperacetazine, acetophenazine dimaleate, carphenazine dimaleate, butaperazine dimaleate and phenothiazine sulfoxide, naphthalenesulfonamides such as N-(6-aminoheptyl)-5-chloro-1-naphthalenesulfonamide, N-(6-aminoheptyl)-5-chloro-2-naphthalenesulfonamide and N-(6-aminoheptyl)-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)benzeneethanamine N-[2-(bis(4-fluorophenyl)methylthio)ethyl]-2-(trifluoromethyl)benzeneethanamine and N-[2-(bis(4-fluorophenyl)methylthio)ethyl]-3-(trifluoromethyl)benzeneethanamine tricyclic antidepressant drugs such as imipramine, 2-chloroimipramine and amitriptyline, penfluridol, haloperidol, pimozide, clozapine, citalopram, and, mixtures and pharmaceutically acceptable salts of any of the foregoing.

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.

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 dosage levels for the anticonvulsants that can be used herein are 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

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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.

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.

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.

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 oxycetanol, 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.

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 non-steroidal 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 neuropathic pain-alleviating composition for administration to a mammal exhibiting, or about to exhibit neu-

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ropathic pain which comprises (a) gabapentin and (b) at least one nontoxic antagonist for the N-methyl-D aspartate receptor or nontoxic substance that blocks a major intracellular consequence of N methyl-D-aspartate receptor activation, the combined amount of (a) and (b) in the composition being a neuropathic pain-alleviating amount and the amount of (b) in the composition being sufficient to potentiate the neuropathic pain-alleviating effectiveness of (a).

2 The composition of claim 1 wherein (b) is at least one member selected from the group consisting of dextromethorphan, dextrorphan, amantadine, memantine and pharmaceutically acceptable salt thereof.

3 The composition of claim 1 wherein (a) and (b) each is present in a sustained release carrier.

4 A neuropathic pain-alleviating composition for administration to a mammal exhibiting, or about to exhibit, neuropathic pain which comprises (a) at least one member selected from the group consisting of lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethosuximide, methsuximide, phenesuximide, trimethadione, benzodiazepine, phenacetamide, acetazolamide, progabide, clonazepam, divalproex sodium, magnesium sulfate injection, metharbital, paramethadone, phenytoin sodium, valproate sodium, clobazam, sulthame, dilantin, diphenylan and L-5 hydroxytryptophan, (b) at least one nontoxic antagonist for the N-methyl D-aspartate receptor or nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation and (c) at least one analgesic, the combined amount of (a) and (b) in the composition being a neuropathic pain-alleviating amount and the amount of (b) in the composition being sufficient to potentiate the neuropathic pain-alleviating effectiveness of (a).

5 The composition of claim 4 wherein (b) is at least one member selected from the group consisting of dextromethorphan, dextrorphan, amantadine, memantine and pharmaceutically acceptable salt thereof.

6 The composition of claim 5 wherein analgesic (c) is a non narcotic analgesic.

7 The composition of claim 6 wherein non narcotic analgesic (c) is at least one member selected from the group consisting of acetaminophen and nonsteroidal anti-inflammatory drug.

8 The composition of claim 7 wherein the nonsteroidal anti-inflammatory drug is at least one member selected from the group consisting of 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.

9 A method of alleviating neuropathic pain in a mammal exhibiting, or about to exhibit, neuropathic pain which comprises administering to the mammal a neuropathic pain-alleviating composition which comprises (a) gabapentin and (b) at least one nontoxic antagonist for the N-methyl-D-aspartate receptor or nontoxic substance that blocks a major intracellular consequence of N methyl-D-aspartate receptor activation, the combined amount of (a) and (b) in the composition being a neuropathic pain-alleviating amount and the amount of (b) in the composition being sufficient to potentiate the neuropathic pain-alleviating effectiveness of (a).

10 The method of claim 9 wherein (b) is at least one member selected from the group consisting of

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dextromethorphan, dextropropan, amantadine, memantine and pharmaceutically acceptable salt thereof.

11 The method of claim 9 wherein (a) and (b) each is present in a sustained release carrier

12 A method of alleviating neuropathic pain in a mammal exhibiting, or about to exhibit, neuropathic pain which comprises administering to the mammal a neuropathic pain alleviating composition which comprises (a) at least one member selected from the group consisting of lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethotoin, mephobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phenisuximide, 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, (b) at least one nontoxic antagonist for the N-methyl-D-aspartate receptor or nontoxic substance that blocks a major intracellular consequence of N methyl D aspartate receptor activation and (c) at least one analgesic, the combined amount of (a) and (b) in the composition being a neuropathic pain-alleviating amount and the amount of (b) in the composition being sufficient to potentiate the neuropathic pain-alleviating effectiveness of (a).

13 The method of claim 12 wherein (b) is at least one member selected from the group consisting of dextromethorphan, dextropropan, amantadine, memantine and pharmaceutically acceptable salt thereof.

14 The method of claim 12 wherein analgesic (c) is a non narcotic analgesic.

15 The method of claim 14 wherein non-narcotic analgesic (c) is at least one member selected from the group consisting of acetaminophen and nonsteroidal anti-inflammatory drug.

16 The method of claim 15 wherein the nonsteroidal anti inflammatory drug is at least one member selected from the group consisting of 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 A method of alleviating neuropathic pain in a mammal exhibiting, or about to exhibit, neuropathic pain caused by accidental trauma which comprises administering to the mammal a neuropathic pain-alleviating composition which comprises (a) gabapentin and (b) at least one nontoxic antagonist for the N-methyl-D-aspartate receptor or nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation, the combined amount of (a) and (b) in the composition being a neuropathic pain-alleviating amount and the amount of (b) in the composition being sufficient to potentiate the neuropathic pain-alleviating effectiveness of (a).

18 The method of claim 17 wherein (b) is at least one member selected from the group consisting of dextromethorphan, dextropropan, amantadine, memantine and pharmaceutically acceptable salt thereof.

19 A method of alleviating neuropathic pain in a mammal exhibiting, or about to exhibit, neuropathic pain caused by accidental trauma which comprises administering to the mammal a neuropathic pain-alleviating composition which comprises (a) at least one member selected from the group consisting of lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin,

phenytoin, mephenytoin, ethotoin, mephobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phenisuximide, 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, (b) at least one nontoxic antagonist for the N-methyl-D aspartate receptor or nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation and (c) at least one analgesic, the combined amount of (a) and (b) in the composition being a neuropathic pain-alleviating amount and the amount of (b) in the composition being sufficient to potentiate the neuropathic pain-alleviating effectiveness of (a).

20 The method of claim 19 wherein (b) is at least one member selected from the group consisting of dextromethorphan, dextropropan, amantadine, memantine and pharmaceutically acceptable salt thereof.

21 The method of claim 20 wherein analgesic (c) is a non-narcotic analgesic.

22 The method of claim 21 wherein non-narcotic analgesic (c) is at least one member selected from the group consisting of acetaminophen and nonsteroidal anti-inflammatory drug.

23 A method of alleviating neuropathic pain in a mammal exhibiting, or about to exhibit, neuropathic pain caused by a tumor which comprises administering to the mammal a neuropathic pain-alleviating composition which comprises (a) gabapentin and (b) at least one nontoxic antagonist for the N-methyl D aspartate receptor or nontoxic substance that blocks a major intracellular consequence of N-methyl D-aspartate receptor activation, the combined amount of (a) and (b) in the composition being a neuropathic pain-alleviating amount and the amount of (b) in the composition being sufficient to potentiate the neuropathic pain-alleviating effectiveness of (a).

24 The method of claim 23 wherein (b) is at least one member selected from the group consisting of dextromethorphan, dextropropan, amantadine, memantine and pharmaceutically acceptable salt thereof.

25 A method of alleviating neuropathic pain in a mammal exhibiting, or about to exhibit, neuropathic pain caused by a tumor which comprises administering to the mammal a neuropathic pain-alleviating composition which comprises (a) at least one member selected from the group consisting of lamotrigine, gabapentin, valproic acid, topiramate, famotidine, phenobarbital, diphenylhydantoin, phenytoin, mephenytoin, ethotoin, mephobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phenisuximide, 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, (b) at least one nontoxic antagonist for the N-methyl D-aspartate receptor or nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation and (c) at least one analgesic, the combined amount of (a) and (b) in the composition being a neuropathic pain-alleviating amount and the amount of (b) in the composition being sufficient to potentiate the neuropathic pain-alleviating effectiveness of (a).

26 The method of claim 23 wherein (b) is at least one member selected from the group consisting of dextromethorphan, dextropropan, amantadine, memantine and pharmaceutically acceptable salt thereof.

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(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 % wt/wt and preferably between 5-70 % wt/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 % wt/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			

Controlled Release Formulations Using Intelligent Polymers

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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, bucal tablets, oral tablets or suppositories.

U S Patent 4,308,251 teaches a tablet formulation comprising an effective
5 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
10 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
15 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
20 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
25 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.
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U.S. Patent 4,692,337 teaches a sustained release pharmaceutical tablet
35 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 (5,1 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.

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

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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 physiochemical 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 encased 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, 5 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, 10 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, 15 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, 20 aluminum carbonate, aluminum chlorohydrate, aluminum hydroxide, alproazolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amoxicillin, amoxicillin, amoxicillin, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoylperoxide, biotin, bisacodyl, bonyl acetate, brompheniramine maleate, bupropion, caffeine, calamine, calcium, 25 calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, cefaclor, cefadroxil, cephalixin, cetylalcohol, cetylpyndrium chloride, chelated minerals, chloramphenicol, chlorcyclizine hydrochloride, chlorhexidine gluconate, chloroxylenol, chloropentostatm, chlorpheniramine maleate, cholestyramine resin, choline bitartrate, cimetidine hydrochloride, cinnamedrine 30 hydrochloride, citalopram, citric acid, cocoa butter, cod liver oil, codeine and codeine phosphate, clonidine, clonidine hydrochloride, clorifibrate, ciprofloxacin HCl, cyanocobalamin, cyclizine hydrochloride, danthron, dextbrompheniramine maleate, dextromethorphan hydrobromide, diazepam, dibucaine diclofenac sodium, digoxin, dimethicone, dioxybenzone, diphenhydramine citrate, diphenhydramine 35 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, griseofulvin, 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, meperidine
 hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate,
 10 methylcellulose, methauximide, 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, pentaerythriol tetranitrate, pentobarbital
 sodium, pheniramine maleate, phenobarbital, phenol, phenolphthalein, phenylephrine
 hydrochloride, phenylpropanolamine, phenylpropanolamine, hydrochloride,
 phenytoin, phenelzine, sulfate, pirmenol, piroxicam, polymyxin 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, quinestrol
 rahitoline, ranitidine, resorcinol, riboflavin, salicylic acid, sesame oil, shark liver oil,
 25 simethicone, sodium bicarbonate, sodium citrate, sodium fluoride, sodium
 monofluorophosphate, sulfamethoxazole, sulfur, tacrine, tacrine HCl, theophylline,
 tramadol, terfenadine, thioperidone, trimetrexate, triazolam, timolol maleate, tretinoin,
 tetracycline hydrochloride, tolmetin, tolnaftate, triclosan, triprolidine hydrochloride,
 undecylenic acid, vancomycin, vidaribine 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 hydroxyethylcellulose (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 ($\text{MPa}^{0.25}$) 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

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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, 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, selegiline, 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, amsalone, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoylperoxide, biotin, bisacodyl, bonyl

- acetate, brompheniramine maleate, buspirone, caffeine, calamine, calcium, calcium carbonate, calcium casinate, calcium hydroxide, camphor, captopril, cascara sagrada, castor oil, cefaclor, cefadroxil, cephalixin, cetylalcohol, cetylpyridinium chloride, chelated minerals, chloramphenicol, chlorcycizme 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, cyclizme hydrochloride, dantrolene, 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, efavirenz, 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, isosorbide, guaifenesin, hexylresorcinol, hydrochlorothiazide, hydrocodone bitartrate, hydrocortisone, hydrocortisone acetate, 8-hydroxyquinoline sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, ketamine, kohl, 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, methasuximide, metomidazole, metomidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen sodium, neomycin sulfate, niacin, nicotinamide, nicotine, nicotinamide, nitroglycerin, nonoxonyl-9, norethindrone, norethindrone acetate, nystatin, octoxynol, octyl dimethyl PABA, octyl methoxycinnamate, omega-3 polyunsaturated fatty acids, omeprazole, oxalic 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, quindine gluconate, quinnestrol, ralitoline, ranitidine,

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 sulfate.
- 35 10 The composition of claim 1, wherein said composition further comprises 10% to 70% by weight channeling agents.

- 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 tablet and has a coating composition comprising anionic copolymers sufficient to
 15 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.

20

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 θ 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

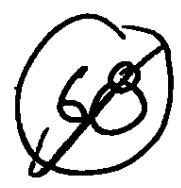
28 The composition of claim 1, wherein the pharmaceutically active substance is
30 selected from the group consisting of glipizide, diltiazem hydrochloride, bupropion, buspirone hydrochloride, Tramadol hydrochloride and verapamil HCl.

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,

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



2020
Bogotá, D C ,

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Opositor

Oficio N° 014267

ASUNTO	Radicación PCT N° 05-7005
	Trámite 011
	Evento 379
	Actuación 330
	Folios 001

Con fundamento en lo previsto por el artículo 42 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición radicada el día 15 de noviembre del 2006, dentro de la solicitud de patente de invención que se adelanta en el expediente de la referencia, no reúne los requisitos formales exigidos por la ley al momento de su presentación, comoquiera que no se precisa el legítimo interés que le asiste en su calidad de opositor, tal como lo dispone el referido artículo, ni se demuestra el detrimento o desventaja de índole patrimonial que pueda sufrir en su esfera individual como consecuencia de la eventual concesión de la patente

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

11 DIC. 2006

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

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