

As. 95.688

Señora

**JEFE DE DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

E. S. D.

REF: Expediente No. 04 121 764 - solicitud de patente de invención a favor
de ASTRAZENECA AB.

Respuesta a oficio No. 13615 del 24 de octubre de 2008

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad ASTRAZENECA AB, según lo acredita el documento de poder presentado ante esa División, me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 3066 notificado por fijación en lista de fecha 24 de octubre de 2008.

En primer lugar, con el fin de atender a todos los requerimientos realizados por el Señor Examinador se adjunta un nuevo capítulo reivindicatorio de 1-6 reivindicaciones. Este nuevo capítulo reemplaza en su totalidad al capítulo inicialmente presentado, no amplía la materia originalmente divulgada y encuentra entero sustento en la descripción; asimismo, las nuevas reivindicaciones definen claramente la presente invención como una formulación oral en tableta, cumpliendo así con todos los requisitos de patentabilidad exigidos por la norma comunitaria.

Dada la limitación realizada en las nuevas reivindicaciones, el solicitante se guarda el derecho de presentar una solicitud divisional con la materia excluida.

Las limitaciones realizadas en el nuevo capítulo reivindicatorio corresponden con las modalidades preferidas de la invención y obvian la excepción anteriormente realizada en la reivindicación 1. Asimismo, estas nuevas reivindicaciones definen la formulación o bjeto de la invención según sus componentes y proporciones y se constituyen como una ilustración acertada de los ejemplos.

Por otro lado, en este nuevo capítulo reivindicatorio se han eliminado las reivindicaciones relativas a uso y métodos de tratamiento.

Sobre la objeción de nivel inventivo realizada por el Señor Examinador es preciso anotar que una diferencia clave entre la presente invención y el arte previo citado es precisamente la formulación de los compuestos de Formula (I) como se reclamada ahora en la reivindicación 1.

Cualquier aproximación a la obviedad de dichas formulaciones sólo puede proceder del análisis retrospectivo de la invención, razonamiento no válido en nuestro entender.

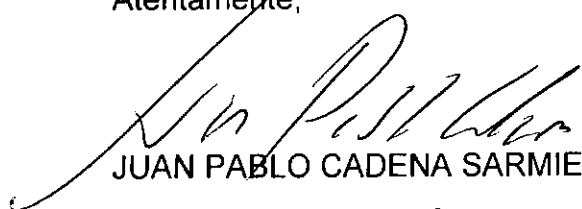
Lo anterior con base en que no existe en el arte previo indicación alguna de una sustitución de un ácido mandélico como la que se propone por los inventores de la presente invención para R1. Ninguno de los documentos citados provee un patrón de sustitución que permitiese el diseño de los compuestos que se reclaman en la presente solicitud.

Adicional a lo antepuesto, un técnico versado en la materia no habría estado motivado de ninguna manera a remover elementos esenciales de los compuestos divulgados en las anterioridades como lo son los grupos sustituyentes nitro de D3 y mucho menos a agregar las sustituciones específicas por halógenos requeridas por la presente solicitud, que no se encuentran indicadas ni en D1, ni en D2, ni en D3. Aún con la divulgación de D2 de formulaciones que incluyen compuestos inhibidores de trombina no habría manera alguna para el experto en la materia de lograr las formulaciones que se reclaman en el nuevo capítulo reivindicatorio a partir de este documento solo o en combinación con D1 o D3. Las falencias de uno y otro documento para llegar a una invención como la presente no son subsanadas por ninguno de los otros.

Así y en vista del nuevo capítulo reivindicatorio respetuosamente solicitamos el retiro de las objeciones a la presente solicitud y la concesión del privilegio solicitado.

De la Señora Jefe,

Atentamente,



JUAN PABLO CADENA SARMIENTO

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C.C. 80.410.337 de Usaquén

Carrera 7 No. 71-21, Torre B, Of. 402

Bogotá, D.C., 22 de enero de 2009

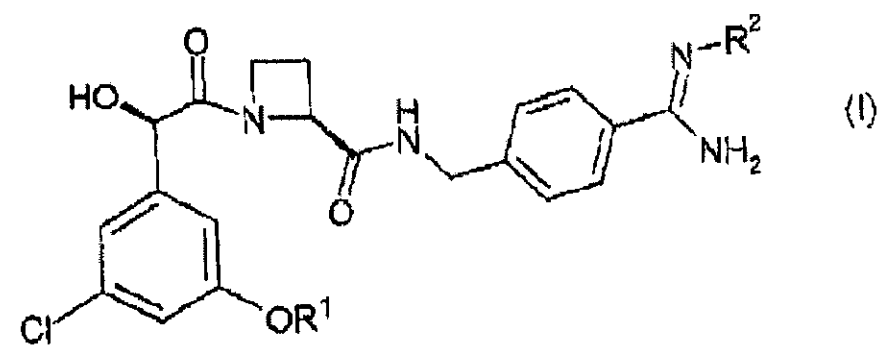
MXBG

Anexos

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REIVINDICACIONES

1. Una formulación farmacéutica de liberación inmediata oral en tableta que comprende, como ingrediente activo, un compuesto de la fórmula (I):



donde

R¹ representa CHF₂ o CH₂CH₂F₂;

R² representa hidrógeno, hidróxi, metoxi o epoxi; o una sal farmacéuticamente aceptable del mismo una celulosa microcristalina en una cantidad de hasta 65% (p/p) de la composición final y al menos otro diluyente o portador farmacéuticamente aceptable seleccionado de fosfato monobásico de calcio, fosfato dibásico de calcio (incluyendo fosfato dibásico de calcio dihidrato y fosfato dibásico de calcio anhidrato), fosfato tribásico de calcio, lactosa, celulosa microcristalina silicada, manitol, sorbitol, almidón (como maíz, papa o arroz), glucosa, lactato de calcio y carboato de calcio; dónde el ingrediente activo y otro diluyentes o excipientes opcionales conforman la composición a su 100% p/p.

2. Una formulación farmacéutica de liberación inmediata como se reivindica en la reivindicación 1, donde la sal farmacéuticamente aceptable del compuestos de Formula (I) es una sal ácido de adición.
3. Una formulación farmacéutica de liberación inmediata como se reivindica en la reivindicación 1 o 2 donde el ingrediente activo es:
 Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe);
 Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe);
 Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab;
 Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(OH);

Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab; o
Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab(OH);
o una sal farmacéuticamente aceptable de cualquiera de estos.

4. Una formulación como se reivindica en la reivindicación 1, 2 o 3 donde el ingrediente activo es una sal cristalina de:

Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe); o
Ph(3-Cl)(5-OCH₂CH₂F)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe).

5. Una formulación como se reivindica en cualquiera de las reivindicaciones 1 a 4, donde el ingrediente activo es Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab(OMe), sal de ácido bencenosulfónico.

6. Una formulación como se reivindica en cualquiera de las reivindicaciones 1 a 5 donde el ingrediente activo es Ph(3-Cl)(5-OCHF₂)-(R)CH(OH)C(O)-(S)Aze-Pab (OMe), sal de ácido bencenosulfónico, caracterizado por un patrón de difracción de rayos X de polvos caracterizado por picos con valores d en 5.9, 4.73, 4.09 y 4.08Å.



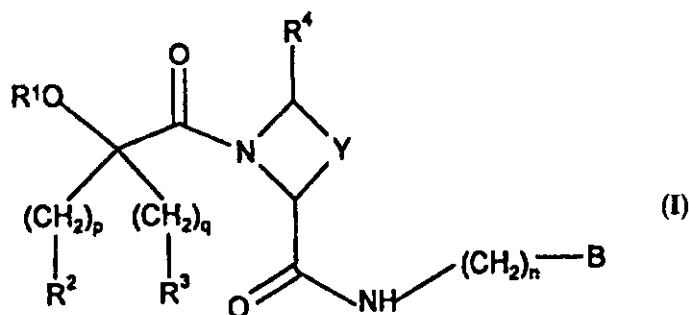
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/SE96/00878 (22) International Filing Date: 2 July 1996 (02.07.96) (30) Priority Data: 9502487-3 6 July 1995 (06.07.95) SE 9502505-2 7 July 1995 (07.07.95) SE 9502504-5 7 July 1995 (07.07.95) SE 9503923-6 7 November 1995 (07.11.95) SE 9504349-3 5 December 1995 (05.12.95) SE 9526411.5 22 December 1995 (22.12.95) GB (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): GUSTAFSSON, David [SE/SE]; Ånghagavägen, Pl 3758, S-429 32 Kullavik (SE). NYSTRÖM, Jan-Erik [SE/SE]; Flintstensvägen 36, S-437 32 Lindome (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).	(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: NEW THROMBIN INHIBITORS, THEIR PREPARATION AND USE

(57) Abstract

There is provided amino acid derivatives of formula (I), wherein p, q, R¹, R², R³, R⁴, Y, n and B have meanings given in the description which are useful as competitive inhibitors of trypsin-like proteases, such as thrombin, and in particular in the treatment of conditions where inhibition of thrombin is required (e.g. thrombosis) or as anticoagulants.



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as coronary arterial disease, cerebral arterial disease, peripheral arterial disease, reperfusion damage, and restenosis after percutaneous trans-luminal angioplasty (PTCA).

Compounds of the present invention that inhibit trypsin and/or thrombin may also be useful
5 in the treatment of pancreatitis.

According to a further aspect of the invention, there is provided a method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound of formula I as defined above, or a
10 pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

Pharmaceutical preparations

15 The compounds of the invention will normally be administered orally, subcutaneously buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route or *via* inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free base, or a pharmaceutical acceptable non-toxic organic or inorganic acid addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and
20 patient to be treated and the route of administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined with any antithrombotic agent with a different mechanism of action, such as the antiplatelet agents acetylsalicylic acid, ticlopidine,
25 clopidogrel, thromboxane receptor and/or synthetase inhibitors, fibrinogen receptor antagonists, prostacyclin mimetics and phosphodiesterase inhibitors .

The compounds of the invention may further be combined with thrombolytics such as tissue plasminogen activator (natural or recombinant), streptokinase, urokinase, prourokinase,
30 anisolated streptokinase plasminogen activator complex (ASPAC), animal salivary gland

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plasminogen activators, and the like, in the treatment of thrombotic diseases, in particular myocardial infarction.

According to a further aspect of the invention there is thus provided a pharmaceutical
5 formulation including a compound of formula I as hereinbefore defined, or a
pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable
adjuvant, diluent or carrier.

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans
10 are about 0.001-100 mg/kg body weight at peroral administration and 0.001-50 mg/kg body
weight at parenteral administration.

The compounds of the invention have the advantage that they may be more efficacious, be
less toxic, be longer acting, have a broader range of activity, be more potent, produce fewer
15 side effects, be more easily absorbed than, or that they may have other useful
pharmacological properties over, compounds known in the prior art.

Biological Tests

20 Test A

Determination of Thrombin clotting Time (TT)

Human thrombin (T 6769, Sigma Chem Co) in buffer solution, pH 7.4, 100 μ l, and inhibitor
solution, 100 μ l, were incubated for one min. Pooled normal citrated human plasma, 100 μ l,
was then added and the clotting time measured in an automatic device (KC 10, Amelung).

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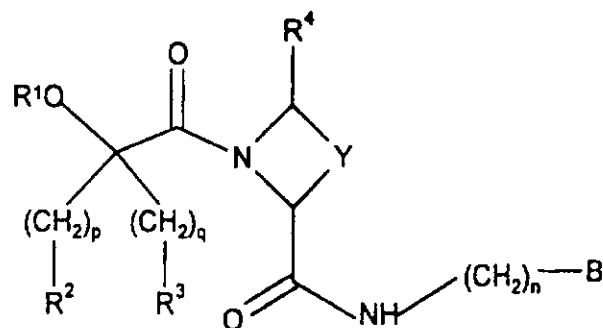
The clotting time in seconds was plotted against the inhibitor concentration, and the $IC_{50}TT$
was determined by interpolation.

$IC_{50}TT$ is the concentration of inhibitor that doubles the thrombin clotting time for human
30 plasma.

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Claims

1. A compound of formula I,

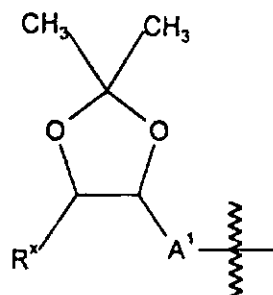


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wherein

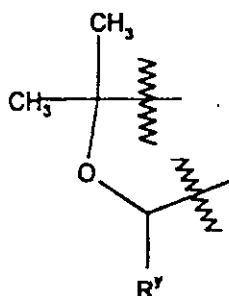
p and q independently represent 0, 1, 2, 3 or 4;

R¹ represents H, 2,3-epoxypropyl, C₁₋₆ alkyl (which latter group is optionally substituted or
10 terminated by one or more hydroxy group), a structural fragment of formula Ia



Ia

wherein A¹ represents a single bond or C₁₋₄ alkylene and Rˣ represents H or C₁₋₄ alkyl,
provided that there are no more than six carbon atoms in the chain Rˣ-C-C-A¹, or, when p
represents 0, together with R² represents a structural fragment of formula Ib,



Ib

wherein R^y represents H or C_{1-3} alkyl;

R^2 represents H, $Si(Me)_3$, naphthyl, indolyl, $CHR^{21}R^{22}$ or C_{1-4} alkyl (which latter group is optionally substituted or terminated by one or more fluorine or hydroxy group) or C_{3-8} cycloalkyl or phenyl (which latter two groups are optionally substituted by one or more of C_{1-4} alkyl, C_{1-4} alkoxy, halo, hydroxy, cyano, nitro, methylenedioxy, trifluoromethyl, $N(H)R^{23}$, $C(O)OR^{24}$), or, when p represents 0, together with R^1 represents a structural fragment of formula Ib;

R^3 represents H, $Si(Me)_3$, naphthyl, indolyl, $CHR^{25}R^{26}$ or C_{1-6} alkyl (which latter group is optionally substituted or terminated by one or more fluorine or hydroxy group) or C_{3-8} cycloalkyl or phenyl (which latter two groups are optionally substituted by one or more of C_{1-4} alkyl, C_{1-4} alkoxy, halo, hydroxy, cyano, nitro, methylenedioxy, trifluoromethyl, $N(H)R^{27}$ or $C(O)OR^{28}$);

R^{21} , R^{22} , R^{25} and R^{26} independently represent cyclohexyl or phenyl;

R^{23} and R^{27} independently represent H, C_{1-4} alkyl or $C(O)R^{29}$;

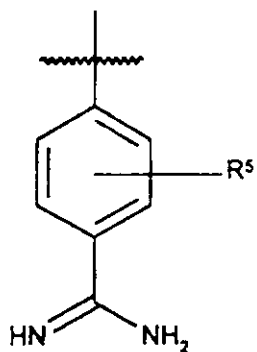
R^{24} , R^{28} and R^{29} independently represent H or C_{1-4} alkyl;

R^4 represents H or C_{1-4} alkyl;

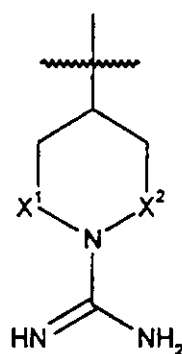
Y represents C_{1-3} alkylene optionally substituted by C_{1-4} alkyl, hydroxy, methylene or oxo;

n represents 0, 1, 2, 3 or 4; and

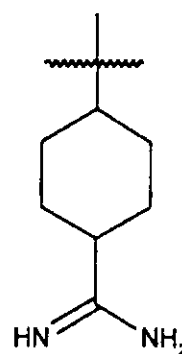
B represents a structural fragment of formula IVa, IVb or IVc



IVa



IVb



IVc

wherein

R^5 represents H, halo or C_{1-4} alkyl; and

X^1 and X^2 independently represent a single bond or CH_2 ;

5 provided that when R^1 , R^2 and R^4 all represent H, p represents 0, Y represents $(CH_2)_2$, n represents 1 and:

(a) R^3 represents unsubstituted phenyl and:-

(i) B represents a structural fragment of formula IVa and R^5 represents H, then q does not represent 0 or 1; and

10 (ii) B represents a structural fragment of formula IVb and X^1 and X^2 both represent CH_2 , then q does not represent 0; and

(b) R^3 represents unsubstituted cyclohexyl, B represents a structural fragment of formula IVa and R^5 represents H, then q does not represent 0;

15 or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein n represents 1 when B represents a structural fragment of formula IVa, IVc or IVb in which latter fragment X^1 and X^2 both represent CH_2 .

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3. A compound as claimed in claim 1 wherein n represents 2 when B represents a structural fragment of formula IVb in which fragment X^1 represents a single bond and X^2 represents either a single bond or CH_2 .

25 4. A compound as claimed in claim 1 or claim 2 wherein R^5 represents H when B represents a structural fragment of formula IVa.

5. A compound as claimed in any one of claims 1 to 4 wherein R^4 represents H.

30 6. A compound as claimed in any one of claims 1 to 5 wherein p represents 0.



US006194000B1

(12) **United States Patent**
Smith et al.

(10) **Patent No.: US 6,194,000 B1**
(45) **Date of Patent: Feb. 27, 2001**

(54) **ANALGESIC IMMEDIATE AND
CONTROLLED RELEASE
PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Ian Keith Smith, Blair Athol; Grant
Wayne Heinicke, Fairview Park, both
of (AU)**

(73) Assignee: **F.H. Faulding & Co., Limited,
Underdale (AU)**

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

(21) Appl. No.: **09/062,060**

(22) Filed: **Apr. 17, 1998**

Related U.S. Application Data

(63) Continuation of application No. PCT/AU96/00658, filed on
Oct. 8, 1996.

Foreign Application Priority Data

Oct. 19, 1995 (AU) 6057

(51) Int. Cl.⁷ **A61K 9/14; A61K 9/20;
A61K 9/22; A61K 9/24; A61K 9/54**

(52) U.S. Cl. **424/458; 424/422; 424/423;
424/436; 424/449; 424/451; 424/455; 424/457;
424/464; 424/465; 424/468; 424/472; 424/473;
424/489; 424/490; 424/483; 424/484; 424/485;
424/486; 424/487; 424/488; 514/770; 514/772.2;
514/772.3; 514/773; 514/777; 514/781;
514/782; 514/783; 514/784; 514/785; 514/786;
514/787**

(58) Field of Search **424/464, 468,
424/490, 422, 423, 436, 449, 451, 457,
458, 483, 473, 455, 489, 472, 465, 484,
485, 486, 487, 488**

(56) References Cited

U.S. PATENT DOCUMENTS

4,859,461	*	8/1989	Chow et al.	424/79
4,859,462	*	8/1989	Chow et al.	424/79
5,084,278	*	1/1992	Mehta	424/441
5,352,683		10/1994	Mayer et al.	
5,502,058		3/1996	Mayer	
5,834,479		11/1998	Mayer et al.	
5,840,731		11/1998	Mayer et al.	

OTHER PUBLICATIONS

Chapman, C.R. et al., "Pain Measurement: an Overview",
Pain, 22 (1985) pp. 1-31.

Hawthorn, Jan et al., "Management of Cancer Pain: Inter-
national Training for Cancer Nurses", developed by Glaxo
Wellcome in collaboration with The International Society of
Nurses in Cancer Care, 1996, 6 pp.

* cited by examiner

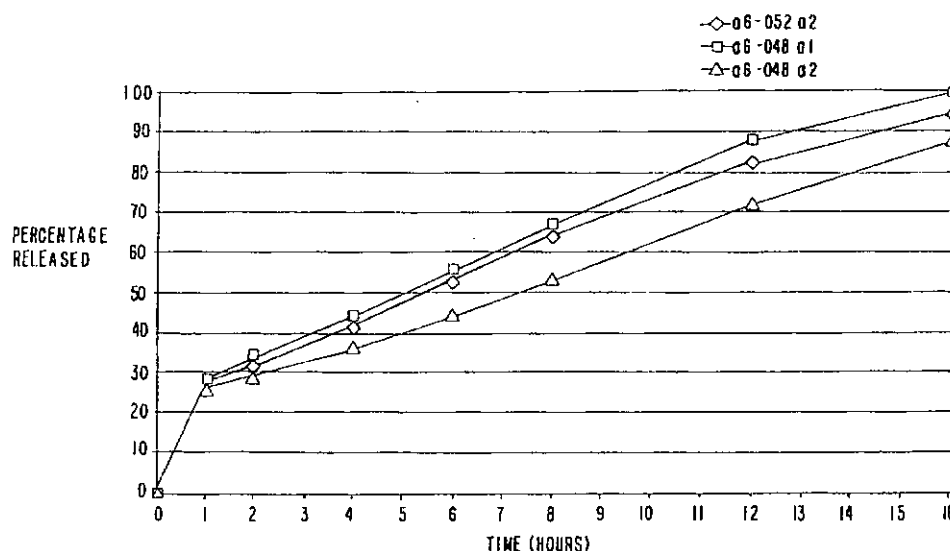
Primary Examiner—James M. Spcar

(74) *Attorney, Agent, or Firm*—Cohen, Pontani, Lieberman
& Pavane

(57) ABSTRACT

Disclosed is a method for the therapeutic treatment of pain
related to wind up in a human or animal. The method of the
invention is practiced by administering to the subject an
effective amount of an analgesic pharmaceutical composition
which includes a NMDA receptor antagonist in an
immediate release form combined with an NMDA receptor
antagonist in a sustained release form. The immediate
release form and sustained release form are present in suf-
ficient amounts to diminish or abolish wind up.

48 Claims, 2 Drawing Sheets



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

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;
- 2) confectionery, for example, chewing gums, lozenges or candy bars;
- 3) powders, for example, drug powder, prilled material, coated actives or granulated materials;
- 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;
- 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.

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

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, chremophor, tweens, spans, pluronics, and the like), insoluble components (microcrystalline cellulose, $\text{Ca}_3(\text{PO}_4)_2$, talc, fumed silica, i.e. aerosil® 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 Pharmacopeia XXII includes extended release dosage forms which allow at least a twofold reduction in dosing frequency as compared to the drug presented as a conventional dosage form and delayed release dosage forms which release the drug at a time other than 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 colorants. The active component 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 components is present in

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amounts of 10 to 80% by weight based on the weight of the total core element. The core may be 200 to 1700µ 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 tableting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, fillers, and excipients known to those familiar with the art. SR tablets may contain granulates, coated powders, pellets, or be multi-layered and the finished tablet may be coated or uncoated.

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

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

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.

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.

The particle sizes of the IR and SR components in the dosage form depends on the technology used. The particle

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sizes component range from submicron to 500 μm for powder technologies (mixtures, spray drying, dispersions etc), 5–1700 μm for coating technologies (wurstler, top spray, bottom spray, spray drying, extrusion, layering etc), to 1–40 mm for tabletting technologies.

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 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 60%. An immediate release NMDA receptor antagonist content of about 15% to 50% is particularly preferred. 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 examples illustrate 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 examples below describes pellet (particle sizes 200–1700 μm) in a capsule. All the quoted ranges are % w/w.

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

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the range 10–90% with a binder in the range 0.1–50% 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 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 enteric 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

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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, polacrilin potassium, and the like.

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

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

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 i.e. 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 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 hydroxypropyl methyl cellulose. A typical matrix tablet would contain the swelling/gelling polymer in amounts from approximately 15 to 70% by weight based on the total weight of the tablet and filler in amounts from approximately 15 to 70% by weight based on the total weight of the tablet. Additional fillers may be included in amounts from approximately 0–60% by weight based on the total 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 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 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 of 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).

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

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

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

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

The coat may be applied as a solution or suspension from aqueous or organic solvents solution concentration in equipment familiar to those skilled in the art. The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. Where solutions are applied the solvent is present in amounts from approximate by 25–99% by weight preferably 85–97% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohols, lower chlorinated hydrocarbons, ketones, or mixtures thereof. Where latexes are applied, the solvent is present in amounts from approximately 25–97% by weight, preferably 60–97% based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

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

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

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

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

The composition of the invention may be produced by providing a core containing the NMDA receptor antagonist

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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 amount of NMDA receptor antagonist for controlled release.

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

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

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

The present invention also provides a kit including a plurality of unit dosage forms, in a container or the like, the container including indicia indicative of a dosage regimen, at least one of the unit dosages being in the form of a pharmaceutical composition in accordance with the present invention.

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.

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.

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.

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BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 shows the dissolution rate of sustain release dextromethorphan capsules; and

FIG. 2 shows the dissolution rate of amantadine pellets.

EXAMPLE 1

A DEXTROMETHORPHAN DISSOLUTION PROFILE

BACKGROUND

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 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 antagonist from a single dose.

METHOD

a) PRODUCTION OF DEXTROMETHORPHAN CAPSULES

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

(i) Granulating Dextromethorphan Solution

Ingredient	% (W/W)
Ethanol 96 PC/BP	95.0
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.

(ii) Coating Solutions

Formulation 1

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

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.

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Formulation 2

Ingredient	% (W/W)
Ethanol 96 PC/BP	93.43
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

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

(iii) Dextromethorphan Cores

Dextromethorphan Cores Part 1

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

Inlet Air Temperature:	50° C.
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 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.

Ingredient	% (W/W)	Typical Amounts (kg)
Ethanol 96 PC/BP	—	0.200
Dextromethorphan Granulating Solution	43.82	1.560
Dextromethorphan HBr	33.71	1.200
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

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

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

Ingredient	% (W/W)	Typical Amounts (kg)
Ethanol 96 PC/BP	—	0.200
Dextromethorphan Granulating Solution	43.82	1.560
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%.

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The final core will have the following composition.

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

(iv) Dextromethorphan Pellets

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

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

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

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

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

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

Ingredient	% (W/W)	Typical Amounts (kg)
Ethanol 96 PC/BP	—	0.2000
Coating Formulation 2	67.80	2.2222
Talc Purified Micronised BP/USP	1.69	0.0555
Dextromethorphan Cores	30.51	1.0000

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The resulting Dextromethorphan Pellets have an excipient breakdown as follows.

Dextromethorphan Pellet A6-052 A2 (10% TPCW)

Ingredient	% (W/W)
Dextromethorphan HBr	68.56
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

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RESULTS

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 dissolution profile in Table 2 and shown in FIG. 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)	% Released	± 20% limit	Actual		
			Aim	A6-048 A1	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

-continued

Ingredient	% (W/W)
Poly Ethylene Glycol (5000) NF	1.86
Talc Purified Micronised BP/USP	4.76

Dextro Pellet A6-048 A1 (8% TPCW)

Ingredient	% (W/W)
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
Ethyl Cellulose N50	4.61
Talc Purified Micronised BP/USP	3.85

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

(v) Capsules

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 potencies of each of the cores and pellets was determined by UV assay.

b) MEASUREMENT OF DISSOLUTION OF DEXTROMETHORPHAN CAPSULES

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

EXAMPLE 2

BACKGROUND

Amantadine is an NMDA receptor antagonist which has been in clinical use many years. Pharmacokinetic data for the drug are as follows: half life about 12 hours, bioavailability is high (assumed to be 100%), absorption rate constant is 0.693 per hr, and elimination rate constant 0.058 per hour. The normal dosage regimen is 200 mg per day given in two divided doses of 100 mg.

In designing a suitable once daily formulation, the primary aim is to ensure that the fluctuations in plasma concentrations (maximum divided by minimum) resulting from a dose of 200 mg once a day (sustained release) are equal to or less than those obtained with the use of immediate release formulation given twice daily. Simulations were performed using the above pharmacokinetic data to calculate a dissolution profile to achieve this minimum plasma concentration fluctuation. The product required had an immediate release component of 30% and a sustained release of the other 70% over approximately a 12 hour period at intestinal pH.

Method

Amantadine capsules were prepared according to the following and dissolution profiles were determined on the sustained release portion thereof.

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Amantadine fast release cores	
Amantadine hydrochloride	2000 g
Microcrystalline cellulose	2000 g
Purified water	1680 g

The materials were blended together and the resulting granulate was passed through a 1.2 mm screen using a Nica E 140 extruder. The extrudate was placed in portions on a Marmeriser (Q400, Fuji Paudal) until the desired roundness had been achieved. The product was dried in a Glatt WSG-3 fluid bed with an inlet air temperature of 50C. for 4 hours and then sieved between 1000 and 1700 um. The yield was 74.5%. The dissolution of these particles (USP XXIII, apparatus II) was rapid at both pH 1.2 and pH 6.8.

Coating solution	
Ethyl cellulose N-50	200 g
Hydroxy propyl methyl cellulose E-5	22.5 g
Triethylcitrate	27.5 g
Ethanol 96PC/BP	4750 g

Ethanol 96PC/BP and hydroxypropyl methyl cellulose E-5 were shear stirred. After the HPMC had dissolved ethyl cellulose N-50 was added and shear stirred until it had dissolved completely.

Amantadine Slow Release Pellets

The fast releasing cores were dispensed into a fluid bed coater. The conditions in the fluid bed coater were as follows:

Inlet air temperature	50° C.
Air flow	80 meters cubed/hour
dew point	0° C.

The pellets were produced by coating methods standard to those skilled in the art.

The final pellets in the size range 1000-1700 um were retained.

Coating formulation	2720 g
Amantadine fast release cores	1000 g
Talc USP	68 g

The talc was suspended in the coating solution and the suspension was sprayed onto the cores in the fluid bed coater. This resulted in a product with a theoretical polymer coat weight of 12%.

The resulting amantadine pellets have an excipient breakdown as follows:

Amantadine hydrochloride	41.53%
Microcrystalline cellulose	41.53%
Talc	5.64%

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Ethyl cellulose	9.04%
Hydroxy propyl methyl cellulose	1.02%
Triethylcitrate	1.24%

Measurement of Dissolution of Amantadine Sustained Release Pellets

Dissolution was measured using USPXXIII apparatus 1, method <711> with pH 6.8 dissolution media. Analysis was performed using the USPXXIII method for amantadine.

The dissolution profile of the sustained release portion was measured and compared with that calculated from the pharmacokinetic parameters. The results appear in Table 3 and are shown in FIG. 2.

TABLE 3

Aim and actual dissolution		
Time	% Released	Aim % Released
2	4	17
4	30	33
6	64	50
8	70	67
10	80	83
12	90	100

The sustained release portion released 13% at 2 hours in pH 1.2 dissolution media, showing that the capsule does not dose dump in the stomach.

A combination of 30% of the dose as the starting core (120 mg of cores, equivalent to 60 mg of amantadine) and 70% of dose as the sustained release pellet (279 mg, equivalent to 140 mg of amantadine) will have dissolution properties substantially like the required profile of a once daily product. The dose combination fits into a size 0 capsule.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in use of such terms and expressions excluding any equivalents of the feature shown and described or portions thereof, it being recognized that various modifications are possible within the scope of the invention.

What is claimed is:

1. A method of preparing an analgesic pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject for the treatment of pain, comprising:

providing a matrix or coated core containing an NMDA receptor antagonist to provide sustained 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

combining the matrix or coated core with the mixture, the immediate release form and sustained release form being present in sufficient amounts to diminish or abolish wind-up.

2. The method of claim 1 wherein the matrix core is a matrix composition selected from the group consisting of a wax; an insoluble matrix polymer; water soluble matrix materials and mixtures thereof.

3. The method of claims 1 wherein the coated core is a core of NMDA receptor antagonist coated with a pharma-

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aceutically acceptable polymer including diffusion barrier polymers with or without porosity enhancers selected from the group consisting of ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups, polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials, sugars, lactose, sucrose, fructose and mannitol, salts, sodium chloride, potassium chloride, organic acids, fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof, enteric polymers, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

4. The method of claim 1 further comprising compressing the core and the mixture into a tablet form and wherein the core and the mixture are dispersed throughout the tablet form.

5. The method of claim 1 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.

6. The method of claim 1 wherein the core and the mixture are combined into a capsule.

7. A method for the therapeutic or prophylactic treatment of pain related to wind-up in a human or animal subject, the method comprising administering to the subject an effective amount of an analgesic pharmaceutical composition including an NMDA receptor antagonist in an immediate release form combined with an NMDA receptor antagonist in a sustained release form being present in sufficient amounts to diminish or abolish wind-up.

8. The method of claim 7 wherein the analgesic pharmaceutical composition is in an unit dosage form.

9. The method of claim 7 for the treatment of chronic or acute pain.

10. The method of claim 9 wherein the analgesic pharmaceutical composition is administered pre-operatively.

11. The method of claim 7 wherein the pain is related to hyperalgesia or allodynia.

12. 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 comprising administering to the subject an effective amount of an analgesic pharmaceutical composition including an NMDA receptor antagonist in an immediate release form combined with an NMDA receptor antagonist in a sustained release form, the immediate release form and sustained release form being present in sufficient amounts to diminish or abolish wind-up.

13. The method of claim 7 wherein the NMDA receptor antagonist is present in an amount of from about 1 to 5000 mg.

14. The method of claim 7 wherein the NMDA receptor antagonist is present in an amount of from about 1 to 1000 mg.

15. The method of claim 7 wherein the NMDA receptor antagonist is present in an amount of from about 100 to 800 mg.

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16. The method of claim 12 wherein the NMDA receptor antagonist in the immediate release form comprises 5% to 90% of the total amount of the NMDA receptor antagonist.

17. The method of claim 16 wherein the NMDA receptor antagonist in the immediate release form comprises 10%-60% of the total amount of the NMDA receptor antagonist.

18. The method of claim 17 wherein the NMDA receptor antagonist in the immediate release form comprises 15%-50% of the total amount of the NMDA receptor antagonist.

19. The method of claim 7 wherein the NMDA receptor antagonist in an immediate release form is combined in a single dosage form with an NMDA receptor antagonist in a sustained released form.

20. The method of claim 19 wherein a portion of the NMDA receptor antagonist is immediately released following administration and a portion is sustained released to provide a therapeutic effect over a period of greater than 6 hours.

21. The method of claim 20 wherein the therapeutic effect is provided over a period of 8 to 24 hours.

22. The method of claim 21 wherein the therapeutic effect is provided over a period of 8 to 12 hours.

23. The method of claim 21 wherein the therapeutic effect is provided over a period of 12 to 24 hours.

24. The method of claim 7 wherein the NMDA receptor antagonist in the immediate release or sustained release form is the same or different.

25. The method of claim 7 wherein the immediate release or sustained release form are in a form selected from the group consisting of active cores comprising; tablets; multi-layered tablets; capsules containing coated active cores and/or uncoated active cores; liquids; powder; coated or uncoated granules; coated or uncoated pellets; suspensions; an injectable solution; a suppository; implant; transdermal patch; and osmotic pump.

26. The method of claim 25 wherein the immediate release and sustained release form of the NMDA receptor antagonist are separate components in a multi-layer tablet and 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 sustained release form.

27. The method of claim 26 wherein the immediate release and sustained release forms of the NMDA receptor antagonist are dispersed throughout the tablet.

28. The method of claim 25 wherein the immediate release and sustained release form of the NMDA receptor antagonist are separate components in a capsule and 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 sustained release form.

29. The method of claim 28 wherein one or more of the components are active cores or pellets and wherein the active cores are uncoated or coated for immediate or sustained release and wherein the pellets are coated for sustained release.

30. The method of claim 29 comprising a blend of cores and pellets wherein a ratio of cores to pellets is 25/75.

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31. The method of claim 7 wherein the NMDA receptor antagonist is a morphinan selected from the group consisting of dextromethorphan and dextrorphan, ketamine, amantadine, memantine, cliprodil, ifenprodil, dizocilpine, remacemide, lamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, a pharmaceutically acceptable salt or ester thereof or a metabolic precursor of any of the foregoing.

32. The method of claim 7 wherein the sustained release form of the NMDA receptor antagonist is in a matrix composition selected from the group consisting of waxes; insoluble matrix polymer; and water soluble matrix material and mixtures thereof.

33. The method of claim 32 wherein the sustained release form further includes an enteric polymer selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, polymethacrylates containing carboxyl groups and combinations thereof.

34. The method of claim 33 wherein the composition further includes a binder selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methyl cellulose, ethyl cellulose, cellulose acetate butyrate, or an enteric binding material, hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate or mixtures thereof.

35. The method of claim 7 wherein the immediate release or sustained release form is coated with a pharmaceutically acceptable coating composition selected from the group consisting of ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups, pharmaceutically acceptable polymers, polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials, sugars, lactose, sucrose, fructose and mannitol, salts, sodium chloride, potassium chloride and derivatives, organic acids fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof and enteric polymers, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

36. The method of claim 35 wherein the coating composition comprises from 0 to 50% by weight of a material selected from the group consisting of silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, polacrillin potassium, or mixtures thereof.

37. The method of claim 36 wherein the composition further comprises 0 to 200 wt.-% of a filler selected from the group consisting of silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, microcrystalline cellulose, polacrillin potassium, or mixtures thereof.

38. The method of claim 37 wherein the composition further comprises a swelling/gelling polymer selected from the group consisting of hydroxypropyl cellulose in the range of 0-50 wt.-% or a hydrophobic material, in the range 10-90 wt.-%.

39. The method of claim 7 wherein the analgesic pharmaceutical composition is in a form suitable for oral or rectal administration or for administration by transdermal,

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intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular means.

40. The method of claim 38 wherein the swelling/gelling polymer is cetyl alcohol.

41. The method of claim 35 wherein the enteric polymer is selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, polymethacrylates containing carboxyl groups and mixtures thereof.

42. The method of claim 2 wherein the wax is selected from the group consisting of carnauba, bees wax, paraffin wax, ceresine, shellac, fatty acids, fatty alcohols; oils, hardened oils or fats, hardened rapeseed oil, castor oil, beef tallow, palm oil and soya bean oil; the insoluble matrix polymer is selected from the group consisting of ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups; and the water soluble matrix material is selected from the group consisting of polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials selected from the group consisting of sugars, salts, and organic acids.

43. The method of claim 7 wherein the immediate release form of the NMDA receptor antagonist is particles admixed with at least one component selected from the group consisting of cellulose, hydroxypropyl methyl cellulose; a surfactant selected from the group consisting of sodium lauryl sulphate, chremophor, tweens, spans, pluronics; an insoluble component selected from the group consisting of microcrystalline cellulose, $\text{Ca}_3(\text{PO}_4)_2$, talc, fumed silica; a coating material selected from the group consisting of polyethylene glycol, hydroxypropyl methyl cellulose, wax, fatty acids and combinations thereof.

44. A method for the therapeutic or prophylactic treatment of pain related to wind-up in a human or animal subject, the method comprising administering to the subject an effective amount of an analgesic pharmaceutical composition including an NMDA receptor antagonist in an immediate release form combined with an NMDA receptor antagonist in a sustained release form, the immediate release form and sustained release form being present in sufficient amounts to diminish or abolish wind-up wherein the analgesic pharmaceutical composition comprises dextromorphan 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 at a pH of between 1.6 and 7.2 at 37° C. is between 22 and 33 wt.-% dextromorphan released after 0.5 hr, between 24 and 36 wt.-% dextromorphan released after 1 hour, between 28 and 42 wt.-% dextromorphan released after 2 hours, between 36 and 54 wt.-% dextromorphan released after 4 hours, between 44 and 66 wt.-% dextromorphan released after 6 hours, between 52 and 78 wt.-% dextromorphan released after 8 hours, between 68 and 100 wt.-% dextromorphan released after 12 hours, and greater than 80 wt.-% dextromorphan released after 16 hours.

45. The method of claim 32 wherein the wax is selected from the group consisting of carnauba, bees wax, paraffin wax, ceresine, shellac, fatty acids, fatty alcohols, oils, hardened oils or fats, rapeseed oil, castor oil, beef tallow, palm

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
JUAN PABLO CADENA
(Apoderado)

ASUNTO Radicación 04121764
 Trámite 002
 Evento 001
 Actuación 430
 Oficio 2166
 Folios 021

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/SE03/00857
Fecha de Presentación Internacional 27-05-2003

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

1.1. Descripción: (Folios: 69 a 181) como se radicó inicialmente.

1.2. Reivindicaciones: 1 a 11 (Folios: 182 a 184) como se radicó inicialmente. Modificadas: 1 a 6 (folios: 240 y 241).

1.3. Prioridad: 31/05/2002, SE 0201658-2.

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. Objeto de la invención:

La presente solicitud se titula: "Formulación farmacéutica de liberación inmediata".

El objeto de la presente solicitud se refiere a una formulación farmacéutica de liberación inmediata que dispone la administración de un fármaco en particular, la manufactura de la citada formulación y la utilización de dicha formulación en el tratamiento o la prevención de la trombosis.

Según la descripción, con frecuencia es deseable formular unos compuestos farmacéuticamente activos para una liberación inmediata después de una administración oral y/o parenteral con el fin de obtener una concentración suficiente en plasma del fármaco dentro del periodo de tiempo requerido para obtener la respuesta terapéutica deseada (ver folio: 69).

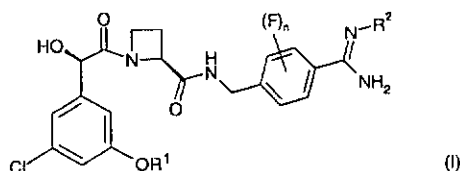
En el caso del tratamiento o de la profilaxis de la trombosis, las formulaciones de liberación inmediata pueden ser necesarias para asegurarse que una cantidad suficiente del fármaco llega al plasma en un periodo relativamente corto para permitir una rápida manifestación de la acción.

Las formulaciones de liberación inmediata son superiores cuando no se requieren múltiples dosis, y cuando no es necesario conservar la concentración en plasma en un nivel constante durante un periodo prolongado.

La solicitud internacional de patente N° PCT/SE01/02657 (WO 02/44145, con la primera fecha de prioridad del 1 de diciembre de 2000, presentada el 30 de noviembre de 2001, publicada el 6 de junio de 2002) divulga un número de compuestos que son, o que se metabolizan en como la trombina. Los tres compuestos del folio: 70 forman parte de aquellos que se divulgan específicamente en la presente solicitud.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 6 (folios: 240 y 241): Una formulación farmacéutica de liberación inmediata oral en tableta que comprende, como ingrediente activo, un compuesto de la fórmula (I):



El problema planteado en esta solicitud es buscar una formulación farmacéutica de liberación inmediata para el tratamiento de un desorden cardiovascular.

La solución propuesta por la presente solicitud consiste en una formulación farmacéutica de liberación inmediata que comprende, como ingrediente activo, un compuesto de la fórmula (I) (ver folio: 72).

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/397; A61P 9/10.

4. De la solicitud de Patente

4.1. Reivindicaciones (artículo 30 D 486)

De acuerdo con lo revelado en el capítulo reivindicatorio modificado, la reivindicación 6 menciona una formulación de las reivindicaciones 1 a 5 donde el ingrediente activo es al parecer una forma cristalina del compuesto de fórmula I, puesto que menciona unos datos del patrón de difracción de rayos X, pero no se define en forma clara la reivindicación como una formulación farmacéutica que es lo que se reclama, sino que se define por un análisis del principio activo que forma parte de la formulación; se le recuerda al señor solicitante que las formulaciones se deben definir por sus componentes es decir, principio activo y excipientes que la hagan diferente de lo ya conocido y no por resultados de uno de sus componentes.

5. Determinación del Estado de la Técnica:

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 31-05-2002.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

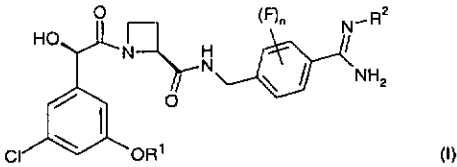
Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	WO 97/02284	New thrombin inhibitors, their preparation and use	23 de enero de 1997
D2	WO 00/13671	Immediate release tablet	16 de marzo de 2000
D3	US 6194000	Analgesic immediate and controlled release pharmaceutical composition	27 de febrero de 2001

6. Análisis de patentabilidad (artículo 14 D486)

6.1. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: una formulación farmacéutica de liberación inmediata oral en tableta que comprende, como ingrediente activo, un compuesto de la fórmula (I):



Donde R₁ representa CHF₂ o CH₂CH₂F₂;

R₂ representa hidrógeno, hidroxilo, metoxi o epoxi; o una sal farmacéuticamente aceptable del mismo, una celulosa microcristalina en una cantidad de hasta 65% (p/p) de la composición final y al menos otro diluyente o portador farmacéuticamente aceptable seleccionado de fosfato monobásico de calcio, fosfato dibásico de calcio (incluyendo fosfato dibásico de calcio dihidrato y fosfato dibásico de calcio anhidrato), fosfato tribásico de calcio, lactosa, celulosa microcristalina silicificada, manitol, sorbitol, almidón (como maíz, papa o arroz), glucosa, lactato de calcio y carboato de calcio; donde el ingrediente activo y otro diluyentes o excipientes opcionales conforman la composición a su 100% p/p.

La anterioridad WO 97/02284 (folios: 242 a 247) hace mención de compuestos derivados de 1-[2-(3-clorofenil)-2-hidroxiacetil] azetidin-2-carboxamida que, al hacer los reemplazos de sustituyentes respectivos, se encuentran los principios activos que se mencionan en la formulación de la presente solicitud. Se menciona además, que estos compuestos se pueden administrar en forma oral, donde el principio activo está en forma de base libre o en una de sus sales inorgánicas u orgánicas farmacéuticamente aceptables y en una forma de dosificación aceptable.

El documento WO 00/13671 (folios: 226 a 228) menciona formulaciones sólidas de liberación inmediata que contienen inhibidores de trombina muy semejantes a los compuestos de fórmula I de las formulaciones de la presente solicitud. Las formulaciones pueden contener celulosa microcristalina, glicolato de almidón, polivinilpirrolidona, manitol, estearil fumarato de sodio, que son los mismos excipientes que se revelan en la presente solicitud (ver ejemplo 44, folio: 166).

El documento US 6194000 (folios: 248 a 257) se relaciona con composiciones farmacéuticas de liberación inmediata y controlada de analgésicos; en esta anterioridad se dice que el principio activo se puede formular con polímeros como por ejemplo hidroxipropilmetilcelulosa (que aparece en los ejemplos de formulaciones de la presente solicitud), componentes insolubles, como la celulosa microcristalina y el fosfato dibásico de calcio (se encuentran en la formulación de la reivindicación 1), azúcares como la lactosa y el manitol (están en la formulación de la reivindicación 1 de la presente solicitud), talco, polivinilpirrolidona (PVP) (se encuentran en los ejemplos de la descripción de la presente solicitud), entre otros componentes usualmente empleados para la preparación de este tipo de formulaciones de liberación inmediata.

De hecho, en la descripción de la presente solicitud, en especial, en los folios: 75 a 78, se especifica que las formulaciones de la solicitud se pueden formular de acuerdo con técnicas conocidas y con excipientes convencionales como son: la lactosa, celulosa microcristalina, talco, PVP, polietilenglicol, fosfato de calcio (dibásico, tribásico, hidrato, anhidrato), glucosa, manitol, sorbitol, almidón, carbonato de calcio, lactato de calcio, hidroxipropilmetilcelulosa, etc.

Asimismo, hay que tener en cuenta que en el capítulo reivindicatorio modificado se especifica una formulación del compuesto de fórmula I, pero que no aparece revelada en los ejemplos de la descripción ni se encuentran datos de liberación como sí aparece con algunas de las formulaciones ejemplificadas. Por lo tanto, no se puede ver con claridad cuál es la ventaja técnica de la formulación que se reclama en el actual capítulo reivindicatorio frente a otras formulaciones de liberación inmediata convencionales, es decir, que emplean excipientes normalmente usados para la preparación de este tipo de formulaciones o composiciones farmacéuticas.

El problema técnico planteado en esta solicitud: buscar una formulación farmacéutica de liberación inmediata para el tratamiento de un desorden cardiovascular, se había resuelto previamente mediante formulaciones farmacéuticas de liberación inmediata ya conocidos(as). Por esta razón se considera que las formulaciones farmacéuticas reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

Las reivindicaciones 1 a 6 de esta solicitud no mencionan una característica que conceda un efecto inesperado o especial a las formulaciones farmacéuticas, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1, D2 y D3 divulgaban previamente formulaciones farmacéuticas de liberación inmediata (folios: 242 a 257 y 226 a 228), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud es decir, una formulación farmacéutica de liberación inmediata; de manera que para una persona medianamente versada en la materia sería obvio utilizar estos documentos. Por lo cual puede no haber Nivel Inventivo.

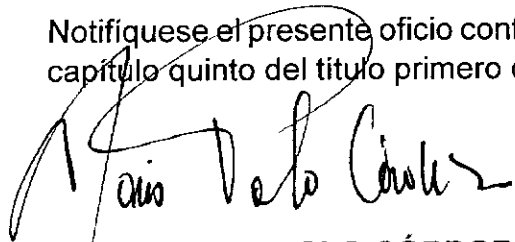
7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO 97/02284	1 a 6	Nivel Inventivo
D2	WO 00/13671	1 a 6	Nivel Inventivo
D3	US 6194000	1 a 6	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará 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 Única Nº 10 de 2001.



DORIS ELENA POLO CÓRDOBA
Jefe de la División de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 20 FEB. 2009

CONCEPTO TÉCNICO No. 376	EXAMINADOR TÉCNICO Código No. 202005
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